Molecular Anatomic Imaging
PET-CT and SPECT-CT Integrated Modality Imaging
SECOND EDITION
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PET-CT and SPECT-CT Integrated Modality Imaging

SECOND EDITION

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To my wife Yela and my children Alexandra, Patrick, and Benjamin.
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Foreword

Within the span of three years since Professor Gustav von Schulthess and his distinguished colleagues first published *Clinical Molecular Anatomic Imaging*, PET-CT scanning has quickly emerged from academic medical centers to become a mainstay in cancer imaging throughout the world. In fact, hospitals and imaging centers use more than 2000 PET-CT scanners to examine well over two million patients annually. This vast dissemination of PET-CT technology has far exceeded initial projections, and thus, experience about the method has been accumulating very rapidly. Because of this exponential growth, it seems likely that much more has been learned about clinical molecular anatomic imaging in the last three years than in the 30-plus years following the introduction of human PET scanning. This explosion of new clinical knowledge and the acceleration of advances in PET-CT hardware, software, and radiopharmaceutical probes have created the need for a new edition of the book three years after its initial publication.

PET-CT is part of a long legacy of important innovations produced by the medical imaging community. Those of us involved in imaging over the past decades have seen revolutionary advances in CT scanning and MR imaging, which have startled the scientific world and transformed the practice of medicine. These discoveries and innovations have been prime examples of so-called “translational medicine” in which the ideas generated in laboratories are rapidly applied to patient care for the improvement of human health. PET-CT is the latest example of an important translational innovation in medical imaging. As detailed in *Clinical Molecular Anatomic Imaging*, PET-CT is being used extensively in clinical practice because it improves the information content of imaging compared to either PET or CT used as a stand-alone method. For cancers that are FDG-avid, the PET-CT method generally improves both the sensitivity and specificity of tumor staging. Furthermore, the method is also very helpful for increasing the confidence of diagnosis. The clinical usefulness of PET-CT is not restricted to the diagnosis and staging of neoplasms. Important investigations have shown the method’s potential for numerous other clinical applications in the cardiovascular system, the central nervous system (CNS), bones, and soft tissues.

The marked growth of PET-CT imaging is occurring during a revolutionary time in medicine in which the molecular basis of health and disease is becoming much better understood. The term “personalized medicine” has been developed and anticipates radically different medical care in which knowledge from molecular-based discovery is used for enhanced diagnosis as well as for therapies directed toward specific molecular targets and pathways in any given patient. It seems inevitable that clinical molecular anatomic imaging will play a key role in transitioning “personalized medicine” from a shadowy concept to a sharply defined reality in the decades ahead. One of the promises of “personalized medicine” is the much earlier detection of disease through genomic and proteomic methods, which can provide a measurement of the likelihood of disease long before there are clinical abnormalities. For those individuals identified by genomic or proteomic methods as having likely disease, the key questions relate to the confirmation of the suspected abnormality and its anatomic localization. Clinical molecular anatomic imaging should be able to prove and localize the presence of early disease as new molecular probes are developed against targets identified by in vitro testing. In this way, we anticipate the conversion of PET-CT from a method that currently provides critical information primarily about the anatomic staging of well-documented and fairly advanced disease to a method that identifies disease when there is far less disease burden or perhaps even before it becomes macroscopic or clinically evident.

Even as we look forward to finding disease in the future far sooner than we do today, we also anticipate the improvement of current therapies through the use of PET-CT. As reflected in the chapters of *Clinical Molecular Anatomic Imaging*, a fundamental shift is changing imaging from a method that has primarily guided surgical and radiation treatment planning to a technique that will direct medical therapies to a far greater extent than occurs today. In particular, in vivo molecular characterization provided by imaging can be used for the earlier monitoring of medical therapy and, perhaps even more importantly, for the selecting of an appropriate therapy for a specific patient. In this way, clinical molecular anatomic
imaging may become a foundation for personalized therapy.

I want to congratulate Professor von Schulthess and his colleagues for their work, which has contributed to the rapid adoption of clinical molecular anatomic imaging as a new standard for patient care. They deserve our added thanks for rewriting *Clinical Molecular Anatomic Imaging* so soon after the first edition was published. Because this rapidly developing field is so vital to current medical practice and to the emergence of the molecular-based practice of medicine, I urge the authors to get some rest now while preparing for the next edition of this important contribution to the medical imaging literature.

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Since the second edition of this book1 appeared in 2002, the use of PET and particularly FDG-PET has grown dramatically and many of the most clinically relevant indications are now reimbursed in many countries. With increased use, a wealth of data is being generated that helps to define the clinical role of PET ever better. The main focus of PET remains on tumor imaging, which accounts for over 80% of the patients examined on most PET scanners in clinical use. SPECT imaging has been used since the 1980s and has become the main way of imaging the brain and the heart with nuclear medicine methods. Body applications in SPECT are still limited as image acquisition is relatively slow and routine extended body surveys with SPECT therefore are not compatible with patient comfort.

While reimbursement was probably the key issue in the clinical acceptance of PET, another remarkable development is the widespread introduction of integrated PET-CT scanners. The introduction of clinical PET started with the installation of a PET-CT scanner with a four-slice CT in March 2001 in our institution, and over the last 4½ years has developed into the fastest growing market for medical imaging equipment with estimated sales of around $1 billion in 2005. Actually, the installed base of PET-only scanners is decreasing as PET owners are replacing their systems with PET-CT. Currently, more than 95% of the newly bought PET systems are PET-CTs and the conclusion is clear: PET in itself will no longer exist in just a few years. This does not mean that PET images in themselves are useless, but it has become amply evident that proper interpretation of a large fraction of all PET body scans requires correlation with anatomic information. Since mental correlation of anatomic images with, for example, a FDG-PET scan is difficult due to the lack of anatomic landmarks, and software image fusion is fraught with problems, "hardware" co-registered molecular and morphological imaging with PET-CT is a very convenient and consistent approach to obtain this correlation. Hence, presenting data on PET mostly integrated with CT data is also critically relevant for owners of PET-only systems. It has been our experience that we have become much better PET image readers with the advent of PET-CT.

Since PET is a costly imaging device, adding a CT adds cost, but only at the level of 20% to 30%. Hence, many who have the money to install PET also will find the extra money to install PET-CT. In fact, PET-CT offers several compelling advantages which may eventually offset the increased cost. Primarily, the addition of CT provides a very speedy way of acquiring attenuation correction data. This increases patient throughput by at least 25% to 30%, makes for efficient use of the PET tracers, which have a short half life, in addition to providing the anatomic correlation information. Many authors have shown in the last 4 years that the availability of matched molecular and anatomic data makes PET-CT a more accurate test than either PET or CT alone. This is of dominant importance, and the second edition reflects this in its contents. As our experience with PET-CT is now based on more than 10,000 examined cases, we have also come to appreciate that teaching the accurate interpretation of PET images is greatly aided by the presence of cross-sectional anatomic images.

In addition, imaging equipment has also been developed which permits the acquisition of "hardware" co-registered SPECT and CT data, hence SPECT-CT has also become a reality. While a system combining a very low-end CT has been on the market for several years now, SPECT systems incorporating more powerful CTs have been available only for the last two years. The speed of adoption of SPECT-CT is much slower than that of PET-CT for two main reasons. First, a SPECT camera costs substantially less than a high-end CT, and second, SPECT cameras are slow data acquisition devices. An integrated SPECT-CT system with a high-end CT system thus leads to inefficient CT use and makes the device difficult to amortize. Nevertheless, all single photon tomographic nuclear imaging can benefit from CT attenuation correction, and tumor imaging with single photon nuclear tracers can benefit importantly from co-registration with anatomical images. In this sense, PET-CT and SPECT-CT are not different imaging modalities. For this reason, we also describe the use of SPECT-CT in topics which we consider of clinical relevance and future potential in this book. An early attempt to incorporate SPECT-CT was already made in the last edition. Thus, applications mainly in tumor SPECT and SPECT-CT imaging are covered in this book. Notable inclusions are the use of SPECT and SPECT-CT in imaging with I-123, I-131, In-111-octreotide as well as some Tc-99m based applications, such as bone, sentinel node, and lung perfusion SPECT-CT. As some of the SPECT tracers will also become widely available as PET tracers, we cannot predict which applications of SPECT-CT will prevail. SPECT-CT with more high-end CT scanners integrated in them will only become a widely
used imaging modality if PET cameras that acquire the data much faster than current systems.

Based on our insights in PET-CT and SPECT-CT imaging, this book has several aims, all of which are centered on clinical utility. Thus, as in the second edition, this book avoids some of the very sophisticated applications of PET, whose use is mainly in research. The introductory chapters have been shortened by omitting financial aspects of PET and PET-CT imaging. Consistent with the accumulating evidence, chapters concerning body imaging have been extended.

- The book should serve as an information source, summarizing current knowledge on how to use and optimize the clinical utility of PET(-CT) and SPECT(-CT).
- By presenting molecular and morphological cross-sectional imaging data side by side, the book is able to demonstrate how synergistic the availability of coregistered data from different modalities often is.
- The initial chapters are devoted to PET-CT and SPECT-CT technology and radiopharmacy.
- Since this book emphasizes clinical imaging, most PET imaging discussed will cover uses of FDG.
- Other PET applications and some SPECT(-CT) applications are also covered.
- The major clinical areas covered are the brain, the heart, body oncology, inflammation, and some special topics as well as pediatric applications.

The book is structured as an easy-to-use reference guide on the relevance of various indications for cross-sectional nuclear imaging, particularly when combined with morphologic imaging. For this reason, each chapter has an abstract with reference to a sample image, when appropriate.

A new feature of this book is a CD-ROM that contains over 80 full cases. The cases are self contained for self-study, but are also referenced from within the book chapters. We believe that this will vastly enhance the teaching effects that this book can provide, because learning by analyzing cases is more effective than being just demonstrated relevant features of cases.

Finally, a word about the contributors to this book. We have been able to enroll several well-known authorities in the field of PET-CT and SPECT-CT and are grateful that they accepted the onerous task to write some of the chapters. Their participation has been critical, since the knowledge in the field is growing rapidly, and no single institution has the accumulated knowledge to discuss all aspects competently. Still, there is a preponderance of contributions coming from our institution, which may add some consistency to the books’ structure.

Gustav K. von Schulthess
The editor of this book is indebted to many people and institutions. Without their help and cooperation, this book would not have been possible and certainly could not have appeared in timely fashion. First, all co-authors from institutions other than mine are gratefully acknowledged. They have delivered excellent chapters at an incredible pace, and for their spontaneous willingness to contribute, I owe them much. They have acknowledged some of their local help in the individual chapters. I also am very grateful to my local collaborators. They all have done a marvelous job not only in writing their contributions, but also by acquiring and analyzing the ever more interesting data coming from our PET-CT and SPECT-CT scanners. While occasionally crunching their teeth at their “slave driver”, they all share my passion about integrated imaging with nuclear methods and CT, the two “ionizing radiation brothers,” and bringing nuclear medicine and radiology closer together than ever before. Important thanks go to many of my clinical colleagues who have adopted PET-CT and SPECT-CT into their daily clinical practice. If they had not appreciated the clinical information provided by these systems, we would not be able to accumulate clinical knowledge at the rate we currently do. My thanks go also to my closest collaborators, Ms. S. Aebi, Ms. E. Hasanic, Dr. N. Loeffel, Ms. J. Valach, and my wife Yela, who bear with me on a daily basis, covering my back so that I have some freedom to undertake such projects as writing and editing this book.

I also acknowledge several institutions and foundations, which are responsible for supporting my endeavours in modern imaging. The Ministry of Health of the Canton of Zurich, the University of Zurich, and the hospital authorities of the Zurich University Hospital have supported modern cross-sectional imaging wholeheartedly and made it possible for us to have the first clinical PET-CT scanner installed worldwide in March 2001. Since this was a risky project, additional foundation and academic money was required and the equipment manufacturer had to help. It is with gratitude that I acknowledge support from the University of Zurich, the Swiss Federal Institute of Technology Zurich, and several foundations such as the Baugarten Stiftung, the Binelli & Ehrsam Stiftung, the Ernst Göhner Stiftung, the Schwyzter Stiftung, and the Jaqueline Seroussi Memorial Foundation for Cancer Research. Without their continued willingness to support PET-CT in Zurich, we would not have been able to accumulate cutting edge knowledge in this exciting field.
Basic Aspects of PET and SPECT Integrated with CT Imaging

In this first part, the physical and technical aspects of positron emission tomography (PET), single-photon emission computed tomography (SPECT), computed tomography (CT), and their integrated forms are discussed. The emphasis is on clinical imaging, and therefore theory is presented in such a way that clinicians can grasp the concepts without difficulty. The goal here is not to give full technical details but to educate the reader on some of the basic aspects that will allow proper understanding of these imaging methods. The references provide adequate reading material for individuals who want to understand the methods in more detail. The integrated imaging modalities PET-CT and SPECT-CT have not been around for very long, and thus a final verdict on several technical aspects has not yet been reached. In addition, the constituent imaging systems are undergoing rapid development. CT in particular has seen an unprecedented development in its capabilities over the last 5 years. Nevertheless, some insights into how to use the integrated techniques have stabilized over the last years and are unlikely to change. The key is thus to conserve the relevant old and adopt the exciting new!
The rapid adoption of positron emission tomography (PET) within the framework of the combined use of PET and computed tomography (CT), or PET-CT, has been astounding. The main reason for this is that the imaging world has seen the limitations of anatomy-based imaging and is now prepared to venture into clinical molecular imaging methods. It should be remembered that nuclear medicine has included clinical molecular imaging right from its birth, in the application of radioactive iodine in the diagnosis and therapy of thyroid disease. The great advantage of fluorodeoxyglucose (FDG)-PET and possibly PET based on other tracers, as well as of single-photon emission computed tomography (SPECT), is that in many instances the lesions are shown with almost no interference from normal anatomic structures. As a consequence, the lesions are very conspicuous, but frequently the morphological information needed to properly locate a lesion is missing. This critical feature of nuclear medicine methods is a result of the “molecular spy” characteristics of most radiopharmaceuticals. The detection systems used are exquisitely sensitive and can locate nano- to picomolar concentrations of tracers, which is the reason nuclear methods are so uniquely useful for molecular imaging. Relevant sensitivities to extrinsic tracer concentration and current spatial resolution ranges are given in Table 1.1. The data show that nuclear imaging methods and anatomic imaging modalities are highly complementary, the former providing high contrast sensitivity, the latter spatial and temporal resolution.

Integrated imaging with PET-CT or SPECT-CT in many ways offers the best of two worlds. This author, in many of his talks, has illustrated this using an example from Richard Scarry’s children’s books. Many readers may recall that the task in these books is to identify “Lowly the Worm,” a little creature placed among a variety of animals and structures depicted on the large pages (Fig. 1.1). This is akin to what a radiologist has to do many times a day when evaluating multiples of 200 or more CT or magnetic resonance (MR) sections to find tumor manifestations in patients who were scanned for staging or therapy follow-up. Tumor PET imaging and SPECT imaging are very different from anatomic imaging: the lesion is readily seen, but the “anatomic” backdrop may be minimal, as shown in Figure 1.2. Thus, precise lesion localization within the anatomic context, which frequently is critical, may be impossible in PET or SPECT. With a combination of the two modalities, the lesions can be identified by virtue of the high sensitivity, specificity, and contrast in PET or SPECT images (represented as the “Lowly the Worm”), and the gray scale background provided by the “hardware coregistered” CT images permits precise lesion localization (Fig. 1.3). It has been well documented over the past years that such multimodality imaging substantially increases the sensitivity and specificity of PET and SPECT examinations and thus make the integrated approach more accurate than the individual modalities by themselves.

SETTING THE STAGE

PET and SPECT imaging are molecular imaging methods. If we define molecular imaging methods narrowly, as methods that permit the measurement of some molecular biological process in vivo, imaging with FDG and some of the SPECT tracers can certainly be classified as molecular imaging. In this narrower definition, nuclear medicine currently encompasses the only clinically useful and utilized molecular imaging methods. If we define molecular imaging more broadly to incorporate the measurement of other functional information, such as perfusion and blood pool imaging, almost all of nuclear medicine qualifies as molecular imaging. In a way, nuclear medicine imaging comprises a multitude of “imaging modalities,” because these differ from other imaging methods in being almost entirely defined by the radiopharmaceuticals used: it is not MRI or CT with contrast, it is 18F fluorodeoxyglucose PET (FDG-PET) or 111In indium octreotide SPECT. Thus, imaging with each radiopharmaceutical represents a different
TABLE 1.1
SENSITIVITIES TO EXTRINSIC TRACER CONCENTRATION AND SPATIAL RESOLUTION RANGES

<table>
<thead>
<tr>
<th>Imaging Method</th>
<th>“Contrast Agent” Concentration (mol/kg Body Weight)</th>
<th>Spatial/Temporal Resolution (mm/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sonography</td>
<td>10^{-3}</td>
<td>1/0.01</td>
</tr>
<tr>
<td>Computed tomography (CT)</td>
<td>10^{-3}</td>
<td>0.6/0.1</td>
</tr>
<tr>
<td>Single photon emission computed tomography (SPECT)</td>
<td>10^{-9}–10^{-12}</td>
<td>10/1</td>
</tr>
<tr>
<td>Positron emission tomography (PET)</td>
<td>10^{-9}–10^{-12}</td>
<td>5/1</td>
</tr>
<tr>
<td>MRI</td>
<td>10^{-5}</td>
<td>0.1–1/0.05–0.2</td>
</tr>
<tr>
<td>MRS</td>
<td>10^{-5}</td>
<td>10/100</td>
</tr>
<tr>
<td>Optical imaging</td>
<td>10^{-9}–10^{-12}</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.1** A page from a Richard Scarry children’s book rendered in gray shades to mimic the appearance of a CT section. “Lowly the Worm,” inserted in the top left-hand corner, has to be identified on this page. This task is similar to the task of a radiologist who has to look for a tumor manifestation in hundreds of sections on a CT scan of a patient with a presumed tumor. “Lowly” is actually sitting in an “apple mobile” (red arrow).
“imaging modality.” Very different normal structures are visible with FDG-PET, lung perfusion imaging, and myocardial perfusion imaging, in addition to the molecular imaging aspects. This is because nothing is seen on a nuclear scan if no radiopharmaceutical is introduced into the patient, and after injection only pathological structures and normal structures labeled by the specific radiopharmaceuticals are visible. A book on PET or SPECT imaging, therefore, also has to define which radiopharmaceuticals are being discussed. Only when we have defined the examinations of interest can we discuss how imaging systems should be optimally designed for them.

In PET, and this is the main topic of this book, identifying the key radiopharmaceutical is easy: it is $^{18}$F fluoro(deoxyglucose. There would be no clinical PET today without the FDG molecule. The reason for the success of FDG is that it accumulates in pathological tissues, notably tumor tissues, which leads to a high lesion-to-background ratio and makes the lesions very conspicuous. This has made FDG-PET a primary method for tumor staging despite the fact that FDG accumulates not only in tumors but also in activated inflammatory cells such as granulocytes and macrophages. The biochemical properties of FDG, combined with the relatively high spatial resolution of state-of-the-art PET scanners, is responsible for the high clinical utility of FDG-PET in tumor staging. Although critics complain about the lack of specificity of FDG, its accumulation in tissues is surely more specific than the accumulation of extracellular fluid agents, such as most iodinated contrast agents and gadolinium chelates used for contrast enhancement in CT and MRI.

There are some other positron-emitting radiopharmaceuticals in clinical use, most notably labeled water ($H_2^{15}O$), $^{13}$N ammonia ($^{13}$NH$_3$), and rubidium-82 ($^{82}$Rb) for brain and heart perfusion imaging. In the last years, various other $^{18}$F-based tracers have received increasing attention, such as choline derivatives, F-ethyl-tyrosine and F-thymidine. Gallium-68 ($^{68}$Ga) DOTATOC and other octreotide analogs have also been clinically evaluated. Although the use of $^{15}$O and $^{13}$N is precluded without an onsite cyclotron, the $^{18}$F-based and generator-based compounds may become more widespread in clinical practice in the coming years. All these tracers are discussed in various detail in this book. The clinical utility of choline derivatives and labeled octreotide analogs currently need to be established.

Most good radiopharmaceutical candidates for clinical PET imaging, except for the perfusion agents, have two things in common: they are $^{18}$F based and mainly used for tumor staging or follow-up and for inflammation imaging. Therefore, any clinical PET scanner must be designed to efficiently scan extended body regions within a time tolerable to patients (i.e., in less than 45 minutes). Despite this, there is a large variety of interesting $^{11}$C-based compounds that have been synthesized and tested in limited numbers of patients. They are only briefly touched upon in this book, as their widespread introduction into clinical practice is prevented by the short half-life of $^{11}$C (20 minutes). Some believe that $^{11}$C-based compounds will find their way into clinical practice. The editor of this book doubts this will happen as long as they remain somewhat difficult to use and low-cost cyclotron-radiopharmacy systems are...
unavailable. Currently, the local application of $^{11}$C compounds and, even more, their distribution make them highly impractical. Providing FDG at a reasonable cost is already difficult to do. Some are optimistic about the use of other PET tracers labeled with radioisotopes, such as iodine-124 ($^{124}$I) and other more exotic positron-emitting isotopes. Although there may be a role in therapy for such isotopes, there are several hurdles preventing the introduction of these radioisotopes, as well as radiopharmaceuticals containing them, into clinical practice. First and foremost, most such isotopes, with the exception of $^{68}$Ga have a relatively long half-life, and since the radiation burden in PET comes from the positron, which is a beta particle, half-lives substantially longer than that of $^{18}$F will result in very high radiation doses to the patient. Second, nuclear medicine has labored for the last 40 years to find interesting radiopharmaceuticals that mimic biochemical properties despite containing odd isotopes such as technetium-99m. The history of Tc radiopharmacy demonstrates that finding "good radiopharmaceuticals" containing such "odd" isotopes is by no means an easy task.

In SPECT imaging, no single radiopharmaceutical is the focus of attention in the way that FDG is in PET imaging. In fact, there are a wide variety of radiopharmaceuticals used in clinical practice. But, again, the most useful agents are large-field-of-view, disease-seeking agents or perfusion agents. Agents of major importance undoubtedly include $^{131}$I for the staging and therapy of thyroid carcinoma; $^{111}$In octreotide for staging in patients with somatostatin receptor–expressing tumors, such as carcinoid tumors; $^{123}$I or $^{131}$I MIBG (methyl-isobutyl-benzyl-guanidine) for detecting pheochromocytomas and their metastases as well as staging neuroblastomas in children and infants; and $^{67}$Ga for tumor and infection staging. Other important extended body scanning applications include bone scanning with Tc-phosphonates. Finally, there are other infection-seeking agents, where SPECT imaging of extended body regions may have some relevance. Still, SPECT is not consistently used when "staging" examinations with these radiopharmaceuticals are performed, and frequently SPECT is only added to clarify a finding suspected on planar scans. Imaging of brain and heart perfusion nowadays consistently

Figure 1.3 PET-CT is really a combination of Figures 1.1 and 1.2. The colored object of interest ("Lowly" in this case but in reality a relevant lesion on PET or SPECT) is easily distinguished on the gray-scale background. The background provides all the relevant structures (in reality CT anatomy) needed to locate "Lowly" exactly.
eventually be replaced by $^{68}$Ga DOTATOC or similar compounds. Second, some of the radiopharmaceuticals available for SPECT examinations have no counterpart in PET imaging, and this book would like to claim some completeness.

SPECT perfusion imaging is the mainstay of nuclear cardiology, and brain imaging with perfusion and other agents using SPECT techniques is done relatively frequently in some centers.

The reasons for adding chapters on SPECT in this book are three in number. First, integrated SPECT-CT cameras analogous to PET-CT cameras have been introduced, and many of the image interpretation issues are similar. Second, some of the radiopharmaceuticals available for SPECT examinations have no counterpart in PET imaging, and this book would like to claim some completeness regarding clinically relevant “staging” compounds. Third, some of the SPECT compounds used may be “precursors” of PET compounds; for example indium octreotide may eventually be replaced by $^{68}$Ga DOTATOC or similar compounds or $^{18}$F fluorodopa. Hence, tumor and infection imaging with some clinically relevant SPECT compounds is discussed in this book.

Staging is one of the most important tasks performed in the current practice of nuclear medicine and PET, and so efficient staging capabilities must define the key features of imaging systems in PET and SPECT. Staging is relevant in identifying tumor spread, but in a wider sense “staging” is also necessary when searching for infectious foci. As stated, there are some examinations that focus on a single organ only, most importantly perfusion imaging of the brain and heart. But imaging capabilities that permit scanning of extensive body regions are critical to SPECT and particularly PET imaging systems. Only a few users will have such a skewed imaging practice that they can afford to buy a scanner optimized for imaging the brain or heart only.

There are a variety of system designs in PET, SPECT, integrated PET-CT, and SPECT-CT. Two design features of clinical imaging systems are essential: the field of view and the method of attenuation correction. The best scanner would surround the whole body—a so-called 4π geometry scanner—because it would permit detection of all radiation emanating from the patient. Since the costs of the detectors in SPECT and particularly in PET are very high, they constitute a substantial obstacle to building scanners with “whole-body” capabilities, and so a clinical scanner has to balance clinical whole-body imaging capabilities against detector cost. Both PET imaging and SPECT imaging are emission based, in that radiation is emitted from within the patient’s body. As the photons emitted travel through the patient, they are attenuated by the patient’s tissues. If an emission scan, be it a PET or SPECT scan, is to accurately reflect the distribution of radioactivity within the patient, the images have to be attenuation corrected. Thus, one key design feature of such systems is the mechanism used to correct for the attenuation of photons. With these key clinical and technical issues in mind, some introductory remarks regarding scanner design can be made.

The task of a PET scanner is to detect with its many detectors the two gamma photons (each 511 keV) that emanate from the site of the positron–electron annihilation reaction occurring close to the radioactive nucleus of origin of the positron. To this end, the electronic circuitry of a PET scanner operates in a so-called coincidence mode: if one PET scanner detector detects a 511-keV photon, the other detectors expect the arrival of the second photon within a narrow window of time, the coincidence window. When a second photon is detected in the coincidence window, the assumption is made that the annihilation reaction has occurred along a straight line connecting the two detectors that detected the photons. In order to achieve such detection efficiently, state-of-the-art scanners make use of a detector ring typically with an axial dimension of around 15 cm. Currently, the best resolution cameras use pixelated detector systems with individual detector blocks resolving 4 to 6 mm in both the axial and transaxial dimensions, and thus many thousands of detectors can be present in a ring detector to detect photons. The axial dimension of 15 cm has been deemed practical because organ scanning of the brain and the heart can be accomplished with a single field of view; thus no scan table motion is necessary during the scan. The diameter of the ring is variable but on the order of 80 to 90 cm. The smaller the ring, the fewer the detectors; thus from a cost perspective a small ring for a given spatial resolution is advantageous. However, the further apart the detector rings, the more homogeneous the spatial resolution of the system across the patient. The detector materials used in PET scanners include BGO (bismuth germanate oxide), LSO (lutetium orthosilicate), and others, as well as NaI (sodium iodide, also used in SPECT scanners). The advantages of the former compounds make them the detector materials of choice for high-performance scanners (see Chapter 3). Issues in detector design are detector speed, energy resolution, and dead time, which are relevant to the suppression of “random” coincidences (i.e., coincidences that occur due to two annihilations occurring almost at the same time) and the suppression of photons that have undergone Compton scattering and therefore will also produce errors in spatial localization of the annihilation event detected.

From the above, it is clear that PET scanning requires numerous corrections in order to produce an adequate image. First, random coincidences have to be minimized, and their number has to be estimated in order to obtain the correct number of true coincidences in a given volume over a given time period. Thus, a PET emission scan has to be corrected for random coincidences. This requires “fast” detectors (see Chapter 3). Correction for Compton scattering has to be achieved, and this requires adequate energy resolution of the detectors. Finally, the scans have to be corrected for attenuation: Radiation from an annihilation reaction deep in the body is attenuated by the patient’s tissues differently than radiation from an annihilation reaction at the body’s surface. As stated, attenuation correction is not unique to PET scanning but is useful for correcting all images obtained by emission scanning methods (i.e., PET and SPECT). In PET, this correction is done by obtaining a...
transmission scan of the patient at 511 keV. This transmission scan provides “attenuation maps” of the patient. The data in such a map are incorporated into the true emission image through a process called attenuation correction (discussed in Chapters 4 to 8). Standard PET scanners provide transmission scans using 511-keV radiation sources that, like the x-ray tube in a CT examination, rotate around the patient to provide projection images. Transmission scanning is a lengthy process, typically taking at least half the time of the also lengthy PET emission scan. Similar attenuation correction designs exist in SPECT scanners, but the transmission maps required have to be adapted to the gamma emission energy of the radioisotope used.

The severe time penalty associated with transmission scanning makes other means of obtaining transmission scans to correct for attenuation in PET and SPECT emission scans more attractive. In fact, a suitable alternative is to use a CT scanner to obtain transmission maps. Systems permitting this consist of PET and CT scanners or SPECT and CT scanners placed in perfect alignment in the axial direction. Such scanners are referred to as PET-CT and SPECT-CT scanners. As typical CT scanners operate with photon energies in the range of 70 to 140 keV rather than at 511 keV (or the relevant SPECT radioisotope energy), the CT transmission maps have to be corrected to obtain maps at the relevant gamma ray emission energy. Fortunately, the necessary correction is relatively easy to achieve. The attractiveness of using a CT for attenuation correction is twofold. First, modern CT scanners are extremely efficient and can scan entire body sections in a matter of a few seconds. As a result, the total PET scanning time can be reduced by 25% to 30%. Second, a CT scan provides detailed anatomical information, which is almost completely lacking in FDG-PET scans and is also not available in the poor photon flux transmission scans obtained from a standard PET scanner. The PET-CT combination has proven to be so successful that PET-only scanners are disappearing and only integrated PET-CT are being sold. The CT scanner replaces the transmission scanning device in the PET scanner, improving PET scanner performance and at the same time making “hardware” coregistered combined molecular and anatomic images available for diagnostic interpretation. Time-consuming and often inaccurate software image coregistration is no longer necessary. Integrating PET and CT into a single system provides the best of two worlds in many ways. The clinical experience with such integrated PET-CT devices has surpassed the hopes of even their most optimistic advocates. As a result, this book draws heavily on images obtained from PET-CT systems, but it is intended to instruct in the practice not only of PET-CT imaging but also of PET-only imaging. In addition to providing better data than a PET scanner alone, PET-CT scanners offer insights that frequently permit a better interpretation of PET images, even if those not obtained using a combined system.

Based on the same arguments, integrated SPECT-CT scanners are now also available on the market. Attenuation correction in SPECT is more complex than in PET, as discussed in Chapter 8, but the purpose of attenuation correction is the same: to produce images that are corrected for the patient’s self-absorption. Attenuation correction in SPECT imaging has been widely used in the past years in nuclear cardiac perfusion imaging, as attenuation by the patient, particularly in the case of a woman with large breasts, significantly lowers the count rate coming from the inferoposterior wall of the heart. This leads to artificial low count regions, which can be misinterpreted as ischemia. Consequently, in the early 1990s several manufacturers equipped their SPECT cameras with radioactive rod or pin sources very much like those present in PET scanners. The attenuation maps obtained in this way are used, as in PET, to correct for self-absorption of photons by the patient. Similar to the PET maps, these SPECT maps also are of poor quality because of the limited photon flux obtainable from the radiation sources. Integrating SPECT and CT provides attenuation maps as well as anatomic information in SPECT imaging. Very much like in PET-CT, these SPECT-CT systems yield “hardware” coregistered combined molecular and anatomic images of importance mainly in tumor-imaging SPECT examinations and heart perfusion imaging, although in the latter only the CT data are of interest for attenuation correction.

Finally, some words about the general strategy for using integrated imaging. A characteristic of all nuclear imaging—except maybe for bone scanning—is the lack of a good anatomic reference. Once a lesion detected on a nuclear scan is referenced anatomically, comparing an integrated PET-CT or SPECT-CT study to any other anatomic imaging study becomes simple: There are enough anatomic features on the integrated scans to mentally coregister these data with those from another anatomic imaging study. The obvious conclusion is this: Frequently, a PET-CT or SPECT-CT study does not need to be performed with a full-scale contrast-enhanced CT. Instead, a contrast-enhanced CT done prior to or after a PET-CT or SPECT-CT study will be able to provide all the additional information. Mental fusion of the two temporally disjoint imaging studies is readily accomplished. This is in fact a common clinical situation. As one example, suppose a contrast-enhanced CT has been obtained in the workup of a bronchial carcinoma patient. Its relevant features can be matched readily to a subsequent unenhanced PET-CT study. Or imagine the biopsy of a lesion detected on PET-CT. When done with image guidance, this does not require biopsy in the PET-CT scanner, because the relevant lesion can be defined anatomically, and a CT-only guided biopsy can identify the lesion by mental coregistration. On the other hand, if it is known that the patient needs a contrast-enhanced CT scan, modern PET-CT scanners can be run so as to obtain a full CT study without much additional time penalty. Strategies on how to use CT imaging in PET-CT are further discussed in Chapter 19. Currently, there is some talk about PET-MR. A major use would be in brain imaging, where MR is the dominant imaging modality.
Three key arguments tend to suggest that the utility of a combined PET-MR system may be very limited clinically. First, integration of PET or SPECT and MR in the brain is readily accomplished by software fusion, which is not true in body imaging. Second, PET and SPECT technology and MR technology exhibit little technical synergy. The technologies do not fit well because the detectors of nuclear imaging systems are disturbed by nearby magnetic fields. Third, the use of MR data for attenuation correction of nuclear scans is not straightforward. The conclusion is that PET-MR systems will likely be very costly and predominantly have research applications.
Radiation Sources for Emission Scanning: Positron and Gamma Emission

Cyrill Burger       Alfred Pfeiffer

Nuclear medicine is based on pharmaceuticals labeled with a suitable radioactive isotope. After such a radiopharmaceutical has been applied to a patient, it takes part in physiologic processes. A radioactive isotope has an unstable nucleus that will undergo one or several transitions (called decays) to finally reach a stable configuration. As a result of these decays, photons can be generated. Depending on their energy, they may penetrate the body tissue and be recorded by external detectors. From the detected photons, the emission images depict the distribution of the radiopharmaceutical in tissues at the acquisition time.

Different types of nuclear decays give rise to photons usable in nuclear medicine. For proton-rich nuclei, a beta-plus or an electron-capture decay may occur. The beta-plus decay ejects a positron. As a secondary event, the positron annihilates with an electron, producing two 511-keV photons that are emitted in opposite directions. In the electron-capture decay, a shell electron is absorbed by the nucleus. The resulting vacancy in the electron shell is filled by an electron from an outer shell, and the energy difference is transformed into a characteristic x-ray photon. Neutron-rich nuclei may decay by a beta-minus transition, by which an electron is ejected. Often the resulting daughter nucleus is in an excited state, from which it will return to the ground state by the emission of characteristic gamma-ray photons.

Radionuclides for medical purposes originate from cyclotrons, nuclear reactors, or secondary decays in generators. In cyclotrons, a suitable target material is bombarded with particles such as protons or deuterons to produce proton-rich radionuclides. From nuclear reactors, radionuclides can be obtained in two ways: one is to put a stable target into the high-neutron flux in the reactor, and neutron-rich radionuclides are then produced in nuclear transformations. The other is to extract fission products of the uranium 235 ($^{235}_{92}$U) fission reaction. The ease and efficiency of radionuclide separation depends on the chemical properties of the radionuclide. The best specific activity is obtained if the atomic number differs from that of the unwanted material, as is the case with proton-enriched cyclotron products. A generator contains a longer-lived parent nuclide that decays into an unstable daughter nuclide suitable for emission imaging. The advantage of generators is that the daughter nuclide can be extracted in regular intervals directly at a clinical site, solving the logistic problem for routine medical investigations (Table 2.1).
INTRODUCTION

Nuclear medicine is based on labeling a pharmaceutical with a suitable radioactive isotope. After application to a patient, the radiopharmaceutical (see Chapters 14–18) takes part in physiologic processes. Radioactive decays are continuously taking place and can be detected from the outside by the emitted gamma rays, allowing monitoring of the distribution of the tracer concentration. Several properties are required for a radioactive isotope to be suitable for nuclear medicine. The half-life of the radiopharmaceutical must be long enough to be delivered to the site of use, if it is not locally produced, and to permit acquisition of patient data; yet it should be short for radiation-protection reasons. The energy of the emitted photons must be high enough to penetrate the body tissues but low enough to be stopped and detected in the detectors of the gamma and positron emission tomography (PET) cameras. Finally, the chemical properties of the isotope should be such that it can be easily bound into stable molecules of interest.

RADIOACTIVE DECAY MODES

A simplified atomic model is used for outlining the most relevant processes that eventually result in gamma rays usable for emission imaging in nuclear medicine. An atom consists of a nucleus surrounded by electrons (Fig. 2.1). The nucleus is formed by a number Z of positively charged protons and a number N of neutrons. Z is called the atomic number and determines the chemical properties of the atom; therefore, the atomic number has a one-to-one relation to a chemical symbol and a corresponding name. For instance, all atoms with Z = 6 are carbon C atoms. The term ”nuclide” is used when referring to an atomic species with a defined number of protons and neutrons. The same number of protons may be combined with different numbers of neutrons. For carbon, configurations with five, six, seven, or eight neutrons are denoted as $^{11}$C, $^{12}$C, $^{13}$C, and $^{14}$C (2, 3) and are called C isotopes. Whether a nucleus is stable depends on the relative number of protons and neutrons: the N/Z ratio. When plotting the stable N/Z configurations as a function of Z, a ”line of stability” starts with 1 and increases with the atomic number, reaching 1.54 for lead 208 ($^{208}$Pb) (1). In nature, about 270 stable configurations occur in elements and hence lie along this line. Unstable nuclides are positioned above the line of stability (neutron rich) or below (proton rich). They undergo transitions also called ”radioactive decay processes” to reach a more stable configuration and by means of which particles or gamma rays are emitted. Hence they are called ”radionuclides.” Of the 2,700 known radionuclides, about

<p>| TABLE 2.1 |
| MEDICALLY IMPORTANT RADIONUCLIDES |</p>
<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>Decay Mode</th>
<th>Photons (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{99m}$Tc</td>
<td>6.0 h</td>
<td>Metastable</td>
<td>$\gamma$:140 (89%)$^a$</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>8.0 d</td>
<td>Beta-minus</td>
<td>$\gamma$:365 (81%)</td>
</tr>
<tr>
<td>$^{123}$I</td>
<td>13 h</td>
<td>Electron capture</td>
<td>$\gamma$:160 (83%)</td>
</tr>
<tr>
<td>$^{133}$Xe</td>
<td>5.2 d</td>
<td>Beta-minus</td>
<td>$\gamma$:81 (37%)</td>
</tr>
<tr>
<td>$^{201}$Tl</td>
<td>3.0 d</td>
<td>Electron capture</td>
<td>$\gamma$:93 (39%), $\gamma$:167 (10%)</td>
</tr>
<tr>
<td>$^{67}$Ga</td>
<td>3.3 d</td>
<td>Electron capture</td>
<td>$\gamma$:300 (15%)</td>
</tr>
<tr>
<td>$^{111}$In</td>
<td>2.8 d</td>
<td>Electron capture</td>
<td>$\gamma$:173 (91%), $\gamma$:247 (94%)</td>
</tr>
<tr>
<td>$^{81m}$Kr</td>
<td>13 s</td>
<td>Metastable</td>
<td>$\gamma$:190 (65%)</td>
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<td>PET imaging</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>20 min</td>
<td>Beta-plus</td>
<td>511 (200%)</td>
</tr>
<tr>
<td>$^{13}$N</td>
<td>10 min</td>
<td>Beta-plus</td>
<td>511 (200%)</td>
</tr>
<tr>
<td>$^{15}$O</td>
<td>2 min</td>
<td>Beta-plus</td>
<td>511 (200%)</td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>110 min</td>
<td>Beta-plus</td>
<td>511 (193%)</td>
</tr>
<tr>
<td>$^{82}$Rb</td>
<td>1.3 min</td>
<td>Beta-plus</td>
<td>511 (191%)</td>
</tr>
<tr>
<td>$^{62}$Cu</td>
<td>9.7 min</td>
<td>Beta-plus</td>
<td>511 (196%)</td>
</tr>
<tr>
<td>$^{68}$Ga</td>
<td>1.1 h</td>
<td>Beta-plus</td>
<td>511 (178%)</td>
</tr>
<tr>
<td>$^{124}$I</td>
<td>4.18 d</td>
<td>Beta-plus</td>
<td>511 (47%)</td>
</tr>
</tbody>
</table>

60 occur naturally; the others are produced using different techniques, mostly in reactors or cyclotrons.

Depending on the configuration of the unstable nuclide, several different transition types may transform the parent nuclide into a daughter nuclide (see Table 2.1). Particularly relevant for PET is the beta-plus decay by which a positron is ejected; such decay typically occurs in proton-rich radionuclides such as carbon 11 (\(^{11}\text{C}\)), nitrogen 13 (\(^{13}\text{N}\)), oxygen 15 (\(^{15}\text{O}\)), fluorine 18 (\(^{18}\text{F}\)), gallium 68 (\(^{68}\text{Ga}\)), and rubidium 82 (\(^{82}\text{Rb}\)). It can be described by

\[
\alpha X \rightarrow \alpha Y + e^+ + \nu
\]  

(1)

and in this type of decay a proton is transformed into a neutron, a positron \(e^+\) (the positively charged counterpart of an electron), and a neutrino \(\nu\). The daughter nuclide has an atomic number that is smaller by 1 and is thus a different chemical element. The positron is emitted with a variable amount of kinetic energy, which lies in a continuous range up to some maximum energy (several hundred keV). As the positron passes through matter, it is slowed by ionizations. By the time it has lost almost all of its kinetic energy (within about 10\(^{-9}\) seconds), it interacts with an electron. In this process, called annihilation, the mass of the two particles (twice the electron mass) is converted into two annihilation photons, according to Einstein’s \(E = mc^2\) law. The resulting two photons of 511 keV are emitted at an almost exact 180-degree angle and can be recorded in PET-detector systems.

An alternative to the beta-plus decay for proton-rich radionuclides is the electron capture transition. The number of electrons in an atom is usually equal to the number of protons. A convenient atomic model states that the electrons are organized in shells of different energy levels around the nucleus (Fig. 2.1A). As the inner shell is close to the nucleus, it is possible for the nucleus to capture an orbiting electron and combine it with a proton, producing a neutron and a neutrino:

\[
\beta X + e^- \rightarrow \beta Y + \nu
\]  

(2)

The electron capture leaves a vacancy in the inner electron shell of the daughter nuclide. It can be filled by an electron from an outer shell with higher energy, and the energy difference between the shells is transformed into a photon called “characteristic x-ray” (Fig. 2.1B). The vacancy left on the outer level is itself filled in the same way, and the process continues as a cascade until all vacancies are filled. There may be different pathways of shell filling, and accordingly percentages can be attributed to the characteristic x-rays occurring. Thallium 201 (\(^{201}\text{Tl}\)) is a radionuclide used in nuclear medicine with characteristic x-rays at 70 to 80 keV, and these characteristic x-rays are used for imaging.

With neutron-rich radionuclides, a beta-minus decay is likely to occur

\[
\beta X \rightarrow \beta Y + e^- + \bar{\nu}
\]  

(3)

and in this type of decay a neutron is converted into a proton, an electron \(e^-\), and an antineutrino. The electron is ejected and delivers a dose to the neighboring tissue. In most cases, this is an unwanted effect, but with iodine 131 (\(^{131}\text{I}\)) it is used for metabolic radiation therapy of thyroid disease. The effect in this decay mode is useful for producing radiation for
Chapter 2: Radiation Sources for Emission Scanning: Positron and Gamma Emission

The types of transitions are different among the decay modes, but the rate at which they occur obeys a common law. The decay of a radionuclide is a random process that is independent of its age. If a set of $N$ radionuclides is considered, the decay probability for each of them is only proportional to the duration during which it is observed; therefore the number of decaying nuclides $dN$ in a time interval $dt$ is given by

$$dN(t) = -\lambda N(t) dt$$

(4)

where the negative sign expresses the decrease in the radioactive nuclides left. The decay constant $\lambda$ denotes the fraction of radionuclides that disintegrate in a unit of time. For instance, if $\lambda = 0.1$ s$^{-1}$ for a given radionuclide, 10% of the radionuclides present at a given time have decayed 1 second later. The number of radionuclides left at a time $t$ can be found by integrating the previous equation:

$$N(t) = N(0) e^{-\lambda t}$$

(5)

The activity $A$ or radioactivity of a sample is given by the number of decays per time:

$$A(t) = -dN/dt = \lambda N(t) = \lambda N(0) e^{-\lambda t}$$

(6)

As the initial activity $A(0)$ is given by $\lambda N(0)$, the activity at a later time point is

$$A(t) = A(0) e^{-\lambda t}$$

(7)

which means that the activity decreases in the same way as the number of radionuclides.

Every radionuclide is characterized by its decay constant, or equivalently by its half-life $T_{1/2}$, which is defined as the time required for the activity to be reduced to one half. The half-life is related to the decay constant by

$$T_{1/2} = 0.693/\lambda$$

(8)

As the initial activity $A(0)$ is reduced by a factor of 2 after each half-life, after $n$ half-lives, it will be $A(0)/2^n$. Specifically, after 10 half-lives, it is reduced by a factor of 1,024, or to $\sim 0.1\%$ of the initial activity.

In radionuclide imaging, the local activity is not reduced by the radioactive decay process alone. Physiologic processes such as fecal or urinary excretion, perspiration, and exhalation remove a pharmaceutical introduced into an individual as well. Pharmaceuticals in general are also frequently removed from the human body according to an exponential law (see Chapter 13) with a half-life $T_b$ of the biologic half-life, or with the decay constant $\lambda_b = 0.693/T_b$. After $T_b$, half of the substance has disappeared from the biologic system (e.g., through urinary excretion). Consequently, radioactively labeled substances disappear from an individual due to both the physical decay of the radionuclide and the biologic elimination of the radiopharmaceutical. The effective rate $\lambda_e$ of radioactivity loss is therefore given by

$$\lambda_e = \lambda_p + \lambda_b$$

(9)

where $\lambda_p$ and $\lambda_b$ denote the physical and biologic decay constants, respectively. It follows that

$$1/T_e = 1/T_p + 1/T_b \quad \text{or} \quad T_e = (T_p \times T_b)/(T_p + T_b)$$

(10)

The effective half-life $T_e$ is always shorter than $T_p$ and $T_b$. If one of the half-lives is much longer than the other, $T_e$ will be almost equal to the shorter half-life.

**PHYSICS OF RADIOACTIVE DECAY**

Emission imaging because often beta-minus decays result in an excited state of the daughter nuclide. It will eventually return to its ground state, and as a consequence photons called “gamma rays” are emitted. Frequently several routes to the ground state are associated with gamma rays of different energy. Usually the return to the ground state is very rapid; however, rare examples exist of exited states with a relatively long half-life. These metastable states are denoted by an “m,” as in technetium 99m (99mTc), the decay product of molybdenum 99 (99Mo) (Fig. 2.2). 99mTc is currently the most valuable radionuclide in conventional nuclear medicine, with a half-life of 6 hours. It can be locally produced in a generator (see “Generation of Radionuclides” discussed later). It emits gamma rays at 140 keV (transition from first excited state to ground state), used in emission imaging. A great advantage of technetium from a radiation-protection point of view is its biologic half-life, or with the decay constant $\lambda_e$. As the initial activity $A(0)$ is given by $\lambda N(0)$, the activity at a later time point is

$$A(t) = A(0) e^{-\lambda t}$$

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(10)

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**Figure 2.2** Decay scheme of 99Mo. Beta-minus transition to metastable 99mTc, which emits a 140-keV gamma ray when returning to the ground state.

Emitted x-rays are characteristic x-rays at 23 keV and 26 keV, and then undergo several transitions from the exited state to the ground state, with gamma rays at 173 keV and 247 keV. The x-rays are absorbed predominantly in tissue because of their low energy. Usually the return to the ground state is very rapid; however, rare examples exist of exited states with a relatively long half-life. These metastable states are denoted by an “m,” as in technetium 99m (99mTc), the decay product of molybdenum 99 (99Mo) (Fig. 2.2). 99mTc is currently the most valuable radionuclide in conventional nuclear medicine, with a half-life of 6 hours. It can be locally produced in a generator (see “Generation of Radionuclides” discussed later). It emits gamma rays at 140 keV (transition from first excited state to ground state), used in emission imaging. A great advantage of technetium from a radiation-protection point of view is its biologic half-life, or with the decay constant $\lambda_e$. As the initial activity $A(0)$ is given by $\lambda N(0)$, the activity at a later time point is

$$A(t) = A(0) e^{-\lambda t}$$

(7)

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(8)

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(10)

The effective half-life $T_e$ is always shorter than $T_p$ and $T_b$. If one of the half-lives is much longer than the other, $T_e$ will be almost equal to the shorter half-life.
The units of radioactivity are Becquerel and Curie. One Becquerel (Bq) is defined as representing one disintegration per second (dps). One Curie (Ci) was historically defined as the disintegration rate of 1 g of radium with $3.7 \times 10^{10}$ dps. Thus

$$1 \text{ kilobecquerel} = 1 \text{ kBq} = 10^3 \text{ dps}$$

$$1 \text{ megabecquerel} = 1 \text{ MBq} = 10^6 \text{ dps}$$

$$1 \text{ gigabecquerel} = 1 \text{ GBq} = 10^9 \text{ dps}$$

$$1 \text{ Ci} = 3.7 \times 10^{10} \text{ Bq} = 37 \text{ GBq}$$

$$1 \text{ mCi} = 3.7 \times 10^7 \text{ Bq} = 37 \text{ MBq}$$

$$1 \mu\text{Ci} = 3.7 \times 10^4 \text{ Bq} = 37 \text{ kBq}$$

**GENERATION OF RADIONUCLIDES**

Radionuclides for medical purposes originate from cyclotrons or nuclear reactors or by secondary decay in generators. Cyclotrons produce particles such as protons and deuterons (nucleus of $^2\text{H}$), accelerate them to a high energy level, and direct them to a target material. During the collisions, the number of protons in some target atoms is typically increased, and thus proton-rich radionuclides are produced during the nuclear reaction. As the atomic number of the radionuclide is different from that of the target material, it can be separated relatively easily by chemical processes. Many radionuclides important in nuclear medicine are cyclotron produced: $^{201}\text{Tl}$, $^{67}\text{Ga}$, $^{123}\text{I}$, and $^{111}\text{In}$, as well as all positron emitters used in PET scanning (Table 2.2).

With nuclear reactors, radionuclides can be obtained in two different ways. One is to put a suitable stable isotope (target) into the high neutron flux existing in the reactor. It will undergo nuclear transformations and likely become radioactive. Typically an isotope with a neutron excess will be produced, hence a radionuclide prone to undergo beta-minus decay. However, separation of the radioactive isotope from the target is difficult, because in most cases the target material and the radionuclide incorporating the neutron have the same atomic number. The second way of obtaining radionuclides is to retrieve by-products of the $^{235}\text{U}$ fission reaction taking place in the reactor. Here the separation tends to be easier because of the different atomic numbers of the fission products. For instance, $^{99}\text{Mo}$ is obtained from nuclear reactors with high specific activity. It is of great practical importance, because it allows the manufacture of an efficient “generator” for the $^{99m}\text{Tc}$

**TABLE 2.2 PRODUCTION OF PET RADIONUCLIDES IN CYCLOTRONS**

<table>
<thead>
<tr>
<th>Target Material</th>
<th>Nuclear Reaction</th>
<th>Radionuclide</th>
<th>Half-time</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{18}\text{O}$ water</td>
<td>$^{18}\text{O}(p,n)$</td>
<td>$^{18}\text{F}$</td>
<td>109.7 min</td>
</tr>
<tr>
<td>$^{20}\text{Ne}$ gas</td>
<td>$^{20}\text{Ne}(d,\alpha)$</td>
<td>$^{18}\text{F}$</td>
<td>109.7 min</td>
</tr>
<tr>
<td>$^{14}\text{N}_2$ gas</td>
<td>$^{14}\text{N}(p,\alpha)$</td>
<td>$^{11}\text{C}$</td>
<td>20.4 min</td>
</tr>
<tr>
<td>$^{18}\text{O}$ water</td>
<td>$^{16}\text{O}(p,\alpha)$</td>
<td>$^{13}\text{N}$</td>
<td>9.96 min</td>
</tr>
<tr>
<td>Enriched $^{15}\text{N}_2$ gas</td>
<td>$^{15}\text{N}(p,n)$</td>
<td>$^{15}\text{O}$</td>
<td>2.07 min</td>
</tr>
</tbody>
</table>

$p$, proton; $n$, neutron; $d$, deuteron; $\alpha$, alpha particle consisting of two protons and two neutrons and corresponding to a helium nucleus.

*The reaction is described by $A(x,y)B$ meaning “start with $A$, bomb with $x$, $y$ comes out, and the result is $B$.”

**Figure 2.3** Principle of the $^{99}\text{Mo}/^{99m}\text{Tc}$ radionuclide generator. Isomeric transition denotes the return from an excited state of a nuclide to its ground state.
A generator consists of a long-lived parent nuclide that decays by beta-plus, beta-minus, or electron capture into a shorter-lived daughter nuclide (Fig. 2.3). As the daughter nuclide is an element different from the parent, it can be chemically extracted. This is done after the decay reaction has been left to build up some amount of daughter nuclide. A mathematical analysis of the simultaneous decays of parent and daughter nuclides shows that a stable relation between the parent and daughter activity has been established after about six half-lives of the daughter nuclide. Because of its continuous generation, the daughter nuclide can be extracted on a regular basis until the activity of the parent is no longer sufficient. The most important generator is the $^{99}$Mo/$^{99m}$Tc system. The mother nuclide $^{99}$Mo has a half-life of 66 hours and decays into $^{99m}$Tc (with a half-life of 6 hours) by a beta-minus transition (Fig. 2.2). $^{99}$Mo can be adsorbed onto an aluminum column. When flushed with saline, the $^{99m}$Tc ions are removed from the column (elution) and can be further processed into the desired radiopharmaceuticals for imaging. The build-up of $^{99m}$Tc is fast enough to serve the daily need of a nuclear medicine department with practical elution intervals of 12 to 24 hours. Several generators are also available for PET imaging, most notably yielding $^{82}$Rb ($^{82}$Sr/$^{82}$Rb) but also $^{62}$Cu ($^{62}$Zn/$^{62}$Cu) and $^{68}$Ga ($^{68}$Ge/$^{68}$Ga).

REFERENCES

Basics of PET Scanning

Cyrill Burger  David Townsend

Positron emission tomography (PET) involves the administration to a patient of a radioactive, positron-emitting nuclide, which tags a biomolecule specific to the physiologic process under investigation by PET. This so-called radiopharmaceutical is usually injected intravenously. If not confined to the intravascular space, it will be partially or completely extracted into the tissues during passage through the capillaries, where it may be metabolized or become bound at a specific receptor site. The ultimate fate of the PET tracer will depend on the outcome of these processes: it may be trapped irreversibly or washed out of the tissue. The radioactive tag allows the path of the pharmaceutical to be mapped noninvasively. The unstable, neutron-deficient nuclide decays by emitting a positron, which will annihilate with a nearby electron to create two 511-keV photons emitted opposite to each other. Detection of the two photons within a narrow time window is called a coincidence event, and the assumption is that the photons originated from a single annihilation occurring along the line of response defined by the direction of the photons (see Fig. 3.1). A PET scanner collects many such coincidence events within the field of view. The events are summed for each line of response and sorted into parallel projections of the positron-emitting distribution. By using standard reconstruction techniques, the underlying radiotracer distribution can then be recovered from the projection data. In principle, with adequate corrections for scattered and attenuated photons and random coincidences, the absolute tracer concentration can be measured by PET in units of kBq/mL averaged over the acquisition duration. Random coincidences arise when a pair of photons is detected within the coincidence time window and acquired as a true coincidence when the photons actually originated from different positron annihilations—hence the terms “random” or “chance” coincidence.

PET is intrinsically a three-dimensional (3-D) imaging technique. Initially, PET scanner designs incorporated lead septa that limit acceptance to photons within transverse planes only. This approach has the additional advantage of limiting the acceptance of scattered photons and requiring only a 2-D reconstruction algorithm, although this is achieved at the expense of reduced sensitivity. Removal of the septa typically increases the scanner sensitivity by a factor of 5, although the fraction of scattered events and the complexity of the reconstruction algorithm will increase.

INTRODUCTION

The basic principle of positron emission tomography (PET) involves the administration to a patient of a pharmaceutical tagged with a positron-emitting isotope. The pharmaceutical is chosen to target a particular metabolic pathway, and the decay of the positron-emitting isotope allows the metabolism to be monitored by detecting the annihilation radiation emitted from the patient. Intravascular tracers such as carbon monoxide (labeled either as $^{15}$CO or $^{15}$O) remain in the blood, whereas most other radiopharmaceuticals will be partially extracted into the tissue during the passage through the capillaries or will diffuse freely, such as oxygen 15 [$^{15}$O]water. After extraction, a tracer will either follow a particular metabolic pathway or bind to a particular receptor system before being washed out of the tissue. Generally, the process is dynamic, and the tracer concentration in the tissue will change continuously with time. One exception is the widely used glucose analogue fluorodeoxyglucose (FDG) (2-fluorine 18 [$^{18}$F]fluoro-2-deoxy-D-glucose), which becomes trapped in the tissue and reaches a near equilibrium state approximately 60 to 90 minutes after injection. More frequently, the injected tracer is metabolized into other chemical forms, so the radioactive tag may also label metabolites in addition to the original pharmaceutical. The PET scanner,
However, measures the total radioactivity in each image voxel, summed over the scan duration, without distinguishing between the different chemical forms. A metabolite analysis of arterial blood samples may be required in addition to the PET images to understand fully the physiologic behavior of the radiopharmaceutical.

The kinetics of a tracer can be monitored dynamically in the PET scanner by acquiring multiple image frames as a function of time. The duration of each frame is related to the tracer kinetics and radionuclide half-life. Typically, short-duration frames are acquired immediately after injection to follow the rapidly changing kinetics, whereas longer-duration frames are acquired later in the scan, once the metabolism or binding of the tracer slows or is completed. Each pixel in each frame represents the tracer concentration in the tissue averaged over the scan duration and corrected for nuclide decay. By applying an appropriate kinetic model to the pixel time-activity curves derived from the PET images, absolute functional maps can be derived that measure tissue perfusion in milliliters per minute per milliliter of tissue or glucose utilization in milligrams per minute per 100 milliliters of tissue (see Chapter 13).

The annihilation radiation from an injected PET tracer is emitted in all directions from the patient, so PET is intrinsically a volume-imaging technique. However, early PET scanners accepted photons from transverse cross sections only, restricting the allowable incident photon directions by interplane septa between the detector rings. Over the past decade, PET scanners without septa, or with retractable septa, have become standard, allowing PET data to be acquired fully in 3-D. Once the volume has been acquired, it can also be displayed as stacked 2-D transverse sections or resliced into coronal or sagittal sections for viewing. The isotropic spatial resolution of many modern PET scanners facilitates reslicing even in arbitrary oblique directions without disturbing artifacts.

**PRINCIPLES OF PET SCANNERS**

**Localization of the Annihilation: Coincidence Events**

PET radiopharmaceuticals are labeled with neutron-deficient, positron-emitting isotopes (see Chapter 2). When a positron is emitted from the nucleus, it interacts randomly with the surrounding tissue, losing energy until it annihilates with an electron, producing two photons of 511 keV, corresponding to the rest masses of the electron and positron. The distance traveled by the positron before annihilation is called the “positron range.” The two photons are emitted essentially in opposite directions at an angle of 180 degrees, although the angle may be slightly less when the electron–positron system is not at rest. The two photons are detected in coincidence by the PET scanner (Fig. 3.1). The locations of the two points of interaction with the scintillators form a line of response (LOR), whereas the actual location of a single annihilation point along the line is unknown. The distribution of positron emissions and hence the distribution of annihilation photons reflect the distribution of the radiopharmaceutical. Although the exact location of a single annihilation point cannot be known, the acquisition of a large number of coincidence events along all lines of response can provide enough information to reconstruct the underlying distribution of the radioisotope. Coincident events are defined as two photons detected within a very short time interval, typically set at approximately 6 to 12 nanoseconds.
A coincident event is recorded for the corresponding LOR, and the event count within the LOR is incremented.

Modern PET scanners acquire data in either 2-D or 3-D mode. In practice, all PET scanners can acquire coincidence data in 3-D, whereas scanners that incorporate retractable septa can acquire data in either 2-D or 3-D. In 2-D mode, only LORs between detectors in the same or immediately adjacent rings are acquired. Coincident events acquired within a detector ring contribute to direct planes, whereas oblique LORs contribute to cross planes, as shown in Figure 3.4. The cross planes interleave the direct planes, sampling the region between two contiguous direct planes. For the direct planes, the sensitivity has a triangular profile, being highest at the center of the plane and decreasing to zero at the edge. The sensitivity profile of the cross planes is different, as shown in Figure 3.4. In 2-D mode, the detector rings are shielded by lead-tungsten septa positioned between the rings (Fig. 3.5A). Photons...
incident at angles larger than those of the cross planes are largely absorbed by the septa, reducing the singles rate on the detectors. Typically, in 2-D mode, 1% or fewer of the annihilation events occurring in the camera field of view (FOV) are used in the formation of the PET images because of the small effective solid-angle coverage in 2-D.

The 3-D imaging mode for PET scanners has been available since the late 1980s. In 3-D mode, the LORs between any pair of detector rings are active, rather than only adjacent detector rings, as in the 2-D mode (Fig. 3.5B). The implementation of the 3-D method required hardware modifications to the scanner to acquire all LORs, the development of suitable 3-D reconstruction algorithms, and an accurate scatter-correction model. The reason for the latter is that, even though the count rate increases by a factor of up to 8 when the septa are removed, the number of scattered coincidences increases by a factor of 3, from a 10% effect to up to a 30% to 40% effect. Therefore, for accurate quantification, it is essential to implement a scatter-correction model. The reason for the increase in scatter is the absence of septa in 3-D, which in 2-D prevent most of the scattered photons from reaching the detectors. The net increase in true coincidences is therefore a factor of 5, owing to the increase in scatter and randoms (Fig. 3.6).

As shown in Figure 3.5, from the geometry of 3-D acquisition, the increase in sensitivity is greatest at the center of the axial FOV and decreases toward the edges. The signal-to-noise ratio in 3-D in the axial end slices may even be less than that in 2-D, because there is an increase in scatter without any corresponding increase in true coincidences (1). Further, in the absence of septa, activity located outside the FOV will emit photons into the detectors, increasing the level of random coincidences and scatter. For brain imaging, the use of a simple annular shield inserted into the patient port to reduce the diameter can effectively reduce the randoms rate by a factor of 2 in $[^{15}\text{O}]$water activation studies (2). Effective shielding presents a greater problem for whole-body imaging in 3-D, and on scanners with retractable septa, many whole-body oncology studies are still acquired in 2-D, even with the reduced sensitivity. A performance evaluation of the GE Advance scanner operated in 3-D showed that the in-plane resolution was the same as that in 2-D for the central part of the axial FOV, degrading by approximately 10% in the end sections (3). The axial resolution in 3-D degraded by approximately 20% compared with that in 2-D, owing to the increased axial length of the crystals compared with the in-plane dimension.

The development of the 3-D method also required more complex procedures for detector normalization and attenuation correction (4). Originally, the large data-set sizes in 3-D and the long reconstruction times were something of a drawback, but more recently significant increases in storage capacity and processing power have essentially removed these limitations. Over the past decade, the 3-D approach has been used extensively for brain studies, particularly activation and neuroreceptor studies, owing to the ability to shield the scanner FOV from external sources of activity. The use of 2-D for whole-body and cardiac imaging may still be preferred when accurate quantification is required, although, as discussed in the next section, many of the large installed base of clinical PET scanners operate in 3-D mode only.

The Emission Scan

The objective of a PET scan is to determine the spatial distribution of the tracer within the FOV averaged over the duration of the scan. Such an acquisition is usually termed a “frame.” When the kinetics of the tracer is to be followed, multiple short-duration frames are acquired from the moment of injection up to maybe 60 to 90 minutes after injection, depending on the actual tracer kinetics and the half-life of the nuclide. To measure tissue perfusion, $[^{15}\text{O}]$water is injected and followed up dynamically for several minutes after injection. Perfusion values are extracted by modeling the tracer kinetics, as shown in Figure 3.7. As described, emission scans can be acquired in 2-D with septa extended or fully in 3-D with septa retracted. Scanners used primarily for clinical studies are often 3-D only, such as the Philips Allegro (PET)/Gemini (PET-CT) or the Siemens ACCEL (PET)/Biograph (PET-CT). A clinical oncology study usually comprises a single-frame emission acquisition at multiple bed positions covering 100 cm or more of axial length. The objective is to survey the body of the patient for disease, particularly the presence of metastases. After the acquisition at multiple bed positions, the reconstructed images are combined into a single data set covering the entire volume scanned. The images can be viewed in transverse, coronal, or sagittal orientation.

When imaging moving objects such as the heart, improved image quality can potentially be obtained by gating the emission scan. Gating synchronizes the movement of the heart with a particular emission frame. The gate is triggered by an electrocardiogram (ECG) signal,
with data for different parts of the heart cycle being stored in different frames. Each phase of the movement can therefore be reconstructed as a separate set of images. The advantage is that the effect of heart movements can be minimized because each frame corresponds to the heart in a different position. The drawback is that the total counting statistics are distributed among several frames, and the acquisition time must be increased to collect sufficient counts for each frame. In practice, clinical gated cardiac studies are still rare.

Reconstruction of a PET Image from Coincidence Events

During the emission scan, each detected coincident event is assigned to the corresponding LOR between the two detectors. Each LOR is characterized by a direction and the distance from the center of the scanner. A matrix, or sinogram, is formed by a 2-D array of position against angle. Each element in the array corresponds to an LOR, specified by a (position, angle) pair. The content of a sinogram element is the sum of the coincident events acquired during the scan in that LOR, as shown in Figure 3.8. Each sinogram assembles all LORs within a detector ring or between detector rings. In 2-D, separate sinograms are acquired for direct and cross planes, and in 3-D, separate sinograms also are acquired for all possible ring differences. A sinogram row contains all LORs at a given angle and represents a 1-D parallel projection of the tracer distribution. In the GE Discovery ST, for example, 315 different angles around the circle yield 315 parallel projections. In 2-D, each sinogram contains the complete data set for a given transverse section, and the data can be reconstructed independently of all other sinograms.

The standard algorithm used since the mid-1970s to reconstruct the underlying 2-D tracer distribution from the 1D projection data is called "filtered back-projection." The implementation involves a two-step process in which the projection data are preprocessed with a filter function, and then the filtered projection data are back-projected into the image space. Back-projection is a mathematical process in which the value of an LOR is distributed uniformly along the line traversing the image space such that all pixels intersecting the LOR are incremented by the same value, as shown in Figure 3.9 for a simple circular object with uniform activity concentration. This process is the reverse of the projection process in which the pixels lying along a given LOR are summed. However, because there is no information about how to distribute the values along the LOR when back-projecting, all pixels on the
modifies the behavior of the ramp at high frequencies, although such a smoothing function will inevitably lead to a loss of spatial resolution (see Chapter 5, Fig. 5.3).

In the past few years, iterative or statistical reconstruction methods have increased in popularity. Although such methods have been available for many years, only relatively recently have computing power and accelerated algorithms attained a level that allows reconstructions to be completed in reasonable times consistent with clinical imaging. Statistical methods allow a more realistic physical model of the imaging process to be incorporated into the algorithm. The basic approach is to assume some initial image, such as a uniform distribution; forward project this initial image; and compare the generated projections with the actual measured ones (5). Correction schemes can then be devised to modify the generated projection data to match more closely the measured projections. The correction factors are applied to the image, and the process is repeated for another projection in a different direction. The cycle is repeated until some criterion for convergence is reached, such as when the absolute change between two consecutive image estimates is less than a given amount. Although generally producing images of higher quality and less streak artifacts than filtered back-projection (Fig. 3.10), statistical methods may take much more computing time to reach an acceptable image than direct methods like filtered back-projection. Because different spatial frequencies may be recovered at different convergence rates, it may be difficult to match the spatial resolution throughout the whole image. Nevertheless, accelerated methods such as ordered subset expectation maximization (OSEM) give high-quality images in acceptable reconstruction times.

In 2-D, the transverse sections can be reconstructed from individual sinograms. In 3-D, however, the situation is more complex, because there are oblique LORs available that must be taken into account when reconstructing the transverse sections they cross. Essentially, they introduce redundant information, which if used properly can improve the signal-to-noise ratio in the images. There are two basic approaches for reconstructing images from a 3-D acquisition. The first approach is to transform the 3-D data set into a 2-D data set by a "rebinning" process that calculates a sinogram for each transaxial section. These sinograms are then reconstructed into slice images using established 2-D reconstruction methods. Several rebinning methods have been developed. Initially, single-slice rebinning (SSRB) was applied in which an oblique LOR was simply rebinned into the slice axially midway between the detectors in coincidence. To overcome some of the limitations of SSRB, the method was refined to multi-slice rebinning (MSRB) and Fourier rebinning (FORE). The combination of Fourier rebinning followed by OSEM has become the method of choice for the image reconstruction of clinical 3-D data sets because it combines fast reconstruction times and accurate results. The second approach is to apply a full 3-D reconstruction process for image reconstruction.
Similar to the 2-D case, there exists a 3-D filtered back-projection (3D-FBP) method as well as iterative reconstructions. The main problem for 3-D reconstructions has been the huge increase in processing time that arises because of the need to process all data at once. Substantial improvements in the computing hardware as well as optimization of the algorithms themselves have been able to bring reconstruction times down to a level that will soon make fully 3-D reconstructions practical in a clinical environment. Figure 3.11 illustrates the improved image quality of the full 3-D reconstruction in comparison with the FORE-OSEM reconstruction.

Figure 3.9 An illustration of projection and back-projection for a homogeneous circular object. A: Five projection measurements acquired with angular increments of 72 degrees yield the indicated profiles. B: Simple back-projection of the five profiles. Initially the image is zero. A profile is back-projected by adding the profile values to the image pixels intersected along the projection direction. The superposition of all five back-projected profiles results in a starlike pattern intersecting at the original object location.

Figure 3.10 Coronal sections of FDG-PET images reconstructed with filtered back-projection (FBP) (A) and iterative reconstruction (B) (OSEM, ordered subset expectation maximization; 28 subsets, two iterations). Attenuation correction was based on CT data.
CORRECTION STEPS FOR QUANTITATIVE PET IMAGES

To obtain quantitative images representing the absolute tracer concentration in tissue, a number of important corrections must be applied to the acquired data. These corrections are to compensate for system effects such as dead time, detector efficiency variations, and random coincidences in addition to corrections for physical effects such as photon attenuation and scattered radiation. Quantification of PET data is also discussed in Chapter 11.
System Limitations

An incident 511-keV annihilation photon that is absorbed in the scintillator generates a pulse of ultraviolet (UV) light that is converted into an electronic signal and amplified by the photomultiplier tubes. The outputs from the photomultipliers are used to localize the incident photon and as a measure of the energy to reject photons that have scattered before reaching the detector. Because the individual crystals may have differing light output and decay times and because photomultiplier tubes have different gains, these parameters must be assessed and correction maps generated to ensure a uniform response from the detectors. When properly normalized, the scanner should exhibit a uniform temporal and spatial response. Time alignment and photomultiplier gain adjustment is part of the detector setup and calibration procedure.

The overall count-rate performance of the detectors is dependent on a number of factors such as pulse pile-up and system dead time. Pile-up within the crystal occurs when two photons from different annihilations arrive so closely spaced in time that they cannot be distinguished as two separate photons. The light output of such an event is the sum of the two photon energies, which will in general exceed the upper energy discriminator level and therefore be discarded. Both photons are subsequently lost. To reduce pulse pile-up at high count rates, scintillators with short decay times are essential. A second source of count-rate losses occurs when the positional and energy determination of a photon is still in process when a second photon arrives. If the detection system is dead when the second photon arrives, the count will be lost. Such a process has the characteristics of a saturating or paralyzing system, as illustrated in Figure 3.12. At low count rates, an increase in count rate is proportional to the increase in activity in the FOV. However, at high activity levels, the proportionality is lost, as the system is unable to handle the increasing count rate. At sufficiently high levels, the count rate actually decreases with increasing activity, as the system becomes paralyzed. Below approximately 50% losses (1), correction factors can be derived to compensate accurately for dead time at the detector level. However, above approximately 50%, the accuracy of the factors is questionable, and operation of the scanner at such high count rates should be avoided.

Corrections for the Interaction of Photons in Tissue (Attenuation)

Annihilation photons must traverse varying thicknesses of tissue before escaping from the body of the patient, and the greater the thickness, the greater the likelihood that one or both photons will interact with the tissue. Such interactions, at 511 keV, will generally involve

Figure 3.12  The principle of dead-time correction. The characteristic response of the PET scanner to different activity levels is measured in phantom scans. Count rates recorded in patient scans are then corrected accordingly.

Figure 3.13  The effect of attenuation correction. A transmission image (20-minute acquisition time acquired using two 68Ge rod sources) represents the linear attenuation coefficient for 511-keV photons (left). When correction for photon attenuation is not applied, basal activity appears reduced in an FDG heart scan (middle) (20-minute acquisition time in 2-D mode), and the artifact disappears when attenuation correction is applied (right).
Compton scattering, in which the photon loses energy and is deflected from its original direction. Absorption of a photon also may occur, although at 511 keV in tissue Compton scattering is the most likely physical process. Whatever the actual physical process, removal of a photon from an LOR attenuates the activity in that LOR, and if the scattered photon is detected, the pair will contribute to an incorrect LOR, resulting in increased (scattered) background.

The attenuation effect obviously increases with depth, activity at the center of the body being more attenuated than the same activity close to the surface. Attenuation is a significant effect, requiring a maximum correction factor for an LOR through the head of approximately 6, whereas for the body the maximum correction factor is approximately 200 for an LOR through the shoulder region. The visual appearance of attenuation is illustrated in Figure 3.13 in an FDG scan of the heart.

Obviously, fully quantitative PET images require correction for attenuation; otherwise, activity deeper within the body will appear reduced relative to activity close to the surface. The PET correction for attenuation is straightforward compared with single-photon emission computed tomography (SPECT), because the detection of two nonattenuated photons is required for a true coincidence (6). The product of the attenuation probabilities of the two photons from a single annihilation results in the same attenuation factor for the LOR independent of the location of the annihilation along the LOR. In PET, attenuation correction factors are therefore independent of depth and depend only on the total thickness of tissue along an LOR. The factors are calculated by measuring the attenuation of 511-keV photons along each LOR by using an external source of positron-emitting activity. This scan, called a “transmission scan,” must be acquired in addition to the emission scan. The transmission is measured relative to a blank scan, which is a transmission scan acquired with no attenuating medium in the scanner FOV (see later). Once the map of attenuation correction factors (ACFs) is calculated from the blank and transmission scans, the attenuation effect for an LOR is corrected by simply multiplying the apparent activity in the LOR by the corresponding ACF.

**Correction for Scatter Coincidences**

As mentioned earlier, attenuation is due mainly to Compton scattering. When one or both of the annihilation photons scatter, the event is removed from the correct LOR. A scattered photon may go undetected either because it scatters out of the acceptance angle of the scanner or because sufficient energy is lost in the scattering process for the photon to be identified as scattered by the lower-level discriminator setting of the detector. However, when a scattered photon is detected but not rejected as scatter, the annihilation is assigned to an incorrect LOR, thus contributing to the scatter background in that LOR (Fig. 3.14). The fraction of total acquired events that are scattered varies from 10% to 15% for the 2-D acquisition mode up to as high as 50% in the 3-D mode. The reasons for the high level of scattered photons in 3-D PET include the relatively poor energy resolution of scintillators such as BGO (approximately 23% for BGO block detectors) and the fact that most scatters are small-angle scatters, with little photon energy being lost by the scattering process. Typically, 73% of scattered 511-keV photons have
an energy of $\geq 350$ keV, and 52% still have an energy of $\geq 450$ keV (1).

For accurate quantification and to avoid significant loss of contrast, particularly in 3-D, such high levels of scatter must be corrected. Although there is no exact method of scatter correction, a number of fairly sophisticated techniques have been developed in the past few years, particularly in 3-D. A good review may be found in Chapter 3 of reference 4. Although simple methods, such as the one that extrapolates the scatter tails from outside the attenuating medium (7), may be adequate in 2-D and for compact 3-D distributions such as in the brain, more sophisticated methods are required for the rest of the body. These techniques remove between 80% and 90% of the overall background due to scatter.

### Correction for Random Coincidences

Random, or accidental, coincidences arise when two photons from different annihilations are detected within the coincidence window and recorded as a coincidence. This situation may arise either when the partner photons are scattered out of the FOV (Fig. 3.15A) or when the two uncorrelated photons simply arrive more closely in time than the true coincidence. The random coincidence rate increases with the singles rate on the detectors because the probability that two uncorrelated photons will arrive within the coincidence window increases. The rate is proportional to the coincidence time window, and an estimate of the randoms rate is given by the expression

$$R = 2\tau S_1 S_2$$

(1)
Figure 3.16  A: A blank scan for normalization of a PET scanner. A radioactive rod source is rotated around an empty field-of-view, and coincidence data are acquired. Based on the source position, only valid LORs are active. B: A representation of the acquired events as sinograms, with one sinogram for each transverse section. The dark diagonal line indicates a problem with one or several detectors.

where $S_1$ and $S_2$ are the singles rates on the two detectors and $\tau$ is the coincidence window. Random coincidences contribute an essentially uniform background to the image, with a mean level given by Equation 1, and when not corrected can lead to a loss of image contrast. Randoms correction can be performed online by acquiring events within a delayed coincidence window (Fig. 3.15B). The delay is chosen to ensure that no true coincidence can be acquired within the window and that all “coincidences” are randoms. Obviously the events acquired in the delayed window are an estimate of the randoms that arise in the coincidence window, and can be either subtracted directly online or stored in sinograms and smoothed before subtraction. The reason for the smoothing approach is that online randoms subtraction increases image noise, and a variance-reduction approach helps to reduce the noise-amplification effect. Noise amplification can be avoided by subtracting an estimate of the randoms level based on Equation 1, although this may result in a residual bias.

**Transmission Scan**

A transmission scan is a “blank” scan acquired with the patient positioned in the scanner (Fig. 3.17). Transmission sources, usually rods of germanium 68 ($^{68}$Ge), are extracted from a shielded housing and rotated around the patient. The LORs from the sources that pass through the 

**Absolute Calibration**

The reconstructed pixel values are expressed in arbitrary count units. When absolute activity concentrations are required, the scanner must be calibrated against a known activity value. This procedure is typically performed by imaging in the scanner a uniform cylinder containing a known activity concentration. The concentration is determined from aliquots of known volume extracted from the phantom. The mean value in a region of interest defined on the images of the cylinder can then be related to the actual concentration (in Becquerels per milliliter) to yield the scanner calibration factor. Multiplication of the image pixel values by this factor converts the values to units of absolute activity concentration. This procedure should be performed periodically to monitor global changes in scanner sensitivity.

**Blank Scan**

A scan acquired by using the PET transmission sources and without a patient or object in the FOV is called a "blank scan" (Fig. 3.16). Such a scan can be used as a daily quality-control procedure, because defective detectors will appear as diagonal stripes of increased or decreased counts in the blank scan sinograms. Blank scan sinograms, acquired before the first patient scan of the day, will be used to generate patient-specific attenuation correction factors, as described later. Finally, a very high statistics blank scan, acquired periodically with rotating rod sources, can be used to generate a lookup table of normalization factors that correct for efficiency differences among the individual detectors.

**Figure 3.17** A transmission scan from which the attenuation-correction factors can be generated. A radioactive rod source is rotated around the patient, and transmission data are acquired. The attenuation factor for a given LOR is calculated from the ratio of the blank and transmission scans on a pixel-by-pixel basis in the sinogram (see text).
patient are attenuated by the body tissues. A transmission scan with $^{68}$Ge rods is acquired at 511 keV, and the corresponding PET attenuation-correction factors can be derived by normalizing the transmission scan to the blank scan. The correction factor for a given LOR is obtained from the ratio $I_0/I$, where $I_0$ and $I$ are the counts in the $^{68}$Ge blank and transmission scans for that LOR, respectively, corrected for differences in acquisition times.

Because the blank scan is acquired without the involvement of a patient, the imaging time can be extended to reduce statistical noise. The transmission scan time is limited by the total acquisition time that can be tolerated by the patient, and the resulting attenuation-correction factors can introduce considerable noise into the reconstructed image. To reduce the effect of transmission noise, segmentation procedures subdivide the reconstructed transmission image into a small number of tissue types (e.g., lung, soft tissue, bone) and assign to each tissue class the appropriate attenuation value corresponding to that class. In some approaches, a weighted sum of the measured and assigned attenuation values is used rather than the assigned value directly. Segmentation reduces the propagation of transmission noise into the reconstructed image and allows the implementation of shorter-duration transmission scans in clinical protocols. The shortest-duration, lowest-noise transmission scans are obtained with x-ray CT as implemented in combined PET-CT scanners. For PET-CT, an energy-scaling algorithm is required to convert the transmission images acquired with a CT energy spectrum from 40 to 140 keV to the equivalent images at 511 keV, as described in Chapter 7.

**PERFORMANCE LIMITS OF PET SCANNERS**

The performance limits of a PET scanner may be expressed in terms of spatial, temporal, and contrast resolution. Spatial resolution is limited not only by the size of the detectors but also by physical effects such as positron range and the lack of collinearity of the annihilation photons (8). Because the positron is ejected from the nucleus with a certain kinetic energy, it may travel some distance from the emission point before annihilating with an electron. The path is somewhat random, but the maximum distance traveled is nevertheless characteristic of the positron-emitting isotope, as shown in Table 3.1. The

<table>
<thead>
<tr>
<th>Isotope</th>
<th>$T_{1/2}$ (min)</th>
<th>Maximum Path Length (mm)</th>
<th>FWHM Resolution Loss (mm)</th>
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</thead>
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<tr>
<td>$^{11}$C</td>
<td>20.4</td>
<td>4.1</td>
<td>0.28</td>
</tr>
<tr>
<td>$^{13}$N</td>
<td>9.96</td>
<td>5.4</td>
<td>0.39</td>
</tr>
<tr>
<td>$^{15}$O</td>
<td>2.04</td>
<td>8.2</td>
<td>1.05</td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>109.7</td>
<td>2.4</td>
<td>0.22</td>
</tr>
<tr>
<td>$^{68}$Ga</td>
<td>68.3</td>
<td>10.0</td>
<td>1.4</td>
</tr>
<tr>
<td>$^{82}$Rb</td>
<td>1.3</td>
<td>&gt;20</td>
<td>2.6</td>
</tr>
</tbody>
</table>

$T_{1/2}$ half-life; FWHM, full width at half-maximum.

**Figure 3.18** A: An illustration of the degradation of the spatial resolution for a ring PET scanner when moving away from the center of the field of view. The radial component is affected to a much greater extent than is the tangential component. The reason for this effect is shown in B; the annihilation photons that contribute to the tangential LORs at the border of the field of view enter the detectors obliquely. Consequently, they may penetrate into a neighboring crystal before interacting and being detected. When this happens, the event may be displaced in the radial direction and assigned to an adjacent LOR.
maximum positron range may vary from 2.4 mm for $^{18}$F up to 20 mm or more for rubidium 82 ($^{82}$Rb). However, because the path is more that of a random walk, the full-width at half-maximum (FWHM) is closer to 0.22 and 2.6 mm for $^{18}$F and $^{82}$Rb, respectively. The range distribution is not Gaussian.

In addition to the range from the emission point, the positron may still retain some residual kinetic energy when annihilation occurs. The momentum of the annihilating system is therefore not zero, and hence, by conservation of momentum, the annihilation photons do not travel apart at exactly 180 degrees. The deviation from 180 degrees is approximately Gaussian, with a FWHM of about 0.5 degrees. The corresponding resolution loss due to acollinearity also depends on the distance between the detectors, and for a detector ring of diameter $D$ the resolution loss at the center, $\Delta$, is given by the expression

$$\Delta = D/2 \tan(0.25^\circ)$$

For a whole-body scanner with a ring diameter of 100 cm, the contribution to the resolution limit due to photon acollinearity is approximately 2.2 mm at the center.

Although the resolution limit for such a whole-body scanner may be approximately 3 mm, it is not usually attained in practice owing to factors related to the specific scanner design. Positioning uncertainty in the detector blocks, for example, may contribute an additional factor of approximately 1 mm. In addition, for ring scanners, the spatial resolution varies throughout the FOV. When the resolution is decomposed into radial and tangential components, it can be seen (Fig. 3.18) that the radial component degrades with increasing distance from the center of the FOV. This is due to the oblique incidence of the radiation on the detectors that can result in malpositioning, even into the adjacent detector element. The effect increases with increasing radial distance from the center of the scanner. The tangential component is essentially unaffected by the ring geometry. Newer designs, however, based on panel detectors with smaller elements, are reporting resolutions down to 2.5 mm over the whole cerebral cortex. The spatial resolution of the panel detectors is maintained constant over the brain by implementing a depth-of-interaction measurement that considerably limits the degradation of the radial component.

The temporal resolution of a PET scanner is a combination of many factors, including the injected radioactivity, the scanner sensitivity, the count-rate performance, and the required signal-to-noise ratio in the image. For certain research studies in which it is important to follow the initial uptake phase of the tracer, frame durations may be as short as 2 to 3 seconds. However, with the sensitivity of current PET scanners, such short-duration frames are count limited, and the frame duration is increased as the kinetics of the tracer slows. Essentially all clinical scans are currently performed with FDG, the scan being initiated 1 hour or more after injection, when the tracer is fixed in the tissue and no longer changing dynamically. For such studies, scan durations of 4 to 20 minutes are typical.

Contrast resolution is a complex combination of scanner spatial resolution; counting statistics; tracer uptake in target and background; corrections for randoms, scatter, and attenuation; and other factors. Correction procedures may increase noise and reduce contrast, as will poor spatial resolution and high statistical noise from low count acquisitions. One of the most important factors, however, is the uptake of the tracer by the target relative to the background. When the target-to-background ratio is sufficiently high, small structures below the resolution of the PET scanner can be visualized with adequate contrast, even in a relatively noisy environment.

REFERENCES

INTRODUCTION

Single-photon emission computed tomography (SPECT) imaging is based on the emission of single photons (γ-rays or x-rays) produced in the decay of certain radionuclides. The most commonly used radionuclide for SPECT imaging is technetium-99m ($^{99m}$Tc). The γ-ray emitted from $^{99m}$Tc has an energy of 140 keV. A summary of some radionuclides used for SPECT is given in Table 4.1.
The data used to form SPECT images are acquired with a gamma camera. The detection of radiation by a gamma camera is depicted in Figure 4.1. A photon is emitted from a radiotracer molecule in a random direction and leaves the body. The gamma camera includes a lead collimator with multiple parallel holes. These holes restrict the acceptance of photons so that only radiation emitted (roughly) perpendicular to the face of the gamma camera will be detected; the rest of the protons are stopped by the lead. The photons that make it through the collimator holes eventually hit the detector material, which is a sheet of thallium-doped sodium iodide [NaI(Tl)]. The vast majority of systems use 3/8-inch (9.5-mm) thick NaI(Tl), although thicker crystals are available and are more appropriate for energies greater than 140 keV. The radiation penetrates the crystal to a depth that depends on the energy of the radiation. The vast majority of 140-keV photons will stop within 3/8 of an inch, which justifies this thickness for 140 keV and lower energies. When a photon stops, some of its energy is released in the form of visible light. This light is measured by photomultipliers on the back of the crystal. The energy of the incident particle is accurately estimated from the sum of all the light energy measured in the photomultipliers. In addition, the position where the photon hit the detector is determined to 3.5- to 4.5-mm accuracy by an electronically implemented algorithm that compares the relative amount of light measured in each photomultiplier. The result for each incident photon that stops in the detector is a set of three numbers: two give the position of the photon in the scintillator (x and y), and the third gives its energy E.

As detected events accumulate, a projection view of the radiotracer in the body develops. The longer the acquisition, the more precisely this image represents the actual projection of the radiotracer distribution. SPECT imaging requires the acquisition of a series of these projections at successive angles around the body. To achieve this, the camera must be mounted on a gantry on which it can orbit the body. A complete data set requires an orbit of 180 degrees, and many acquisitions use 360 degrees of angular coverage. A typical angular increment is 3 degrees, which results in 60 total projections for a 180-degree orbit. Projection views and reconstructed slices from a cardiac SPECT study are shown in Figure 4.2. In this case, the field of view of the camera in the axial direction is 40 cm, much larger than necessary to image the heart.

Compared with positron emission tomography (PET), SPECT acquisition is a less efficient way of acquiring data, because only the photons leaving the body (roughly) perpendicular to the detector (about 1/1000, depending on the specific collimator design) will pass through the collimator and be detected. With PET, any photon pairs leaving the body in the same plane as the detector ring will be detected. Another disadvantage of SPECT is that only a single projection view is acquired at a time, whereas in PET all angles are acquired simultaneously.

Most single-photon emitters used with SPECT are longer lived (more than 6 hours; see Table 4.1) than the conventional PET radionuclides (less than 2 hours). The implications are great for producing and delivering radiotracers, because half-lives less than 2 hours require either on-site production or careful delivery planning, whereas longer-lived tracers allow more flexibility in production, delivery, and use.

### TABLE 4.1

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Symbol</th>
<th>Half-life (h)</th>
<th>Emitted Photon Energies (keV)</th>
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</thead>
<tbody>
<tr>
<td>Thallium 201</td>
<td>201Tl</td>
<td>73</td>
<td>~70–80, 167</td>
</tr>
<tr>
<td>Technetium 99m</td>
<td>99mTc</td>
<td>6</td>
<td>140</td>
</tr>
<tr>
<td>Iodine 123</td>
<td>123I</td>
<td>13</td>
<td>159</td>
</tr>
<tr>
<td>Iodine 131</td>
<td>131I</td>
<td>8</td>
<td>364</td>
</tr>
<tr>
<td>Indium 111</td>
<td>111In</td>
<td>2.8</td>
<td>172, 245</td>
</tr>
<tr>
<td>Gallium 67</td>
<td>67Ga</td>
<td>78</td>
<td>93, 184, 300, 393</td>
</tr>
</tbody>
</table>

SPECT images are degraded by several physical factors (1) that ultimately limit SPECT image quality and accuracy. Collimator blur, statistical noise, scatter, and attenuation each have specific negative effects.

**IMAGE-DEGRADING FACTORS**

SPECT images are degraded by several physical factors (1) that ultimately limit SPECT image quality and accuracy. Collimator blur, statistical noise, scatter, and attenuation each have specific negative effects.
Spatial Resolution

The ideal collimator would have long, small-diameter holes so that only photons arriving exactly perpendicular to the collimator face would be accepted. In reality, the collimator accepts photons over a range of incidence angles. The result is that a small point source would look like a blurred dot in a SPECT image. The amount of blurring depends on the collimator characteristics and the distance of the source from the camera, as depicted in Figure 4.3. The best spatial resolution results when the source is close to the camera and when the collimator has holes that are long or have a small diameter, or both.

For a given scan, the distance from the photon-emission sites to the collimator is dictated by the patient’s size, the particular body section being imaged, and the proximity of the camera to the body. To achieve the highest possible spatial resolution, many modern SPECT systems feature autocontouring. In this mode, the system uses sensors on the collimators to keep the camera as close to the patient as possible at each projection angle.

Noise

Image noise (statistical variation from one pixel to the next) results from the acquisition of a limited numbers of photons. Increased counts result in reduced noise. Increases in counts can result from using a higher injected radiotracer dose, using a longer scan time, having more detectors on the gantry, and modifying the collimator design. The simplest collimator modifications to increase sensitivity are to decrease hole length and to increase hole diameter. Such modifications, however, work directly against the goal of high spatial resolution. In practice, the collimator design represents a trade-off between the need for more counts to reduce image noise and the need for better spatial resolution. The ideal configuration depends on the imaging situation.

In addition to the acceptance angle, which dictates spatial resolution and sensitivity, an important feature of a collimator is its ability to stop the undesired (oblique) photons. Collimators designed for low-energy (140 keV or less) imaging can have very thin (less than 1 mm) lead septa. Higher energies require thicker septa to prevent penetration of the septa, which results in ineffective collimation.

**Figure 4.2** Selected projection views (every 15 degrees) from a cardiac SPECT acquisition are shown in the top two rows. In the bottom row are six of the transaxial slices reconstructed from these projections.

**Figure 4.3** Collimator blur. The image of a point source is blurred out on the detector face because of the acceptance of the holes. Increased blurring resulting from short holes, larger-diameter holes, and increased distance between the source and collimator.
Other modifications to the standard parallel-hole design for SPECT collimators include designs in which the holes focus to a spot (cone beam) or to a line (fan beam). Among the advantages of such collimators is that more radiation from the middle of the field of view is collected, meaning higher detection efficiency. The disadvantages include a decreased field of view and more complex image reconstruction.

**Scatter**

Of all the photons detected in the gamma camera, many will have scattered at least once in the body. The probability of a photon’s scattering depends on its energy and the amount and type of tissue traversed. For example, a 140-keV photon has a 15% chance of scattering as it traverses 1 cm of soft tissue. On scattering, the photon loses some energy. If the energy loss is great enough, the photon can be rejected by the gamma camera. However, the energy measurement of the gamma camera is not precise enough to reject all scattered photons. (A typical window is 10%; events measuring more than 10% greater than the emission energy or less than 10% below the emission energy are excluded.) Approximately 30% of photons detected and processed in the gamma camera are scattered. The detection of a scattered photon is depicted in Figure 4.4 by the ray labeled 1. It should be noted that, unlike in PET and in various transmission imaging contexts, the SPECT collimator does not preferentially limit the detection of scattered radiation.

The effect of scattered events on the final reconstructed image is to add counts over a broad area of the image. A variety of scatter-correction algorithms have been proposed and evaluated for SPECT. The simplest of these uses an additional measurement of photons at a lower energy than the primary emitted photon energy. Such a sample of photons will all have scattered and can serve as an estimate of the scattered photons in the primary sample.

**Attenuation**

In Figure 4.5, ray 2 depicts attenuation, where a photon is either absorbed or is scattered away from a path that would have allowed its detection. Although only a small number of scattered photons are detected (which entails that scatter has only a moderate effect on SPECT images), all scattered or absorbed photons contribute to attenuation effects. Only 22% of 140-keV photons are unscattered through 10 cm of water (or soft tissue). Only 5% of 140-keV photons are...
unsctracted through 20 cm of water, comparable to the amount of soft tissue traversed by a photon emitted deep in a large body.

Attenuation has several effects on the resulting images. First is the loss of quantitative accuracy by very large factors. Second is the increase in image noise due to lost counts. Third is the nonuniformity caused by the different amounts of attenuation for photons emitted in different parts of the body. Generally, the photons emitted from deeper in the body are more likely to be lost. Regions of the body with uniform uptake of the radiotracer will appear nonuniform because of attenuation. Other effects, such as distortions, are possible but less prevalent than they are in PET.

**EXISTING SYSTEMS**

The systems designed to do SPECT imaging also are designed to do planar single-photon imaging. Planar imaging is the acquisition of a single projection view, with no reconstruction into cross-sectional slices. For some studies, planar views provide sufficient information. Historically, planar imaging with gamma cameras was widespread long before SPECT imaging became technically feasible. The advantages of SPECT over planar imaging include separation of underlying structures, increased contrast due to attenuation for photons emitted in different parts of the body. Generally, the photons emitted from deeper in the body are more likely to be lost. Regions of the body with uniform uptake of the radiotracer will appear nonuniform because of attenuation. Other effects, such as distortions, are possible but less prevalent than they are in PET.

Attenuation of photons emitted by the radiotracer results in a variety of undesirable effects, including overall loss of counts, loss of quantitative accuracy, nonuniformity (e.g., more counts are lost from sources deep in the body than from superficial sources), and even the appearance of excess activity in low-attenuation areas. It is possible to correct these effects (except noise effects due to lost counts) if the attenuating properties of the body are known.

Attenuation correction is possible by using the emission data alone if the outer contour of the body can be determined from the emission data and if it can be assumed that all regions within this contour are of uniform density (attenuation). SPECT attenuation corrections based on these assumptions have been in use for a long time (2). However, because of the presence of bone, lungs, abdominal gas, and errors in the estimated body contours, it is best to measure the body’s attenuating properties with a transmission scan.

Multiple transmission-scanning techniques have been proposed and implemented for SPECT cameras. With the exception of x-ray CT scanning for attenuation correction (discussed more fully in Chapter 8), all systems use the gamma camera to detect the radiation from an external radioactive source. As with PET, the data measured during a SPECT transmission scan are compared with the data from an identical scan done without a patient in the scanner, sometimes called a “blank scan.” Figure 4.6 shows a transmission measurement for a particular path through the body. A ratio of the transmission scan counts $T$ (at right) and the blank scan counts $B$ (at left) yields the attenuation factor $A$ for that path:

$$A = \frac{T}{B}$$

(1)
The attenuation factors for all paths (all projection lines at all angles) can be reconstructed into a cross-sectional attenuation map. The resulting attenuation map can be used to correct attenuation during the reconstruction of the emission data. Several features are necessary for practical transmission scanning on SPECT cameras. First, the radiation exposure to the patient should not be excessive (e.g., greater than the exposure from the radiotracer). Second, adequate attenuation maps should be attainable without a substantially longer total acquisition time (for emission and transmission). Third, the transmission scans must be feasible after the patient has been injected with the radiotracer. That is, it must be possible to perform the transmission scan immediately before, during, or after the emission scan.

Because different radionuclides emit photons of different energies, it is possible to use transmission sources whose photons can be differentiated from emission photons by energy. In Figure 4.7, a measured energy spectrum of $^{99m}$Tc ($E = 140$ keV) in a phantom and gadolinium 153 ($^{153}$Gd) ($E = 100$ keV) in a transmission source is shown. In this case, the 140-keV peak can be measured cleanly, whereas the 100-keV peak will be contaminated somewhat by $^{99m}$Tc photons that have scattered and lost some energy.

**Moving Line Source**

One transmission-scanning technique uses a scanning line source (3). As it moves, the line source sweeps out the area of the detector on the opposite side of the patient (Fig. 4.8A). Because of the camera collimation, as the line source moves, true transmission counts register only in the region currently in front of the line. An electronic mask that moves with the source is used to exclude emission events from the transmission data set. An inverse of this mask can be used to exclude transmission events from the emission data if the transmission source has the higher energy. Among the benefits of this technique, it can be done in conjunction with a normal collimator on the camera and also done simultaneously with the emission scan. Instead of a single moving-line source, another approach uses multiple fixed parallel-line sources, exposing more of the body at once (4).

**Symmetric Fan-Beam**

If a fan-beam collimator is used on one head (Fig. 4.8B), a line source can be placed at its focus to achieve an x-ray CT-like geometry (5). This system allows very efficient detection of transmission radiation, because all holes focus on it simultaneously. If the source photons have higher energy than the emission photons, a very fast transmission scan can be done before or after the emission scan, and the source is covered during the emission scan. One limitation of this technique is that the field of view is reduced compared with that of a parallel-hole geometry, and a large patient will not be fully sampled.

**Offset Fan-Beam**

A modification to the fan-beam geometry is to use a collimator that focuses to one side (6) (Fig. 4.8C). If a 360-degree rotation is performed, this system has the same full field of view as a parallel-beam system.

Finally, transmission scanning in SPECT can be done by using a rotating x-ray source. This approach is discussed in detail in Chapter 8.

Although multiple adequate methods exist for transmission scanning on SPECT systems and options are commercially available on many systems, very few clinical SPECT
studies are performed with transmission scans, and few systems are purchased with transmission-scanning options. This is in stark contrast to PET. No PET scanner is sold without transmission-scanning capability, and routine use of transmission scanning for attenuation correction is widespread. There are many possible reasons for this disparity, including the larger effect of attenuation in PET, the relative ease of implementing attenuation correction in PET from an algorithmic point of view, the history of using PET for quantitative research purposes, and the smaller incremental fraction of total system cost.

Figure 4.8 Methods of transmission scanning on SPECT systems. A: Moving-line source. B: Fixed-line source, symmetric fan-beam. C: Fixed-line source, offset fan-beam.

REFERENCES
Design Criteria for PET Scanners: What Is Important and Why

Charles Stearns  Alexander Tokman

Positron emission tomography (PET) image quality is a function of scanner resolution and the statistical quality of the data acquired. For most clinical PET studies, image quality is limited not by the intrinsic resolution of the scanner but by the signal-to-noise characteristics of the data. The PET signal is the true coincidence count during the scan; noise comes from the Poisson statistics of the combined true, scattered, and random coincidence counts. The task of systems design is to maximize acquired true counts (i.e., signal) while minimizing the scatter and random coincidence contamination (i.e., noise). This is not straightforward, because many design parameters have multiple influences, and all design decisions must be weighed against their impact on the cost of the scanner. Noise-equivalent count rate (NECR) analysis is a method of demonstrating the relationship among true, scattered, and random coincidences and their impact on signal-to-noise in the PET data set (see Fig. 5.5). Although NECR analysis is a valuable tool, it is dependent on the particular imaging task under consideration.

The primary imaging performance metrics (per National Electrical Manufacturers Association [NEMA] methods) of PET and PET-CT scanners are a function of many variables, and no single scanner component determines the imaging performance of the PET scanner. The intrinsic characteristics of the detector crystal material (e.g., its stopping power, speed, and energy resolution) are important, but other aspects of PET system design (e.g., system and crystal geometry, crystal volume, septa design, and electronics) are also key determinants of PET imaging performance. True coincidence sensitivity, for example, is a function not only of the sensitivity of the detector (probability that a 511-keV photon hitting the detector is recognized by the system) but also the geometric sensitivity of the scanner (what fraction of annihilation photon pairs hit the detector). Similarly, scattered and random coincidences depend on detector and system properties as well.

One significant question in PET system design is the presence of slice septa. For current clinical applications, a septa-less design has a much higher geometric sensitivity for both signal and noise coincidences. The merits of a septa-less scanner (or the septa-retracted mode of a retractable septa scanner) hinge on whether the benefits of increased true coincidences are outweighed by the costs in increased scatter and randoms. The answer to this question is very dependent on the imaging application. Brain imaging with relatively modest scatter and random coincidence benefits from septa-less imaging; however, the advantages of septa-less whole-body imaging are less clear.

INTRODUCTION

The exceptional clinical utility of positron emission tomography (PET) in diagnosing, staging, and restaging oncologic as well as other disorders has led to a dramatic growth of PET applications worldwide in the last few years. This growth has been further spurred by factors such as expanded reimbursements, the growth of the entrepreneurial segment,
fluorodeoxyglucose (FDG) dose availability, overall improved cost-effectiveness, and the introduction of PET-computed tomography (CT) technology. The first three factors are the primary reasons for the exploding U.S. PET market.

As PET emerges from being a research tool used by selected luminary institutions to become a mainstream medical imaging modality, the new users ask typical questions when inquiring about the technology. What is a good PET scanner? Which scanner is better and why? What is the minimum performance I must have and can I afford it given my budget constraints? What PET detector technology should I go with: bismuth germinate (BGO), lutetium oxyorthosilicate (LSO), gadolinium oxyorthosilicate (GSO), or sodium iodide (NaI)? These questions do not have simple answers, especially because they all are open-ended. For example, two PET scanners based on the same PET detector technology may perform completely differently. In one case, scanner A will outperform scanner B because it has better scanner geometry, better crystal geometry, more crystal volume, more crystals, and better electronics, but it will be more expensive. In another case, two scanners may be of comparable cost, but scanner A performs better for oncologic procedures whereas scanner B excels at neurological applications because of crystal geometry differences. Thus, the performance parameters trade-off is key in PET scanner design, and no single component makes one scanner better than the other.

What does “better” mean in clinical terms? Does it improve the accuracy of the diagnosis or staging? Does it allow one to see finer objects in the image? Do objects exhibit better a contrast-to-noise ratio and therefore are more easily seen? Of course, the objective way to get answers to the questions is to scan a number of patients on several scanners, conduct objective observer studies, and then compare the accuracy and effectiveness of each scanner with respect to others, not forgetting the other important clinical attributes, such as the time it took to complete the patient examination and the injected patient dose. In reality, this is not feasible, so standardized phantom studies are used as predictors of scanner performance.

The objective of this chapter is to provide the reader with the pragmatic overview of the top-down principles of PET scanner design without “drowning” him or her with the underlying scanner and detector physics. In this top-down process, the clinical application requirements drive scanner requirements, which in turn determine the critical scanner components and specifications.

**CLINICAL APPLICATION REQUIREMENTS**

The clinical efficacy of any medical imaging device, including PET scanners, is determined by the following factors (note that in the remainder of this chapter, unless referring to a specific scanner model, the terms “PET” and “PET scanner” will be used to mean either a stand-alone PET scanner or the PET component of a PET-CT scanner):

- **Lesion detectability:** the ability to detect objects of various sizes and contrast-to-background ratios.

- **Examination time:** the elapsed time between when the patient is placed on the table to when the images are reconstructed and the patient is dismissed. Although the overall examination time typically comprises five elements, including patient check-in time, injection time, the postinjection wait period, and patient positioning time and imaging time (acquisition and reconstruction time), the latter two are most dependent on the design and operation of the PET scanner.

- **Dose:** how can one minimize the dose to patients and staff without sacrificing the clinical efficacy of the examination?

- **Applications capability:** scanner ability to perform routine and advanced clinical and research applications. Although FDG oncology imaging is currently the dominant clinical imaging procedure in many institutions, the growth of applications in cardiology and neurology may place additional demands on the PET scanners. Applications involving other isotopes, particularly positron emitters such as iodine 124 (124I) and copper 64 (64Cu), which are characterized by low positron fractions and high incidence of coincident or noncoincident γ-ray emission, also may become important in the future, although there are radiation protection issues (see Chapter 9).

Note that these factors are also highly interrelated: for example, one can reduce the examination time by simply increasing the dose to the patient or by accepting a reduced image quality. The following section outlines what drives these clinical parameters.

**PET IMAGING PERFORMANCE ATTRIBUTES**

The top-level requirements for the PET scanner fall into one of the these categories: image quality, examination time or throughput, extended features and functionality, ease of use, connectivity, reliability, serviceability, and cost. This chapter focuses on the scanner parameters that impact image quality and examination time.

In the 1990s, the PET manufacturers and academic experts developed the National Electrical Manufacturers Association (NEMA) standard for measuring the performance of PET scanners. They jointly agreed on the important parameters affecting clinical image quality and patient imaging time.

**Spatial Resolution**

Spatial resolution is defined as the ability of the PET scanner to discern small objects. Resolution is generally assessed by measuring the response of the system to a point source emitter (typically approximately 1 mm). It is typically reported as “full width at half maximum” (FWHM), or the width of the region where reconstructed pixel values exceed half the maximum pixel value of the point source response. This is shown in Figure 5.1. It is theoretically impossible to distinguish two objects closer together than one FWHM, because there is no discernible
valley between the two point spread responses in the image. Spatial resolution is typically presented in transaxial and axial directions.

It is well known that PET resolution is limited by the range of the emitted positron and by the noncollinearity of the annihilation photon pair (see Chapter 3). These factors provide a fundamental resolution limit for PET images at roughly 2 mm FWHM for human whole-body imaging. This limit may only be achieved with a perfect detector system that is able to locate each annihilation photon precisely. Real detectors fall short of this ideal in two important ways:

- First, the detector is composed of finite elements. This is true whether the detector is assembled from individual crystals (as in a block detector) or is the digitized readout from a continuous detector (as in an Anger camera). The line of response between two detector elements is therefore not a line but a tube of nonzero width, as shown in Figure 5.2A. At the midpoint of the line between the two detectors, the sensitivity profile across this tube is triangular, so the FWHM of the profile is one-half the detector element width. Away from the midpoint, the sensitivity profile becomes trapezoidal, with a FWHM somewhat larger than half the element width.

- Second, precise localization is possible only if the annihilation photon has a single (photoelectric) interaction with the detector, depositing all of its energy at the site of that interaction. Unfortunately, 511-keV photons are fairly energetic and will frequently undergo Compton scatter. A secondary photon leaves the Compton scatter site, making it possible to have multiple interactions in the detector (Fig. 5.2B). In this example, the top photon has a Compton scatter in detector A, and the scattered photon has a photoelectric event in detector B. Only a small amount of energy is deposited in detector A; most of the energy is deposited in detector B. The detector will likely determine that the photon interacted in detector B, and will assign the coincidence event to line of response BC instead of AC. Quantifying the impact of this effect on scanner resolution is difficult, because it is a complex function of the detector configuration, detector material properties, and scanner electronics design. However, it is clear that a detector material with a higher photofraction (i.e., a higher probability of photoelectric vs. Compton interaction with the incident photon) will have more single-interaction events in the detector and therefore less resolution loss due to multiple detector interactions.

However, detector designs that attempt to approach this limit in human imaging are confronted by signal-to-noise issues that prevent the completed system from utilizing the high resolution the detector can provide.

A demonstration of the importance of signal-to-noise in reconstructed PET images is shown in Figure 5.3. For this study, a resolution phantom was simulated in which the smallest features are 2.5 mm in diameter and spaced by 10 mm. Three data sets were created with $10^5$, $10^6$, and $10^7$ true counts, each using a hypothetical PET detector with...
resolution of 4 mm FWHM. The top row shows the reconstruction of the three data sets with a standard ramp filter. Each of the images has the same theoretical or intrinsic resolution properties, but it is clear that much more detail is evident as the total count increases. The middle and bottom rows show the effect of applying smoothing filters to the images during reconstruction. Filtering reduces the resolution of the imaging system and decreases the detail visible in the high-count image. However, even though the theoretical resolution of the filtered images is reduced, feature visibility in the lower count images is improved by reducing the background noise.

Resolution uniformity refers to the consistency of spatial resolution across the scanning field of view (FOV). In many PET scanner designs, the detectors are all oriented at the center of the imaging FOV; therefore, photons entering the detector volume from off-center locations may interact in one of several detector elements. The resulting uncertainty in event localization leads to an elongation in the point-spread function in the radial direction; a larger detector ring in a PET scanner will lessen this effect. The effect of the resolution degradation away from the center is shown in Figure 5.4. In clinical applications, the patient represents a finite emission volume and not a point source; hence the off-center resolution is a critical imaging attribute.

Signal-to-Noise Level: Noise Effective Count Rate

The noise effective count rate (NECR) is a composite imaging metric originally proposed by Strother et al. (1). The NECR takes into account the fact that although true coincident events represent the signal in PET imaging, the Poisson statistics of the combined true, scatter, and random coincidences contribute to image noise. Even if the scatter and random corrections are perfect—that is, they accurately and noiselessly estimate the expected level of scatter and random coincidences in the data set—the corrections cannot compensate for the additional counting noise introduced by those coincidences. Factors affecting NECR

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**Figure 5.3** The importance of counts in reconstructed image quality. Simulated images with $10^5$ (left column), $10^6$ (center column), and $10^7$ (right column) counts; reconstructed with a Ramp filter (top row), Hann window with 4-mm cutoff (middle row), and Hann window with 8-mm cutoff (bottom row). Although the high-count images demonstrate that the intrinsic resolution of the images is degraded by filtering, filtering increases feature detectability in the low-count images.

**Figure 5.4** At the center of the ring (left), events are detected in one line of response, independent of their depth of interaction in the detector. Away from the center, the events are distributed over several detector elements. The result is a loss in radial resolution away from the center of the field of view, as depicted in the graph at the right.
The value of the NECR provides a quantitative framework in which to assess their impact on imaging performance. It is important to note that the true, scatter, and random coincidence rates, and hence the NECRs, are functions of scanner design, patient characteristics such as size, and the amount and distribution of activity within the patient.

Notwithstanding these factors, the NECR is a useful predictor of the PET scanner performance because it combines the effects of signal and noise in the system in a single metric. The NECR provides a quantitative framework in which to analyze design options that may increase true, scatter, and random coincidences by varying degrees and thus to assess their impact on imaging performance. It is important to distinguish between the often quoted peak NECR and the clinically relevant NECR performances. This is further discussed in the “Imaging Performance Assessment” section later.

### Sensitivity to True Events

Sensitivity is the rate at which the system detects coincidence events per unit of activity in the FOV. The rate of event detection is referred to as the “count rate” and is usually measured in kilo counts per second. The activity in the field of view is measured in microcuries (µCi) per cubic centimeter (cc) per unit time (second). Note that the more counts collected in an image, the better the image looks; also, the faster the counts are accumulated, the faster an image of the desired image quality can be acquired. So for any given set of scanners, the scanner with the highest sensitivity (in 2-D or 3-D) will produce an equivalent counts image faster than the other scanners. In turn, it will produce more counts than other scanners during the same acquisition time. The commonly used sensitivity metrics are 2-D/slice, 2-D system, and 3-D system. All are measured in kilo counts/s/µCi/cc.

Maximizing sensitivity is critical for maximizing the NECR. The true coincidence rate is a function of the following three factors: (a) the activity, or total number of positron annihilations occurring per second, in the FOV of the ring; (b) the fraction of annihilation photon pairs reaching the detector ring (which may be referred to as “geometric” sensitivity); and (c) the probability that a photon reaching the detector ring is detected (or the “detector efficiency”).

Detector efficiency is especially important in PET imaging because each of the two annihilation photons must be detected: a 10% efficient detector will only capture 1% of the available coincidence events because the probability of both detectors detecting a photon is proportional to the product of the capture efficiency of a single detector.

Derenzo et al. (2) provide a mathematical framework for estimating coincidence event rates as a function of the PET system design parameters and for computing the true coincidence rate of a single slice of a PET scanner:

$$\text{Trues} = \left[\epsilon^2 P^2 e^{-\mu l} \right] \frac{\beta aS^2}{4r}$$  \hspace{1cm} (2)

where $\beta$ is the activity density of the equivalent line source in microcuries per axial centimeter, $a$ is 37,000 positron annihilations/s/µCi, $S$ is the slice thickness or axial distance between septa, $L$ is the average path length (in centimeters) of a $\gamma$-ray photon pair through the object; $\mu$ is the attenuation coefficient (per centimeter), which is a function of the effective atomic number and density of the material; $r$ is the radius of detector ring; $P$ is the packing fraction, or the probability that a photon that hits the detector ring will then hit a crystal (this is the ratio of the actual detector front surface to the total surface area, including the gaps); and $\epsilon$ is the detector efficiency, the probability that if a $\gamma$ photon hits it, the detector crystal will convert it to light (as used in this analysis, this factor also incorporates the probability that the processing electronics will detect and process the single event).

From this formula, it can be seen that the sensitivity of the scanner is proportionally increased with the square of the packing fraction of the detector material and the detector efficiency. Per-slice sensitivity is also proportional to the square of the slice thickness. Sensitivity is inversely proportional to the radius of the detector ring. Note that the above equation is based on the data acquired in the 2-D mode. The extrapolation of the Derenzo equation to 3-D performance is explained later in the chapter.

![Figure 5.5](image-url) The noise effective count rate (NECR) as a function of specific activity. The curves are discussed in the text. Curves drawn from data provided by the manufacturers of each scanner.
The packing fraction is improved by increasing the detector volume while decreasing the gaps between detector crystals and can be negatively affected by saw-cutting the crystals out of the blocks. Detector efficiency is improved through a higher scintillator stopping power, better light conversion ability, and a higher decay constant as well as by improvement in the dead-time processing logic.

**Scatter**

A scatter coincidence occurs when one or both of the γ-ray photons from a positron annihilation undergo Compton scattering and then proceed to be detected (see Fig. 3.14). The subsequent noncollinearity of the detected pair results in a substantial malpositioning of the originating event. Not surprisingly, scatter is a function of factors similar to those that affect system sensitivity, specifically:

- the activity, or total number of positron annihilations occurring per second, in the FOV of the ring,
- the probability of the unscattered photons reaching the detector ring,
- the probability of the scattered photons reaching the detector ring, and
- the probability that a photon reaching the detector ring will be detected and converted to light.

Derenzo (2) computes scatter as

\[
\text{Scatter} = k_e^2 p^2 \frac{\beta_0 S^3}{2T} \tag{3}
\]

where \(T\) is the length of septa (in centimeters) and \(k_e\) is the probability of detectable scatter occurring in the patient, given by

\[
k_e = 2g_1(e^{-\mu/2} - e^{-\mu}) + g_2(1 - e^{-\mu/2})^2
\]

where \(g_1\) is the probability of single scattering photons and \(g_2\) is the probability of dual scattering photons, both of which are functions of the maximum scattering angle \(\theta_m\) (which in turn is defined by the geometry of the coincidence fan and the energy threshold).

The scatter equation stresses several important points:

- The same factors (i.e., \(e, p, t\)) that boost or reduce sensitivity also increase or decrease scatter at the same rate and vice versa.
- Slice thickness has even larger impact on scatter than it has on sensitivity (cubic vs. quadratic).
- Increasing septa length proportionally decreases scatter.
- Increasing maximal scattering angle \((g_1\) and \(g_2\)) through widening of the coincidence fan or energy threshold also increases scatter.

The last three points are important because they clearly demonstrate the value of having septa (i.e., in 2-D mode) on the PET scanner and the importance of proper design when high-scatter objects (e.g., large patients) are imaged.

**Randoms**

A random coincidence occurs when individual γ-rays from two separate, simultaneous positron annihilations strike two detectors and create a false coincidence event (see Fig. 3.15). The second γ-ray photon of each annihilation event may have been lost, either by leaving the scan plane or by attenuation.

Since randoms are the result from any two single γ-rays arriving at the same time, the randoms rate as sensitivity is a function of the following three factors: (a) the activity, or total number of positron annihilations occurring per second, in the FOV of the ring; (b) the fraction of the photons reaching the detector ring; and (c) the probability that a photon reaching the detector ring will be detected and converted to light.

It can be again shown that randoms rate is described as

\[
\text{Randoms rate} = f[\frac{\beta_0^2 S^3}{T} + \frac{k_R}{N_0}, \frac{S}{T} + \frac{1}{T} + \frac{1}{T} - 1 - e^{-\mu/2} + g_2 e^{-\mu/2}]
\]

where \(k_R\) is the probability of the singles rate; \(t\) is the coincidence time window; \(f\) is \(N_0/N\), the fraction of total detector crystals in coincidence with one detector crystal; and \(N_0\) is the number of opposing detector crystals in coincidence with any one detector.

Note that the randoms rate increases with the square of the activity injected into the patient, so randoms become a significant issue at increased activity levels in the patient. Randoms per slice also increase by \(S^3\); however, this increase can be balanced by increasing the length of the septa \(T\) and reducing the coincidence window \(t\) of the detector. The coincidence window is affected by the speed of the scintillation material of the detector, as it must be wide enough to accept essentially all true coincidences while remaining narrow to limit acceptance of random coincidences. Typically, a detector material with a faster decay constant will permit a decreased coincidence window.

**2-D and 3-D Acquisition**

All PET images are "3-D" in that they represent an image of the activity distribution in the patient over multiple transaxial planes. However, PET acquisitions are performed in one of two modes:

- 2-D, or multi-slice acquisition, where septa are used to help define the imaging planes and reduce the effect of scatter and random coincidences, and
- 3-D, or volumetric acquisition, where septa are not used and coincidences are accepted at an increased axial angle.

Some PET scanners have both 2-D and 3-D capability, with septa that are automatically retracted for 3-D acquisitions and replaced for 2-D acquisitions (see Fig. 3.5).

The Derenzo equations can be adapted for volumetric acquisition by considering the full axial extent of the scanner.
as one slice and replacing the septa term \( T \) with the extent of the side shields at the ends of the axial FOV. This yields a large increase in true event detection, which is the primary motivation for volumetric acquisition. However, it produces an even larger increase in scatter and random coincidence events.

The NECR formulation provides a mechanism to assess the balance between the positive impact of the increase in true coincidences versus the negative impact of the increase in scatter and randoms. In imaging conditions in which the scatter and randoms fraction is low, such as low-activity imaging, the sensitivity increase prevails, and 3-D imaging is demonstrably superior to 2-D imaging due to improved imaging time and reduced dose. In other imaging conditions, such as in body imaging, which is the most common kind of imaging in oncology, 2-D exams are still considered the gold standard. However, it is expected that the use of 3-D imaging will increase as the technology improves. In clinical oncology, 2-D exams are still considered the gold standard of PET imaging, primarily because of the septa effectiveness in shielding the increased body scatter.

### SCANNER DESIGN PARAMETERS

The previous section described the relation between several scanner design parameters and true, scatter, and random coincidence events recorded by the system. This section analyzes those design parameters in light of these relationships to determine their impact on the NECR, on resolution, and, by extension, on PET image quality. All PET scanner design parameters fall into two important categories: (a) intrinsic detector parameters and (b) scanner geometry and systems parameters.

#### Intrinsic Detector Parameters

The intrinsic properties of the detector determine many important attributes of image quality available from a PET system. For the purposes of this discussion, we restrict our considerations of detectors to designs consisting of scintillator crystals and photomultiplier tubes. Table 5.1 lists several important properties of the scintillators most commonly used in PET scanners today.

**Detector Efficiency**

Detector efficiency is defined as the probability that if a \( \gamma \)-ray photon hits a detector, the detector crystal will capture it and convert it to light. As discussed earlier, detector efficiency is of critical importance to true event sensitivity, since both of the annihilation photons must be detected to register a true event. Efficiency is driven by the crystal stopping power, which is a function of crystal density and its depth. Because of the likelihood of multiple photon interactions in the detector, it is not possible to calculate the detector efficiency exactly. An upper bound on sensitivity can be established by recognizing that if there is no interaction, then there can be no detection. This can be expressed by the equation

\[ \varepsilon \leq 1 - e^{-\mu L} \]

where \( \mu \) is the attenuation coefficient for the material and \( L \) is the crystal depth.

**Detector Timing Resolution**

Light photon and photoelectron statistics limit the ability to resolve the arrival time of a photon, which in turn limits how small the coincidence window width can be set. The objective is to minimize the coincidence time window in order to minimize the random coincidence events while maintaining optimal sensitivity. This attribute is a function of the scintillator decay constant, and the coincidence time window can be shortened if the scintillator material possesses faster decay times. Faster “decay time” crystal detectors generally are more expensive and therefore add cost to the scanner.

**Detector Energy Resolution**

Energy resolution represents the ability of the detector to differentiate 511-keV photons from scattered protons of less energy and is a function of the detector scintillator material properties. Improved energy resolution permits increasing the minimum threshold for measured energy of accepted \( \gamma \)-ray photons (or narrowing the energy window), which will have a positive impact on system performance by reducing the detection of scattered coincidences.

**Detector Dead Time**

“Dead time” refers to the inability of the detector, or subsequent processing electronics, to process more than one event at a time; additional events are lost because the detector channel is “dead” to them. The fundamental component of dead time is the integration time of the signal in the detector. Integration time is improved by reducing the scintillator time constant so that the dead time is shorter and by reducing the volume of the detector that is consumed by processing each event (the “dead zone”).

Additional dead time occurs when detector signals must be multiplexed en route to the coincidence processor. The extent of these dead-time losses can be minimized, but

### TABLE 5.1

**PROPERTIES OF PET SCINTILLATOR MATERIALS**

<table>
<thead>
<tr>
<th></th>
<th>BGO</th>
<th>GSO</th>
<th>LSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attenuation ( \mu ) (cm(^{-1}))</td>
<td>0.95</td>
<td>0.67</td>
<td>0.89</td>
</tr>
<tr>
<td>Photofraction</td>
<td>(-40%)</td>
<td>(-35%)</td>
<td>(-30%)</td>
</tr>
<tr>
<td>Light output (relative)</td>
<td>20–25</td>
<td>35</td>
<td>75</td>
</tr>
<tr>
<td>Decay constant (ns)</td>
<td>300</td>
<td>65</td>
<td>50</td>
</tr>
</tbody>
</table>
only at the cost of additional (or more complex) electronics to process the detector signals.

**Scanner Geometry and Systems Parameters**

Although the detector properties described above play a key role in determining image quality, the use of those detectors in an appropriate system geometry is also of vital importance. A detector that has "superior" intrinsic properties but is placed in the wrong system geometry will not yield superior image quality. The question of 2-D versus 3-D imaging is a significant scanner geometry issue that was addressed previously. In addition, the following factors affect image quality in a PET scanner.

**Scanner Ring Diameter**

In a full-ring system design, the ring diameter is increased or decreased by adding or removing detector elements, with obvious implications for system cost. The primary impact of increasing ring diameter (see Fig 5.4) on image quality is to improve the peripheral spatial resolution of the scanner. A smaller ring diameter has a larger parallax effect away from the center of the scanner, providing less constant resolution over the whole-body field of view.

A very significant secondary benefit of an increased ring diameter is the opportunity to increase septa length (or side shielding length in a 3-D–only system) in the space between the patient port and the detector surface. This will improve scatter and randoms rejection in the system design.

**Detector Axial Extent (or Axial Field of View) and Overlap**

The imaging time is inversely proportional to the product of the length of the axial FOV (AFOV) (see Fig 3.2) and the number of AFOVs required to cover a specific anatomy. The larger the AFOV, the fewer FOVs or bed positions required to cover a given distance and thus the shorter the examination time. For a fixed AFOV, the factor that determines the number of FOVs required to scan a given volume is called the "percent overlap." The percent overlap varies from 1% to 3% during 2-D scanning to 20% to 30% for 3-D acquisitions. This is primarily driven by the "triangular" sensitivity response (i.e., the decrease in the sensitivity from the center to the edges) observed in 3-D applications. This directly translates into an additional requirement of 20% to 30% extra bed positions for 3-D scanning. This is counterbalanced by the increased count rate exhibited by 3-D acquisitions (with increased scatter; see Chapter 3). As a practical example, consider two PET scanners each with an AFOV of 15 cm. The first scanner (scanner A) is operated in 2-D with the emission time of 4 minutes per bed position or AFOV, and the second scanner (scanner B) is operated in 3-D with 3 minutes per bed position. The anatomic area of coverage for a typical oncologic procedure is approximately 90 cm. Both scanners will cover this patient anatomy in 24 minutes because scanner A will require six AFOVs or bed positions and scanner B eight bed positions (assuming typical 25% overlap).

**Detector Crystal Dimensions**

Each of the three dimensions of the detector element—transaxial (width), axial (height), and depth—has a significant impact on imaging performance. Transaxial and axial dimensions determine the spatial extent of the line of response and therefore determine image resolution. In 2-D imaging, the axial dimension of the detector is the primary determinant of slice thickness, which we have seen has a profound effect on true, scatter, and random coincidences. We have also seen that detector depth has a profound impact on detector efficiency.

These effects must be considered in light of the crystal cost. Although smaller detector elements favorably impact image resolution, decreasing crystal width and height will increase the cost dramatically, as more crystals are required to complete the detector. Increasing the detector depth increases the volume of the detector material required to complete the detector.

**Detector Packing Fraction**

The gaps between crystals and between blocks determine the packing fraction of the detector for a given detector crystal volume. A high packing fraction is important for boosting system sensitivity; however, it also increases scatter and randoms. Once again, having septa or a fast scintillator will allow a boost in sensitivity but mitigate scatter (septa) and randoms (septa and fast scintillator). Cost is generally a factor when it comes to improvement of this design attribute.

**Electronics Dead Time**

Additional dead time occurs when detector signals must be multiplexed en route to the coincidence processor. The extent of these dead-time losses can be minimized, but only at the cost of additional (or more complex) electronics to process the detector signals.

**Imaging Performance Assessment**

The imaging performance attributes of several commercial PET-CT scanners based on the NEMA NU 2-2001 standard are summarized in Table 5.2. “N/A” implies that a specific metric is not applicable for a given device. “NP” implies that the information has not been published by a manufacturer. The information presented here is based exclusively on the data published by the manufacturers of the respective equipment and is available from the product data sheets, at the manufacturers’ Web sites, and at trade press Web sites such as www.itnonline.net.

Table 5.2 shows that Discovery ST has the highest 3-D sensitivity but also the highest scatter fraction. The other scanners each have essentially the same 3-D scatter fraction.
Spatial resolution is largely determined by crystal size. The Siemens Biograph, with the smallest crystals, achieves the lowest spatial resolution values. Resolution at 10 cm is comparable to resolution near the center of the FOV, as the resolution effects of detector curvature (as shown in Fig. 5.4) are minimal at this radius in whole-body scanners.

The 3-D NECR data based on the NEMA NU-2 2000 standard are shown in Figure 5.5, and the peak values are summarized in Table 5.2. The highest NECR values are achieved by the Biograph in 3-D mode and the Discovery ST and STE in 2-D mode. The value of the NECR curve is that it allows comparisons at different activity levels, which correspond to different injected doses in a patient or different delay times from injection to imaging. For example, although the Siemens biograph has the highest peak NECR and the best NECR performance at high activity rates, it fares less well than the other scanners at low activity rates.

What does this mean in clinical terms? Extrapolating the activity of 6 kBq/mL to the activity seen in a 70-kg patient translates into 420 MBq (11.4 mCi) of activity at the time of imaging. This is approximately equivalent to about 610 MBq (16.5 mCi) of FDG injected 1 hour before imaging begins, which may be considered excessive in some settings. Even this extrapolation should be considered cautiously; because most adult patients are considerably larger than the 20-cm-diameter NEMA phantom, the effects of attenuation and scatter, and hence their “effective” NECR...
performance, will be considerably different than that measured in the standard measurement configuration.

**SUMMARY**

The key characteristics that determine the overall value of a PET scanner include image quality, examination time or throughput, extended features and functionality, ease of use, connectivity, reliability, serviceability, and cost. The emphasis of this chapter has been on the important imaging attributes that establish the baseline for PET scanner imaging and throughput performance.

The limiting factor in most PET studies is not the intrinsic resolution of the scanner but the signal-to-noise characteristics of the data in the PET acquisition. This predictor (NECR) is a function of the true, scatter, and random coincidence events acquired during the PET scan. Although the NECR is a valuable tool in assessing the image quality potential of a particular PET scanner design, it is important to remember that NECR performance on a particular phantom does not fully capture the breadth of imaging conditions a PET scanner may encounter.

The imaging performance metrics are a function of many variables, and there is no a single scanner component that determines the imaging performance of a PET scanner.

The intrinsic characteristics of the detector crystal material, such as its stopping power, speed, and energy resolution, are important, and other aspects of PET system design, including the system geometry, crystal geometry, septa design, and electronics, are also key determinants of PET imaging performance. There are many ways to “skin a cat”; thus, when deciding on a particular PET scanner, the choice should be based on the system performance results (with the main applications in sight) and not on the building blocks or the variables that determine it. For example, when buying a car, we make the decision based on the overall performance results, such as acceleration, breaking distance, reliability, features, and cost, not on which car has a better carburetor.

Image quality is also dependent on the imaging task at hand, in terms of both the radiopharmaceutical being imaged and the location in the body under examination. A system that is optimal for imaging F-DOPA in the brain may not be well suited to image FDG in the thorax or abdomen, where attenuation is greater and the scatter fraction much higher. As a result, a good understanding of the applications at hand is key when selecting an optimal PET scanner.

**REFERENCES**

Basics of CT Scanning and Issues Relevant to Integrated Imaging

Willi A. Kalender

X-ray computed tomography (CT) has evolved to be one of the most important imaging modalities due to the introduction of spiral CT and of multi-row detector technology. Multi-slice spiral CT (MSCT) allows coverage of complete organs in typically 5 to 10 seconds or "whole-body" scans in less than 30 seconds with isotropic spatial resolution of typically 0.5 mm or better. This chapter focuses on technical developments, scanner performance, image quality, and the expanded range of clinical applications. Dose issues are dealt with briefly, in particular, the options for dose reduction offered by modern CT. MSCT constitutes a perfect match with molecular imaging using PET and SPECT. Given the current high performance levels, the latest advances in CT technology, including cardiac CT, can and should be utilized without any restriction in PET-CT and SPECT-CT scanners.

INTRODUCTION

X-ray computed tomography (CT) has gone through a number of development cycles since its introduction in the early 1970s. Although the goals and the future of CT developments were rated differently at different points in time, in particular when compared with competing modalities, such as magnetic resonance imaging (MRI), that emerged in parallel, a general trend has been observed throughout these years: it has been a primary aim to speed up measurements, both for the scanning of single slices and for the scanning of volumes. The introduction of spiral CT scanning in 1989 was a decisive step in this direction and has led to a renaissance of CT: CT is largely regarded as equivalent to spiral CT today. Since the end of the 1990s, rotation times of 0.5 seconds and below and multi-row detectors have become available. Today they allow measuring up to 64 slices simultaneously. In combination with the short rotation times, this provides for unprecedented volume scan times: single-organ examinations take less than 10 seconds, and whole-body examinations can be completed in less than 30 seconds. CT is a universal imaging modality covering all organs and body regions; even cardiac imaging, including CT coronary angiography, is performed routinely in spiral mode today. As an illustration of the performance levels, Figure 6.1 shows typical results achieved with 64-slice scanners. The introduction of "dual source CT" (DSCT) systems—scanners with two x-ray tubes and two detectors intended to improve cardiac CT and provide dual-energy CT—is the latest of many recent innovations.

This chapter offers a short review of the principles and technology involved in modern CT, an assessment of its performance in clinical imaging as a balance of image quality and dose, a brief overview of special applications, and a statement regarding the suitability of modern CT technology for combination scanning with positron emission tomography (PET) and single-photon emission computed tomography (SPECT).
SPIRAL CT PRINCIPLES

Traditionally, CT images were acquired by sequential scanning of single slices; 3-D volumes were built up sequentially from such 2-D scans. In spiral scanning, the patient is transported continuously through the field of measurement while the x-ray tube and the detector rotate continuously (1,2). Relative to the patient, the x-ray focus travels on a spiral path (Fig. 6.2A). The technological basis, continuous rotation of the measurement system, became available in the late 1980s and is now generally used in all types of scanners, in high-performance as well as in low-cost scanners, and also in combination scanners used for PET-CT and SPECT-CT. The spiral scan mode provides two major principal advantages: (a) decisively faster volume coverage than sequential slice-by-slice scanning would ever allow and (b) increased 3-D resolution, both for low-contrast and for spatial resolution, due to the continuous data sampling along the z-axis (1).

Image reconstruction is the same in principle for sequential CT and for spiral CT. However, in spiral CT the data sets representing a single slice have to be generated from the spiral volume data set in an additional preprocessing step, the so-called z-interpolation. This step is not
computationally expensive but it provides a decisive advantage: images can be reconstructed for any arbitrary position. Both the position of the image and the effective slice width can be chosen retrospectively. Reconstructing overlapping images is the basis for improved low-contrast and high-contrast resolution. Details on aspects of image reconstruction in spiral CT are given elsewhere (1) but are not necessary for understanding this chapter.

TECHNOLOGY

Many technical components of a modern CT scanner with subsecond rotation times represent cutting-edge technology and are constantly upgraded. Detector technology was the focus of interest for many years, as the detector was viewed as the most important component, and new concepts for its design have made multi-slice scanning possible and have advanced CT to its present level. But other components are gaining in importance too.

The importance of the mechanical setup increases with shorter and shorter rotation times. For rotation times of 0.3 seconds, centrifugal forces of about 30 g result, which are far beyond what humans could tolerate. For a mechanical system, it would be possible to go beyond the typical rotation times of 0.3 to 0.4 seconds currently offered by the top-performance systems. However, not only would adapting the components involved (e.g., the rotating-anode x-ray tube) involve added expense, there is the problem of available x-ray power, which is the main limiting factor. The numbers of photons necessary to generate an image with acceptable quality is fixed and has to be provided in shorter and shorter time intervals when the rotation speed is increased. This limitation, which was an essential reason for the failure of electron-beam CT, has to be kept in mind. It provided the motivation to think about multi-source systems again, which are addressed below.

The main improvements in x-ray tube technology for CT over the years consisted of increasing the mass and the diameter of the rotating anode to allow higher and continued power levels. Today, the most powerful CT systems offer 80- to 100-kW x-ray sources. An important technological innovation has been introduced just recently, the so-called rotating vacuum vessel technology (1,3). In this technology, the complete vacuum vessel, held by dual bearings, rotates, and the anode is an integral part of the vessel (Fig. 6.3A). This allows for direct cooling of the anode’s back surface and alleviates the need for a large and massive anode. This new technology offers an additional advantage: since the electron beam has to be steered electromagnetically from the centrally placed cathode to the anode, the focus position can be controlled and switched precisely. This feature is utilized by generating a so-called z-flying focal spot, which allows for double-sampling in the z-direction and has beneficial effects on resolution and artifact behavior (1,4). A tube of this design, the Siemens Straton tube, is shown disassembled in Figure 6.3B to illustrate the reduced mass and dimensions. The anode has a diameter of only 12 cm but allows 80-kW power levels. It has been in successful use in clinical CT for more than 2 years. Such designs will likely become preferred for CT x-ray sources in the future.

The multi-row detectors necessary for MSCT constitute a mature technology. They are offered as isotropic or non-isotropic arrays. Isotropic arrays are regular matrices in which slices are defined by single rows or by combinations of rows (i.e., by multiples of the detector pitch). An example of a nonisotropic array of 40 rows is presented in Figure 6.2B, which shows the solution for the Sensation 64 (Siemens Medical Solutions, Erlangen, Germany), a scanner that can acquire 64 slices of 0.6-mm width simultaneously. In the standard scan mode, the inner 32 detector rows are exposed, and 64 overlapping slices are generated using the z-flying focal spot technology. Alternatively, 20 slices of 1.2-mm width can be acquired simultaneously. Similar patterns of submillimeter and millimeter slice acquisition are offered by all manufacturers at present. The trend is toward thinner and thinner slices, with many institutions
using the thinnest slices only, as the combination of data into thicker slices retrospectively is always an option.

As wider and wider detector arrays have become available, new paradigms for image reconstruction have become necessary. The traditional assumption that all fans are oriented in parallel to each other and to the central plane does not hold true anymore. The cone-beam nature of the scan has to be taken into account explicitly. Appropriate solutions now exist; so-called approximate reconstruction algorithms, such as the advanced single-slice rebinning (ASSR) algorithm (5), provide excellent results for scanners from 16 to 64 slices. In fact, image quality is generally improved compared with that of the earlier four-slice scanners, where four parallel fans were still assumed and the cone beam nature of the geometry was simply ignored. It is still an open question whether perfect algorithms (i.e., image reconstruction algorithms that provide optimal image quality within acceptable time intervals) will be available for the higher numbers of slices and the concomitant increases in the cone angle sometimes postulated as a necessary development. It is possible that 256-slice CT scanners may eventually become available. But there are alternative development paths.

The first dual-source system primarily aimed at providing high-quality cardiac imaging in practically all clinical situations was recently introduced. The basic geometry of the system, the Siemens SOMATOM Definition, is sketched in Figure 6.4A. The components and technology are largely identical to those of the corresponding single-source system. Integrating two complete measuring systems into a single housing offers distinct advantages. It has to be noted that increasing the number of sources and detectors by 2 is a more efficient way to reduce effective scan times than increasing the rotation speed by a factor of 2 (1). A DSCT system automatically provides twice the x-ray power and thus allows exploitation of the higher temporal resolution. Yet it does not require increased gantry speed and is comparable to a standard system (Fig. 6.4B).

**IMAGE QUALITY AND DOSE ISSUES**

MSCT allows speeding up examinations by a factor $M$ equal to the number of simultaneously acquired slices. This means that a volume $M$ times larger can be covered in a given time with otherwise unchanged parameters. Alternatively, and more importantly in most cases, a given volume can be covered with thinner slice collimation. Thus MSCT allows enhancing the most important achievements of spiral CT: (a) short examination times per organ and (b) high isotropic spatial resolution.

Since the increase of detector rows in modern scanners has brought about a reduction in the detector pixel size, higher isotropic spatial resolution levels have become available. Today submillimeter resolution, even at a level below 0.5 mm, is available routinely (Fig. 6.5), and it does not require a compromise regarding volume coverage any more. High volume coverage in the shortest possible time is a primary demand of CT angiography, for example; volumes with an extent of more than 100 cm can easily be covered during the time of maximum vascular enhancement by MSCT (Fig. 6.1). Image quality has risen continuously with the introduction and refinement of MSCT.

**Technical Developments for Patient Dose Reduction**

Although it is generally recognized that CT offers reliable high performance, its use of ionizing radiation is continually quoted as an inherent problem. Patient dose issues are discussed in detail in Chapter 9. Today’s scanners typically work at levels of effective dose on the order of the annual...
Chapter 6: Basics of CT Scanning and Issues Relevant to Integrated Imaging

exposure to natural background radiation: 1 to 10 mSv per organ scan and typically 10 to 20 mSv for examinations of the complete trunk (1,6). Nevertheless, a number of technical efforts at dose reduction have been implemented in the last few years.

The introduction of spiral scanning did not cause an increase in patient dose. On the contrary, a reduction of dose in clinical practice was observed (1), and spiral CT led to the development of new techniques directly linked to the spiral scanning mode: attenuation-based online tube current modulation (7) and multi-dimensional adaptive filtering (MAF) techniques (8). Both techniques offer substantial means for reducing dose or improving image quality; both have undergone successful clinical evaluation already. The continuation

Figure 6.4  Dual-source CT systems combine two complete measuring systems on one rotating gantry and provide double the x-ray power without an increase in space requirements. A: Principal sketch of the system. B: Photograph of the installation at the IMP in Erlangen. (Reprinted with permission from Kalender WA. Computed Tomography. New York: Publicis Corporate Publishing; 2005.)

Figure 6.5  Submillimeter MSCT scanning allows provision of isotropic submillimeter spatial resolution with adequately short scan times. For 0.6-mm collimation and double z-sampling, isotropic resolution of 0.4 mm is achieved both in the xy plane (A) and in the z direction (B). (Reprinted with permission from Kalender WA. Computed Tomography. Erlangen: Publicis Corporate Publishing; 2005.)
of these developments is the concept of an automatic exposure control for CT, which constitutes an automated and online adaptation of the tube current to achieve a defined noise level for a given patient. This means that tube current levels will be reduced for smaller patient cross sections, in particular, for children. All manufacturers meanwhile are working on product options. There is reason to hope that patient dose can be limited, although MSCT lends itself to more examinations, extended volume examinations, and repeated multi-phase examinations. These developments are of high relevance to ensure general acceptance of CT, which is associated with the use of ionizing radiation.

**Applications**

Modern spiral CT is capable of covering all anatomic regions with excellent quality. Even neuro-imaging, which was completely assigned to MRI for a long time, has...
become a frequent CT application again. Although CT cannot match many of the capabilities of MRI, it provides the relevant diagnostic answers fast and reliably.

The dominant new applications of MSCT are CT angiography and cardiac imaging. In the case of all organs in which contrast medium can be kept at a high level after an intravenous injection, MSCT allows complete coverage in the short time of 5 to 30 seconds. Such imaging is now a standard CT application, with high relevance for combination imaging. Cardiac imaging already has become available, with subsecond single-slice spiral CT proving the principles of retrospective phase-selective image reconstruction involved. It has reached very high image quality and reliability with rotation times of 0.5 seconds and below and advanced multi-slice capabilities. Since about 2003, cardiac CT has been an established CT application for coronary calcium measurement and for coronary CT angiography. The latter application is widely accepted as an alternative to invasive catheter angiography as a first diagnostic test. Nevertheless, results remained inconclusive in a percentage of examinations (estimated to be roughly 10%). This has resulted in the development of dedicated dual-source systems for cardiac CT that offer effective scan times of 50 to 100 milliseconds (1). First results with a system of this type (Siemens SOMATOM Definition) demonstrate clear improvements; an example showing the heart both in systole and in diastole is presented in Figure 6.6. CT thus is able to cover almost all aspects of anatomic and morphologic imaging.

CONSIDERATIONS FOR PET-CT AND SPECT-CT COMBINATION SCANNERS

Modern MSCT provides excellent morphological imaging, but its deficits regarding functional imaging remain. Only perfusion imaging has gained acceptance for some indications, such as in the evaluation of acute brain infarct patients, where CT offers the advantage of a direct match to anatomy. Combining CT and PET in a single modality is now established. The same development is underway with respect to SPECT (Fig. 6.7).

In general, there are no restrictions on the use of CT in these combination scanners, although there was an initial tendency to provide CT with only limited capabilities, particularly those necessary for coarse anatomic matching and for providing the data needed for attenuation correction. CT with such limitations can still be sufficient in many cases. However, there are just as many cases where the full diagnostic potential of CT is required. Therefore, it is the personal opinion of this author that all recent developments in CT are of direct interest for clinical use in PET-CT and SPECT-CT combination scanners.

In conclusion, MSCT offers very high performance in anatomic imaging at moderate doses. Whole-body scanning unimpared by patient motion is routinely available. MSCT offers the perfect match for molecular imaging with SPECT and PET.

REFERENCES

**INTRODUCTION**

The recent introduction of combined, dual-modality PET-CT tomographs allows the PET emission data to be routinely corrected for photon-attenuation effects by using the CT images acquired as part of the PET-CT scan protocol (1). The advantages of such an approach include (a) attenuation-correction factors that are essentially noiseless owing to the high photon flux used for CT, and (b) short transmission scan times compared with standard PET scanning. As part of the attenuation-correction procedure, it is necessary to scale the CT images from the mean CT energy of approximately 70 keV to the PET photon energy of 511 keV. This is typically achieved using a bilinear function that associates a unique 511-keV linear attenuation value with each measured Hounsfield unit. The use of a bilinear function originates from the different constituent characteristics of soft tissue and bone. After scaling, the attenuation-correction factors are generated by integration (forward projection) along each line of response in the emission data. In practice, however, the CT images may be acquired with intravenous or oral contrast present and they may contain artifacts because of truncation of the arms and patient respiration. Furthermore, there may be foreign objects present, such as dental implants or prosthetic devices. For these reasons, even a scaling algorithm that correctly identifies the proper 511-keV linear attenuation values for human tissue may still not allow for exact attenuation correction. In particular, there is the possibility of introducing spurious hot spots in the attenuation-corrected PET images corresponding to very dense structures seen on CT. Nevertheless, despite this potential for artifact, CT-based attenuation correction has become a routine practice, with resulting artifacts in the attenuation-corrected PET images either being too small to be of clinical significance or, in the case of more substantial artifacts, being easily interpreted as such and therefore not impairing diagnosis. Remedies, including modified scan protocols and scaling procedures, have been proposed to reduce or eliminate these artifacts, in spite of their limited significance in routine oncologic imaging. These remedies become more important in cases where the need for precise attenuation correction is more critical, an example being cardiac PET-CT imaging, where the elimination of metal artifacts and motion artifacts may be necessary for proper clinical interpretation.
will be biased unless the energy difference between CT (approximately 70 keV) and PET (511 keV) is accounted for by an appropriate scaling of the CT images, as described later. After scaling, the attenuation-correction factors are generated by integration (forward projection) of the CT image volume along each line of response in the emission data.

Although in principle such a straightforward method can be used to generate CT-based attenuation-correction factors, a number of practical issues may limit the accuracy of the approach. Clinical CT scans of the thoracic region are generally acquired with the arms above the head and with breath-hold at full inspiration; clinical CT of the head and neck is performed after injection of intravenous contrast; and clinical CT of the abdomen and pelvis is generally performed after administration of both oral and intravenous contrast. However, such clinical protocols may affect the accuracy of the CT-based attenuation-correction factors unless appropriate modifications are made to the standard scaling algorithm (discussed later). The duration of the PET scan may not easily be tolerated by patients with their arms above their heads, and the scan may be performed with arms in the field of view. If the PET-CT scan is to be used for radiation treatment planning, it is desirable to have the patient in the treatment position. For the CT images, this can result in complete or partial truncation of the arms or other regions due to the 50-cm-diameter transverse field of view. Attenuation-correction factors generated from truncated CT images may be inaccurate. When the CT scan is acquired with breath-hold at full inspiration and the PET scan is acquired during free breathing owing to a typical scan duration of several minutes, the images will not match, especially in the thorax, again resulting in potentially inaccurate correction factors. Finally, the use of intravenous or oral contrast will introduce pixels into the CT images with enhanced Hounsfield units that may scale incorrectly for attenuation purposes, as may also be the case with x-ray–dense foreign objects such as dental implants and prostheses. Various modifications to the basic scaling procedure and PET-CT scan protocol have been proposed to eliminate or minimize the bias that can result, although these effects are generally seen to have little clinical significance in routine PET-CT imaging, which is primarily focused on oncology. In more specialized applications, such as the use of PET-CT in cardiac imaging, these considerations may take on increased importance.

This chapter summarizes the standard algorithm for CT-based attenuation correction and then discusses modifications and protocols intended to address the issues of patient movement, including respiration; truncation of the CT images; and the presence of intravenous or oral contrast (or both) and foreign objects in the CT images. These modifications to the standard algorithm are required to ensure accurate and unbiased CT-based attenuation-correction factors, although in most cases artifacts associated with the standard approach are not of clinical concern or are well understood and well tolerated.

**Figure 7.1** Bilinear transformation to convert measured CT Hounsfield units into 511-keV linear attenuation values for the purpose of performing CT-based attenuation correction as defined by Kinahan et al. (solid line; see ref. 2) and Burger et al. (dashed line; see ref. 3).

**Figure 7.2** Linear attenuation per unit density as a function of energy for soft tissue/water (solid line), bone (long dashes), and iodine (short dashes).
for the different soft-tissue types cannot be resolved separately and are taken to be the same. Bone has the higher linear attenuation coefficient per unit density at the lower CT energies because of the larger photoelectric component of the higher-atomic-number constituent, calcium, and consequently the ratio of the linear attenuation per unit density at the PET energy to that at the mean CT energy is lower for bone than for soft tissue or water by approximately 20%.

It is this difference due to the mineral content present in bone and the subsequent different attenuating properties that motivates the use of a bilinear function. In Figure 7.1 both methods assume that for Hounsfield units below 0 HU the tissue may be taken to be essentially equivalent to a mixture of air and water; the air (−1,000 HU) and water (0 HU) points can be mapped to their known linear attenuation values at 511 keV, and this defines the linear transformation for all points in between. Above 0 HU, in the approach of Burger et al. (3), a variable mixture of water and bone is assumed, giving increasingly lower values at 511 keV than if a waterlike material of varying density was assumed. Kinahan et al. (2) adopted a slightly different approach, identifying bone pixels as those pixels above 300 HU, with all pixels below this value assumed to be a waterlike material of varying density. This leads to a discontinuity in the transformation, as seen in Figure 7.1. Nevertheless, both these bilinear methods are reasonably successful at transforming human tissue CT values into 511-keV linear attenuation values, as has been demonstrated in studies comparing CT-based attenuation-corrected images with germanium 68 transmission-based attenuation-corrected images (4,5).

Also shown in Figure 7.2 is the curve for iodine which (bound to specific molecules) serves as a CT contrast agent. The higher atomic number of this element results in an increased photoelectric contribution at the lower CT energies compared with fluids or soft tissues, leading to a much larger linear attenuation per unit density than even that for cortical bone. At 511 keV, however, iodine has essentially the same value as that of bone and soft tissue, indicating that only the Compton scattering contribution is significant at these energies, and the concentrations of iodine in oral contrast agents used to enhance the CT image are found to have little effect at 511 keV, as is discussed in detail in the section on contrast agents. Despite the general success of the transformations in Figure 7.1 in scaling the CT images for attenuation-correction purposes, they are not adequate for precise attenuation correction in all cases. For instance, a one-to-one mapping cannot correctly scale both bone pixels and oral contrast–enhanced pixels, since they may have the same Hounsfield unit in the CT images and yet have different linear attenuation values at 511 keV. Furthermore, it is well known that measured Hounsfield units for a particular material can differ depending on the tube voltage (kVp) setting that is chosen as part of the CT protocol. Values for dense bone in particular will be dependent on this choice of kVp setting. Consequently, scaling procedures that are not dependent on the kVp setting cannot be optimized for all possible kVp settings. However, since scans are typically performed at a setting of approximately 120 kVp, for which the methods (2,3) are optimized, this is generally not an issue. Other settings that may be available, such as 80 kVp, are generally not employed, except perhaps in special cases such as pediatric cases. Nevertheless, the elimination of bias due to an unusual choice of kVp setting does require a more generalized method to take account of these effects (6).

The 2-D transverse CT images transformed to linear attenuation maps and scaled to 511 keV are then stacked to form a 3-D transmission volume image of the attenuating medium. The corresponding attenuation-correction factors for the PET emission data are generated by integrating (forward projecting) through the scaled CT volume. The attenuation-correction factor for a coincidence line of response L is given by

\[ ACF_L = \int d\mu_{511}(x, y, z) \]

where \( \mu_{511}(x, y, z) \) are the stacked, scaled linear attenuation values from the CT images and \( \ell \) is the integration variable along the coincidence line of response L.

**PATIENT RESPIRATION**

Usually CT studies of the chest and abdomen are performed with breath-hold and at full inspiration, thereby eliminating respiratory motion. This is possible because of the short scan time of modern CT scanners. Such an approach is not possible for PET scans because of their longer duration; instead, the patient is breathing freely, and the acquired PET emission data correspond to an average over the respiratory cycle. This leads to the question of the most appropriate breathing protocol for the best handling of respiratory motion when performing PET-CT scans. The patient will be breathing during the PET acquisition, although it is possible to instruct the patient to adopt a different breathing protocol during the initial CT scan. Adopting the approach of conventional CT studies (i.e., instructing the patient to maintain full-inspiration breath-hold during the CT portion of the study) will tend to maximize the discrepancy between the PET and CT acquisitions due to respiration. This is because breath-hold is typically maintained at full or deep inspiration; it is not practical to expect patients to maintain breath-hold for longer periods except at full inspiration. In some respiratory protocols, most patients can do this during the critical imaging passage of CT data acquisition through the chest, which with a multi-slice device lasts only approximately 10 seconds. However, the state of full forced inspiration is far removed from any of the states of shallow or even normal breathing, and although the CT acquired in this way will be free of motion artifacts from respiration, anatomic structures will tend to be maximally displaced...
from their mean position during shallow or normal respiration. For example, the anterior chest wall in full forced inspiration can be so displaced from the range of its position during shallow breathing that the anterior chest wall is not even apparent in the attenuation-corrected PET emission image.

Another approach in PET-CT studies is to acquire both scans with the patient performing shallow breathing. However, the CT images will now exhibit motion artifacts because the patient is not maintaining breath-hold, which can lead to artifacts in the attenuation-corrected PET image unless the CT is of the most recent multi-slice vintage. Similar problems regarding respiratory motion arise in using CT for radiation therapy planning, and many studies (7–10) have used MRI or sonography to investigate the movement associated with respiration, looking at normal, shallow (or quiet), and deep (or forced) breathing. In Korin et al. (7), MRI studies were used to examine the relative motions of the upper abdominal organs in the cranio-caudal (CC), right-left (RL), and anteroposterior (AP) directions. The reported ratio for motion in the CC direction to motion in the AP direction was approximately 5 for both normal and deep breathing, and the ratios for motion in the CC direction to motion in the RL direction were approximately 6 and approximately 8 for normal and deep breathing, respectively. The main conclusion of Korin et al. is that the movement of the upper abdominal organs is primarily in the CC direction. Studies reporting the maximal excursion of the upper abdominal organs due to respiration, as determined by ultrasound or MRI, are generally consistent in the values found for both deep and normal breathing. For example, Suramo et al. (8) report the mean excursion in the CC direction as 2.5 cm for the liver, 2.0 cm for the pancreas, 2.0 and 1.9 cm for the kidneys in normal breathing. Values for deep breathing generally exceed those for normal breathing by a factor of 2 or more. Instructing the patient to breathe shallowly is expected to lead to excursions less than those for normal breathing. In shallow breathing, there also will be motion in the lower abdomen, including significant motion in the AP direction, although the motion of the upper abdominal organs at the boundary of the lungs leads to the largest artifacts in the PET image.

In shallow breathing, the motions of the rib cage tend to be minimized (although this can depend on the patient; e.g., if he or she is a strong thoracic breather as opposed to an abdominal breather), and it is seen that there can be excellent registration of nodules in the lung between CT and PET, even close to the chest wall. Patient studies have confirmed that the preferred CT breathing protocol during the PET-CT exam is free or shallow breathing or, to the extent that it is possible, midexpiration or normal expiration breath-hold (11–13). However, even with shallow breathing, significant artifacts still can be present. As discussed in Balter et al. (10), because of the short per-slice CT sampling time compared with the respiratory cycle, respiratory motion does not lead to a significant loss of resolution or blurring of the images but instead leads to geometric distortions. CC movements of the diaphragm and the upper abdominal organs lead to an improper axial sampling. Figure 7.3 shows a PET-CT study acquired with shallow breathing, with coronal and sagittal views of both the CT images and the corresponding PET images using the CT images for attenuation correction. In the coronal CT image, we see a geometric distortion of the liver dome at the lung boundary because of CC movement of the liver. The top of the liver dome is imaged in the exhalation position; however, for neighboring inferior slices corresponding to the inhalation stage, the liver has moved so that the liver dome is now below this position, leading to the artifact of a portion of
the liver dome “hanging” in the lung volume. This is expected to lead to the most serious artifacts in the attenuation-corrected PET image because of the strong sensitivity to both the large changes in attenuation and activity across the boundary defined by the diaphragm. Other geometric distortions are present because of SI motion in the kidneys, stomach, and spleen, although these are not expected to lead to very serious artifacts, as the attenuation is roughly uniform except at the lung or air boundaries. In the sagittal CT image, artifacts from AP movement in the lower abdomen below the ribs are apparent. In the coronal PET image, an artifact in the region of upper liver dome is associated with the geometric distortion of this region in the CT image. In the sagittal view, a slight artifact corresponds to the CT artifact due to AP movement of the lower abdomen. Generally artifacts in the attenuation-corrected PET image due to respiratory motion artifacts in the CT image will not be so apparent away from the upper abdomen–lung boundary or skin–air boundary because of the rough uniformity of attenuation values for soft tissue.

The extent of the “hanging” liver dome artifact in the case of single-slice and dual-slice PET-CT tomographs has been discussed by Beyer et al. (14). However, with the advent of PET-CT tomographs incorporating CT components with 16 or more slices, the shorter scan times and corresponding increased bed translation speeds have largely eliminated this type of severe artifact, even with the patient breathing freely. There will still be artifactual distortions in the CT images due to respiratory motion, but severe misordering of slices in the lung field and liver dome region is much less likely, as the speed of organ motion is less than these faster bed translation speeds. Although this represents an improvement in attenuation correction, this still does not guarantee that the CT image obtained is the most appropriate for attenuation correction in terms of the respiratory phase it describes. A more sophisticated approach is to perform respiratory gating of the PET acquisition during the PET-CT exam (15) and to then select the PET frame that most closely corresponds to the respiratory phase seen on the CT image for the purposes of generating a quantitative attenuation-corrected image. Other studies have involved acquiring fully 4-D CT data (16), capturing the full respiratory cycle using CT. These CT images can then be averaged to correspond to the acquired PET data, which, in the absence of gating, is necessarily averaged over the whole respiratory cycle. The problem of CT-based attenuation correction in the presence of respiratory motion may ultimately be addressed, given assumptions concerning the reproducibility of the respiratory cycle, by a combination of a respiratory-gated PET acquisition and a temporal fully 4-D CT scan in which all phases of the respiratory cycle are identified in both modalities. It remains to be seen how widely such a comprehensive solution will be adopted in the future given the implications for patient dose and the data reconstruction burden. The clinical implications of respiration for image quality in PET-CT is further discussed in Chapter 33.

## TRUNCATION OF THE CT IMAGES

CT scans of the abdomen and thorax are generally performed with the arms raised above the head, out of the CT field of view, thus avoiding exposure of the arms and improving the signal-to-noise ratio for lines of acquisition that would otherwise pass through the arms. In PET scans, this may not be possible because of the longer duration and ensuing discomfort of this position, which is more strained than keeping the arms resting on the bed alongside the body. Even if the patient is able and willing to keep the arms out of the field of view, maintaining this strained position might lead to patient movement and subsequent misalignment between the PET and CT images. The CT field of view, except in the case of some specialized scanners, is 50 cm, less therefore than the typical PET field of view of ~60 cm and less than the typical patient port opening of 70 cm. If the PET-CT study is performed with the arms in the field of view, the CT projections may be truncated, even when the torso itself fits completely inside the CT field of view. If the patient is very large, there may be other portions of the body that are truncated in the CT image, even if the arms are kept raised. It may also be desirable to scan the patient in an unusual position, for example, to correspond to the treatment position in radiation therapy or to better match the likely patient positioning in a subsequent interventional procedure. Such positions, combined with the 50-cm CT active field of view, may lead to truncation.

Truncation of the CT projections may lead to a spurious ring artifact at the edge of the CT field of view (although modern CT scanners tend to remove this artifact by modifying the truncated projections), and the attenuation values outside the CT field of view are set to zero. The absence of nonzero attenuation values outside the CT field of view will result in the underestimation of attenuation-correction factors (ACFs) through the affected region, whereas the presence (if at all) of the spurious ring artifact will lead to the overestimation of ACFs through that artifact. Some ACFs, such as those passing through both arms, can be affected in both ways. Note that typically the PET field of view is larger than the CT field of view, so the acquired PET emission data might not be truncated even if the CT projections are. In such cases, the attenuation-corrected PET emission images can then be affected by the CT truncation through errors in the ACFs (Fig. 33.4).

Methods for correcting for truncation in CT projections include extending the truncated projections (17) and using the Radon transform consistency conditions (18). Using statistical algorithms such as the ordered subset expectation maximum (OSEM) method to reconstruct CT images (19), rather than filtered back-projection, can allow better handling of missing projection data. However, these studies are concerned with reconstructing a diagnostic CT image without the artifact of truncation, whereas for attenuation correction in PET, the concern is only the effect on the ACFs corresponding to line integrals through the scaled...
CT image, which suggests that a very simple treatment may be sufficient in the case of truncation of the arms. To see the effects of truncation on the ACFs compared with no truncation, a study was identified in which the patient just fit inside the CT field of view. The original CT images are shown in Figure 7.4A: a coronal slice and a transverse slice through the abdominal region. The CT projections were then artificially truncated and reconstructed (Fig. 7.4B) to exhibit the typical artifacts associated with truncation. A simple method for removing the truncation artifacts consists of identifying the truncated projections and linearly extending them to zero by using an estimate of the size of the true image. Figure 7.4C shows the same slices now reconstructed from the truncated projections with linear extension of those projections. In Figure 7.4C, the ring artifacts are not present (because the CT projections are no longer abruptly truncated), and the attenuation values outside the truncated CT field of view are recovered. There are still some artifacts (e.g., the definition of the contour of the shoulder in the coronal slice in Figure 7.4C is poor); however, the primary concern here is that the resulting ACFs will be accurate, rather than the CT image itself. The reason such a simple approach is sufficient is that typically only the projections at a small range of angles about the AP and posterior-anterior (PA) directions are actually truncated.

The concern is with the difference between the true ACFs (calculated from Fig. 7.4A) and those obtained when the truncation artifacts are present (calculated from Fig. 7.4B) and also with the difference between the corrected ACFs calculated from the images corrected for truncation (Fig. 7.4C) and the known true ACFs. Figure 7.5 shows the ACFs corresponding to lines of response in the AP direction through the transverse abdominal slices shown in Figure 7.4, comparing those calculated from the image without truncation, with truncation introduced, and corrected for truncation. The differences between the ACFs calculated from the image with no truncation and those calculated from the image corrected for truncation are slight, indicating that the simple method of linearly extending truncated CT projections works adequately well. The ACFs calculated from the truncated images are zero for the outermost part of the arms (as this is outside the CT field of view), whereas the true projections are nonzero there. In Figure 7.6, we show the ACFs corresponding to lines of response in the LR direction through the transverse abdominal slices shown in Figure 7.4 (including lines passing through both arms and the torso, corresponding to the lines of greatest attenuation). Again it is seen that the...

Figure 7.5  Attenuation-correction factors (ACFs) corresponding to an anteroposterior projection through the transverse images shown in Figure 7.4. The ACFs for an image with no truncation and an image corrected for truncation are generally in agreement.
attenuation-correction factors. However, clinical PET-CT obtains the attenuation map at 511 keV and hence the PET water or bone or some admixture thereof in order to measured Hounsfield units as corresponding to air or may be scaled using a bilinear mapping that interprets the presence of foreign objects such as prostheses, the CT image administration of CT contrast agent and without the presence studies may involve the administration of intravenous (IV) or oral contrast, or both, to enhance structures in the diagnostic CT images. There may also be a variety of foreign objects present in the body, including, but not limited to, prosthetic devices, dental implants, cardiac valves, pacemakers and implanted defibrillators, and subcutaneous chemotherapy ports. These objects may be entirely or partially constructed from materials that are highly x-ray dense, such as metals, which are very different from the materials in the body and will therefore not be scaled correctly using the methods appropriate for bone and soft tissue. The effect of IV contrast, at the PET resolution, is to enhance soft-tissue structures by tens of Hounsfield units. Conversely, oral contrast can lead to enhancements by hundreds of Hounsfield units for large regions of the bowel structures in the abdominal region. However, although the contrast agent has a large effect at CT energies of approximately 70 keV, it has little effect at 511 keV, as can be seen by imaging solutions of contrast agent corresponding to clinical situations by using 511-keV transmission sources. Therefore, scaling the CT images by using the algorithms will introduce a bias into the ACFs as the enhanced CT values are scaled, giving an overestimation of the attenuation at 511 keV. This in turn will lead to an overestimation of the PET emission activity through the attenuation correction in regions corresponding to contrast agent enhancement in the CT image.

An IV contrast agent will lead to enhancement, by tens of Hounsfield units, of soft-tissue structures throughout the body. Note that higher concentrations of IV contrast in small vessels will not be apparent at the PET resolution. The solutions of oral contrast administered (e.g., approximately 2% solution of meglumine diatrizoate [Gastrografin]) correspond at delivery to approximately 200 HU; however, these solutions become increasingly concentrated during passage through the gastrointestinal tract so that the colon, when properly opacified, will have values of up to approximately 700 HU. Because the attenuation at 511 keV is close to that of water, scaling these enhanced values will lead to an overestimation of the attenuation. Carney et al. observed a 20% effect in which the calculated PET activity was overestimated in the ascending colon due to the presence of oral contrast agent. Other studies have also compared patient groups with and without the administration of oral contrast agent and observed higher uptake values in the ascending colon for the group that received oral contrast.

Similar comparisons of patient groups with and without the administration of intravenous contrast agent revealed a global increase in uptake values associated with the presence of the contrast agent, although the effect was small. Situations can arise, however, that lead to a larger overestimation of the PET activity. In the case of intravenous contrast, if the CT is acquired very soon after injection of intravenous contrast, which is typically the case when CT data are

**CT CONTRAST AGENTS AND FOREIGN OBJECTS**

As discussed previously, for PET-CT studies without the administration of CT contrast agent and without the presence of foreign objects such as prostheses, the CT image may be scaled using a bilinear mapping that interprets the measured Hounsfield units as corresponding to air or water or bone or some admixture thereof in order to obtain the attenuation map at 511 keV and hence the PET attenuation-correction factors. However, clinical PET-CT
acquired in a multi-row detector CT for vascular delineation, a bolus of high attenuation values appears in the CT image, leading a spurious hot spot in the PET image. Thus in such systems, it may be advisable to acquire intravenous contrast–enhanced data after acquisition of an initial unenhanced CT scan and the PET emission scan, to use a post–contrast injection saline flush, or to adjust the contrast injection timing (see also Chapter 19). Similar effects can be seen if a too concentrated solution of oral contrast is administered or if contrast precipitation occurs, as is the case in Figure 7.7 (see also Fig. 33.6). The highly enhanced CT values in the CT image (arrow in Fig. 7.7A) lead to a region of high uptake in the PET image (arrow in Fig. 7.7B). An alternative is to use a modified scaling algorithm in which the oral contrast–enhanced pixels are distinguished from bone by using a region growing technique to identify the whole skeleton (23). The oral contrast–enhanced values can then be segmented and replaced with the proper 511-keV values as part of the attenuation-correction procedure so that the artifact is no longer present in the attenuation-corrected PET image (arrow in Fig. 7.7C). As oral contrast has to be given an hour before CT data acquisition, post–PET emission imaging contrast enhancement is not achievable. Thus the lowest possible concentration of oral contrast agent should be used for bowel enhancement in PET-CT studies. Nevertheless, contrast agents are routinely administered as part of PET-CT protocols, and any bias that is introduced does not appear to be clinically significant.

The effects on the attenuation-corrected PET images of metals in the body, which appear highly x-ray dense on CT, are similar to the effects of bolus and precipitated contrast agent. Metal objects that may be present in the body include dental implants; various prostheses; and cardiac valves, pacemakers, and implanted defibrillators. It is well documented that these metal objects can lead to artifacts in the PET images when CT-based attenuation correction is used (28,29). This again is because the scaling procedures appropriate for human tissue overestimate the 511-keV linear attenuation of these objects. Fortunately, the resulting artifactual foci will be correlated with the metal object, thereby revealing their true origin. The introduction of these artifactual foci may be mitigated by limiting the associated 511-keV linear attenuation values for very high measured HU. More detailed information about the particular composition of x-ray dense objects may be obtained in CT by using an extended CT scale (30), which could then be used to determine a more reasonable value for the 511-keV linear attenuation, by using lookup tables for known materials, for example.

Although precise attenuation correction at the level of tens of percent or better may not be critical for routine oncology applications, there will be situations where it can be important, such as the use of standard uptake value (SUV) determinations to monitor response to therapy over time or the use of PET-CT as a noninvasive tool for evaluating cardiac disease. The emergence of PET-CT tomographs

**Figure 7.7** Highly enhanced CT values are seen in the CT image from a prior oral contrast media scan (A, arrow), and these lead to a spurious region of high uptake in the attenuation-corrected PET image (B, arrow). This region is removed when the enhanced values are segmented and replaced with the correct attenuation values at 511 keV prior to their use for attenuation correction (C, arrow).
incorporating 64-slice CT scanners, the state of the art in cardiac CT imaging, is driving the development of PET-CT cardiac applications, whether for assessing myocardial viability or performing perfusion studies. These applications require a more detailed consideration of the CT-based attenuation-correction procedure as relative uptake in different areas of the myocardium is interpreted. One issue of particular relevance, similar to that involving reported artifacts associated with metallic prostheses and dental implants (28,29), is the presence of artifacts in the PET image resulting from implanted cardiac defibrillators. Studies have shown that such artifacts can cause the myocardial uptake values to be incorrect by 30% or more (31), indicating that more sophisticated methods of attenuation correction are required.

CONCLUSION

The benefits and utility of CT-based attenuation correction for the purpose of obtaining quantitative PET images in PET-CT exams are now well established. The experience of large numbers of routine studies over the past few years, as well as dedicated studies comparing CT-based attenuation correction with transmission-based attenuation correction, has shown that the established procedures for transforming the CT images for the purpose of performing attenuation correction work well. Nevertheless, the relatively simple methods used to generate the needed attenuation-correction factors from the CT images are not exact, and the presence of foreign objects in the body, patient motion, and the limitations of the smaller CT field of view can lead to artifacts and inaccuracies in the attenuation-corrected PET images. These inaccuracies may range from effects at the few percent level (or tens of percent level in the case of normal CT contrast enhancement or a small metal object) to dramatic artifacts, such as result from large foreign objects or a contrast bolus, occur near the diaphragm due to respiration, or occur in regions that are truncated on CT. These artifacts will not generally be a problem due to the correlation with features readily apparent in the CT images. PET-CT has been routinely and successfully utilizing relatively simple CT-based attenuation-correction procedures largely for diagnosis and staging in oncology. Simultaneously, modifications and improvements in these procedures have been underway, and while not necessarily required for many routine exams, they are desirable and take on increased importance for specialized applications, such as cardiac applications, and other quantitative applications, such as longitudinal studies evaluating response to cancer therapy by monitoring SUV values.

REFERENCES

CT-Based Attenuation Correction for SPECT

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The addition of x-ray computed tomography (CT) to a conventional single-photon emission computed tomography (SPECT) system allows attenuation correction and anatomic localization of SPECT lesions, similar to positron emission tomography (PET)-CT. Compared with PET, SPECT images are generally of lower quality because of fewer collected counts and lower spatial resolution. Transmission scanning, which is considered to be an essential feature of any dedicated PET scanner, is commercially available for SPECT but is not widely used, even though attenuation correction is essential to providing uniform images with quantitative accuracy.

Many SPECT radiotracers provide very little anatomic information, warranting the use of correlated CT images to help with lesion localization. The issue of aligning the SPECT and CT images is minimized if both are performed by the same system in the same session, minimizing changes in body morphology between the two scans.

SPECT-CT systems are now commercially available from three manufacturers. One system uses the same rotating gantry for both SPECT detectors and x-ray CT tube and detectors. A very low current x-ray tube is used, matched to the relatively slow rotation speed, compared with diagnostic CT systems. The resulting CT images are adequate for attenuation correction and provide anatomic detail for many lesion-localization tasks (Fig. 8.1). The other two systems use CT systems with their own fast gantries and correspondingly high flux x-ray tubes.

INTRODUCTION

The possibility of including single-photon emission computed tomography (SPECT) and x-ray computed tomography (CT) in a single combined system was first investigated by Lang et al. (1). This group investigated the use of separately functional CT and SPECT components put together into a larger system as well as a single solid-state detector design that could be used to count the gamma rays emitted from the body in addition to measuring the flux of x-rays from an x-ray tube (2).

The appeal of combining CT and SPECT is largely the same as the appeal of combining CT and positron emission tomography (PET). SPECT imaging suffers from effects of photon scatter and absorption. SPECT images are made more accurate, therefore, by the application of attenuation correction. In most regions of the body, appropriate attenuation correction can be done only when the attenuation of the body is measured directly with a transmission scan. X-ray CT images that are aligned with the SPECT data can be used for attenuation correction if appropriate adjustments are made to the attenuation values. In addition, the anatomic information that can be deduced from radiotracer distributions is sometimes insufficient for accurate localization of SPECT lesions. The inherently registered x-ray CT resulting from dual-modality scanning can provide the required anatomic localization, alleviating the problems that occur in the very complex task of retrospectively matching SPECT and x-ray CT images by using software algorithms.

DIFFERENCES BETWEEN PET AND SPECT

Although PET and SPECT are quite similar in concept and use, important differences may have implications for how
the addition of CT to either modality should be designed and implemented.

**Attenuation**

The absorption or scatter of photons emitted from radio-tracers, whether positron emitting or single-photon emitting, results in a reduction of detected events. This loss of events can dramatically degrade both the quantitative accuracy and visual quality of the resulting images. In Figure 8.2, attenuation of a single photon and an annihilation photon pair is illustrated.

The single photon must traverse a path length $d$ in tissue before leaving the body. The probability that this photon survives attenuation is given by

$$P = e^{-\mu d}$$

where $d$ is the path length of the photon through the body and $\mu$ is the linear attenuation coefficient. For the photon pair, the probability that both photons survive is the product of the individual survival probabilities:

$$P = P_1 P_2 = e^{-\mu d_1} e^{-\mu d_2} = e^{-\mu (d_1 + d_2)}$$

where $d_1$ and $d_2$ are the path lengths of the two photons in the body. Although these equations assume a constant $\mu$ (uniform attenuation within the body), the following points also are true for more general body features, including bone, lungs, and gas. These two important points can be made in comparing the single-photon case with the positron case. The first is that because both photons must survive for the event to be detected, attenuation effects are greater in PET imaging than in SPECT, at least from a quantitative perspective. The magnitude of this effect is illustrated in Figure 8.3.
The second point is that whereas the attenuation probability would be the same for any photon pair emitted along a path shown for the pair in Figure 8.2, regardless of where the annihilation point is on that path (because the final answer depends only on the total path length $d_1 + d_2$, with single-photon emission, the amount of attenuation depends on the particular emission point of the photon on any particular path. This feature makes accurate attenuation correction of single-photon imaging more difficult. For PET, because all photon pairs emitted and possibly detected in a given line are attenuated by the same probability, the raw data (the counts obtained for that line) can be corrected by a well-defined factor before reconstruction. For SPECT, the most accurate attenuation correction can be done only once an estimate of the radioactivity distribution has been made. An iterative algorithm is therefore required that can simultaneously improve the tracer distribution estimate with each update and use accurate attenuation compensation.

### Attenuation Correction: Required Quality

High-performance whole-body PET scanners have an intrinsic spatial resolution of 4 to 6 mm full width half maximum (FWHM), with processed images yielding 7- to 10-mm resolution in the body (some spatial resolution is sacrificed to reduce the statistical noise, by either smoothing the images or limiting the number of reconstruction iterations). At least 0.5 million counts per slice would be typical. Because of the limits of mechanical collimation, SPECT images typically have 10- to 20-mm spatial resolution in the body (depending on the collimator used, size of the patient, radius of rotation, etc.) and can have far fewer counts (depending on the radionuclide used, size, number of the patient, etc.). The lower resolution and lower statistical quality of typical SPECT imaging have several implications.

For optimal attenuation correction, the spatial resolution of the transmission data should not be worse than the emission data (with possibly acceptable compromises coming from, e.g., axially degraded transmission data due to the body’s symmetry along its axis). PET attenuation correction therefore requires higher spatial resolution transmission scanning. In addition, the statistical noise of the transmission data should be low compared with the emission data being corrected so that the noise of the emission data is not inflated noticeably during the correction process. Therefore, high-count PET data require higher-count transmission scans than do SPECT data if radionuclide transmission sources are used. Radionuclide transmission sources on SPECT systems can obtain sufficient counts in a short time, which is a highly desirable feature. With PET, however (where transmission scanning is actually much more common), relatively short transmission scans can be achieved only with the use of segmentation algorithms that use known body attenuation properties to reduce the noise of the resulting attenuation map.

Even a relatively low performance x-ray CT image has much lower noise and much higher spatial resolution than a radionuclide-base transmission scanning system. For example, noise low enough to differentiate the subtle attenuation differences between soft-tissue types would not be possible with radionuclide sources. Additionally, the spatial resolution of x-ray CT images (2 mm at worst) is much better than any whole-body emission data. From this perspective, almost any conceivable x-ray CT system should provide data of adequate quality for accurate attenuation correction.

### Anatomic Localization: Required Image Quality

The CT image quality needed for localization of fused SPECT lesions is higher than that needed for attenuation correction. The actual quality needed, though, greatly depends on multiple variables, including the size of the SPECT lesion, its location, and the difference in CT contrast between the lesion and surrounding tissue, with or without administered contrast media. In some cases, the CT image quality for SPECT lesion localization needs to match that obtained for diagnostic CT purposes.

The combination of x-ray CT and SPECT or PET brings an additional image-quality concern, that of accuracy of alignment between the PET or SPECT image and the x-ray CT image. The alignment accuracy depends on both patient issues (movement, patient comfort, high patient throughput, and reduced probability of motion between emission and transmission scans are all benefits of fast scans. A unique benefit of a very slow transmission scan is that the resulting data will be averaged over respiratory and cardiac cycles, similar to the emission. All of these factors are true for both PET-CT and SPECT-CT.

### Scan Speed

Current CT systems are able to acquire whole-body image sets in very short times (~15 seconds to ~1 minute). For most purposes, the short scan time is highly desirable. Elimination of motion effects with breath-hold, patient comfort, high patient throughput, and reduced probability of motion between emission and transmission scans are all benefits of fast scans. A unique benefit of a very slow transmission scan is that the resulting data will be averaged over respiratory and cardiac cycles, similar to the emission. All of these factors are true for both PET-CT and SPECT-CT.

### SPECT ATTENUATION CORRECTION WITH CT

To use x-ray CT attenuation maps in PET or SPECT attenuation correction, the pixel values must be transformed from the typical Hounsfield units to appropriate attenuation coefficients. For soft tissue, the transformation is simply a linear scaling from one unit to another, by using the ratio attenuation values for PET or SPECT energies versus x-ray CT in water as the scaling constant. In bone, however, the relatively higher photoelectric component results in a different scaling constant (see Chapter 7). A simple function has been...
proposed and implemented to work over the whole range of tissue types (3), and experimental measurements have been published (4). Other issues include the effects of contrast agents on attenuation correction. Although the attenuation coefficients are different for SPECT and PET photons (typical SPECT energies start near the peak x-ray energies, whereas PET energies are much higher), the nonlinear conversion from Hounsfield units to linear attenuation coefficients must be accurate in either case.

The simplest and historically most widely implemented attenuation correction for SPECT is that of Chang (5). In its simplest form, only the body contour (as deduced from the emission data) is used. It is assumed that entire region within the contour has a single attenuation value. A correction is applied to each pixel, after reconstruction, based on the average attenuation factor over each projection angle for that pixel. This technique can be generalized to allow the use of a better attenuation map, such as one measured in a transmission scan. An iterative version of the Chang algorithm allows more accurate correction than the simpler multiplicative method.

Many algorithms have been developed to include attenuation correction in the reconstruction process (6–9). Generally speaking, these iterative algorithms take an estimate image of the radiotracer distribution and then simulate projection of this distribution by modeling the known attenuation properties of the body (as well as other factors such as collimator blur and scatter). The image is then updated, based on discrepancies between those simulated projections and the projections actually measured. Each repetition produces an image that is more consistent with the measured projections. All attenuation correction algorithms for SPECT could use a CT-based attenuation map.

Implementation of SPECT-CT

Three manufacturers currently offer SPECT-CT products. The first product was the Hawkeye (10), originally an option on the Millennium VG and currently an option on the Infinia (GE Healthcare Technologies, Milwaukee, WI). It uses an x-ray CT tube and detector attached to the rotating gantry to which the gamma camera heads are mounted (Fig. 8.4). The benefits of having a single rotating gantry include reduced space requirements. On this system, the gantry can rotate continuously because of the use of slip rings for power transmission and optical coupling for signal transmission, allowing continuous imaging as the table steps for each successive slice. One of the drawbacks is that the CT speed is limited to the gantry rotation speed; a gantry that can rotate quickly while supporting very heavy SPECT detector heads with collimators would be a mechanical challenge.

Figure 8.4  Hybrid CT-SPECT scanner, schematic view (A) and photograph (B). Two gamma camera heads are 180 degrees apart. The x-ray tube and detector are located axially between the gamma camera heads and the gantry housing. During use, the table would be extended into the gantry hole, supported by the rollers shown. This support is critical to maintain the same table height for a given body section, between SPECT and CT, because the table must extend farther for CT than for SPECT, and an unsupported table would increasingly sag with extension.
The limited rotation speed of this system allows the use of a very low-current x-ray tube (2.5 mA). The dose measured in a 20-cm cylindrical phantom is 425 mrad per slice at the surface, decreasing to 336 mrad per slice at the center. A total dose per scan at 1 m axially from the phantom is 1 mrad (10). A complete rotation of the gantry takes 14 seconds; sufficient CT data to reconstruct a slice are acquired during 10 seconds of partial rotation. The slice thickness is 1 cm. Including the table stepping time, it takes 10 minutes to acquire 40 slices corresponding to the 40-cm axial field of view of the gamma camera. Reduced transmission scan time is possible for studies with limited axial field-of-view requirements, such as cardiac studies.

Figure 8.5 shows a $^{[111}\text{In}]$ ProstaScint (capromab pendetide) study of a prostate cancer patient performed with this system. In this case, attenuation correction based on the x-ray data has been applied to the emission data. The x-ray images show the presence of implanted radioactive seeds in the vicinity of the prostate used for therapy.

Compared with typical modern CT systems, the slow rotation and low-power x-ray tube have several implications. First, image quality is limited in the regions where breathing motion is significant. Second, the low power allows the system to be used by nuclear medicine technologists in many areas, without CT training. Finally, less shielding is required (if any is required at all) to keep exposure outside of the imaging room within regulatory limits.

More recently, two other companies have introduced SPECT-CT systems. These systems use separate rotating gantries for the CT and gamma cameras, allowing faster CT rotation and acquisition. The Precedence (Philips Medical Systems, Andover, MA) features 16-slice CT with all of the capabilities of systems used for diagnostic CT studies, including a rotation time of 0.5 seconds or less, submillimeter slice thickness, multiple kVp settings from 90 to 140 keV, and a 60-kW generator, allowing tube currents of hundreds of mA.

The Symbia (Siemens Medical Systems, Malvern, PA) has two- and six-slice CT options, with rotation times from 0.6 seconds and up, one millimeter or less slice thickness, 80- to 130-keV kVp settings, and a 40- or 50-kW generator, allowing tube currents up to 240 and 345 keV for the two-slice and six-slice options, respectively.

In addition to providing higher-resolution, lower-noise images in a much shorter time, these systems have the capability to perform additional types of studies. Both systems are capable of cardiac calcium scoring, and the Precedence allows cardiac angiography. These capabilities come at a price, of course, and whereas the latest CT capability can be added to PET without doubling the system cost, adding high-performance state-of-the-art CT to SPECT can increase the system cost severalfold. In fact, from a cost (and practice) perspective, it may be more appropriate to view the combination of SPECT and high-end CT as a CT with an added gamma camera. Since attenuation correction can be achieved with much lower-performance CT, it is clearly other applications that have driven the design of these new systems.

### CONCLUSION

Using x-ray CT data from a low-dose and low-end CT product for attenuation correction is an attractive option for SPECT imaging. In designing such a system, various aspects have to be taken into account: appropriate quality of the attenuation map, appropriate quality for anatomic definition of organ structures in the transmission images, and scan speed. Overall, requirements may be lower when using CT attenuation correction for SPECT images than for PET images.

In contrast to PET imaging, attenuation correction is not used frequently in SPECT, and there has been little clinical experience with attenuation-corrected SPECT-CT images. One important application will be in cardiac imaging, where attenuation correction results in improved image quality in the inferoposterior myocardial wall. Whether CT scanning for transmission correction of partial body imaging (e.g., in SPECT scans for tumor imaging) will become routine has yet to be seen. However, in such scans, the
anatomic reference information provided in SPECT-CT is as relevant as it is in PET-CT.

REFERENCES
Radiation Doses and Radiation Protection

Alfred Pfeiffer  Cyrill Burger

Introduction

Nuclear medicine examinations deliver a certain amount of radiation to the patient as well as to the personnel involved with the patient before, during, and after the examination. In most countries, laws impose limits for the radiation burden of the personnel. The radiation dose that can be delivered to the patient is generally not restricted but recommended by the DRL.

Patient Radiation Dose

Generally the dose absorbed by the patient for any radiopharmaceutical depends on several factors:

- type of decay
- radiation energy
- radionuclide half-life (physical half-life)
- clearance from the body (biologic half-life)
- kinetics of distribution in the body

Positron emission tomography (PET), single-photon emission computed tomography (SPECT), and computed tomography (CT) use ionizing radiation, and therefore when these examinations are used, the ALARA principle (radiation dose As Low As Reasonably Achievable) must be observed. Even though there is no legal limitation to the radiation dose given for diagnostic or therapeutic purposes, one should try to minimize patient radiation exposure in PET, SPECT, and CT. A guideline to improve the management of patient doses in medical imaging is the DRL (diagnostic reference level) concept.

A fluorodeoxyglucose (FDG)-PET scan with 370 MBq (10 mCi) of $^{18}$F-FDG delivers a radiation dose of approximately 11 mSv to a patient, which is comparable to that from a diagnostic CT, which is in the range of 10 to 20 mSv. This radiation dose is predominantly due to the $\beta^+$ particles (positrons) emitted from PET isotopes and not from the 511-keV $\gamma$-rays resulting from the annihilation process. With shorter-lived PET radioisotopes, radiation exposure is substantially lower, and higher or multiple doses can be given safely, as frequently is the case in water or ammonia studies.

Doses of SPECT examinations are typically much lower because technetium-99m, the most widely used radioisotope in SPECT imaging, exclusively emits $\gamma$-rays. It is state of the art to use short-lived and pure $\gamma$-emitters. This is different when other isotopes with much longer effective half-lives and/or additional $\beta$-ray emission are used.

Therefore, attenuation correction of PET and SPECT data by using radioactive line or point sources in a conventional PET or SPECT scanner does not add much to this dose. Adding CT for attenuation correction and anatomic coregistration conversely results in an additional dose. This dose depends on the quality of the CT scan and the protocol used (unenhanced vs. contrast enhanced, etc.). A low-dose CT with 40 mA, which we believe to yield adequate image quality for most PET-CT and SPECT-CT applications, results in a radiation burden of approximately 2 to 8 mSv. Thus an integrated PET-CT or SPECT-CT examination results in a typical dose of between 10 and 20 mSv and is therefore comparable to a contrast-enhanced CT. The "CTs" (e.g., GE Hawkeye) used for attenuation in SPECT-CT use a much lower tube current (typically 2 mA), and the radiation burden added to SPECT in SPECT-CT thus is in the range of 0.5 mSv, which is negligible.
As discussed in Chapter 2, the physical half-life $T_{\text{phys}}$ and the biological half-life $T_{\text{biol}}$ together yield the effective half-life $T_{\text{eff}}$, which is the relevant parameter for the radiation dose received by the patient:

$$\frac{1}{T_{\text{eff}}} = \frac{1}{T_{\text{phys}}} + \frac{1}{T_{\text{biol}}}$$

A brief mathematical analysis shows that $T_{\text{eff}}$ is close to the shorter of the two times $T_{\text{phys}}$ and $T_{\text{biol}}$ if the other one is much longer. Thus, for the short-lived positron-emitting nuclides oxygen 15 ($^{15}\text{O}$) ($T_{\text{phys}} = 2.04$ minutes) and nitrogen 13 ($^{13}\text{N}$) ($T_{\text{phys}} = 9.97$ minutes), the clearance from the body is of minor relevance. It becomes more important in the longer-lived nuclides such as fluorine-18 ($^{18}\text{F}$) ($T_{\text{phys}} = 109.775$ minutes), iodine 124 ($^{124}\text{I}$) ($T_{\text{phys}} = 4.18$ days), and the various “conventional” radiopharmaceuticals marked with technetium 99m ($^{99m}\text{Tc}$) ($T_{\text{phys}} = 6.02$ hours) or other nuclides emitting single photons.

The radiation dose in nuclear medicine and positron emission tomography (PET) is importantly influenced by the biologic nature of the radiopharmaceutical used. The result is a much wider range of organ doses received in a specific examination than in a computed tomography (CT) examination, in which the absorbed dose is in essence proportional to the absorption coefficient of the irradiated tissue. The calculation of single-organ doses (measured in grays; 1 Gy = 1 J/kg) and the whole-body effective dose (measured in sieverts; 1 Sv = 1 J/kg multiplied by a weighting factor for the biologic effectiveness of different decay types) is sophisticated and based on complex calculation models, which take the uptake values for different organs and the spatial neighborhood of the organs into account.

**PET TRACERS**

It is important to note that the major radiation dose in PET comes from the positron and not from the $\gamma$-rays produced in the annihilation reaction. The most widely used radiopharmaceutical in clinical PET imaging is $^{18}\text{FDG}$. Physiologically, it is taken up by the brain and, depending on the fasting state, by the myocardium. It is excreted via the kidneys into the bladder. Thus the organs with the greatest radiation exposure in $^{18}\text{F}-\text{FDG}$ studies are the brain, the myocardial wall, the kidneys, and the bladder wall (Table 9.1) (1–3). These single-organ doses are weighted for the calculation of the effective whole-body dose. From Table 9.1, we conclude that for a standard dose of FDG of 400 MBq the whole-body effective dose is approximately 8 mSv, which is comparable to the dose received when being examined by full-dose CT. Also note that the radiation exposure with ammonia and water is much smaller because of the shorter half-lives of these compounds (4). The clinical use of long-lived radionuclides such as $^{124}\text{I}$ (physical half-life 4.2 days) is only acceptable if they are bound to a radiopharmaceutical with short biologic half-life.

**SPECT TRACERS**

The patient radiation exposure from single-photon emission tomography (SPECT) tracers varies over a wide range.

### TABLE 9.1

**TARGET ORGAN DOSES OF PET AND SPECT TRACERS**

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>$^{18}\text{F}-\text{FDG}$</th>
<th>$^{15}\text{O}-\text{H}_{2}\text{O}$</th>
<th>$^{99m}\text{Tc-Mibi}$</th>
<th>$^{99m}\text{Tc-Phosphates}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorbed Dose ($\mu\text{Gy/MBq}$)</td>
<td>Absorbed Dose ($\mu\text{Gy/MBq}$)</td>
<td>Absorbed Dose ($\mu\text{Gy/MBq}$)</td>
<td>Absorbed Dose ($\mu\text{Gy/MBq}$)</td>
<td>Absorbed Dose ($\mu\text{Gy/MBq}$)</td>
</tr>
<tr>
<td>Brain</td>
<td>28</td>
<td>0.71</td>
<td>5.2</td>
<td>1.7</td>
</tr>
<tr>
<td>Heart</td>
<td>62</td>
<td>0.67</td>
<td>6.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Kidneys</td>
<td>21</td>
<td>0.95</td>
<td>36</td>
<td>7.3</td>
</tr>
<tr>
<td>Liver</td>
<td>11</td>
<td>0.75</td>
<td>11</td>
<td>1.2</td>
</tr>
<tr>
<td>Lungs</td>
<td>10</td>
<td>0.57</td>
<td>4.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Red marrow</td>
<td>11</td>
<td>1.49</td>
<td>5.5</td>
<td>9.2</td>
</tr>
<tr>
<td>Spleen</td>
<td>11</td>
<td>1.19</td>
<td>6.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Bladder</td>
<td>160</td>
<td>1.16</td>
<td>11</td>
<td>4.8</td>
</tr>
<tr>
<td>Thyroid</td>
<td>10</td>
<td>1.11</td>
<td>5.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Ovaries</td>
<td>15</td>
<td>1.79</td>
<td>9.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Testes</td>
<td>12</td>
<td>1.11</td>
<td>3.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Effective Dose Equivalent ($\mu\text{Sv/MBq}$)</td>
<td>19</td>
<td>1.2</td>
<td>8.5</td>
<td>5.7</td>
</tr>
</tbody>
</table>

The estimated absorbed radiation dose to various organs in healthy subjects. The data are quoted from ICRP no. 80.

International Commission on Radiological Protection.

ICRP Publication 80: Radiation Dose to Patients from Radiopharmaceuticals.
Radionuclides with an advantageous combination of γ-ray energy and effective half-lives such as $^{99m}$Tc in general deliver lower doses to the patient than do long-lived nuclides with a low energy such as thallium 201 ($^{201}$Tl). Table 9.1 summarizes the radiation exposures arising from intravenous application of some frequently used SPECT radiopharmaceuticals in comparison to PET tracers.

**TRANSMISSION COMPUTED TOMOGRAPHY DOSIMETRY**

Dedicated PET scanners without a CT unit use positron-emitting sources such as germanium 68 ($^{68}$Ge) and gallium-68 ($^{68}$Ga) for transmission scans, which are crucial for the reconstruction of quantitative PET images. The patient’s radiation exposure caused by these transmission scans is about 2 or 3 orders of magnitude below the effective dose resulting from the administration of radiopharmaceuticals and is therefore negligible (5,6). As stated earlier, this is because the photon flux of the line sources used for the transmission scan in PET is very low, and the radiation burden in PET examinations is dominated by the positron radiation. However, with use of a CT scan for transmission correction and for anatomic localization of suggestive lesions, the radiation dose becomes relevant because of the much higher photon flux used in CT and the lower energy of the x-rays used compared with the γ-rays. The radiation dose stemming from the CT portion of PET-CT or SPECT-CT scans must therefore be taken into account.

Unlike the radiation dose delivered by tracers, the radiation exposure from a CT scan depends on some operator-dependent factors (7–10):

- tube current
- exposure time
- scanner geometry
- slice thickness and slice distance
- scanning mode (step-based vs. spiral technique, single-slice vs. multi-slice)

Because repeating a CT scan results in a doubling the radiation exposure, care must be taken to choose the appropriate CT-scanning parameters.

The radiation exposure is directly proportional to the tube current (measured in milliamperes [mA]) and the exposure time (measured in seconds). However, as in other scanning techniques using ionizing radiation, the signal-to-noise ratio in the resulting image, which corresponds to the image contrast, grows only in proportion to the square root of the product of these two parameters (measured in milliamperes). Thus there is no benefit to be gained from increasing the milliampere product to very high values, considering the trade-off between patient radiation burden and resulting image quality. In our experience with PET-CT, a CT run at a very low milliampere product is sufficient for transmission correction (11); for anatomic localization, a better image quality is needed, and on the basis of some serial experiments, we believe that 40 mA is adequate in standard size patients (12), which is still lower than in diagnostic “CT only” scans. Imaging protocols for these examinations are discussed in detail in Chapter 19.

The average dose delivered to one slice of the scanned volume can be estimated by using the “CT dose index” (CTDI), which is equivalent to the dose distribution integrated over the z (longitudinal) patient axis divided by the slice thickness (13):

$$C_{TDI} = \frac{1}{d} \int_{-\infty}^{+\infty} D(z) \, dz$$

where $D(z)$ denotes the radiation dose in one slice as a function of axial location and $d$ denotes the slice thickness. A normalized form of this index ($nCTDI$) is obtained by dividing the CTDI by the milliampere product. The product of CTDI and the scanned length in the z axis is called the “dose-length product” (DLP), which is a measure of the total radiation energy received by the patient’s body (14). The U.S. Food and Drug Administration (FDA) and its European counterparts require CT scanners to display CTDI and DLP during scanning procedures (15) and have published quality criteria for CT procedures (Table 9.2). With whole-body PET-CT scans, the CTDI in mGy is approximately equal to the whole-body effective dose in mSv, because the weighting factor for x-rays equals 1, and the whole body is irradiated at the given dose rate. For smaller volumes, the resulting effective dose must be adapted properly according to the irradiated target organs (16,17).

Typically, $nCTDI$ values vary between 0.05 and 0.2 mGy/mA and further depend on the other factors mentioned earlier. Assuming a whole-body PET-CT scan and a milliampere product of 40 (which we consider to be a reasonable compromise between image quality and patient radiation exposure) (12,18), the total radiation burden can be estimated to be between 2 and 8 mSv, which is in the range of the radiation burden from the intravenous administration of 400 MBq of $^{18}$FDG.

### TABLE 9.2

<table>
<thead>
<tr>
<th>Organ</th>
<th>CTDIw (Slice) mGy</th>
<th>DLP (Exam) mGy × cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine head</td>
<td>60</td>
<td>1,050</td>
</tr>
<tr>
<td>Routine chest</td>
<td>30</td>
<td>650</td>
</tr>
<tr>
<td>Routine abdomen</td>
<td>35</td>
<td>780</td>
</tr>
<tr>
<td>Routine pelvis</td>
<td>35</td>
<td>570</td>
</tr>
<tr>
<td>Face and sinuses</td>
<td>35</td>
<td>360</td>
</tr>
<tr>
<td>HRCT lung</td>
<td>35</td>
<td>280</td>
</tr>
</tbody>
</table>

RADIATION PROTECTION FOR SCANNER PERSONNEL

The radiation exposure of the scanner personnel is generally higher in PET scanning units than in their conventional nuclear medicine counterparts (10–21). This is due to the higher γ-ray energy of positron-emitting nuclides and the correspondingly more difficult shielding. Moreover, γ-ray energy is emitted twice per single decay event (Table 9.3), and close to the syringe a high dose is emitted by the positrons. To reduce the radiation exposure, one can take the following protection measures.

Reduction of Exposure Time

Optimal planning of the work to be done can significantly reduce the exposure time. The intravenous line for radiopharmaceuticals should be placed before the injection; if possible, automated systems for syringe preparation and injection should be used. If it is necessary to draw blood samples or to take repeated blood pressure measurements, these should be performed using automated systems.

Shielding

Effective shielding for 511-keV photons requires thick layers of lead (half-value layer for fluorine 18 [18F] is 6 mm; see Table 9.3) or another shielding material; thus shields are heavy and in most instances cannot be carried around. Mobile shields mounted on wheels are available but are also not easy to handle. The positron component of the radiation can be effectively shielded with Plexiglas, which should be done especially when handling syringes, as in addition this increases the distance between the radiation source and the fingers of the handling technician or physician.

Distance

The dose rate is proportional to the inverse square of the distance between the radiation source and the point of measurement. In addition to appropriate instruction of the scanning staff, an adequate architectural construction of rooms for nuclide preparation, administration, and patient uptake, maximizing various distances to the patient, substantially contributes to the reduction of the radiation burden for the scanner personnel.

Whole-body and finger doses must be monitored with thermoluminescence dosimeters (TLDs). To check for potential contamination, hand and foot monitors and monitors checking contamination of clothes are part of the mandatory standard equipment in nuclear medicine scanning and radiopharmaceutical preparation areas. Incorporation of positron emitters by personnel in the course of preparing for, carrying out, and cleaning up after PET examinations is rare. Because of the short half-life of the standard PET radionuclides, such incorporation poses a minimal radiation hazard to the personnel.

REFERENCES


TABLE 9.3

RADIATION EXPOSURE OF THE PERSONNEL AND SHIELDING FOR PET AND SPECT TRACERS

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Skin Dose</th>
<th>Organ Dose</th>
<th>Lead</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>h0.07</td>
<td>h0.07</td>
<td>h10</td>
</tr>
<tr>
<td>99mTc</td>
<td>300</td>
<td>0.2</td>
<td>0.022</td>
</tr>
<tr>
<td>123I</td>
<td>400</td>
<td>0.3</td>
<td>0.043</td>
</tr>
<tr>
<td>131I</td>
<td>1000</td>
<td>1.4</td>
<td>0.062</td>
</tr>
<tr>
<td>11C</td>
<td>1000</td>
<td>1.7</td>
<td>0.161</td>
</tr>
<tr>
<td>18F</td>
<td>2000</td>
<td>1.7</td>
<td>0.160</td>
</tr>
</tbody>
</table>

h0.07 = (mSv/h)/GBq at 0.1 m distance, depth = 0.07 mm; h0.07 = (mSv/h)/(kBq/cm²) for contamination, depth = 0.07 mm.

h10 = (mSv/h)/GBq at 1 m distance, depth = 10 mm.

Plastic, total absorption.

Lead, half and tenth value thickness.


**SUGGESTED READING**


INTRODUCTION

Image coregistration and fusion (coregistered image rendering) was one of the prominent nuclear medicine imaging topics during the decade before the first multi-modal systems appeared. Although positron emission tomography (PET) and single-photon emission computed tomography (SPECT) systems were able to acquire images showing unique tissue function, their accurate interpretation was sometimes difficult due to the lack of anatomical

There is a growing need to compare medical images of the same organs viewed on different modalities or acquired under different conditions. Examples include the comparison of newly acquired patient images with prior images retrieved from a picture-archiving system or the correlation of functional information in positron emission tomography (PET) images with the anatomy visible in cross-sectional images. The problem is that the images to be compared generally show the organs with different orientation and position. These differences in geometry result from differences in patient positioning and acquisition geometry in the studies being compared. A processing step called image registration can be used to undo the geometric differences and calculate congruent images from both studies. Various image-registration methods are available, and most of them assume that the object is rigid and that no distortions occur during the acquisition. The optimum method would perform the registration fully automatically for any type of studies, but practical methods often require user interaction and impose restrictions on the images they are able to register.

The most robust and flexible method is full manual registration (see Fig. 10.4). The physician rotates and translates one of the data sets until the displayed images from both studies appear to be aligned in a combined rendering of both images. Another method is based on the interactive definition of corresponding points (landmarks) in both data sets. An algorithm then calculates the spatial offsets and rotations to bring the two arrangements of landmarks into optimal agreement. A popular matching method is the AIR (Automatic Image Registration) program which is able to register images of a single modality without user interaction. It is freely available.

More recently, the maximization of mutual information has been introduced as a matching criterion and is successfully used in a broad range of application domains. A different class of registration methods perform not only rigid alignments but additionally introduce elastic deformations to better match the shapes within the images. The typical domain for this kind of registration is the adaptation of an individual's brain image to an atlas image representing the “standard” brain. After each of the registration processes described, both image sets are in a common coordinate system and can be compared directly. Visualization tools support this comparison by providing a coupled cursor in both images or by calculating different types of rendered images from two corresponding images.
Many research was carried out to develop methods for combining anatomical images acquired on magnetic resonance (MR) and computed tomography (CT) scanners with images from nuclear medicine modalities. The situation has been relieved to some extent with the advent of the combined PET-CT systems and more recently the SPECT-CT systems, which yield inherently matched images. However, because most medical images are and will be acquired on separate systems, there remain many situations where image coregistration is relevant.

Let us illustrate the involved tasks with a typical example, the coregistration of a FDG brain PET with a corresponding T1-weighted MR image. Whereas PET shows the glucose uptake with a resolution of about 7 mm, MR presents much better resolved anatomic images. As the patient had been differently positioned in the two scanners, the head was differently oriented within the field of view. Thus the PET images appear rotated and reduced relative to the MR images. When reading these images in a traditional way by just showing the image sections in a viewbox (Fig. 10.1), we find it difficult to co-localize a lesion visible in PET precisely on a corresponding MR section. Image coregistration supports this comparison in two steps. The first step of “registration” brings the tissue structures in the two data sets into spatial alignment; that is, acquisition-related geometric differences are undone. As a result, this first step leads to two directly comparable (“registered,” “matched,” or “aligned”) image stacks. The congruent slices can now be presented in the traditional side-by-side fashion, but this still burdens the observer’s mind with the information-integration task. Thus, the second step is to support the comparison process by applying explicit visualization tools. For the example mentioned, a simple solution would be to project a lesion or its outlines from PET into the MR images. More sophisticated dynamic tools allow even better assessment of the extent and severity of the lesion and facilitate subsequent surgical planning.

**IMAGE REGISTRATION FOR GEOMETRIC REALIGNMENT**

Image registration is always required for data sets acquired in different studies because a patient will always be differently positioned unless very cumbersome or unpleasant procedures are applied. Similar, although smaller, dislocations are likely to happen between consecutive acquisitions of one study because of involuntary patient motion. To prepare the ground for the ensuing discussion of different registration techniques, we start with a quick summary of the conceptual models and classification criteria involved.

**Overview of Registration and Classification Criteria**

A registration procedure that allows the matching of two data sets consists of the following components:

1. **Role of the data sets.** Although registration entails that both data sets end up aligned in a common coordinate space, it does not entail that both should actually be transformed. Transformations such as rotations involve interpolations that may degrade image quality, especially if the spatial resolution is nonisotropic (Fig. 10.2). Therefore, only the better resolved data set (the “model”) is transformed, whereas the other one (the “reference”) remains fixed.

2. **Information type.** Registration procedures do not always operate on the full images but may rely on a set of derived...
information features common to the objects represented in the two data sets. Examples include a set of anatomical landmarks and an organ surface detected in the images. These information features are collected in a preprocessing step. Often, user interaction is required, such as to point out corresponding anatomical landmarks or to guide the edge detection algorithm in segmentation procedures. However, depending on the image characteristics, the pixel values themselves can also be employed directly.

3. Allowed geometric transformation. There are two distinct classes of transformations, rigid transformations and elastic transformations. Rigid transformations assume that the object’s geometry is identical in both acquisitions and that the acquisition is distortion free. In this case, the transformation consists of a three-dimensional displacement (three parameters) and of a three-dimensional rotation (three more parameters). Differences in the size of the pixel edges are accounted for by three scaling factors. A rigid transformation is therefore determined by nine parameters. In most cases, however, the scaling factors are known from the image headers and need not be estimated. Elastic transformations allow a certain degree of image warping to cope with the fact that the boundaries of organs outside the brain change across acquisitions.

4. “Goodness-of-match” criterion. For an automatic registration method, the goodness of the alignment after a candidate transformation must be measurable. Only then can the transformation parameters be found that provide the best match between the reference features and the transformed model features.

5. Optimization. If the registration is not interactively done by the user him- or herself, an automatic optimization algorithm is required that brings the two image sets into agreement based on the extracted information and the allowed transformation. Usually it is not possible to find the optimal transformation by a single calculation. In these cases, iterative schemes are employed whereby the transformation parameters are systematically varied until no better match can be found. One problem with these algorithms is that they can find approximate solutions and miss the optimal match.

While a registration method can be characterized by the above five criteria, there are some additional relevant criteria with respect to a clinical application:

1. Prior requirements. The issue concerns the extent to which the registration method depends on special setups of the acquisitions. Examples include patient fixation techniques (Fig. 10.3) and the placement of external landmarks visible in the images. Further requirements might be related to image contrast and resolution or to the extent of organ coverage. If there are no such requirements, image data sets from previous studies or acquired at remote institutions can at any time be matched with newly generated images. It is clear that the ability to implement retrospective registration is very helpful in a clinical environment.

2. Objectivity and automation. Fully automatic registration techniques are highly desirable. In addition to being user-friendly, they offer operator independence and hence exact reproducibility. However, automatic methods are only a true advantage if the registration achieved is accurate enough. Usually, the input data for fully automatic methods cannot be arbitrarily acquired, but image acquisition must obey strict quality criteria. West et al. (1) point out that careful visual inspection of the results obtained from automatic registrations is crucial in a clinical setting.

3. Multi-modality registration. The image registration problem is easiest to solve for images acquired with one protocol on a similar scanner because they show the same information with the same resolution. If this condition is not fulfilled, registration becomes more difficult. Differences in resolution may not be a severe obstacle within certain limits. More difficult is the frequent case comparing functional and anatomical images where the images look very different.

In the rest of this section, several widely used registration techniques are discussed. We begin with rigid registrations and end with an elastic transformation that is frequently applied to transform functional patient data into
the normalized coordinate space of the stereotactic Talairach atlas (2). For a more in-depth review, the reader is referred to the reviews by Evans (3) and Maintz and Viergever (4), and for a performance evaluation, to the assessment of 16 retrospective registration methods by West et al. (1).

Interactive Registration

Interactive registration fully relies on the pattern-matching capabilities of a trained human professional, which is hard to surpass. An interactive registration tool can be used to specify trial transformation parameters, calculate the transformed model images, and present them jointly with the reference to allow the user to judge the goodness of the match. An example of a commercially available image fusion tool (http://www.pmod.com) is illustrated in Figure 10.4. The translation and rotation parameters of a rigid transformation can be specified by means of button presses or by directly dragging or rotating the model images, while the scaling factors are taken from the acquisition information in the image header. Three orthogonal slices of both data sets are shown in parallel, plus the fusion image, using the current transformation. Once the match is completed, corresponding slices will be shown. Assessment of the match is facilitated by various fusion display options, such as the inclusion of contours or a spyglass. The user incrementally modifies the transformation until the fusion confirms an adequate match.

The only prerequisites for interactive registration are (a) a trained user who understands the anatomy and the characteristics of the two modalities and (b) sufficient common features in the two studies. Thus, it is the solution if the automatic matching methods fail, and it can be applied retrospectively even for multi-modality registration. Owing to the interactive nature of the procedure, there is some subjectivity in the resulting match. However, systematic studies of intraobserver and interobserver variability (5) have shown that its influence is not significant if a standard processing protocol is followed. The authors concluded that the reproducibility and accuracy are comparable to or even better than those of published automatic registrations or fixation systems such as head holders or face masks in a large variety of registration situations.

Landmark-Based Registration

The information feature used in landmark-based registration is the homologous point pair. Such a point pair identifies the same anatomical location in both data sets. In order to calculate the registration parameters, a whole set of point pairs is needed. The two image sets are reduced to two spatial arrangements of points, the reference points and the model points, which must be brought into optimal agreement. We assume here that the transformation performing this alignment is rigid, but this is not mandatory, and approaches with elastic transformations have been described. The criterion for the match is some norm based on the distance between the reference points and the model points, which must be brought into optimal agreement. We assume here that the transformation performing this alignment is rigid, but this is not mandatory, and approaches with elastic transformations have been described. The criterion for the match is some norm based on the distance between the reference points and the corresponding model points after transformation. Usually the sum of the squared distances is minimized by an iterative algorithm.

In general, the point pairs are obtained in an interactive preprocessing step. A trained user repetitively explores the two image sets and each time tries to identify an anatomical location in both of them. This assignment happens in three dimensions and is therefore quite difficult to perform. Consequently, the point locations are specified with

Figure 10.3 Fixation aid to restrict patient motion during examinations of the chest on two separate scanners. A: The patient is embedded into a mattress that, when evacuated, fits itself to the body contours. The shape is maintained throughout successive scans and efficiently limits patient motion, but this device is not liked by patients, as they tend to perspire profusely in it. B: To prevent errors arising from the table curvatures, a flat equalization board is used on both scanners.
a measurement error $\sigma$, which has an impact on the registration accuracy. It is clear that the number $N$ of point pairs used also affects the accuracy, as measurement errors tend to cancel themselves out on average. These issues have been investigated by Evans et al. (3,6). These authors found that the registration accuracy is proportional to $\sigma/\sqrt{N}$ and propose to use about 10 to 20 point pairs. As the quoted measurement error is in the range of 5 to 15 mm, a registration accuracy of 2 to 3 mm can be expected.

The definition of the point pairs is crucial for this registration method. The user must therefore be supported by powerful visualization tools to efficiently browse through the image volume. With dedicated systems, 10 to 20 point pairs can be specified in about 15 to 20 minutes. Retrospective and multi-modality registration is possible provided that enough anatomical landmarks can be located in the two studies. If one of the studies has poor anatomical information, one can resort to preplanned acquisitions with external landmarks. These are devices that are attached to the patient during both studies and contain material visible in both types of acquired images. They show up as fiducial structures in the images and can be used to define landmarks additional to the anatomical ones.

**Surface Matching**

The information feature used in this initially popular registration method by Pelizarri et al. (7) is the three-dimensional surface of an object visible in both image sets. In the classical implementation for brain studies, a rigid matching transformation is assumed and estimated together with the scaling factors. The criterion of measuring the goodness of match can be illustrated by the “hat over head” metaphor: The surface from the modality with higher resolution usually takes the role of the “head.” The other, the “hat,” is considered to consist of points. For each of the hat points, the residual is defined as the distance between the point and the head surface along the direction of the head.
The centroid (the center of gravity of the volume enclosed by the head surface). The sum of all squared residuals yields the criterion, which is minimized to find the optimal match. During an iterative optimization procedure, the transformation parameters are varied until the residual criterion of the transformed hat points is minimal.

As with other automatic techniques, this registration method has been mostly applied in the head, using the outer skull or the brain surface. The required contour lines are relatively easy to segment in most modalities without interaction. In PET, the transmission images instead of the emission images can be used for segmentation (Fig. 10.5). Retrospective and multi-modality registration is possible provided that a common object can be located in the two studies. It should be pointed out that the technique does not require the object to be covered by the same extent in both studies. A common part of the surface may be sufficient if there is not too much symmetry, which prevents the calculation of a unique solution. The registration accuracy is limited by the lower-resolution pixel size. In phantom studies, Pelizzari et al. (7) found errors in the range of 0.7 to 2.5 mm for various cross-modality registrations (MRI, CT, PET).

Figure 10.5 The PET transmission images show the linear attenuation coefficient at 511 keV and therefore resemble CT images. They can be used to find the coordinate transformation between the whole-body CT study and the PET emission study, which is assumed to be aligned with the PET transmission study. To assess the match, the PET contours are overlaid on the CT images.
Besides the classical implementation described above, there are numerous extensions of surface matching, as reviewed by Audette et al. (8).

**Automatic Image Registration (AIR)**

This widely used registration method was introduced by Woods et al. (9) and aimed at PET studies of the brain. As the name suggests, it was developed for fully automatic registration. AIR directly uses the values of all pixels in the image volumes as the information feature. It is based on the assumptions that both data sets show the objects very similarly and that they are related by a rigid transformation. To be more specific, the idealized assumption is that the pixel value in each model point equals the value in the corresponding reference pixel multiplied by a global factor F. In practice, the two data sets will differ because of noise, sampling effects, and, depending on the clinical or experimental situation, physiological differences. Therefore, the assumption is relaxed to the criterion that the match is optimal if the variance of the transformed model:reference ratio (F) ideally is minimal. An iterative optimization algorithm is applied that updates one parameter at a time to approach a better match until further improvements, as expected by the derivatives, fall below a preset threshold. In practice, areas outside the head pose difficulties when forming the ratio. Therefore, the ratio is only considered within a masked area obtained by applying an empirical threshold value to the reference data set.

The registration as described above is fully automatic. The only input value is the mask threshold, which can experimentally be determined once for a certain study type. Retrospective registration is possible with AIR, but cross-modality registration is not directly supported. However, there exists an extension of the technique that makes it suitable for MRI–PET alignment (10). In addition to modifications of the criterion that incorporate grouping of pixels with similar behavior in MRI, manual preprocessing of the MR data is involved to mask out structures not visible in PET, such as the scalp, skull, and meninges. The accuracy as determined by Woods et al. (9) in phantom experiments simulating H215O-PET studies is 0.7 mm. These authors also show that prior smoothing of the images improves the registration at high noise levels. The latest developments in AIR include nonrigid transformations and different methods for quantifying the goodness of the image alignment.

**Registration by Maximization of Mutual Information**

A more recently evolved class of registration techniques is based on the maximization of mutual information, with the seminal papers by Collignon (11) and Viola (12) in 1995. Mutual information is a criterion from information theory and is explained with reference to medical images in Wells et al. (13). It is related to the entropy (as a measure of uncertainty, variability, or complexity) in both image sets as well as their joint entropy. The mutual information is maximal if the images are coregistered, that is, if each of the images provides the most information about the other. The mutual information can be calculated directly from the image pixel values, and there exist efficient optimization algorithms for the task of image alignment.

Image registration by maximization of mutual information has been applied in a broad range of domains (14) with rigid and nonrigid transformations. Experience has shown that it is an accurate and robust method for aligning mono-modality and multi-modality medical images, notably PET, SPECT, MRI, and CT. Therefore, mutual information based registration has become the method of choice for many applications and is used predominantly in commercial packages. It has the great advantages that it can be applied retrospectively, does not require preprocessing, and operates fully automatically.

**Elastic Registration to the Talairach Atlas**

Stereotactic normalization is based on the work of Talairach and Tournoux (2). They set up a proportional system that adapts itself to the proportions of each individual brain. This means that each pixel in a brain image can be mapped into a coordinate of the stereotactic “average” brain, the brain atlas. In order to estimate the mapping transform, it is important to localize the line passing through the anterior and posterior commissures (AC-PC line). In PET, this has been accomplished by an additional lateral skull radiograph in the first approach (15), but automatic methods have since been developed (16,17) that estimate the AC-PC line directly from the PET images. After this line has been found and realigned with that of the atlas by rotations and translations, the stereotactic transformation only consists of linear scaling along the three dimensions. Although a certain degree of anatomical alignment is ensured by this transform, some regional variations among subjects still remain. When averaging such normalized images of different subjects, the mismatches might cause artifacts. As a remedy, an additional step has been introduced. It minimizes the shape differences of structures in the atlas images (the reference) and in the normalized patient images by applying a nonlinear “plastic” (18) or “warping” transformation (19).

The implementations of stereotactic normalization differ in the information feature they use for estimating the plastic deformation. Although Friston et al. (18) use the pixel values themselves, landmarks are employed by Minoshima et al. (19). Consequently, they also apply different matching criteria. Stereotactic normalization is most commonly applied within a modality, with the atlas images serving as a reference and the actual images normalizing shared similar features. In this case, the differences are primarily due to the brain shapes and only to a lesser extent caused by variations in pixel intensity. The methods referred to above are fully automatic and can be applied retrospectively.

One typical domain of stereotactic normalization is in stimulation experiments. There the provoked signal changes
are often too small to be reliably assessed by few acquisitions. Study data from several subjects must therefore be pooled for a single analysis in modalities, such as PET, where experiments cannot be repeated arbitrarily. Hence all the images are first normalized and then subjected to statistical analysis. The results can then be directly reported in stereotactic coordinates. Another domain is the formation of a normal uptake pattern (normal database) against which patient images can be compared, as described in Chapter 11.

Matching Outside the Brain

With modern hybrid in-line systems such as PET-CT or SPECT-CT, patients are examined using two complementary imaging modalities, obviating the need for patient repositioning. This setup results in inherently matched multimodal images, although the match may be compromised to some extent by the motion of organs or by posture changes during lengthy acquisitions.

There has been some debate whether modern algorithms are capable of bringing images acquired on separate systems to a match comparable to that of combined systems. Although there is sufficient evidence that this is the case for brain scans where the organ can be assumed to be rigid, a recent study (20) clearly documents that automatic matching frequently fails in other parts of the body, which require the compensation of elastic deformations.

**Figure 10.6** Rendition of coregistered images in single fusion images. A: $^{18}$F fluoroethyl tyrosine (FET) PET image. B: $T_1$-weighted MR image. As a result of registration, images A and B are congruent and have the same pixel sizes. C,D: Images rendered by weighted blending of the PET and MR pixel values. E: Single image obtained by displaying all PET pixels above a certain threshold and MR pixels elsewhere. F: FET PET information displayed on the MR image in a movable spyglass window.
because otherwise disturbing interpolation effects might occur (see Fig. 10.2).

In a broad sense, coregistered image rendering includes all techniques that allow the user to integrate the information of two or more aligned image studies. The following two interactive approaches are simple, yet helpful and accurate:

- Contours can be defined and exchanged between the studies.
- A coupled cursor can be moved about the images and mark the same anatomic position in both studies. The coupled cursor is particularly useful if it is combined with interactive triangulation, which allows rapid updating of the display with orthogonal slices through a new point of interest.

Several methods can generate images within which the information of the congruent images of two matched studies is explicitly rendered. One of the following approaches may be applied to generate such fusion images, as illustrated Figure 10.6:

- The pixels from two data sets are alternated and combined in a new image as a checkerboard-like pattern. Because only half of the information in the source images is used, the result is often not pleasing.

- Instead of alternating the pixels from the two data sets, their color values can be added directly. As a pixel color is defined by three numbers representing the contributions of red, green, and blue (RGB), the new pixel color can be easily calculated by adding each color channel separately. Using weighted summing allows control of the relative importance of the components in the fusion image. It is very helpful for the comparison process if a slider supports smooth blending from one image over different degrees of mixing to the other. The advantage over pixel alternation is that no resolution is sacrificed.

- A threshold can be defined for one of the studies, the "lesion study." All pixels with values above the threshold are transferred from this lesion study to the fusion image, whereas the remaining pixels are filled with values from the other study. This approach retains the full resolution of the two information components in specific regions. It is particularly powerful if the threshold is interactively changeable and combined with image blending.

- A movable spyglass allows the inspection of the functional information at specific anatomic locations, or vice versa.

Figure 10.7 illustrates the rendering display of coregistered images by clinical software (Xeleris View Workstation, GE Healthcare, Milwaukee, WI), which includes a rotating maximal intensity projection window of the PET image data.
GE Medical Systems, Milwaukee, WI) designed to review PET and matched CT images jointly. This software has many different display configurations to rapidly and accurately localize and assess lesions visible in PET. It has turned out that a rotating maximum intensity projection (MIP) image of the PET data allows a fast overview of the situation. If the user points to a lesion in the MIP image, the orthogonal images at this location are immediately calculated and displayed.

A current topic in image fusion development is the combining of anatomical virtual reality (VR) rendering with functional information. The latest radiological devices are able to acquire images with such a high resolution and contrast that appropriate postprocessing techniques are able to produce stunning VR renderings of the organ in question. The example in Figure 10.8 shows the volume rendering of a heart assessed by an angio-CT procedure using a short bolus of intravascular contrast agent.

Although the virtual anatomy of the coronary arteries—in combination with the original CT images and additional measuring tools—allows review and examination of the state of the vessel tree, the consequences of obstructions or malformations on myocardial perfusion remain unknown. This information can be added to the scene from a rest–stress perfusion PET or SPECT study that has been matched to the CT acquisition.

Explicit image rendering of coregistered images represents a significant improvement over the classic method of correlative image reading. No longer are physicians given only a set of static slice or projection images, the information from which they have to integrate mentally. They now have a set of powerful interactive visualization tools that allow them to explore the information with different methods until the situation has been clarified.

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Figure 10.8 Combination of CT virtual reality rendering with PET image fusion (PMOD 3D tool, http://www.pmod.com). Volume rendering of angio-CT study (A) and CT slice images (B). C: Fusion of 13N ammonia perfusion PET with CT after image registration. D: The color of the PET images representing perfusion is combined with the volume-rendered CT.
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**Quantifying PET**

Cyrill Burger  Alfred Buck

Although subjective reading of positron emission tomography (PET) images is still the basis of clinical diagnosis, strategies to extract quantitative information of disease processes will permit more objective diagnosis and comparisons among patient groups. Some quantification methods require the measurement of the true concentration of the tracer in tissue. Such data can be acquired only with a PET system that is correctly calibrated and routinely maintained.

The aim of lesion quantification is to calculate an index related to the severity of the lesion. To this end, a volume of interest is generally defined around the lesion, and the average pixel value calculated (see Fig. 11.1). In doing this, a problem called the partial-volume effect occurs. Because of the limited spatial resolution of the PET system, the actual activity distribution becomes distorted. Depending on whether a lesion takes up more or less tracer than the surroundings, the true tracer concentration is underestimated or overestimated at the edges. A semi-quantitative index often used for brain tumors is the lesion-to-reference ratio, which uses, for example, normal white matter as the reference tissue. The advantage of the method is the general availability of the internal standard and the removal of many distortion effects by the operation of division.

An index that has become popular during the last years for fluorodeoxyglucose (FDG) studies and is used for tumor grading is the standardized uptake value (SUV). In the initial definition, the tissue FDG concentration was normalized by the injected dose per gram body mass. Criticism led to the refinement of the SUV definition by replacing the total body mass by some measure of the lean body mass. The recommended way to measure lean body mass is using a fat and body weight scale rather than deriving it by an anthropometric formula. It is important to note that FDG uptake is not representative of the metabolic rate of glucose due to the potential change of the lumped constant in lesions. In some situations, patient images can be compared against the standard uptake pattern of normal controls to detect lesions and derive a quantitative measure of disease. A recent example is the fully automatic discrimination of patients with suspected Alzheimer dementia from normal controls on the basis of FDG data.

**INTRODUCTION**

In most situations, positron emission tomography (PET) imaging is done just like any other imaging modality. Images are acquired, reconstructed, and then reviewed with the aim of identifying pathologic lesions. Once a lesion is found, the decision about the lesion’s significance is based mainly on a visual comparison of its uptake with that of tissue considered to be normal, qualified by the physician’s experience. In this process, the numbers attributed to the lesion pixels by the reconstruction algorithm do not matter. Such relative assessments have been proven to be successful in clinical diagnostic routine, but they do not permit comparison between studies. This can be done with several more or less quantitative approaches. They allow comparison of the data for a patient group in order to arrive at a certain measure of the disease process (e.g., malignancy) or to assess numerically a therapy-induced effect in follow-up studies. Furthermore, they are mandatory for many types of research studies in which a baseline image is compared with an image in a specific condition, such as the brain perfusion before climbing Mount Everest and afterward (a study actually done in our PET center).

**CALIBRATION AND QUALITY CONTROL**

As quantitative analyses require the reconstructed values in the image pixels, these have to be calibrated in absolute values to reflect the true tracer activity concentration in
kilobecquerels per cubic centimeter (kBq/cc) of the imaged tissue. To this end, a whole sequence of procedures must be performed (see Chapter 3). First, the procedures correct for the different types of signal distortions occurring during an acquisition, such as event losses due to detector dead time and photon attenuation, wrong "random" and scattered events, and differences in detector properties. With these corrections, true scanner “counts” represent the number of signals detected from each resolved tissue voxel. However, different scanners have different sensitivities for activity in the field of view, resulting in different count images for the same tracer distribution. Therefore, a calibration measurement must be performed with a homogeneous phantom (usually a cylinder containing a fluorine 18 [18F] solution of known activity concentration). The ratio of activity concentration to reconstructed counts represents the calibration factor that transforms the count image into a quantitative activity–concentration image in kilobecquerels per cubic centimeter. As the sensitivity varies among slices, one calibration factor per slice is applied. Because correct calibration is vital for quantitative analyses, quality control procedures must be performed on a regular basis, and the calibration repeated according to a schedule and after every significant system maintenance.

DISTORTION EFFECTS

In most numeric analyses, the PET signal is averaged over a set of image pixels (a “volume of interest” [VOI], Fig. 11.1), based on the assumption that they represent homogeneous tissue. With such VOI methods, a problem arises related to the limited resolution of PET: the generation of so-called partial-volume effects (known also in CT and MR). An ideal imaging system would acquire perfect images of object shapes. Real systems, however, have a limited resolution and thus produce blurred images. The process of unsharp imaging can be modeled by a convolution of the true image with a function representing the impulse response, typically in the form of a Gaussian function. This function represents the characteristics of the imaging system, and its full width at half maximum (FWHM) is often used to define the resolution. PET systems typically have a resolution of approximately 5 to 10 mm in clinical imaging, so considerable blurring occurs.

Figure 11.2 illustrates the effect for a 20-mm-diameter synthetic hot lesion containing a count per pixel of 1,000 imaged with three systems. The perfect system yields the true image, and the second and third systems yield the true image convolved with a 7-mm and 12-mm Gaussian function. Applying a circular VOI of 20 mm to the images results in average pixel values of 1,000, 761, and 603, respectively. The reason for this progressive loss is obvious from the profiles in Figure 11.2B: a part of the activity is smeared to the neighborhood of the hot lesion. The loss is described by the “recovery coefficient,” which is defined as the fraction of the true counts that is measured in a VOI analysis. In the examples given, the recovery coefficients are 76.1% and 60.3%.

The recovery coefficient depends on several factors, such as the object size, the VOI size, the resolution of the scanner, and the lesion-to-background ratio. If a lesion takes up fewer trace than the surrounding tissue, the actual tracer concentration will be underestimated at the edges. An approach to reducing the partial-volume effect in lesions that are hotter than the surroundings is to use the maximum pixel value in the VOI instead of the pixel average (1). The advantage is that the impact of the partial-volume effect and of the VOI geometry, such as shape, size, and location, is greatly reduced.
RATIO METHODS

Many factors can influence the tracer concentration in tissue measured at some time point after the administration, as listed in Table 11.1 (2). Apart from the primary biochemical process of interest, confounding factors moderate the uptake. Any quantification method must try to minimize their impact so that the results are minimally biased. Kinetic modeling (see Chapter 13) is the ultimate method for accounting for various confounding factors. However, it imposes high demands regarding data acquisition and processing and is therefore often not applicable in clinical routine. For some tracers and some of the studies, simplified approaches can achieve a similar goal of reducing the effect of the confounding factors.

One approach sometimes helpful for assessing the severity of lesions is to compare the tracer uptake in the lesion with the uptake in healthy tissue. To this end, VOIs are defined around the lesion and a suitable reference tissue, and the average tracer concentrations are calculated. Then the ratio of the lesion concentration to the reference concentration is formed and used as a potential indicator to grade the lesion. This approach has several advantages: first, the calibration errors are eliminated by the division process, and second, an internal standard is used as a reference, which is available in most situations. The ratios of tumor to white matter and of tumor to contralateral tissue have been used for differentiating low-grade and high-grade cerebral tumors with FDG (3) (Fig. 11.3). A recent receiver operating characteristic (ROC)–based comparison of the ratio methods and visual grading, however, concluded that visual grading of cerebral tumors is at least as accurate as grading based on a ratio (4). Additionally, the study showed that gray matter or white matter represents a better reference than does contralateral tissue.

STANDARDIZED UPTAKE VALUES FOR FDG

An approach that has come into widespread use for FDG studies in the past few years is the SUV. This represents an index for FDG accumulation in tissue. The principle of the SUV, introduced by Strauss and Conti (5), is to normalize the measured FDG concentration to the injected activity per gram body mass. Thus the measured tracer activity in kBq/cc is converted into an SUV value by the expression

\[
SUV_{\text{bm}} = \frac{A[kBq/cc]}{D[kBq]} \text{ mass}[g]
\]

where \(A\) is the tissue activity and \(D\) is the injected dose, both decay corrected to the same time point. Initially, there was considerable criticism regarding the use of the SUV\(_{\text{bm}}\) (6), as several factors affect the usefulness of the SUV\(_{\text{bm}}\). The patient size and habitus was recognized as a source of considerable variability. Differences in the uptake time in clinical PET imaging and differences in the patient-scheduling practices at different institutions were also shown to have important effects. It was even found that the time lag between cradle positions of a single whole-body scan

| TABLE 11.1 |
| FACTORS THAT CAN AFFECT TRACER UPTAKE IN TISSUE |

- Tracer dose administered to patient (MBq)
- Route of tracer administration
- Biochemical processes in which the tracer is involved
- Perfusion of the tissue of interest
- Body mass and constitution (body fat content)
- Condition of the systems in the body (uptake of tracer in other tissues, excretion rate, metabolism of the tracer in the body, etc.)
- Competition endogenous substrate/tracer
- Nonspecific biochemical environment in tissue
- Biochemical properties of labeled metabolites in plasma
- Vascular volume in tissue
- Time of measurement after tracer administration

Molecular Anatomic Imaging

might cause significant differences in the $SUV_{\text{bm}}$. Several refinements have therefore been proposed to overcome some of the problems with SUV calculation.

$$SUV_{\text{bm}}[g/ml] = \frac{1000}{A} \left( \frac{D}{45.5 + 0.91 \left( \frac{\text{height}[cm]}{152} \right)} \right)$$

$$SUV_{\text{bm}}[g/ml] = \frac{1000}{A} \left( \frac{D}{1.07 \text{weight}[kg]} \right) - 148 \left( \frac{\text{weight}[kg]}{\text{height}[cm]} \right)^2$$

$$SUV_{\text{bm}}[g/ml] = \frac{1000}{A} \left( \frac{D}{1.1 \text{weight}[kg]} \right) - 128 \left( \frac{\text{weight}[kg]}{\text{height}[cm]} \right)^2$$

$$SUV_{\text{bm}}[m^2/ml] = \frac{A}{D} \left( \text{weight}[kg] \right)^{0.425} \times \left( \text{height}[cm] \right)^{0.725} 0.007184$$

where $b$ is a constant independent of the particular patient being studied, $\text{Glc}$ is the glucose content in arterial plasma, and $\text{LC}$ is a lumped constant that accounts for the transport and phosphorylation difference between glucose and FDG. Two questions arise with this formula. First, how stable is the value of the LC that describes the relative overall uptake efficiency of glucose and FDG? It is of utmost importance to realize that the lumped constant is really known only in healthy brain tissue. In tumors, it can be radically different. For example, it has been shown in brain tumors by using $^1$H$^1$C glucose that tumor $\text{MR}_{\text{glc}}$ was decreased relative to cortex, whereas FDG uptake was increased (10). It is therefore not possible to measure $\text{MR}_{\text{glc}}$ in lesions by using FDG. The second question is whether the glucose content should be included in the SUV calculation or not. From the perspective of the FDG utilization characteristics, the inclusion of the $\text{Glc}$ factor into the SUV calculation seems appropriate for most tumors (2). However, a recent study revealed that the inclusion of $\text{Glc}$ increases the variability of the resulting SUV (11) and recommended that correcting for blood glucose not be done.

**COMPARISON AGAINST NORMAL DATABASES**

Most quantification methods are based on a reader who detects a lesion in the images and performs some sort of volume-of-interest analysis. Due to the manual contour placement, this always entails some degree of operator dependence. In certain situations, it is possible to overcome this shortcoming with methods that compare the patient’s images against a reference image representing the normal uptake pattern. There are three requirements for such methods:

1. **Anatomical normalization.** To compare the patient images with the reference, the patient anatomy must be adjusted to the standard anatomy. There are two domains where this task has proven to be successful. With heart studies, the anatomy is reduced to a simple geometrical model such as an ellipsoid. With brain studies, an elastic transformation is derived that warps the patient’s images into the stereotactic coordinate system (see Chapter 10). If the functional brain images do not show sufficient anatomical details, the transformation may indirectly be obtained using an anatomical brain image of the same patient, such as a MR image.

2. **Standard uptake pattern.** Studies must be performed with a large enough set of normal controls, the data anatomically normalized, and the results statistically analyzed. It is important to bear in mind that patient preparation, the acquisition protocol, and reconstruction usually have an impact on the resulting images, and therefore guidelines must be established and followed. As tissue function tends to change with age, the control group should be age-matched to the target patient group. The statistical analysis has to demonstrate a consistent uptake pattern with a sufficiently small standard deviation.

3. **Comparison against standard.** In addition to highlighting differences, the ultimate aim is to derive some sort of statistically sound criterion of the disease degree.

A recent example is the discrimination of patients with suspected Alzheimer dementia (AD) from normals on the basis of FDG brain PET scans (12). In summary, the data are processed as follows: The images are spatially normalized and smoothed, the value range is normalized, and the pixel values are corrected to compensate for age-related effects and are transformed into $t$-values. All abnormal $t$-values within an Alzheimer-specific mask are then summed to form a criterion (AD $t$-sum), which is tested for significance of abnormality, and an error probability is derived. In conjunction with clinical symptoms, an abnor-
mal finding supports the diagnosis of AD (Fig. 11.4). This fully automatic method, which has demonstrated 93% sensitivity, is commercially available (PMOD Technologies, Adliswil, Switzerland, www.pmod.com).

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Figure 11.4 Alzheimer discrimination analysis result (www.pmod.com) of FDG PET data from a 77-year-old patient. The spatially normalized patient images in gray are overlaid with clustered t-values. Red pixels represent abnormal pixels belonging to a cluster of at least 216 contiguous voxels. The main outcome is the AD-t sum, which is abnormal, with an error probability of <0.0001.
INTRODUCTION

In single-photon emission computed tomography (SPECT) imaging, the term “quantitation” has taken on many meanings. In all cases, the goal is to produce from the SPECT data not only a visual image of the radionuclide distribution but also a number that describes some underlying parameter represented by the image. The particular aspect of the image that the number describes has been wide ranging and is the source of the many meanings of “quantitation.”

For our purposes, “SPECT quantitation” refers to using SPECT imaging methods to measure the detected count rate from a “feature” of interest within the image, such as a tumor or organ. This detected count rate typically is then used to compute a functional parameter of the image feature. “SPECT quantitation” also can refer to the measurement of the feature size (length, area, or volume).

The detected count rate of an image feature usually does not, by itself, provide meaningful physiologic information, but it does when compared with the count rate in another image or in a different region of the same image. For example, in tumor imaging, a change in detected count rate over time can indicate the response of the tissue to a drug or radiation therapy. In myocardial perfusion imaging, the ratio of the lung count rate to the myocardium count rate has been used as an indicator of cardiac function. In gated blood pool imaging, the ratio of the count in the ventricle at end diastole to that at end systole is used to compute ejection fraction and stroke volume. We can refer to these clinical applications as relative SPECT quantitation.

Relative quantitation can provide important physiologic information, but in some contexts it is important to know the absolute amount of radioactivity in the tissue. A prime application of this occurs in the area of radiation dosimetry. To calculate the radiation dose to organs of interest, the SPECT image must provide information on the total activity (e.g., μCi or MBq) in the image feature. Another application of absolute SPECT quantitation occurs in kinetic modeling. In this case, the goal is to compute functional parameters of an organ (e.g., blood flow) based on the SPECT-measured absolute activity concentration and activity measured from blood samples obtained over time. Here we focus on absolute SPECT quantitation.

Absolute SPECT quantitation is performed in two separate steps: (a) generation of a quantitatively accurate reconstructed SPECT image and (b) definition of the boundary of the feature of interest (i.e., segmentation of the image) and computation of its activity. The goal of the first step is to obtain a SPECT image in which the intensity of each voxel represents the true activity concentration within the body at that point. The goal of the second step is to
compute the activity from within the feature of interest only, excluding activity from background regions. Both of these steps are critical for the accuracy of the overall SPECT quantitation.

**QUANTITATIVE SPECT RECONSTRUCTION**

SPECT quantitation requires a reconstructed image that accurately represents the rate of photon emission, or activity, per unit volume throughout the imaging field of view. Because it is impossible to detect all of the photons emitted at all points in the field of view, a calibration factor is required to relate the rate of photon detection to the rate of photon emission at all points of interest. In this section, we (a) summarize the important physical factors that affect SPECT quantitation and give examples of correction methods, (b) describe methods for calibrating the SPECT image for absolute activity quantitation, and (c) describe in greater depth current methods for compensating for an important factor in SPECT quantitation, attenuation.

**Physical Factors Affecting SPECT Quantitation**

A large number of physical factors can affect the SPECT quantitation of a particular image feature (1), but three factors stand out: attenuation, scatter, and detector response (or finite spatial resolution limited by the collimator). Other factors can play more prominent roles under special conditions (e.g., organ or patient motion and count losses due to detector dead time at high count rates), but these three are significant factors under most SPECT imaging conditions. Attenuation is the process whereby an emitted photon moving on a trajectory that would allow acceptance through the collimator undergoes a Compton interaction in body tissue and is deflected to a trajectory that is not accepted through the collimator. Scatter is a Compton interaction in body tissue with the opposite result: an emitted photon is deflected from a trajectory that would not allow acceptance to one that would. Thus attenuation removes counts from the detected image, whereas scatter adds counts, but adds them at the wrong position with respect to the point of emission. Detector response is the spatial blurring of image features, and its effect on SPECT quantitation is greatest for small features.

**Attenuation**

In most instances, attenuation has the greatest impact on SPECT quantitation and can result in order-of-magnitude errors if left uncorrected (4). This can be illustrated with the simple example of a point source at the center of a water-filled cylinder. For a 15-cm radius cylinder, the fraction of emissions (technetium 99m [99mTc]) not affected by attenuation is $e^{(-\mu \times 15)}$, where $\mu$ is the linear attenuation coefficient of water at 140 keV, or 0.151/cm. Thus attenuation results in almost a 90% decrease in reconstructed intensity at that point. For distributed sources, the effect is more complicated to analyze but can be illustrated with a slightly more complicated example: a uniform source distribution within the same cylinder. In this case, a profile through the resulting reconstructed image with and without attenuation correction is shown in Figure 12.1. As the figure shows, the reconstructed intensity without attenuation correction is erroneously small throughout the image but particularly so near the center of the cylinder. In more complicated (and more realistic) situations in which the body has nonuniform attenuating characteristics, more complicated artifacts result. The general trend still holds, however: deeper features are affected more by attenuation. Attenuation-correction methods are addressed later.

**Scatter**

Scatter effects are more difficult to analyze than attenuation effects, but they are much smaller in magnitude. Typically, scatter results in an approximate 30% increase in detected counts compared with an idealized case in which scatter was excluded. This percentage will vary with the size of the attenuating medium. Many scatter-correction methods have been proposed for SPECT. The methods vary greatly in the extent of physical modeling that is used; however, a relatively simple method has been shown to reduce scatter effects effectively (2). The method uses data acquired within a second, lower-energy window. These “scatter” data, after appropriate scaling, are assumed to represent the scatter component of the primary energy window data and are subtracted from the primary energy window data. Because this method uses two energy windows, it is often referred to as the "dual-energy window method."

**Detector Response**

Detector response, or finite spatial resolution, becomes an increasingly important factor in SPECT quantitation as the image feature size decreases. It is observed that for features smaller than approximately twice the spatial resolution of
The detector, the measured activity concentration decreases with the volume of the feature (3). The reason for this effect is that the detected counts in the SPECT image are spread across a larger region than that occupied by the emission source. Thus the measured concentration is necessarily reduced (see also Chapter 11). For larger sources, the spreading of counts away from a point in the SPECT image is balanced by the spreading into the point from surrounding areas of activity. Effective methods for detector-response correction involve linear deconvolution filtering with, for example, Wiener or Metz filters. An example of a Metz filter is shown in Figure 12.2. The filter exceeds unity gain at low spatial frequencies to deconvolve, or sharpen, the detector response blurring. The filter “rolls-off” to zero gain at high frequencies to control high-frequency image noise.

**Calibrating the SPECT Image**

In the ideal situation, after correcting for the effects of attenuation, scatter, and detector response, the intensity at each voxel in the SPECT image is the same as if it were an isolated point of activity in air. The final factor that needs to be considered, then, is the detector efficiency. The detector efficiency can be characterized by a calibration factor that relates the detected count rate to the emission count rate. The calibration can be performed by acquiring an image of a simple point source (syringe) of known activity in air. From the image, the total detected count rate is obtained, and this value is divided by the known activity. This calibration factor, with units of counts per second per activity unit, can then be applied to all subsequent SPECT images to obtain absolute quantitation.

One other calibration method deserves mention. In the special circumstance in which the entire distribution of injected radioactivity is contained within the SPECT image, one can use the injected dose for the calibration. The procedure for obtaining the activity in a local region of the SPECT image is to compute the ratio of the reconstructed counts in the region to the total counts in the SPECT image and multiply this ratio by the total injected dose. In this case, it is still necessary to perform attenuation, scatter, and spatial-resolution correction to the SPECT image to achieve an accurate relative-count distribution across the image, but a separate calibration scan is not required. A clinical example in which this approach can be applied is lung perfusion imaging. In this case, essentially all of the injected radiopharmaceutical, $^{99m}$Tc MAA (macroaggregated albumin), localizes in the capillary beds of the lungs.

**ATTENUATION CORRECTION IN SPECT**

The approaches to attenuation compensation in SPECT can be grouped into two categories: those that make the simplifying assumption that the body is composed of a uniformly attenuating medium (water) and those that consider the nonuniform attenuating nature of the body. A survey of these approaches is beyond the scope of this chapter, but an excellent review can be found in reference 4. In areas of the body where the tissue density is highly nonuniform (e.g., in the thoracic region because of the presence of the lungs, heart, ribs, and spine), the uniform density approximation approach can result in substantial quantitative inaccuracies and image artifacts.

Although methods have been suggested for compensating for nonuniform attenuation by using only the SPECT data, the more common approach is to measure the attenuation distribution by using CT techniques. Relatively recently, commercial systems have become available that combine SPECT and x-ray CT and provide attenuation correction from CT. The alternative to using x-ray CT is to use a radionuclide source. This technique typically has involved mounting a line source of radioactivity, or a set of line sources, to the gantry of the rotating SPECT camera at a point that allows transmission data to be acquired in an opposing detector. The measured transmission data are then reconstructed to obtain the nonuniform attenuation distribution used for correction within the SPECT reconstruction. Although CT-based attenuation correction of SPECT-CT is attractive because of the additional benefits the CT provides, radionuclide-based transmission data are certainly adequate for attenuation correction, and this method has historically been used for most quantitative SPECT development.

Two general designs for radionuclide transmission data acquisition on a SPECT camera have been used: (a) parallel-beam collimation with a scanning source (5) or multiple line sources (6–8) and (b) fan-beam collimation with a nonscanning line source (9–14) (see Fig. 4.8). The parallel-beam approach traditionally has been used to increase the limited field of view of the fan-beam geometry. The fan-beam approach has inherently greater spatial resolution and detection efficiency, and recently methods have been used to increase the effective field of view by using an offset fan-beam geometry (11,12,14). In addition to field of view,
spatial resolution, and detection efficiency, other important issues are involved in the design of a SPECT system with transmission correction. Two of these are the choice of the radionuclide for transmission correction and the issue of simultaneous versus sequential emission and transmission SPECT scanning. The radionuclide for transmission correction ideally should have a long half-life, be affordable, and emit at an energy that is relatively close to the SPECT radionuclide energy. In addition, the effect of cross-talk between emission and transmission data—confusing transmission photons for SPECT photons and vice versa—must be considered, and it should be assumed that the SPECT radionuclide will be distributed within the patient at the time of the transmission scan. To date, the most commonly used radionuclide for transmission scanning is gadolinium153 (153Ga; 100 keV), but other choices include tellurium 123m (123mTe; 159 keV), americium 241 (241Am; 60 keV), and cesium 139 (139Ce; 165 keV). In addition, x-rays from a conventional low-end–design CT mounted on the camera gantry can be used to provide data for attenuation correction. In this setup, the transmission data have a higher photon flux and thus can provide CT-quality images with detailed anatomic information (see Chapter 8). As for the issue of simultaneous versus sequential scanning, the former is more efficient, but cross-talk effects are of greater concern. The optimal systems design for a SPECT camera with transmission correction capabilities is still an unsettled question and one on which much research is being focused.

We have developed and evaluated a method for transmission imaging that uses a long focal length, offset fan-beam geometry, and a three-headed detector system (Fig. 12.3). Because we believe that the system can acquire adequate transmission data with a relatively short scan time (e.g., 2 minutes), our approach is to use two-step acquisition: a short simultaneous transmission–emission scan followed by a longer SPECT-only scan during which the transmission source is shielded. By using a transmission source (e.g., 123mTe or 139mCe) with greater emission energy than the SPECT emission source, cross-talk effects are effectively eliminated. During the transmission–emission scan, the detector nearest the transmission source must be fully retracted so it does not block the TCT beam (detector 2 in Fig. 12.3). Therefore, during the short scan, this detector is idle, while SPECT data are acquired in detector 3, and transmission data are acquired in detector 1. During the SPECT-only scan, detector 2 is moved close to the patient, and data are acquired in all three detectors.
The results of transmission imaging with this system are illustrated in Figure 12.4. The figure shows reconstructed transmission images from a patient. Short (2-minute) and long (14-minute) scans were performed. The long scan image again reveals the high spatial resolution of this system, and the short scan images demonstrate that good-quality transmission images can be obtained within clinically practical time constraints.

**Evaluation of Quantitative Accuracy**

One of the challenges in developing quantitative SPECT methods is to test them in realistic ways. The ultimate test of quantitative accuracy would be based on human images. Unfortunately, the true radioactivity concentrations are not known in humans. Therefore, phantoms are used, with the goal being to design phantoms that challenge the imaging system in the same ways as human subjects. A phantom study was performed to evaluate the accuracy of a commercially implemented CT-based attenuation correction for SPECT for a range of radionuclides with emission energies from 70 to 511 keV (15). In this study, identical bottles filled with the same radioactive solution were imaged simultaneously, one in air and one in the middle of a large phantom. Errors between ROI measurements of the reconstructed, attenuation-corrected bottles ranged from 6% to 12% for the different radionuclides. (Errors of 72% to 60% were present without correction.) This level of error should be expected for attenuation correction, with additional errors introduced by imperfect scatter correction and collimator blurring effects.

**Image Segmentation**

The final task in extracting quantitative values from SPECT images is to determine which pixels are of the tissue of interest. In this regard, SPECT is not different from other imaging modalities. Relatively low resolution, however, adds to the problem of defining edges, and automated, threshold-based techniques have the appeal of being objective and less operator dependent. SPECT-CT adds the possibility of using the CT to aid in defining the region of interest. It should be noted that with blurring it may not be desirable to identify and average all pixels within the tissue of interest. A more accurate measure of the tissue uptake concentration may come from using a small region not affected by the blurring at the region boundary.

**SUMMARY**

SPECT imaging has the potential for accurate quantitation of radionuclide concentrations. As with PET, multiple corrections and calibrations must be performed. Unlike PET, the vast majority of SPECT systems do not currently have the required capabilities for quantitation. The biggest obstacle is attenuation measurement and correction. If SPECT-CT becomes widespread, the potential will exist for quantitative SPECT to flourish.

**REFERENCES**

A Primer in Compartment Modeling

Cyrill Burger   Alfred Buck

The information contained in nuclear medicine images represents the average concentration of the tracer compound in tissue during the acquisition of the emission counts. If all distortions such as photon scatter or attenuation have been corrected for during image reconstruction, this concentration is quantitative in the sense that the amount of tracer per tissue volume is known. However, in most cases, tracer concentration cannot be directly transformed into a quantitative tissue parameter such as perfusion in milliliters per minute per 100 mL of tissue or receptor concentration in picomoles per milliliter. Prerequisites for absolute quantification are a suitable tracer, an optimized acquisition protocol, and an adequate data analysis procedure. Often compartment models are used to describe processes mathematically in living systems, including tracer uptake and metabolism (see Fig. 13.3). Different forms or spaces of tracer are distinguished (the “compartments”) between which material is continuously exchanged.

A classic example is the one-tissue compartment model that actually has two compartments: tracer in blood plasma and tracer in tissue. Exchange between these compartments occurs by tracer extraction into tissue, a perfusion- and endothelium-related process, and some backflux from tissue. Quantification then consists of adjusting the model parameters so that the tissue concentration predicted by the model based on the measured tracer concentration in arterial plasma optimally matches the tracer concentration in a tissue structure measured at different times during tracer uptake. The one-tissue compartment model can be refined by differentiating between distinct forms of tracer in tissue (free, nonspecifically bound, specifically bound). Although refined models are better able to describe the complex physiology, they require more unknown material transfers. More unknowns in matching a model to measured data of limited quality in general reduce the reliability of the results. The “art” of compartment modeling, therefore, is to find a model with the least number of parameters and the best information about significant tissue parameters.

INTRODUCTION

Imaging in nuclear medicine is based on the application of radioactively labeled compounds (tracers) that are distributed throughout the body by the vascular system and take part in physiologic processes according to the properties of the tracer molecule. Each tracer is designed to assess a specific property of tissue (e.g., perfusion, metabolic turnover, or the concentration of a specific receptor). To obtain optimal images, a protocol defines how the tracer is administered and at what timepoints single images or a sequence of images is acquired. The information contained in the images represents the average tracer concentration during the image acquisition, and in most cases it cannot be directly transformed into a quantitative parameter of the target process. For instance, “perfusion-weighted” images cannot be translated directly into images representing tissue perfusion in milliliters per minute per 100 mL of tissue.
Although functionally weighted images bear valuable diagnostic information, some situations require absolute quantification, such as therapy monitoring and group comparisons. Hence there is an interest in using nuclear medicine techniques for the quantitative assessment of tissue parameters not only for the scientific evaluation of tracer characteristics but also for clinical purposes.

The transformation of the measured data into absolute metabolic parameters is based on physiologic models, often compartment models. Hereby the relevant transport and uptake parameters are mathematically modeled and a prescription derived that predicts the tracer concentration in tissue given a measured plasma concentration. Quantification of the measurement then consists of solving the following inverse problem: Which model parameters predict the measured tissue concentration most closely? It must be possible to find a model that adequately describes the processes with a small number of parameters. Otherwise, with too many parameters in the model, there is a high chance that different parameter combinations will result in approximately the same predicted tissue response, and an optimization algorithm will then have difficulty finding a definite optimal solution. Whether such a model—one that is considerably simplified with respect to the underlying physiology—still provides valuable information is a question that must be answered for each tracer individually.

Compartment modeling has the following requirements:

- A tracer with favorable properties regarding distribution and uptake dynamics;
- Sampling of the tracer concentration in blood plasma (input curve) from the time of tracer administration until the end of image acquisition;
- Observation of the dynamic tracer distribution in tissue by a series of image acquisitions (Fig. 13.1); and
- Appropriate correction of the image information (e.g., attenuation correction) and conversion into absolute tracer concentration in becquerels per milliliter (as a result of which the time course of the tracer activity concentration [TAC, tissue time–activity curve] is available in each image pixel).

**COMPARTMENT MODELS**

To describe a physiologic system, it is often helpful to decompose it into a number of interacting subsystems, called *compartments*. Each compartment represents a homogeneous distribution of material and may exchange material with other compartments. Note that compartments...
should be understood not as a physical volume but rather as a mass of well-mixed material that behaves uniformly. Examples of frequently used compartments include these:

- Tracer in the arterial plasma that can be extracted into the tissue;
- Free tracer in tissue that can be bound or that may diffuse back into the blood;
- Tracer in tissue that has been nonspecifically bound to other than the targeted cell components; and
- Tracer in tissue that has been specifically bound, for instance, at the target receptor site.

Compartment models are visualized by diagrams in which the rectangles symbolize compartments and the arrows represent material exchange, as illustrated in Figure 13.2. Although the mechanisms of material transport may be diverse, models that can be reasonably analyzed with standard mathematical methods assume first-order processes. As a consequence, the change of tracer concentration in one of the compartments is a linear function of the concentrations in all other compartments. Put into mathematical terms,

$$\frac{dC_i}{dt} = f_i(C_A, C_1, C_2; \ldots)$$  \hspace{1cm} (1)

It is assumed that the observed system is not disturbed by the administration of the tracer. Because of the tiny amounts of tracer material applied in nuclear medicine investigations, this assumption is highly justified in most cases.

To illustrate the properties of compartment models, let us consider a tracer that is not freely diffusible and is injected intravenously as a bolus. When the tracer arrives at the heart, it is well mixed with blood and distributed by the arterial circulation. It finally arrives at the capillary bed, where exchange with the tissue can take place. Nonextracted tracer is transported back to the heart, from which a new circulation starts. This highly simplified "physiologic" model can be translated into a one-tissue compartment model, as illustrated in Figure 13.2A. It is assumed that, because of mixing, the arterial tracer concentration is the same throughout the body, so it can be measured in a peripheral artery. The tracer concentration in tissue increases by the extraction of tracer from the blood plasma, and as this is described by a first-order process, the transfer of material is proportional to the concentration in plasma $C_A(t)$. Conversely, it is reduced by a backward transfer, which is proportional to the concentration in tissue $C_i(t)$. Both processes compete, so the change over time of the net tracer concentration in tissue $(dC_i(t)/dt)$ can be expressed by the following differential equation:

$$\frac{dC_i(t)}{dt} = K_1 C_A(t) - k_2 C_i(t)$$  \hspace{1cm} (2)

The two transfer coefficients, $K_1$ and $k_2$, have a somewhat different meaning, indicated by using capital and small letters. $K_1$ includes a perfusion-dependent component and has units of milliliter per minute per milliliter of tissue, whereas $k_2$ [min$^{-1}$] indicates the fraction of mass transferred per unit of time. For example, if $k_2$ equals 0.1 [min$^{-1}$], the material leaves the compartment at a rate of 10% per minute. The plasma concentration $C_A(t)$ is not modeled but is considered a measured quantity and appears as the input curve driving the system.

By solving differential equation (2), the following equation for the concentration of tracer in tissue can be derived:

$$C_i(T) = K_1 C_A \otimes e^{-K_1 T} = K_1 \int_0^T C_A(t) e^{-K_1(T-t)} dt$$  \hspace{1cm} (3)

Hence, the time course of the tissue concentration essentially results from a convolution $\otimes$ of the input curve with a decaying exponential, and the convolution operation $\otimes$ is defined by the last term in the equation. $K_1$ acts as a scaling factor for the concentration course, whereas $k_2$ has an effect on its form.

The more complex models shown in Figure 13.2B,C distinguish different forms of tracer in tissue, which is usually interpreted as follows. After entering a cell, the tracer is available for binding in a free form at a concentration $C_1(t)$. From this form, it can directly be bound to its target molecule, $C_3(t)$, but it also may bind to some cell components that are not known in detail, $C_2(t)$. Considering these pathways, model C distinguishes three tissue compartments with six transfer coefficients, whereby $C_2$ and $C_3$...
communicate only by $C_1$. The system of differential equations can be derived in analogy to the one-tissue compartment model but is much more complex. The equations describing this model are given by

$$\frac{dC_1(t)}{dt} = k_1 C_1(t) - (k_2 + k_3 + k_4) C_1(t) + k_5 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_6 C_2(t)$$

This system contains six unknown parameters ($K_1$ to $K_4$) that are difficult to assess experimentally. For practical purposes, the system is therefore usually reduced to the simplified model B by treating free and nonspecifically bound tracer as a single compartment. This simplification is justified if the exchange free $\leftrightarrow$ nonspecific binding is significantly faster than the exchange free $\leftrightarrow$ specifically bound. Otherwise, specific and nonspecific binding cannot be distinguished, and the resulting transfer coefficients cannot be attributed to specific binding alone. The simplified two-tissue compartment model is given by

$$\frac{dC_1(t)}{dt} = k_1 C_1(t) - (k_2 + k_3 + k_4) C_1(t) + k_5 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_6 C_2(t)$$

By using a mathematical method called Laplace transformation, analytic solutions can be derived for linear multicomartment models, but the mathematical formulas for two compartments are already long. They show that $K_1$ represents a scaling factor like in the solution (Equation 3) given for the one-tissue compartment.

As mentioned earlier, $K_1$ is related to tissue perfusion $F$. With a capillary model, the relation

$$K_1 = EF \quad \text{(6)}$$

can be derived. $E$ represents the unidirectional first-pass extraction fraction (i.e., the fraction of tracer that penetrates the capillary wall and is extracted into the tissue during the first pass of tracer through the capillary). The reverse transport is not regarded in the calculation. Renkin (1) and Crone (2) calculated the extraction as

$$E = 1 - e^{-P S F} \quad \text{(7)}$$

where $P$ denotes permeability and $S$ the surface of the endothelium by which the capillary exchanges with the tissue. The relation demonstrates that the extraction depends on the properties of the endothelium with respect to the tracer ($PS$) as well as the perfusion $F$. The higher the perfusion, the smaller the extraction, because the average time spent close to the capillary wall decreases. However, total mass transport in general still increases with flow, as the reduced extraction is more than compensated for by the higher abundance of tracer ($F$ in the term $EF$ in Equation 6).

For tracers with very high permeability, the extraction is virtually independent of perfusion and approaches 1. In this case, $K_1$ equals perfusion according to (Equation 6).

### Fitting of Compartment Models to Measured Data

The aim of modeling a tracer is to characterize its properties (i.e., to find the structure of a suitable compartment model and to estimate the values of the transfer coefficients from measured data). To this end, an operational equation is formed as follows. The signals arising in emission measurements cannot be assigned to the different compartments. Therefore, the expected tracer concentration measured by, for example, positron emission tomography (PET) imaging, $C_M(t)$, for a specific volume consists of contributions from the capillary bed and from the different tissue compartments

$$C_M(t) = V_b C_A(t) + (1 - V_b) \sum C_i(t) \quad \text{(8)}$$

$V_b$ denotes the vascular fraction per volume and is ~5% for brain tissue. The instantaneous concentrations in the individual compartments, $C_i(t)$, are needed for evaluation (8). They can be calculated for a model configuration given a set of transfer coefficients and a known plasma concentration $C_A(t)$, either by numeric integration of the system of differential equations or by using an analytic solution. The task then consists of finding a set of transfer coefficients such that the operational equation $C_M(t)$ optimally matches the measured tracer concentration $C_M(t)$. To this end, the transfer coefficients are varied until the sum of squared residuals becomes minimal.

$$X^2 = \sum \frac{(C_M(t_i) - C_M(t_i))^2}{\sigma_i^2} = \text{Min} \quad \text{(9)}$$

The residuals in this expression are divided by the measurement variance $\sigma_i^2$ so that more reliable measurements have a higher impact on the optimization than do unreliable ones. In practice, however, the distribution of the measurement error is hardly ever known, so one often resorts to unweighted optimization with $\sigma_i^2 = \sigma^2$.

The compartmental analysis of measurements requires appropriate software that supports the following tasks:

- Simple specification of different compartment models;
- Calculation of the operational equation (i.e., the expected activity concentration given a set of transfer coefficients and the plasma concentration);
- Optimization of the cost function given by Equation 9 by systematic variation of the transfer coefficients; and
- Visualization of the residuals, because a trend in the residuals indicates that the chosen model does not explain the kinetics well enough.
Figure 13.3 illustrates the notions discussed so far by using commercial software dedicated to quantitative processing of data (PMOD Software, www.pmod.com).

**MODEL SIMPLIFICATION AND VERIFICATION**

Huang and Phelps (3) summarized the fundamentals of model development and assessment. They describe model development as a sequence of steps that starts with a comprehensive physiologic model and derives a simplified mathematical model whose significance for the application must be carefully assessed. The final step is the definition of protocols for both the data acquisition and the data processing so that the most accurate and detailed information can be obtained in patient studies. It is a general rule that more complex models allow a better fit to the measured data. At the same time, however, the number of approximate solutions increases. For compartment models, this means that transfer coefficients may vary significantly without major changes in the resulting model curve. This situation is commonly described by the term "low identifiability." Under such conditions, the transfer coefficients cannot be reliably assessed. As a general rule, one model should be applied that predicts the measurements with the least number of parameters. This is in line with a statement attributed to Einstein, who apparently once said that a model should be as simple as possible but not simpler!

Carson (4) described a statistical procedure for comparing models. In this procedure, the significance of the information gained by means of a more complex model with additional parameters is quantified on the basis of the F-statistics of $\chi^2$. In past years, it was found that because of the structure of the models and the limited signal-to-noise ratio, only simple models with one or two tissue compartments should be applied to PET and SPECT data. In practice, one deals with the questions whether a second tissue compartment has to be considered and what the lumped parameters really mean.
INTERPRETATION OF THE MODEL PARAMETERS

As outlined above, the configurations usable in kinetic modeling represent highly simplified models of the underlying physiology. Therefore, the question arises how the parameters obtained from model fitting can be related to the observed process. The answer depends highly on the kinetics of the tracer used, and only if a meaningful relation can be derived is the tracer useful for quantification. For receptor tracers, for example, it is important that the extraction from plasma into the tissue is sufficient so that the kinetics is not limited by perfusion. Additionally, the relation of the transfer coefficients for specific and nonspecific binding determines whether these different types of bindings can be distinguished. Often one must resort to considering the entire tracer concentration in tissue as an indicator of specific binding. The measure used in these cases is called the "total distribution volume" (DV) and can be computed by

\[
DV = \frac{K_1}{k_2} 1 \text{ - Compartment Model (A)}
\]

\[
DV = \frac{K_1}{k_2} \left( 1 + \frac{k_3}{k_4} \right) 2 \text{ - Compartment Model (B)}
\]

(10)

The distribution volume in general is defined as the ratio of the tracer concentration in tissue to that in plasma at equilibrium. A DV equal to 20 hence means that the tracer is being concentrated in tissue at a ratio of 20:1. The relation of other parameters in different models is elegantly recapitulated by Koeppe et al. (5).

Figure 13.4 Generation of images showing the total distribution volume (DV) by use of pixelwise Logan plots. The DV corresponds to the slope of the regression line fitted to the Logan-transformed time–activity curve.
**RELATED QUANTIFICATION METHODS**

**Graphical Methods**

Compartment models are valuable tools for modeling physiologic systems and simulating their behavior. When fitting experimental data, however, numeric instabilities may occur because of low structural identifiability and noisy data. To avoid these problems, numeric alternatives were developed that deliver less detailed information but are less prone to erroneous estimations. One class of methods comprises "graphical plots." These are based on certain integral transformations that smooth the noise contents. A regression line is fitted to the transformed data, and this in itself is a robust method. The two most frequently used representatives of this kind of data analysis are the Patlak plot (6) and the Logan plot (7). The Patlak plot requires the existence of an "irreversible" compartment (i.e., a binding of a tracer that cannot be reversed any more \( k_t = 0 \)). In this case, the slope of the regression line equals the rate of tracer uptake \( R_i \) into the irreversible compartment and is given by

\[
R_i = \frac{K_i k_t}{k_2 + k_3},
\]

The Patlak plot is ideally suited to the processing of FDG-PET data (8), because this glucose analog is irreversibly trapped in the cells. From the slope \( R_i \) the metabolic rate of glucose MRGlu can be quantified by the expression

\[
MRGlu = R_i \frac{\text{PG}}{\text{LC}}
\]

where \( \text{PG} \) denotes plasma glucose and \( \text{LC} \) (lumped constant) represents a correction to account for the slight difference in the uptake of the glucose analog. The Logan plot is complementary to the Patlak plot. It is applicable only in the absence of irreversible binding and yields the total distribution volume in tissue as the slope (Fig. 13.4).

**Reference Methods**

The requirement to draw and analyze blood samples throughout the acquisition in order to measure the plasma activity curve entails a severe practical difficulty for quantitative PET measurements. Therefore, methods have been sought to obviate the need for invasive blood sampling. The solutions found replace the arterial input curve by a sort of indirect input curve, namely, the time activity curve of a reference tissue, and are therefore called "reference methods." Reference methods are not able to provide a full kinetic analysis. However, assuming certain relations between the kinetics of the tissue of interest and the reference tissue, they are able to calculate a valuable measure of interest.

Most of these reference methods are dedicated to reversibly binding neuroreceptor tracers. A reference tissue is chosen that is devoid of receptors, and generally it is assumed that the distribution volume of the nondisplaceable compartment (free tracer in tissue and nonspecific binding) is the same in both tissues. Under these assumptions, a measure of the receptor concentration called "binding potential" can be calculated from the two time–activity curves. The reference methods differ in their mathematical approaches, and they show substantial differences with regard to noise sensitivity and processing speed. A method based on multilinear regression analysis developed by Ichise et al. (9) is noteworthy because it is fast and robust enough to calculate a binding potential estimate in single image pixels with minimal bias and variability.

**Pixelwise Models**

Because of the high noise level in dynamic nuclear medicine data, the signals must be averaged in homogeneous tissue volumes in order to apply compartmental analysis. With robust methods such as the graphical plots mentioned before, however, the signals from individual pixels can be analyzed with reasonable accuracy. Such pixelwise models provide absolute functional images, as illustrated in Figure 13.4 with the data from a measurement with the tracer carbon 11 \(^{11}\text{C}\)([+]MeN-5652) (10), which addresses the serotonergic receptor system. Structures with a high density of receptors have a high distribution volume and therefore are represented by the white areas in the slope images of the Logan plot.

**REFERENCES**

Making PET, PET-CT and SPECT-CT a Clinical Reality

SPECT and PET imaging require radiation sources and systems that can detect the radiation emanating from these sources. In Part I, the technical basis of PET-CT and SPECT-CT imaging systems was discussed. The other prerequisites for making these imaging examinations a clinical reality are discussed in Part II. These are the radiopharmaceuticals required for molecular imaging with PET and SPECT and the imaging protocols used to produce successful studies.

The emphasis in this book is on clinical applications of PET and SPECT. Currently, 90% of clinical PET uses FDG as a tracer. Still, the ensuing chapters are intended to give a somewhat broader perspective on the radiopharmaceuticals in clinical use and those with a definitive clinical potential. This book also discusses some uses of SPECT-CT. For SPECT-CT, the radiopharmaceuticals in use are more numerous, but again the most relevant radiopharmaceuticals that could benefit from SPECT-CT anatomic coregistration can be counted on two hands. Chapter 14 summarizes some of the important considerations regarding radiopharmaceuticals and their potentially desirable properties. Chapter 15 deals with the fluorinated PET compounds, which best lend themselves to distribution to satellite PET facilities. Chapter 16 discusses the perfusion radiopharmaceuticals that have established clinical utility, and Chapter 17 discusses the carbon 11 compounds, which have the obvious shortcoming of having a very short half-life. Finally, single photon compounds of clinical relevance for SPECT-CT are addressed in Chapter 18.
Some basic rules for the proper performance of PET-CT and SPECT-CT imaging have emerged over the last few years. These protocols are summarized in Chapters 19 and 20. It is worth perusing these chapters, as they indicate how physicians and technicians can avoid much unnecessary work and also avoid subjecting patients to unnecessary radiation exposure. Although some early PET-CT users advocated the use of CT contrast agents in all PET-CT examinations, we feel that this should be avoided if no additional clinical information can be gained. This is in keeping with the ALARA principle (see Chapter 9), which is relevant in PET-CT because the examination, if improperly performed, results in a sizable radiation exposure. As the use of SPECT-CT is less established, SPECT-CT protocols are less fully elaborated, and only some general guidelines can be given.
Designing good radiopharmaceuticals for imaging is a more difficult task than one might think. It is therefore not surprising that equipment manufacturers change the technology they offer almost on a yearly basis, while the introduction of a new radiopharmaceutical may take 5 years or more from its first appearance in the literature. In general, a contrast agent or radiopharmaceutical should provide high sensitivity, relatively high specificity, and low toxicity. Agents that are too specific are typically too costly for clinical use, as their development cost can be recovered from employing them with only a small number of patients. They nevertheless may eventually prove their value as we move into the age of personalized medicine, where such expensive tracers may prevent giving even more expensive drugs to a patient.

Although toxicity restrictions essentially do not exist for radiopharmaceuticals, many aspects of their design are still tricky. The number of radioisotopes available is limited, and the PET radiopharmaceuticals in widespread use will predominately be $^{18}$F based. Too short a half-life makes a radioisotope impractical for performing chemistry on it, too long a half-life leads to unacceptable radiation doses to the patient, particularly when part of the emission is in beta particles, as is the case in PET. Radiopharmaceuticals need to be relatively easy to synthesize and have good kinetic properties, binding strongly but not to strongly, for example, to the receptor intended for study (see Chapter 13). Furthermore, since only the label and not the pharmaceutical is seen in the nuclear imaging process, the radiopharmaceutical should not be metabolized extensively. It turns out that in regard to many of these issues FDG has excellent properties.

Nuclear imaging, be it conventional nuclear imaging or PET imaging, requires radiation sources in the form of radioisotopes alone or bound into biomolecules. These labeled biomolecules participate in physiological processes and thereby become “metabolic spies.” The “art” of radiopharmacy is thus to identify molecules that are suitable for labeling a given metabolic process, synthesize them reliably, and, in the case of PET, where the short half-lives of the radioisotopes drastically limit the time of their usefulness, synthesize them in the shortest possible time. This chapter outlines some general principles of contrast enhancement and discusses considerations regarding the design of radiopharmaceuticals.
BASIC PRINCIPLES OF CONTRAST ENHANCEMENT IN IMAGING

In general, external contrast enhancement in imaging is used to enhance the contrast between structures and their background. Except in the case of nuclear imaging, this enhancement is superimposed on the contrast already existing between various body structures (i.e., structures are already seen on the images), but the external contrast media make the structures more conspicuous. In nuclear imaging, the situation is completely different, in that the human body contains virtually no radioactivity. Thus, no structures in the body are seen without the administration of a nuclear contrast agent, which in nuclear imaging is called a “radiopharmaceutical.” The potential advantage of this unique situation is that a very high lesion-to-background or structure-to-background ratio can be achieved, typically causing the lesion or structure to be very conspicuous in the image. In nuclear imaging, the radiopharmaceutical provides the entire contrast; in the other medical imaging modalities, external contrast merely adds some contrast in most instances.

Radiopharmaceuticals also differ entirely from the contrast agents used in other imaging modalities in the dose range at which they have to be injected to produce adequate contrast in the images (see Table 1.1).

Whereas in ultrasound, CT, and MR, the concentration of contrast agents needed to affect the images is in the 1 mmol to the 10 µmol range, nuclear imaging operates at radiopharmaceutical concentrations 10,000, 10,000,000 times lower. (For the sake of completeness, optical imaging, whose properties are similar to those of nuclear imaging, is also listed in Table 1.1, but due to difficulties of transmission of light through the body, optical imaging is so far can only be used in small animal imaging experiments.) This difference in the effective concentration of contrast agents and radiopharmaceuticals is critical. In nuclear imaging, no physiological or pharmacological side effects are observed after the injection of a radiopharmaceutical, except in the rare case of extremely toxic receptor imaging agents. Thus, allergic and other reactions to radiopharmaceuticals are not observed. This is in stark contrast to the contrast agents used in other imaging modalities, where adverse reactions are known to occur after their injection. Consequently, most of the molecular mechanisms that can be targeted with radiopharmaceuticals are inaccessible to imaging with the contrast agents used in the other modalities. Thallium, which was in routine use in nuclear cardiology, is rat poison, but in myocardial perfusion scanning it was given at a concentration 50,000 times lower than the LD50. Compounds such as Tc-MIBI and Tc-Myoview could in principle also be labeled with gadolinium, but the resulting MR contrast agent would be too toxic for use. The same is true of fluorodeoxyglucose, as the stable $^{13}$F isotope is amenable to fluorine-MRI. Although it is possible to amplify the MR signal by using, for example, small ferrite particles linked to biomolecules, such complexes have very unfavorable accumulation biokinetics.

Thus, “molecular imaging” and “nuclear imaging” are currently synonymous in clinical practice. This is important to understand given the current “hype” about molecular imaging engulfing MRI.

Another important general principle concerns the specificity of contrast agents and radiopharmaceuticals. In principle, the ideal agent would be a “magic bullet” that specifically identifies a disease. Imagine an agent that when injected would show only bronchial carcinoma cells, but all of them. Unfortunately, creating such agents remains largely a dream. But in some cases developing very specific agents may be possible. The problem is their development cost. Developing a pharmaceutical agent—and contrast agents and radiopharmaceuticals are nothing but pharmaceutical agents—costs a lot of money. If that agent can only be used in a very small number of patients, the expense per patient will be large, as the development costs will have to be offset by very limited sales. It is therefore not surprising that companies providing contrast agents hesitate to invest their resources in the development of very specific agents.

This may change as regulatory agencies start to appreciate that, because of the differences in their toxicity profiles, radiopharmaceuticals requires much less scrutiny than the contrast agents used in other imaging modalities. As personalized medicine becomes a reality, some expensive imaging tests may become useful nevertheless. The cost of new personalized medicine therapies are in the tens of thousands of dollars, and so a radiopharmaceutical costing $3,000 per application may not be outrageously expensive if it can prevent the use of therapies predicted by the imaging study to have no beneficial effect.

The current reality is still the following. Rather nonspecific extracellular fluid x-ray and MR contrast media, as well as bubbles in ultrasonography, are currently in clinical use. The extracellular fluid contrast agents are widely usable and useful in imaging. In nuclear imaging, the same holds true. But in nuclear medicine and PET, radiopharmaceuticals with other molecular properties are also widely in use. One example consists of bone-seeking agents, which allow very sensitive but not very specific examinations of bone disease. A second example—possibly approaching the definition of the “ideal” radiopharmaceutical, as it is highly sensitive and relatively specific—is FDG, which is the radiopharmaceutical used in most PET applications described in this book. FDG is further discussed in the next section.

Exceptions to the rule that a contrast agent or radiopharmaceutical should be relatively unspecific so that it can be used widely are the technetium-based myocardial perfusion nuclear imaging agents. They are very specific but can be widely used because they are markers of the most widespread disease: coronary artery disease. But this disease is the only human disease that is very widespread and relatively nonheterogeneous. This is in contrast to tumor imaging, where ideally one would like to have a marker that is sensitive and very specific for each type of tumor. PET radiopharmaceuticals so far have not been developed by industry.
but rather by individual cyclotron or radiopharmacy units. A wide variety of them have been synthesized and tested in small patient groups. But as with other contrast agents and radiopharmaceuticals, getting such PET radiopharmaceuticals to a level where they can be introduced for widespread clinical use is very costly, and their introduction has to be considered carefully. This author’s guess is that the next PET radiopharmaceutical to become clinically mature will be F-choline or one of its derivatives.

SPECIFIC ISSUES REGARDING THE DESIGN OF CIADIOPHARMACEUTICALS

Radioisotopes

When considering a radioisotope as a potential label of a pharmaceutical for nuclear imaging, several conditions have to be met. First, the energy of the emitted gamma rays or x-rays during the decay process of the radioisotope should not be below 100 keV. The reason is that a sizable part of the radiation must leave the body: note that a technetium ray is reduced to half its intensity after traversing 15 mm of soft tissue! Second, the half-life of the isotope should be long enough to make imaging practical but short enough to minimize the radiation burden. Third and finally, the radioisotope should not emit beta or alpha particles during its decay, as the ionizing radiation results in a much higher radiation dose to the patient than gamma rays or x-rays (see Chapter 9).

Unfortunately, in PET imaging, the latter condition cannot be met, because the positron is a beta particle, and the largest fraction of the radiation burden in PET imaging (see Chapter 9) is due to the beta decay process and not to the annihilation photons relevant for detection in PET. Thus the requirement that the PET radioisotopes have a short half-life has to be stringently adhered to. Fortunately, the currently used isotopes $^{18}$C, $^{11}$N, $^{15}$O, and $^{18}$F all have half-lives that are shorter than 2 hours, leading to acceptable patient radiation doses (indeed, doses comparable to or less than those encountered in CT imaging). However, other positron-emitting radioisotopes with half-lives of days, such as $^{124}$I, cannot be considered candidates for diagnostic examinations, although they may eventually play a role in metabolic therapy.

Radiopharmaceuticals

The rules given above for designing good contrast agents apply to radiopharmaceuticals as well. A radiopharmaceutical should have a wide range of applications so it is not too costly per patient. On the other hand, it should not be overly nonspecific. Furthermore, in order to yield interpretable results, it should not be metabolized into many different daughter molecules. Here is not the place to analyze this in depth. This topic would be covered in a textbook on designing radiopharmaceuticals, but following is a brief account of some of the issues.

In order to be practical, we use FDG as a reference radiopharmaceutical. In many ways, FDG is an ideal radiopharmaceutical, which probably explains why it has become so successful. FDG has a wide range of applications: imaging for many frequent malignant tumors, inflammation imaging, and imaging of some major brain diseases such as dementia. Despite this wide range of applications, it is relatively specific: when looking for Alzheimer dementia, we are usually not concerned to find a tumor or an infection, and if we happen to find such a disease, the distribution pattern is different. Note that here morphology starts to play a role, as it helps to specify what metabolic process we are looking at. It turns out that in clinical practice the question of whether a lesion is a manifestation of tumor or infection does not frequently arise. Thus, FDG is highly sensitive and relatively specific. It certainly is more specific than the extracellular fluid agents used as contrast agents in CT and MR: those label all processes with hyperemia and hyperperfusion, and there are many diseases other than tumors and inflammatory processes that present with these characteristics. Also, probably the most successful conventional radiopharmaceuticals, the bone-seeking phosphonates, are clearly less specific than FDG but are still reasonably good agents. There are more specific radiopharmaceuticals, octreotide and MIBG, but they are more costly to prepare than FDG—the price of their specificity. The experience with $^{18}$F-labeled tyrosine suggests that it may be more specific than FDG, as it is not as avidly taken up into inflammatory cells, but unfortunately it appears to be less sensitive than FDG. In looking for tumor metastases, this is clearly a major disadvantage, although it may not be so in brain imaging, where FDG is also not very sensitive because of the relatively poor cortex-to-lesion contrast (FDG accumulates strongly in the cerebral cortex). Another fluorine-based label that has become a major focus of interest is $^{18}$F choline and other choline analogs. The compound is probably as specific or unspecific as FDG. However, it accumulates well in prostate cancer, which FDG does not. On the other hand, it accumulates strongly in the liver, which makes it less suitable for malignant tumors with a preponderance for liver metastases.

Designing more specific radiopharmaceuticals than FDG is difficult. One very useful characteristic of FDG is that it is only 6-phosphorylated when in a cell but is not further metabolized. Hence, activity in a PET scan corresponds to FDG-6P and nothing else. This makes image interpretation relatively simple. Another critical aspect has to do with the affinity of the radiopharmaceutical for a specific process. If we aim, for example, at labeling a dopamine receptor in the brain, this is more difficult than it appears at first sight. If we find an agent that has a very high affinity for the receptors under consideration, this agent will saturate all receptors during the first pass through the brain. A compartment model analysis (Chapter 13) will demonstrate that this is not desirable: it is important that the label comes off the receptors at a reasonable rate. Why is this so? If upon first pass all the radiopharmaceutical sticks to the receptors, it is
an excellent perfusion agent, extracted during first pass very much like macroaggregates of albumin are extracted upon first pass in the lungs. On the other hand, if the radiopharmaceutical comes off too fast, it will not be suitable for labeling the dopamine receptors. Thus, the radiopharmaceutical needs to have just the “right” properties, where “right” is defined by what exactly one desires to see.

In summary, finding the “right” contrast agents is a difficult task even when toxicity is not an issue, as in radiopharmaceuticals, which are given at very low concentrations. This may be an important reason why not many interesting contrast agents and radiopharmaceuticals are available to label specific processes at a reasonable cost.

With the increasing interest in clinical PET and the much less stringent toxicity restrictions on radiopharmaceuticals compared with other contrast agents, the situation may change, and an increasing variety of clinically relevant radiopharmaceuticals may eventually appear. We are eagerly awaiting this. The following chapters discuss some of the clinical or clinically promising radiopharmaceuticals. Since widespread use of PET radiopharmaceuticals requires that they be labeled with $^{18}$F, special emphasis is placed on such radiopharmaceuticals (see Chapter 15). The other relevant PET radiopharmaceuticals are discussed in Chapters 16 and 17, and the current spectrum of SPECT radiopharmaceuticals is summed up in Chapter 18.
INTRODUCTION

The availability of radiopharmaceuticals labeled with fluorine-18 ($^{18}$F) has made possible the widespread clinical use of PET. The chemical and nuclidic properties of $^{18}$F have led to a steady increase in the number of tracers concomitant with the increase in the variety of biochemical and pharmacological principles applied in molecular imaging. Various reviews have appeared recently describing the preparation of $^{18}$F radiopharmaceuticals and those being presently established. It is clear that the most relevant fluorinated radiopharmaceutical is fluorodeoxyglucose (FDG), as amply documented in this book. It can now be produced consistently and reliably at 40 to 60 GBq (1 to 1.5 Ci) per batch and is being widely distributed; the only limitation for distribution is its short half-life of $\sim$110 minutes. However, additional fluorinated compounds are now available as potent diagnostic tracers for tumor imaging, such as $^{18}$FDOPA, $^{18}$FLT, and $^{18}$FET (Fig. 15.1), and for the diagnosis of receptor systems. Several selected new $^{18}$F-tracers with possible further diagnostic applications in the brain and heart and for tumor imaging are also discussed.

THE RADIONUCLIDE $^{18}$F AS A LABEL

$^{18}$F is the most important radionuclide for PET imaging besides carbon-11, and in the form of $[^{18}\text{F}]$FDG it is the most often used in clinical studies. Whereas carbon-11 allows authentic labeling of biomolecules and pharmaceuticals, as well as repetitive studies (often for therapy control), because of its short half-life of 20.4 minutes, the decay properties of $^{18}$F provide different advantages. The low energy (635 keV) of the emitted $\beta^-$-particle allows the highest spatial resolution among all PET radionuclides. Here the border of 1 mm
is attained with recently introduced small-animal PET scanners (4). The relatively longer half-life of 109.8 minutes offers the possibility of extended synthetic procedures and of following slower tracer kinetics of 6 hours or less. Thus, the time frame of study protocols is much less severe, with advantages for a clinical setting. Above all, 18F-labeled tracers can be provided to clinical services without a cyclotron, according to the so-called PET satellite concept.

Tagging a molecule with 18F in place of a hydrogen atom almost does not change its steric shape, and in general metabolically stable compounds are obtained. Its electronic influence, however, renders an analogous compound with changed physicochemical properties and with possibly altered biochemical, pharmacological, and toxicological features. This necessitates an evaluation of new 18F-labeled compounds with respect to their anticipated use as in vivo radiopharmaceuticals.

**PRINCIPAL RADIOFLUORINATION METHODS**

18F can be produced in good yields, even with modern low-energy medical cyclotrons (5). Quantities of greater than 150 GBq of 18F can be produced through the (p,n) nuclear reaction on enriched oxygen-18 (18O) at proton energies of less than 15 MeV. Most often [18O]water is used as target material, from which [18F]fluoride is obtained with a high specific activity of greater than 500 GBq/μmol. There is now no other practical way to produce the radionuclide in electrophilic form, besides adding elemental fluorine, but this limits the specific activity to less than 1 GBq/μmol. Thus, despite many new methodological improvements and various new pathways, the principal features of no-carrier-added (nca) radiofluorination, continuously reviewed over the last 20 years, are still valid (1,6–9).

Thus nucleophilic substitution with nca [18F]fluoride is still the only practical way to obtain labeled products with high specific activity. This is always necessary if a mass action of established radiopharmaceuticals or new tracers under development would lead to pharmacodynamic or toxic effects and hamper the tracer signal, especially in cases of low concentrations of the target molecules, as with receptors or enzymes (cf. ref. 10). For tagging 18F to aliphatic carbon, nucleophilic substitution is the method of choice, and various leaving groups for replacement are known for effective labeling. This also is true for activated aromatic derivatives (i.e. those that bear electron-withdrawing groups in addition to good leaving groups on the benzene ring). If electron-rich aromatic compounds have to be radiofluorinated on an nca level, electrophilic substitution is excluded, and products must be built up by multi-step synthetic procedures starting from a simple nca [18F]fluorobenzene derivative. This is generally tedious, makes automation difficult, and often hinders broad clinical use of a potent compound. For this purpose, however, many versatile nca 18F-labeled synthons have been developed (1,8,9).

As another alternative, prosthetic group labeling can often be used. In this method, a small functionalized nca [18F]fluoroalkyl or -aryl group is tagged to a target molecule of higher molecular mass. It is the method of choice for radiofluorination of oligomeric compounds like nucleotides (11) and especially peptides and proteins, as recently reviewed (12). It is also receiving increased interest as exemplified for markers of angiogenesis (13) and somatostatin receptors (14).
ESTABLISHED ¹⁸F-RADIOPHARMACEUTICALS

From the several hundred ¹⁸F-labeled tracers prepared for PET over the last 3 decades, only a few actually have reached the status of "established" ¹⁸F-radiopharmaceutical (Fig. 15.2). None has attained the importance and frequency of use of 2-[¹⁸F]fluoro-2-deoxy-D-glucose (¹⁸FDG), which is therefore referred to as the "work horse" of PET. Since its first proof as an indicator of energy metabolism (glucose consumption) (15), the number of indications for which it is a useful diagnostic compound have steadily increased, especially in oncology (16,17). Recently a complete compilation of the ¹⁸FDG-PET literature has been published (18).

A key prerequisite for the broad routine application of a radiopharmaceutical is its general availability (i.e. there must be a reliable radiochemical method of preparation). First developments of electrophilic labeling methods did not deliver ¹⁸FDG in high activity, and only a stereochemically impure product was available. Through the introduction of a nucleophilic nca radiofluorination on a tetraacetylmannose triflate precursor (19), the pure 2-fluorodesoxyglucose became available in batch yields of 40 GBq or more. This method has been in use now for 20 years, with small improvements, especially a switch to basic hydrolysis of protecting groups (20,21). Thus ¹⁸FDG became the first PET radiopharmaceutical licensed in many countries. For a recent review on ¹⁸F-labeling of sugars, see Beuthien (22). The availability of this important diagnostic compound was and is the basis for the worldwide establishment of clinical PET.

The other established radiopharmaceuticals fall short in comparison with ¹⁸FDG because they are appropriate for a much more limited number of clinical indications and in many cases lack availability (i.e. ease of radiosynthesis). The latter shortcoming does not apply to nca ¹⁸F-fluoride, which only must be transferred upon its production in a ¹⁸O-water target to an isotonic injectable solution. The chemically most stable form of fluorine, its anion, represents (as ¹⁸FNaF) a radiopharmaceutical for bone imaging, as suggested 30 years ago (23,24). After ¹⁸FDG and 6-[¹⁸F]fluoro-L-dopa (¹⁸FDOPA), it ranks third in frequency of clinical use and is specifically employed for detection of bone metastases.

In contrast to ¹⁸FDG, ¹⁸FDOPA and 5-[¹⁸F]fluorouracil (5-FU) are generally still produced by electrophilic methods, with the disadvantage of relatively small batch yields and limited availability. The chemotherapeutic analog 5-FU is produced by an addition–elimination sequence of

Figure 15.2  Established ¹⁸F-radiopharmaceuticals.
electrophilic fluorine species on dihydouracil (25). It is used for therapy control (26) and has been discussed as a means of predicting therapy response in liver metabolism in patients with colorectal carcinoma (27). Although nucleophilic procedures were established for the routine production of $^{18}$FDOPA, they are difficult to implement because of multi-step radiosyntheses. Most efforts were devoted to improve the carrier-added (ca) electrophilic radiofluorination. To date, a fluordeoxynililation reaction (28) appears to be the best option for regioselective labeling with satisfactory yields. This allowed automation (29), and recent improvements in precursor preparation and quality control (30) ensure reliable production for in-house application.

After introduction of $^{18}$FDOPA (31), it became a well-established tracer for studying presynaptic integrity of dopaminergic innervation, mainly in Parkinson disease (32,33). Although the uptake of $^{18}$F-labeled DOPA in melanomas has been known for 15 years, it has only recently found applications in oncology, with great promise as complementary tracer to $^{18}$FDG (for review, see ref. 3). In neuroendocrine tumors, for example, it has been shown to be superior to somastatin receptor scintigraphy (34). The report of a carcinoid crisis induced by $^{18}$FDOPA points to the necessity of a practical nca labeling method for this tracer (35).

Generally, tumor accumulation of amino acids is dominated by transport much more than by protein synthesis. Thus various attempts were aimed at $^{18}$F-labeled amino acid analogs specific for different transporter systems; for reviews on $^{18}$F-fluoroamino acids, see refs. 36 and 37. The most potent one appears to be O-(2-$^{18}$F)fluoroethyl-L-tyrosine (FET), which was first prepared using a two-step fluoroalkylation method (38) but can now be produced using direct substitution, one-pot synthesis, with high batch yields like $^{18}$FDG for broader clinical use (39). Besides the logistic advantages, it was found not to accumulate in inflammatory tissue like $^{18}$FDG (40) or methionine (41), although it shares a similar amino acid transporter profile. Above all, biopsy samples of human gliomas have proved that in cases of FET-PET and MRI mismatch the amino acid indicated the solid tumor with high specificity (42) (see Fig. 15.1). Meanwhile, it has led to convincing results, especially in the diagnosis of brain tumors, suggesting perspectives as a clinical standard tracer (43).

Based on the findings from imaging prostate cancer with $^{11}$C[18]Choline, $^{18}$F-fluorocholine was prepared and shown in initial patient studies to detect prostate cancer and metastases thereof clearly (44). Because the radiosynthesis involved intermediate gas chromatographic purification steps, the $^{18}$F-fluoroethyl analog was also prepared. Although poorer biologic compatibility was found in in vitro cell experiments (45), it proved very effective for detecting prostate cancer with PET (46). The biodistribution of both compounds is very similar to that of $^{11}$C[18]Choline, but their urinary excretion is much more rapid, demanding appropriate imaging protocols (Chapter 49) or bladder catheterization (45). $^{18}$F-fluorocholine seems advantageous and is also detected in intracranial lesions (47).

Another very promising tracer for tumor imaging is 3-deoxy-3-$^{18}$F-fluorothymidine ($^{18}$FLT), as it is an indicator of cell proliferation (48), is stable in vivo, and is a false substrate of thymidine kinase. Whereas the first nucleophilic nca synthesis starting from an anhydro precursor had low radiochemical yields, a new precursor allows better and reliable radiosynthetic results, thus improving clinical availability (49). Accumulation of the compound in normal proliferating tissue is a drawback with respect to bone marrow dosimetry, as this compound accumulates strongly in the hematopoietic bone marrow. Conversely, FLT scans may thus permit control of the action of chemotherapy on critical organs. Based on recent findings, this radiotracer shows clinical suitability (2,50,51) in comparison with $^{18}$FDG (52) and $^{11}$C[18]Thymidin (53).

A high specific activity of the radiopharmaceutical is an absolute necessity for imaging of receptors because of their low concentration (see ref. 10). This requirement has been met for several radioligands of central and peripheral neurotransmission systems by using nca nucleophilic substitution procedures. Examples for the 5-HT$_{2A}$ serotonin receptor are $[^{18}$F]setoperone and $[^{18}$F]altanserin, with the latter more widely accepted (54–56). Both ligands are prepared from the nitro-substituted precursor, with good radiochemical yields (54,57,58). A database on the binding of $[^{18}$F]altanserin to 5-HT$_{2A}$ receptors was recently constructed using normal volunteers (59).

Fluoroalkylated butyrophenones, such as N-(2-[$^{18}$F]fluoroethyl)psiperone (60), are useful for monitoring 5-HT$_{2A}$ in the frontal cortex as well as D$_{2}$ dopamine receptors in the striatum (61), but they are of minor use compared with the corresponding $^{11}$C-labeled ligands. Fluoroalkylation of these and other tracers was developed as an alternative to multi-step radiosyntheses to meet the nca requirements of radioligands. With the advent of improved labeling conditions with nca $^{18}$F in the authentic position of butyrophenones (62), other derivatives have become available (e.g., N-methyl-[$^{18}$F]-benperidol) that exhibit specific and reversible binding to D$_{2}$ receptors (63).

Another established radiopharmaceutical, $[^{18}$F]fluoromisonidazole, is finding increasing clinical use. It is used as indicator of hypoxic tissue (64,65), although it suffers somewhat from slow uptake kinetics and high background. In contrast to earlier syntheses, however, a one-pot substitution reaction with high radiochemical yield makes this tumor tracer widely available (66). It has proved useful for delineating hypoxia in various tumor entities and for showing the relevance of hypoxia in radiotherapy (3,67,68). $[^{18}$F]fluoro-6-thia-heptadecanoic acid ($^{18}$FTHIA), used for the assessment of the myocardial activity of free fatty acids (69) and skeletal muscle uptake (70), has only limited application.
Many newer potent \(^{18}\text{F}\)-labeled compounds are not yet fully established for clinical use but are being tested in initial or extended human PET studies (Fig. 15.3). Some compounds, such as derivatives of tyrosine, underwent preclinical evaluation and had promising results in the first patient studies but have not found a broader application. Among these, 4- and 6-\(^{18}\text{F}\)fluoro-meta-L-tyrosines are to be mentioned; like \(^{18}\text{F}\)FDOPA, they are easily prepared by electrophilic fluorination (71) and serve the same purpose of measuring the presynaptic integrity of dopaminergic neurons. Although they do not exhibit fast metabolism in plasma or storage in vesicles, in contrast to \(^{18}\text{F}\)FDOPA (72,73), the 6-isomer in particular was shown to be a selective indicator of aromatic amino acid decarboxylase (74); however, it is not generally accepted in clinical practice.

In contrast, 6-\(^{18}\text{F}\)fluorodopamine does not penetrate the blood-brain barrier but lends itself to the monitoring of cardiac sympathetic innervation, as recently demonstrated (75). The most efficient method described for its preparation uses direct electrophilic fluorination of dopamine (76); however, a nca but more tedious multi-step procedure (77) appears advantageous with respect to the toxicity of 6-fluorodopamine.

In the case of 2-\(^{18}\text{F}\)fluoro-L-tyrosine, which is a tracer of amino acid transport and protein synthesis in brain tumors (78,79), its broader use was hampered by the low yield of its electrophilic synthesis. Also, in comparison with \(^{18}\text{F}\)FDG it falls short in the diagnosis of peripheral tumors (80). As mentioned above, many more \(^{18}\text{F}\)-labeled amino acids are being clinically evaluated (for review, see refs. 2, 3, 37, and 81), some of which show potential for special indications. In this context, the surprising preferred stereoselective transport of the D-isomer of cis-4-\(^{18}\text{F}\)fluoro-proline at the brain-brain barrier is of special interest (82).

For newer radioligands of several neurotransmitter systems, direct or multi-step radiosyntheses were developed to ensure both high specific activities and high batch yields for clinical evaluation. Among the newer radioligands, \(^{18}\text{F}\)cyclofoxy (6-deoxy-6-\(\beta\)-\(^{18}\text{F}\)-fluoronaltrexone), an antagonist of opiate \(\mu\) and \(\kappa\) receptors, is almost an established radiopharmaceutical. Besides being used for epilepsy (83), it is being examined for clinical use in Alzheimer disease (84,85) and heroin addiction (86), for example. The radiosynthesis is based on nucleophilic substitution in a protected triflate precursor (85).

A newer \(^{18}\text{F}\)-ligand is the xanthine derivative \(^{18}\text{F}\)-CPFPX, which appears as the first functioning PET ligand for purinergic receptors. In vitro and ex vivo experiments in rodents and baboons proved that it has a high affinity and
specificity for the A1-adenosine subtype (87). Human PET studies delineated an uptake pattern in normal brain in agreement with the known cerebral distribution of A1 adenosine receptors (88,89), which can be quantified with a standard three-tissue compartment (90). Given the broad range of indications with proven and suspected involvement of adenosine receptors (91), this radioligand may find wide application, as demonstrated with Huntington disease (Fig. 15.4; comparable FDG images are presented in Fig. 26.8).

As an 18F-labeled analog of the selective 5-HT1A ligand WAY-100635, the para-[18F]fluorophenyl derivative [18F]MPPF was developed by using again a nucleophilic aromatic substitution of a nitro group, with approximately 25% radiochemical yield (92), and preclinical evaluation in rodents and in monkeys has been summarized (93). Although the uptake and signal-to-noise ratio are smaller than those of the original 11C-compound, [18F]MPPF proved useful for quantification of the 5-HT1A receptor distribution in humans (94,95) and exhibits the logistic advantages of fluorine-18.

Under intense clinical evaluation is [18F]fallypride, a newer high-affinity dopamine D2 18F-ligand suitable for measuring both striatal and extrastriatal receptors. It has been effectively prepared (96) and evaluated in rodents and monkeys (97). A recent PET study on healthy subjects pointed to comparable results with this radioligand, its desmethoxy-congener, and [11C]raclopride (98). For imaging of the nicotine acetylcholine receptors (nAChRs), the most promising ligands appear to be the 2-isomer and 6-isomer of [18F]fluoro-3-[2(S)-2-azetidinyl-methoxy]-pyridine ([18F]A-85380), which are readily prepared by nucleophilic substitution (99,100). Because the compound is much less toxic than 18F-derivatives of epibatidine, developed for the same purpose, the 2-isomer in particular holds great potential (99,101), which was confirmed in
recent PET studies in Alzheimer patients and controls (102, 103).

NEW POTENTIAL 18F TRACERS

Especially in the field of tracer development, several new radioligands are already or close to being used in human applications (Fig. 15.5). Here the ongoing development of radiohalogenated estrogen ligands such as 16α-[18F]fluoro-17β-estradiol ([18F]FEES) (104) should be mentioned. Complementary to receptor ligands, those for reuptake transporters of the neurotransmitters are of great interest, and a recent review summarized both types of tracers (105). Especially many 18F-ligands are based on the tropone structure, such as [18F]FP-β-CIT (106) and [18F]FECNT (107), used for imaging the dopamine transporter. However, many more ligands are under development in order to find the most suitable candidate. This is even more true for serotonin reuptake transporters, although high affinities for the derivatives [18F]ACF (108) and [18F]AFB (109) were recently reported.

Improved alternatives are being sought for misonidazole, such as [18F]EF5 (110) and [18F]fluoroazomycin arabinoside ([18F]FARA) (111), as new hypoxic cell markers. Especially the latter showed improved properties over 18F-MISO (112) and is easily available by nca nucleophilic substitution, while [18F]EF5 demands an electrophilic ca method of preparation. Similarly, compared with [18F]fluorodopamine, 4-[18F]fluorometaraminol exhibits improved properties for monitoring myocardial innervation (113), but it lacks a simple preparation method (114).

A completely new field is opened by tracers for imaging of amyloid plaques in Alzheimer disease, such as [18F]FDDNP, already tested in first PET studies on patients and controls (115), and intense research is going on (2), with promising results, using 18F-labeled stilbenes (116). Another new field of research concentrates on the imaging of reporter gene expression, such as the false nucleoside 8-[[18F]fluoroganciclovir for the thymidine kinase (HSV1-tk) (for reviews, see refs. 2 and 117). Although the research is just beginning, this field is an encouraging example of the use of physiological concepts like angiogenesis (113,118) and apoptosis (119) in 18F-tracer development for research and clinical application.

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Molecular Anatomical Imaging


Cerebral and cardiac perfusion studies by PET provide quantitative measurements and permit assessment of perfusion abnormalities in patients with cerebrovascular and cardiovascular disease. Regional cerebral blood flow measurements with PET also are useful in the evaluation of new drugs. Oxygen 15–labeled water ($^{15}$O)water), nitrogen 13–labeled ammonia ($^{13}$N)ammonia), and rubidium 82 ($^{82}$Rb) are the most common PET tracers used in clinical routine for perfusion measurements. These PET imaging agents are taken up in the cells of normal myocardium or brain in relation to blood supply. In practice, studies using these radiopharmaceuticals require repeated measurements in the same individual and during the same experimental session. Whereas $^{15}$O and $^{13}$N are produced by cyclotron irradiation of appropriate target materials, $^{82}$Rb is generator produced and thus does not require an on-site cyclotron. Other generator products are copper 62 ($^{62}$Cu) and gallium 68 ($^{68}$Ga). They may be of interest as labels of various compounds. Clinically most relevant is probably $^{68}$Ga-OTATOC and similar compounds, which serve as markers of endocrine active tumors such as carcinoids and may eventually replace $^{111}$In-octreotide.
**[13N]AMMONIA: RADIONUCLIDE PRODUCTION AND SYNTHESIS**

Nitrogen 13 (13N; T1/2, 10 minutes) is produced by bombarding a natural water target with 16.5-MeV protons via the nuclear reaction 16O(p,α)13N. The target material is usually aluminum, but targets made of nickel or titanium also are in use. Of all the [13N]-labeled radiopharmaceuticals, [13N]ammonia is the most commonly used agent for PET studies. There are two methods for its production. In the first method, the 13N-labeled nitrates/nitrates formed by proton irradiation of water are reduced by either titanium (III) chloride, titanium (III) hydroxide, or DeVarda’s alloy in alkaline medium (1). After distillation, trapping, and sterile filtration, the [13N]ammonia is ready for clinical application. In the second method, oxidation of 13N to [13N]nitrates/nitrates is prevented in situ by the addition of ethanol as free radical scavenger to the target content (2). The target content is transferred to a small cation-exchange column to trap [13N]ammonium ions. A final injectable solution of [13N]ammonia is obtained upon eluting with saline and after passage through a sterile filter.

**[15O]WATER: RADIONUCLIDE PRODUCTION AND RADIOISYNTHESIS**

A number of nuclear reactions are used for the production of 15O (T1/2, 2 minutes), but the 14N(d,n)15O is most widely used (3). The energy of the deuterons lies in the range of 8 to 10 MeV, and the target material is aluminum. The target content is a mixture of nitrogen and 0.2% to 1% of oxygen. The 15O atoms formed react with the carrier oxygen to give [15O]O2. The 15O-labeled water then is produced by reacting hydrogen with [15O]O2 over a palladium–alumina catalyst at 200°C. The [15O]water vapor formed is trapped in sterile isotonic saline by bubbling the solution with nitrogen as carrier gas.

**82RB: RADIONUCLIDE PRODUCTION AND RADIOISYNTHESIS**

Rubidium 82 (82Rb; T1/2, 75 seconds), a monovalent cationic analog of potassium, is a generator-produced radionuclide, and as such its production does not require an on-site cyclotron. In the strontium 82 (82Sr)-82Rb generator system, the 82Sr has a half-life of 25.5 days and decays to 82Rb by electron capture. 82Sr belongs to the second group of elements in the periodic table and is a divalent cation. The difference in the charge number between 82Sr and 82Rb and their particular chemical properties lead to a rather simple separation technique. The preferred method, which produces by far the largest quantities of 82Sr, is the spallation of molybdenum by using high-energy accelerators (4). The 82Sr is loaded on a SnO2 column and eluted every 15 minutes with saline. Due to the ultrashort half-life of 82Rb, it is almost impossible to elute the generator, collect the eluate, and inject it by means of a syringe into a patient. Consequently, only a direct infusion of the eluate is feasible. The infusion system needed for this process has to fulfill several requirements. The activity, flow, and pressure of the eluate must be measured and controlled. Safety tests, including calibration and validation of all components, must be done on a regular basis to make sure that the infusion system always works properly. An excessive pressure in the infusion system might lead to injury of the patient, too-low activity might lead to poor-quality PET studies, and too-high activity might subject the patient to unnecessary radiation exposure.

The cost of the infusion equipment is around $55,000 and that of a single generator around $30,000, with additional supplies and a service contract estimated at a total of $10,000 per year. The suggested life span of a single generator is around 1 month; thus, ascertaining the permanent availability of radionuclide requires the purchase of 12 generators per year. This is only a feasible proposition when the generator is used in a high-throughput cardiac environment. The 82Sr-82Rb generator system (Cardiogen-82) is commercially available from Bracco Diagnostics, Princeton, NJ.

**OTHER GENERATOR PRODUCTS OF CLINICAL RELEVANCE**

Other positron-emitting diagnostic nuclides that are generator produced and have found application in the clinical environment as diagnostic nuclides are gallium 68 (68Ga) and copper 62 (62Cu). In the 68Ge-68Ga generator system, 68Ge has a physical half-life of 271 days and 68Ga 68 min. The generator is made up of alumina loaded in a glass column. The 68Ga is eluted from the column with 0.005 M EDTA or 1 M HCl when 68Ge is absorbed on a stannous dioxide column. When, however, the 68Ga is eluted with EDTA, prior dissociation of the 68Ga-EDTA complex is necessary provided 68Ga-EDTA is not the desired radiopharmaceutical. 68Ga-EDTA is used mainly for brain tumor imaging. Octreotide has been labeled with 68Ga (5), and the first clinical results are promising (Chapter 43), but more work is needed before 68Ga-octreotide can be used as a routine clinical diagnostic agent.

62Zn, with a half-life of 9.3 hours, decays to 62Cu (T1/2 = 9.7 minutes) by electron capture. In this generator system, 62Zn is loaded on a Dowex 1 × 10 anion exchange column, and the 62Cu is eluted with 2 M HCl. Because of the short physical half-life of 62Zn, the generator is prepared and shipped on a daily basis. Two well-known copper 62 radiopharmaceuticals are 62Cu-ATSM [diacetyl-bis(N4-methylthiosemicarbazone)] and 62Cu-PTSM [pyruvaldehyde-bis(N4-methylthiosemicarbazone)]. Whereas 62Cu-ATSM is being used as a hypoxia imaging agent (6), 62Cu-PTSM has found application as a myocardial and brain perfusion PET imaging agent (7).
QUALITY CONTROL OF THE RADIOPHARMACEUTICALS

Because of the short physical half-lives of $^{15}$O, $^{13}$N, $^{82}$Rb, $^{62}$Cu, and $^{68}$Ga, there are some inherent limitations in performing all the necessary quality control tests formulated in USP, European, or local pharmacopoeia before the radioligands are administered to humans. Tests such as sterility and pyrogenicity are normally verified after administration but are inherently assured by performing the syntheses according to rigorous established standard procedures. Isotonicity; radionuclide, chemical, and radiochemical purity; and pH are integrated in the production process by appropriately controlling the nuclide production, purification, and formulation steps so that these aspects of quality control are monitored before application.

REFERENCES


\[ ^{11}\text{C}\text{-Based PET-}\]

Radiopharmaceuticals of Clinical Value

Kjell Någren  Christer Halldin

Positron emission tomography (PET) imaging with carbon 11 (\(^{11}\text{C}\)) radiopharmaceuticals is challenging because of the short half-life of the radionuclide \(^{11}\text{C}\), which is approximately 20 minutes. Usually 300 to 370 MBq (8 to 10 mCi) is injected intravenously into the patients. The synthesis time is 30 to 40 minutes (the time from end of cyclotron irradiation until availability of the radiopharmaceutical for injection), and the imaging time is 40 to 90 minutes. The radioactivity available for the first patient is 4 to 8 times lower than that obtained from the cyclotron, whereas for a potential second patient the radioactivity is 16 to 32 times lower. This quick calculation shows that it is difficult to introduce \(^{11}\text{C}\) radiopharmaceuticals into a routine clinical environment, and thus they are more frequently used in research environments partway between clinical practice and research.

Nevertheless, \(^{11}\text{C}\) radiopharmaceuticals play an important part in the development of PET tracers, as it is usually simpler to test principle concepts with \(^{11}\text{C}\)-labeled substances than with fluorine 18 (\(^{18}\text{F}\))-labeled substances. Endogenous molecules do not contain fluorine, and thus it is important to compare the in vivo distribution of the endogenous molecule, traced with \(^{11}\text{C}\), and the \(^{18}\text{F}\) labeled analog to confirm that the analog retains important properties of the endogenous molecule. One such substance is \(^{11}\text{C}\)methionine, which several institutions are using for brain tumor imaging. Other tumor-imaging agents clinically used in some institutions are \(^{[\text{\text{15}\text{N}}]}\)choline and \(^{[\text{\text{13}}\text{C}]h}\)thymidine. They have shown promise for the imaging of prostate tumors and for the imaging of cellular proliferation, respectively. Both also have become available as \(^{18}\text{F}\)-labeled analogs. In cardiac imaging, the most important clinically useful compound, \(^{[\text{\text{13}}\text{C}]h}\)ydroxyephedrine, appears to yield relevant information in heart transplant recipients and patients with myocardial hypertrophy. In the brain, the most widely used \(^{11}\text{C}\) compounds are \(^{[\text{\text{11}}\text{C}]f}\)lumazenil for the assessment of epilepsy and \(^{[\text{\text{11}}\text{C}]r}\)aclopride for the evaluation of diseases of the dopaminergic receptor system. Clinical examinations with such compounds can realistically be done only if an in-house cyclotron and a radiopharmacy unit are available.

Most clinical PET scanning is performed with \(^{[\text{\text{18}}\text{F}]f}\)luoro-deoxyglucose (FDG) as the radiotracer. However, an increasing number of clinical studies are performed with \(^{11}\text{C}\) tracers in oncology, cardiology, and brain receptor studies (Table 17.1). This chapter focuses on PET \(^{11}\text{C}\) radiopharmaceuticals of special clinical value.

RADIOCHEMISTRY AND RADIOPHARMACY REQUIREMENTS FOR CARBON 11 RADIOPHARMACEUTICALS

Compounds labeled with the ultrashort-lived isotope carbon 11 (\(^{11}\text{C}\)) are not commercially available and must be prepared in the vicinity of a cyclotron (1–3). In a PET facility, the cyclotron, the radiochemistry laboratory, and the PET scanner(s) constitute the three main operative units. Today, most centers that do PET scanning use low- or medium-energy cyclotrons to produce one or more of the positron-emitting radionuclides: \(^{11}\text{C}\), nitrogen 13 (\(^{13}\text{N}\)),...
oxygen $^{15}\text{O}$, and fluorine $^{18}\text{F}$. The ultrashort half-life of $^{11}\text{C}$ implies that it must be produced immediately before use by an adjacent cyclotron. $^{11}\text{C}$ is formed by means of nuclear reactions that occur upon bombardment of target mediums with charged particles. The production of $^{11}\text{CO}_2$ is an example of this hot-atom chemistry. The irradiated material is, in the case of $^{11}\text{C}$, typically in a gaseous state. Irradiation yields are dependent on such factors as target shape, the design of the target foil, and the efficiency of target cooling. The amount of radioactivity that can be obtained is regulated by the energy of the accelerated particles and the beam current imposed on the target.

Labeling of a compound without affecting its biochemical properties is possible by exchange of stable atoms present in the parent molecule. For instance, carbon 12 ($^{12}\text{C}$) is replaced with the corresponding positron-emitting radionuclide $^{11}\text{C}$. The small kinetic isotope effect due to the different atomic weights of $^{11}\text{C}$ and $^{12}\text{C}$ that may occur is considered negligible for most applications. The ultrashort half-life especially of $^{11}\text{C}$ make it advantageous for sequential investigations with short time intervals in the same individual (animal or human), allowing the subject to be its own control. The use of radionuclides with relatively longer half-lives, such as $^{18}\text{F}$ or bromine 76 ($^{76}\text{Br}$), provides an opportunity to follow the radioactivity from the radiolabeled compound for a longer time but leads to the use of analogs of natural compounds and also to a higher radiation dose to the patient.

In the preparation of compounds labeled with radionuclides such as $^{11}\text{C}$, a series of requirements related to the ultrashort half-life of the radionuclide must be taken into account. The radioactivity from the radiolabeled compound for a longer time but leads to the use of analogs of natural compounds and also to a higher radiation dose to the patient.

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<table>
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NHL: non-Hodgkin lymphoma, H&N: head and neck
Online and one-pot reactions shorten the total synthesis time and reduce radioactivity losses.

Commercially available dedicated cyclotrons (10 to 18 MeV) are well suited for the production of $^{11}$C for PET radiochemistry purposes. A large number of $^{11}$C-labeled precursors can either be produced directly in the target or obtained via rapid online reactions starting from $^{11}$CO$_2$ or $^{11}$CH$_4$. The most widely used $^{11}$C-labeled precursor has been $[^{11}C]methyl$ iodide. Recently a more reactive precursor, $[^{11}C]methyl$ triflate, was demonstrated to give higher yields with shorter reaction times and smaller amounts of precursors for many commonly used PET radiopharmaceuticals. Today, most PET centers have either commercially available or in-house–constructed units for the production of $^{11}$C-labeled methyl iodide or methyl triflate. Among the radiopharmaceuticals listed in this chapter, $^{11}$C-labeled methionine, MeAIB, choline, metomidate, PK 11195, HED, raclopride, flumazenil, $\alpha$-methyl-tryptophan, and PIB can all be produced from such a production unit by using, in most cases, commercially available des-methyl precursors (3). $[^{11}C]acetate$ can be prepared by simple reaction and purification conditions, whereas $^{11}$C-labeled 5-OH-$\beta$-tryptophan, tyrosine, thymidine, CGP 12177, and WAY-100635 production is more complicated, demanding a well-established in-house collaboration between skilled radiochemists and technicians.

Radiopharmacy regulations vary somewhat between countries, but guidelines can be found both in the European and U.S. pharmacopeias, which have entries for $^{11}$C-labeled radiopharmaceuticals such as raclopride and methionine. From a radiopharmacy viewpoint, two crucial steps of the production are purification and quality control, with high-performance liquid chromatography (HPLC) the standard method in both steps. The specific radioactivity (SA) of a radiopharmaceutical is defined as the ratio of radioactivity per mole of the labeled compound, with a maximum SA inversely related to the physical half-lives of the radionuclide. The maximum theoretical SA for $^{11}$C is 107 mCi/nmol, but because of difficulties in completely eliminating external sources of $^{12}$C, this high specific radioactivity is never obtained. An SA higher than 2,000 mCi/µmol (74 GBq/µmol) is sufficient for most of the radiopharmaceuticals used in PET investigations of receptors and transporters. For high-affinity $^{11}$C radiopharmaceuticals that require a higher SA, like $[^{11}C]FLB$ 457, the new method of $[^{11}C]methyl$ iodide/triflate production from $[^{11}C]$methane has opened up the possibility of routinely obtaining a higher SA. $[^{11}C]methane$ can be produced within the target or externally (post-target), with the former method giving a higher SA. When producing endogenous compounds such as amino acids, acetate, and choline, a high SA is not needed. Efficient PET investigations require an unusually high degree of interdisciplinary collaboration and coordination in a very tight time frame, and this is especially evident in the case of ultrashort-lived radionuclides such as $^{11}$C. Thus PET centers must optimize all steps in this sequence of events to be able to achieve smooth operation and cost-effectiveness.

**CARBON 11 RADIOPHARMACEUTICALS IN CLINICAL USE**

Although a large number, more than a thousand, of $^{11}$C-labeled compounds have been prepared, only a few have been proven clinically useful (3) (Fig. 17.1). The first $^{11}$C radiopharmaceutical that became established in clinical PET is $[^{11}C]$methionine, which is by far the most extensively

![Figure 17.1 Carbon 11 radiopharmaceuticals in clinical use.](image-url)
used amino acid in PET neuro-oncology as well as in pituitary adenoma investigations (4–6). $[^{11}C]$methionine is conveniently prepared using $[^{11}C]$methyl iodide or $[^{11}C]$methyl triflate (7). Measurements relate to tissue concentrations of $[^{11}C]$methionine as a percentage of injected dose or as the ratio of concentration between tumor and healthy tissue. Several studies have shown that most of glial tumors exhibit a higher amino acid uptake than that of the healthy tissue. The high-grade tumor accumulation tends to be greater than that in low-grade tumors. $[^{11}C]$methionine

**Figure 17.2** Carbon 11 radiopharmaceuticals under clinical evaluation.

**Figure 17.3** T1W Gd-enhanced MR image, early arterial phase (left) and $[^{11}C]$metomidate summed dynamic PET image, 0 to 25 minutes (right), of a 58-year-old male with histologically confirmed hepatocellular carcinoma (arrows). (Courtesy of M. Seppänen, Turku PET Center.)
imaging is being used clinically in several institutions (Chapters 22 and 23).

PET studies of myocardial blood flow and metabolism have identified the human heart as an organ that is fully integrated with the general function of the human body (8). The neuronal function of the heart is altered in several cardiac disorders such as heart failure, ischemia, and cardiac arrhythmias, and several $^{11}$C-labeled radiopharmaceuticals have been proven useful in PET studies of the human heart. The most commonly used $^{11}$C radiotracer designed and tested to assess cardiac neurotransmission at a presynaptic level is $[^{11}C]$hydroxyephedrine ($[^{11}C]$HED) (9). At the postsynaptic level, $\beta$-antagonists such as $[^{11}C]$CGP12177 are available to assess $\beta$-adrenoceptor expression and density (10). The clinical usefulness is considerable. In heart transplantation, $[^{11}C]$hydroxyephedrine studies support the concept that spontaneous reinnervation takes place after transplantation. By using both $[^{11}C]$hydroxyephedrine and $[^{11}C]$CGP12177, researchers demonstrated that both the presynaptic myocardial catecholamine reuptake and the postsynaptic $\beta$-adrenoceptor density were significantly reduced in hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy (11,12). A decline in oxidative metabolism has been shown by reduced oxidation of $[^{11}C]$palmitate and delayed turnover of $[^{11}C]$acetate; $[^{11}C]$acetate is a widely used radiotracer for measurement of myocardial oxygen consumption. PET findings in early postinfarction as well as in stable chronic coronary disease have demonstrated the utility of this radiotracer (8).

PET has made important contributions to the understanding of epileptic disorders and has identified patients who were not previously considered to be surgical candidates. $[^{18}F]$FDG is the most widely used radiotracer for the presurgical evaluation of patients with medically refractory epilepsy. A reduced benzodiazepine-receptor density has been demonstrated in epileptic foci by using the benzodiazepine-receptor antagonist $[^{11}C]$flumazenil (13,14). $[^{11}C]$flumazenil was found to be a more sensitive and more accurate focus localizer than $[^{18}F]$FDG, especially in patients with nonlesional MRI (Chapter 25). $[^{11}C]$flumazenil could even be used as a biochemical marker of epileptogenicity and neuronal loss in stroke (15).

Recently one area of clinical research has been growing: PET studies with $^{11}$C radiotracers in neuropsychopharmacologic drug development (16). A basic problem in the discovery and development of novel drugs to be used in, for example, the therapy of neurologic and psychiatric disorders is the absence of relevant in vitro or in vivo animal models that can yield results to be extrapolated to humans. Drug research now benefits from the fast development of functional imaging techniques such as PET. The most frequent approach is to study how an unlabeled drug inhibits specific binding of a well-characterized selective PET radiopharmaceutical such as the dopamine $D_2$ antagonist $[^{11}C]$raclopride (Chapter 26).
CARBON 11 RADIOPHARMACEUTICALS UNDER CLINICAL EVALUATION

Many $^{11}$C radiotracers are presently evaluated for their usefulness in clinical PET (Fig. 17.2), especially in oncology. $^{11}$C-labeled amino acids such as $[^{11}$C$]$tyrosine (17) and $[^{11}$C$]$MeAIB (18), as well as $[^{11}$C$]$choline (19), $[^{11}$C$]$acetate (20), $[^{11}$C$]$metomidate (21) (Fig. 17.3), $[^{11}$C$]$5-OH-β-tryptophan (22), and $[^{11}$C$]$hydroxyephedrine (23), have been used for studies of tumor uptake and metabolism, and their clinical value is still evaluated at different PET centers. Tumor proliferative activity has been shown by $^{11}$C-labeled purine bases such as $[^{11}$C$]$thymidine in preclinical studies, but this correlation has not been found in vivo (24). The peripheral benzodiazepine-type ligand PK 11195 has been labeled with $^{11}$C and used to visualize the glial–macrophage reaction in ischemia, glial tumors, and dementia (25, 26).

A new concept for the study of Alzheimer disease using PET is radiotracers that bind to amyloid deposits in the brain. $[^{11}$C$]$PIB is the most extensively studied amyloid-binding tracer, and it enables clear separation of Alzheimer disease and control subjects (27) (Fig. 17.4).

CARBON-11 RADIOPHARMACEUTICALS OF POTENTIAL CLINICAL USE

A large number of $^{11}$C radiotracers are of potential clinical use. Structures of a few of them are shown in Figure 17.5. The tracer $\alpha-[^{11}$C$]$methyl-β-tryptophan (14) has been used in a attempt to differentiate between epileptogenic and nonepileptogenic tubers. Recently, the serotonin 5-HT$_{1A}$-receptor antagonist [carbonyl-$^{11}$C]WAY-100635 has been used to demonstrate the temporal epileptic foci where $[^{18}$F$]$FDG imaging was not sufficient (28).

A large number of receptor radiotracers have been labeled with $^{11}$C and used in basic research protocols in patients with different diseases, and their distribution has been compared with the regional distribution of the radiotracers in healthy volunteers. However, the results have usually not been fully implemented in clinical practice. In drug development, a direct approach is to radiolabel a new potential drug and to trace its uptake, anatomic distribution, and binding in brain. Furthermore, the effects of a novel drug on physiologic–biochemical parameters, such as glucose metabolism or blood flow, also can be assessed. The
demonstration of quantitative relations between drug binding in vivo and drug effect in patients is used to validate targets for drug action, correlate pharmacologic and physiologic effects, and optimize clinical treatment. Several selective \(^{11}C\) radiopharmaceuticals such as \[^{11}C\]raclopride, \[^{11}C\]FLB 457, \[^{11}C\]SCH 23390, and \[^{11}C\]PE2I (dopaminergic) and \[^{11}C\]WAY-100635, \[^{11}C\]DASB, and \[^{11}C\]MADAM (serotonergic) have successfully been used for this purpose (3,16).

Cardiac neurotransmission imaging has improved our understanding of the pathophysiology of these diseases. Future directions may include the development of more selective radiotracers that would help in implementing studies of cardiac neurotransmission in clinical practice (29).

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INTRODUCTION

SPECT imaging is widely available, and some very useful imaging agents have been developed since the inception of nuclear medicine. The most effective and most widespread agents are used in perfusion imaging of various organs or organ systems, tumor imaging, and imaging of inflammation. Although the perfusion imaging agents are typically used to image one organ, the tumor- and inflammation-seeking agents are intended in most instances to search foci of activity in the entire body. Some interesting agents exist that are directed against specific components of receptor systems, but few of these agents are in widespread use, and it is not clear whether they will find widespread introduction or are only precursors to similar “higher resolution” PET agents (see, e.g., Chapter 26).

PERFUSION IMAGING AGENTS

The ideal perfusion radiopharmaceutical is one that is completely extracted from the blood upon passing the target organ, after which the radioactive label remains in the
cells for a long time without being washed out so as to enable ample imaging time of a “quasi-steady-state tracer distribution” at a convenient time after injection. In practice, none of these conditions are fully met. A high extraction fraction with slow washout of the label afterwards is the normal situation. Perfusion imaging with SPECT tracers is an organ-specific procedure that requires different radiopharmaceuticals for various organs. Using radiopharmaceuticals for first-pass perfusion measurements has long ago lost attractiveness in view of the better organ-specific perfusion agents. Here, nuclear medicine has a clear advantage over other imaging techniques, where first-pass agents are the only ones that can be used for perfusion imaging, as dictated by toxicity considerations. The nuclear perfusion agents thus are described under organ system headings.

**Brain Perfusion**

Technetium 99m \[^{99m}\text{Tc}\]exametazime ([RR,SS]-4,8diaza-3,6,6,9-tetramethylundecane-2,10-dione bisoxime or HM-PAO) is an uncharged lipophilic and low molecular weight complex that easily crosses the blood–brain barrier. Approximately 3.5% to 7% passes into the brain by passive diffusion during the first minute after injection. After some initial washout during the first 2 minutes, the remainder of the activity is retained in the brain without loss for the next 24 hours. It is thought that the complex probably reacts with glutathione in the cell and thus becomes trapped (1).

During the labeling procedure, there is a risk of making a secondary \[^{99m}\text{Tc}\]exametazime complex that is hydrophilic and thus is not extracted quickly from the blood, causing higher background activity. This especially occurs in the presence of oxygen, and thus the labeling should be done with freshly eluted \[^{99m}\text{Tc}\]pertechnetate, eluted from a generator that was last eluted within the previous 24 hours. If the eluate has to be diluted before the labeling procedure, it is helpful to dilute with saline that does not contain oxygen (e.g., stored under nitrogen).

Unless stabilized by chemical additives (cobalt [II] chloride), the labeled complex is not stable over longer periods of time and must be injected within 30 minutes after labeling; if stabilized, it must be injected within 5 hours. Quality control has to be performed before application to ascertain radiochemical purity.

\[^{99m}\text{Tc}\]bicisate (\(N,N'\)\-[1,2-ethylenediyl]bis-1-cysteindithylester dihydrochloride, \[^{99m}\text{Tc}\]-ECD) is a stable complex 5% to 6.5% of which is taken up by the brain during the first few minutes (2,3).

The complex is slowly eliminated from the brain, but the regional distribution in the brain remains the same for at least 6 hours. The two-step labeling procedure should be done quickly with fresh, oxidant-free \[^{99m}\text{Tc}\] eluate in phosphate buffer, and quality control has to be performed before application to ascertain radiochemical purity. The preparation is stable for at least 8 hours.

**Lung Perfusion**

\[^{99m}\text{Tc}\] human albumin macroaggregates are particles with a diameter of 10 to 100 \(\mu\text{m}\) (4). Following injection into a superficial vein of the systemic venous circulation, the macroaggregates (6 \(\times\) 10\(^4\) to 7 \(\times\) 10\(^5\) particles in an adult) are carried to the first capillary filter (i.e., the capillary tree of the pulmonary artery system). The albumin macroaggregate particles do not penetrate the lung parenchyma (interstitial or alveolar) but remain in a temporary occlusive position in the lumen of the capillary. The technetium-labeled macroaggregates remain in the lungs for variable periods of time, depending on the structure, size, and number of particles. The larger aggregates have a longer biological half-life, whereas particles between 5 and 90 \(\mu\text{m}\) in diameter have a half-life ranging from 2 to 8 hours. This perfusion measurement is the paradigmatic wash-in perfusion experiment, as during the first pass 100% of the radiopharmaceutical is extracted.

The decrease in the pulmonary concentration is caused by the mechanical breakdown of the particles occluding the capillaries. The resulting recirculating albumin microcolloid is quickly removed by the macrophages of the reticuloendothelial system (essentially the liver and the spleen). The microcolloid is metabolized with the introduction of the radioactive label \[^{99m}\text{Tc}\] into the systemic circulation, from which it is removed and excreted in urine. The application of the radiopharmaceutical should be done within 8 hours after preparation.

**Heart Perfusion**

Monovalent, positively charged metals and metal complexes are taken up and retained by the myocardium, enabling the estimation of myocardial perfusion (5).

\[^{201}\text{Tl}\] thallous chloride (T\(_{1/2}\) = 3.04 days) provides a cationic \(\text{Tl}^+\) solution. After intravenous injection of \[^{201}\text{Tl}\] thallous chloride, the thallium rapidly leaves the blood, and approximately 90% is cleared after the first pass. The relative uptake depends on regional perfusion and on the cell extraction efficacy of different organs. The myocardial extraction fraction of \[^{201}\text{Tl}\] is about 85% during the first pass during stress, and the peak myocardial activity is 4% to 5% of the injected dose and relatively constant for about 20 to 25 minutes. The precise cellular uptake process is still questionable, but the sodium–potassium ATPase pump is probably involved, at least in part.

The muscular uptake is dependent on myocardial workload during the injection and compared with the resting condition, the uptake into myocardium and skeletal muscle is increased two- to threefold during exercise, with a consequent reduction of uptake into other organs.

\[^{99m}\text{Tc}\] sestamibi \(([^{99m}\text{Tc}]2\text{-methoxyisobutylisonitrile})_n\) \[^{99m}\text{Tc}\]MIBI] is a cationic complex that accumulates in vital myocardium in proportion to perfusion (1.2% of the injected dose [during rest] to 1.5% [during stress]). Under hypoxic conditions, extraction is diminished. The regional
myocardial distribution is comparable to that of 201TI and remains stable from 0.5 (stress) or 1 (rest) up to at least 2 hours. Labeling must be done with oxidant-free 99mTc eluate (from a recently eluted generator) under heating. The radiopharmaceutical purity should be checked before application. The application should occur within 6 hours after labeling (6).

The regional uptake of [99mTc]tetrofosmin is comparable to that of [99mTc]sestamibi. The relative regional myocardial distribution is proportional to myocardial perfusion and remains the same from 5 minutes to at least 4 hours. The application should occur within 12 hours after labeling.

**TUMOR-LOCALIZING AGENTS**

Some molecules accumulate in some tumors to a higher extent than in normal tissue because of various mechanisms. Several of these mechanisms form the basis for radiopharmaceuticals used as tumor-seeking agents. Increased metabolism and faster biochemical and physiologic processes because of rapid cell growth and proliferation are the reasons for the rather nonspecific but sometimes useful increased tumor uptake of (radioactive) molecules. Increased energy consumption is shown by increased sugar consumption and results in increased [18F]FDG uptake. Increased protein synthesis is sometimes shown by higher uptake of labeled amino acids ([11C]methionine, [18F]fluorothyrosine). These PET radiopharmaceuticals are discussed in Chapters 15 and 17. They were sometimes used as single photon tracers, but with the widespread use of PET this application has disappeared. Perfusion imaging agents may show abnormal patterns in organs if the organ structure and/or function is disrupted by neoplastic growth. Thus the cerebral perfusion imaging agents may show abnormal perfusion patterns in the brain and disruption of the blood–brain barrier due to tumor.

The myocardial perfusion agents may visualize tumors and metastases in different organs, especially brain tumors and thyroid tumors. These agents are used for thyroid tumors that do not accumulate iodide. Sometimes the mechanisms are related to specific molecular structures on the tumor cells (receptors), and thus binding is more specific. The clinically most relevant tumor-seeking molecules are discussed here.

[99mTc]diphasosphonates ([hydroxymethylenediphosphonate [HMDP, HDP], 3,3-diphosphono-1,2-propandicarboxylate [DPD]) seem to be actively taken up during bone mineralization, and consequently most abnormal lesions in bone are visualized, along with bone metastases of various tumors. The solutions of the labeled products are virtually stable and may be applied until 8 hours after preparation (7).

[131I]sodium iodide (T1/2 = 8.04 days) and [123I]sodium iodide (T1/2 = 13.2 hours) are used for diagnosis, and [131I]sodium iodide is also for the treatment of thyroid carcinoma. The iodine is needed to produce the thyroid hormones, and thus thyroid tumors whose cells have at least an intact iodine uptake mechanism accumulate sodium iodide. Due to the fact that the decay of [123I]iodide does not involve the emission of a beta particle, it is only useful for diagnosis, whereas [131I]iodide is also used for metabolic radiation therapy. [123I]meta-iodobenzylguanidine ([123I]MIBG) (T1/2 = 13.2 hours) and [131I]meta-iodobenzylguanidine ([131I]MIBG) (T1/2 = 8.04 days) are iodinated aralkylguanidines. MIBG contains the guanidine group from guanethidine, linked to a benzyl group, into which iodine is introduced. Like guanethidine, the aralkylguanidines are adrenergic neuron-blocking agents. Thus tumors originating in tissues that embryologically stem from the neural crest can be visualized: pheochromocytomas, paragangliomas, chemodectomas, ganglioneuromas, and neuroblastomas. Pheochromocytomas and neuroblastomas are sensitive in approximately 90% of patients, carcinoids in 70%, and medullary carcinomas of the thyroid in only 35%.

The regional uptake of [99mTc]tetrofosmin is comparable to that of 201TI and remains stable from 0.5 (stress) or 1 (rest) up to at least 2 hours. Labeling must be done with oxidant-free 99mTc eluate (from a recently eluted generator) under heating. The radiopharmaceutical purity should be checked before application. The application should occur within 6 hours after labeling (6).

Transport of MIBG across the membranes of cells originating from the neural crest is an active process when the concentration of the drug is low (as in diagnostic dosages). The uptake mechanism can be inhibited by uptake of inhibitors such as cocaine or desmethylimipramine. When the drug is administered in higher concentrations (as in therapeutic dosages), passive diffusion processes also become important. Subsequently, an active mechanism transfers at least part of the intracellular MIBG into the storage granules within the cells (11).

[131In]indium octreotide (T1/2 = 67 hours) binds to the somatostatin receptor and thus accumulates in tissue expressing this receptor. Thus it shows gastroenteropancreatic (GEP) tumors (9–10). The stability of the physiologic solution of [131In]indium octreotide is 6 hours. For not clearly understood reasons, the labeling process is not always successful, and therefore quality control before application is obligatory.

[67Ga]gallium citrate (T1/2 = 78 hours) is widely used but is rather nonspecific; it also accumulates in lesions due to inflammatory disease and abscesses. The mechanism of the tumor uptake of [67Ga]gallium is poorly understood. The uptake varies with tumor type, among patients with the same tumor, and at tumor sites in one patient. [67Ga]gallium is transported through the body bound to transferrin as the carrier protein, and its uptake may be mediated by transferrin receptors on the cell membrane (8). [67Ga]gallium uptake is influenced by vascularity, increased permeability of tumor cells, rapid proliferation, and the somewhat lower pH in tumor cells. At low pH, [67Ga]gallium dissociates, and the gallium ions bind to the intracellular proteins.

[99mTc]nanocolloid (colloidal rhenium sulfide, 100-nm diameter; human albumin colloidal particles, less than 80-nm diameter; tin sulfide, less than 50-nm diameter). If applied by subcutaneous injection into connective tissue, 30% to 70% of the administered 99mTc colloidal particles (depending on particle size) are filtered into lymphatic capillaries, whose main function is the drainage of proteins from the interstitial fluid back into the blood pool.
This enables lymph node scintigraphy and identification of the sentinel lymph node(s), the first lymph node in the regional lymphatic basin to receive metastatic cancer cells. Surgical removal of sentinel lymph nodes and their histologic analysis permits the detection of microscopic or macroscopic cancer involvement. The working hypothesis is that if the sentinel nodes have no tumor cells in them, a distant metastatic spread is unlikely for most tumors (12).

The $^{99m}$Tc colloidal particles are then transported along the lymphatic vessels and are finally trapped into the reticular cells of functionary lymph nodes. A fraction of the injected dose is phagocytized by histiocytes at the injection site. Another fraction appears in the blood and accumulates mainly in the RES of the liver, spleen, and bone marrow; traces are eliminated via the kidneys.

**INFLAMMATION-LOCALIZING AGENTS**

Infection and noninfectious inflammation are characterized by physiological alterations that can be targets for radiopharmaceuticals used to detect inflammatory changes. Inflammation imaging is described in Chapter 58 (13). Most tumor-localizing agents also accumulate to some extent in inflammatory tissue. Here the main clinically used radiopharmaceuticals are listed.

**Labeled Leukocytes**

Despite the elaborate procedures to label leukocytes and the developments of alternative radiopharmaceuticals, the gold standard in inflammation-localizing agents still consists of the radiolabeled leukocytes, which enter the inflamed tissue by diapedesis (14,15).

In the case of $^{111}$In-labeled leukocytes ($T_{1/2} = 67$ hours), indium forms a saturated (1:3) complex with 8-hydroxyquinoline (oxine). The complex is neutral and lipid soluble, which enables it to penetrate the cell membrane. Within the cell, indium becomes firmly attached to cytoplasmic components; the liberated hydroxyquinoline is released by the cell. It is thought likely that the mechanism of labeling cells with $^{111}$Inindium oxine involves an exchange reaction between the hydroxyquinoline carrier and subcellular components that chelate indium more strongly than hydroxyquinoline. Upon reinjection, $^{111}$Inindium-labeled blood cells follow the pathways of the nonlabeled cells and thus allow visualization of areas of accumulation. After injection of labeled leukocytes into normal volunteers, about 60% of the dose is taken up immediately by the liver, spleen, bone marrow, and other tissues. There is only a very short transient holdup in the lungs. The remainder shows exponential clearance from the circulation with a half-life between 5 and 10 hours, resulting in a final uptake of about 20% in the liver, 25% in the spleen, 30% in the bone marrow, and 25% in other organs. The in vitro survival time of the leukocytes determines the time available for labeling and reinjection; obviously this time should be kept as short as feasible.

$[^{99m}Tc]$exametazime ($[^{99m}Tc]$HM-PAO) is a neutral lipophilic molecule that crosses fatty cell membranes by passive diffusion (it also crosses the blood–brain barrier; see "Brain Perfusion" above). After reacting with glutathione, the complex becomes trapped. $[^{99m}Tc]$-labeled leukocytes distribute between the marginalizing pools of the liver (within 5 minutes) and spleen (within about 40 minutes) and the circulating pool. Approximately 37% of the cell-associated $^{99m}$Tc is recoverable from the circulating pool 40 minutes after injection. The labeling is not completely irreversible, and a small portion is eluted from the labeled cells and is excreted partly by the kidneys and partly via the liver into the gall bladder. The in vitro survival time of the blood cells determines the time available for labeling and reinjection; obviously this time should be kept as short as feasible, partly because of the slight reversibility of the cell labeling.

$[^{99m}Tc]$antigranulocyte monoclonal antibodies are antibodies against the antigen NCA and can thus bind with more than 90% of the granulocytes in peripheral blood and with granulocytes in bone marrow. Immediately before application, quality control on the $[^{99m}Tc]$-antibodies must be done.

$[^{67}Ga]$gallium citrate ($T_{1/2} = 78$ hr) accumulates in lesions due to inflammatory disease and abscesses (see also "Tumor-Localizing Agents" above). The accumulation of gallium in tumor tissue and in sites of inflammation is thought to be due to its behavioral similarity to iron. Binding of gallium to transferrin, ferritin, and lactoferrin (present in polymorphonuclear leukocytes) has been demonstrated.

$[^{99m}Tc]$diphosphonates (hydroxymethylene diphosphonate [HMDP, HDP], 3,3-diphosphono-1,2-propandicarboxylate [DPD]) show uptake into bone and joint structures that are infected or inflamed (see also "Tumor-Localizing Agents").

$[^{99m}Tc]$albumin nanocolloid (human albumin colloidal particles less than 80 nm in diameter; see also "Tumor-Localizing Agents"). The increased uptake in the interstitial space of inflamed tissue results from increased extravasation, which is caused by the enlarged pore diameter (from 3.7 to 3.8 nm up to 5 to 20 nm) under the influence of the inwardly directed osmotic gradient of the plasma in the capillaries. After intravenous injection, reticuloendothelial cells in liver, spleen, and bone marrow are responsible for blood clearance. A small fraction of $^{99m}$Tc radioactivity passes through the kidneys and is eliminated in urine. The maximum concentration in the liver and spleen is reached after about 30 minutes, but in the bone marrow after only 6 minutes. The proteolytic breakdown of the colloid begins immediately after its uptake by the reticuloendothelial system, the products of degradation being excreted through the kidneys into the bladder. Labeled nanocolloid is stable for at least 6 hours.

After intravenous injection, $[^{99m}Tc]$ human immunoglobulin (HIG) remains for a longer period of time in the blood pool. The increased uptake in the interstitial space of chronic inflammation results from increased extravasation. The labeled HIG is stable for 4 hours (16).
REFERENCES


INTRODUCTION

Since only coincidence events of photons generated by annihilation are detected, different positron-emitting radiopharmaceuticals can be used in the same PET scanner. In a sense, each radiopharmaceutical generates a new type of imaging study. Thus imaging protocols are strongly dependent on the radiopharmaceutical used. The most frequently used metabolic marker is fluorine 18 $^{18}$F-fluorodeoxyglucose (FDG), whereas nitrogen 13 $^{13}$N-ammonia and oxygen 15 $^{15}$O$\text{H}_2\text{O}$ are used for perfusion measurement in neurology and cardiology PET imaging. For every single tracer, specific data acquisition protocols have to be used. Essentially, all PET imaging can be performed on PET alone scanners, but the introduction of PET-CT scanners does allow for faster patient throughput. With the availability of diagnostic CT imaging in a single machine, oral and intravenous contrast agents can be added and can make protocols more complex. In FDG-PET-CT, it is useful to opacify bowel with dilute contrast agent. A CT scan with the application of intravenous contrast agent is best done after the PET emission scan to avoid image artifacts. Once a PET-CT has been obtained, it is easy to correlate its information with other anatomic cross-sectional imaging documents available from prior studies or studies acquired after PET-CT.

QUALITY ASSURANCE AND QUALITY CONTROL

Quality control is mandatory for reliable data acquisition in PET imaging (5). The accuracy of PET source data is based on optimal tuning of the PET scanner, which is obtained by continuous quality control. Quality control includes the control of the following system characteristics: function control of the scintillation detectors (blank scan), photo-multipliers (updating of gain calibration), and a check of the coincidence timing correction (CTC). For system sensitivity measurements of each line of response (line between any two detectors in the PET ring detector; see Chapter 3), a normalization has to be performed, which is used to correct the emission scanning data (normalization). Furthermore, a standard dose of radiotracer is measured during several minutes in a standard phantom (2-D and 3-D well counter correction) in order to ascertain proper calibration of quantitative values of PET radiotracer activity measured in the 2-D and 3-D modes. The daily quality control in the morning includes only the blank...
scan. The weekly quality control includes a extended blank scan and updated gain calibration and CTC. Bimonthly and after major maintenance work, a 2-D and 3-D well counter calibration is necessary. Overall, the above-mentioned procedures do not represent the standard of care, and quality control and quality assurance procedures have to be performed in compliance with the individual manufacturer of the PET or PET-CT machine.

**PATIENT SCHEDULING**

Optimization of patient throughput in a PET center depends critically on the PET radiopharmaceuticals and the PET protocols used. Due to the relatively long production time and the half-life of FDG, which permits scanning for approximately half a day, most PET centers use their cyclotron or radiopharmacy unit for FDG production early in the morning. Consequently, PET scanners with on-site cyclotrons and satellite PET centers will receive FDG for scanning in the morning. Additional FDG scanning can be done if an end-of-morning second FDG production is available. Otherwise, and in PET centers with cyclotrons, imaging with tracers like $[^{13}N]$ammonia and $[^{15}O]$H$_2$O, which have to be produced for individual patients, is scheduled in the afternoon. For proper patient scheduling, knowledge of the average scan times is helpful, and the use of ad hoc complex FDG protocols should be avoided.

**GENERAL CONSIDERATIONS REGARDING PATIENT PREPARATION FOR FDG APPLICATIONS**

**Prior to FDG Injection**

Patients have to fast for at least 4 hours prior to the FDG injection. There are no restrictions for intake of prescribed daily medications. Note that many intravenous infusions contain glucose; they have to be replaced for that amount of time by an infusion free of glucose. A pre-FDG-injection blood glucose measurement should be performed in all patients to ensure patient fasting status as well as to detect patients with elevated blood glucose levels due to unknown causes or possibly tumor-related diabetes mellitus. Based on our experience, patients with blood glucose level above 160 to 200 mg/dL should be rescheduled for another day.

**At FDG Injection**

As patients should be injected in a quiet room and in a supine or reclining relaxed position, FDG injection is done in so-called uptake rooms. A single uptake room is sufficient if the PET scan lasts longer than the minimum uptake time of approximately 40 to 60 minutes necessary for FDG. If scans are shorter than this time, which is typically the case in brain FDG studies or FDG-PET-CT exams, the availability of additional uptake rooms is needed, because more than one patient will be awaiting scanning at any point in time. For the injection, intravenous access is obtained via a 20-gauge indwelling catheter. Function control of the intravenous access is strongly recommended to prevent paravenous injection of the radiotracer. Note that aspiration of blood into the FDG-containing syringe should not occur, as the formation of FDG-containing microemboli lodging in the lungs has been reported (6). Sufficient saline flushing of the syringe containing the activity and the catheter after injection is necessary for complete application of the dose.

In adult oncologic patients, a standard dose of 370 MBq (10 mCi) is injected independent of patient weight in our center. Other centers use doses up to 740 MBq (20 mCi) to speed up data acquisition and maintain image quality. In our experience, this is not necessary, because even with the lower dose high-quality scans are obtained in overall imaging times of less than 40 minutes. Furthermore, radiation protection issues should not be ignored (see Chapter 9). For dedicated brain imaging, a dose of 200 MBq is sufficient.

Note that pre- and postinjection dose measurements of the syringe in a dose calibrator are needed to reconstruct attenuation-corrected, semiquantitative PET images and make standardized uptake values (SUVs) available (see Chapter 11). In addition, meticulous measurements of the other factors required for this calculation (i.e., patient weight, patient height, injected dose, time of injection, and time of data acquisition) are mandatory in order to obtain reliable results (7). PET scans allowing SUV measurements can now be easily reconstructed with commercially available software, and their calculation as standard imaging documents is highly recommended for PET-CT imaging.

**After the Injection**

Patients are required to rest in the darkened, quiet uptake room with eyes closed for at least 20 minutes. The patient should be asked to refrain as much as possible from speaking. When space limitations are critical, it may be possible to remove the patient from the uptake room after 20 minutes and keep him or her in the waiting room for the rest of the uptake phase. Just prior to imaging, the patient is asked to void as completely as possible in order to minimize PET image artifacts in the pelvic region, which can stem from high bladder activity. For PET-alone imaging in a patient with suspected pelvic disease (cervix or uterus cancer, involvement of the bladder), catheterization of the bladder with continuous saline flushing can be useful. However, this procedure is not needed in FDG-PET-CT imaging. For patient imaging, no premedication is given routinely. However, some institutions prefer the application of diazepam for the reduction of muscular uptake and/or furosemide for artifact reduction due to high activity in the renal pelvis (8,9).
WHOLE- AND PARTIAL-BODY FDG-PET AND FDG-PET-CT IMAGING PROTOCOLS

General
Whole-body FDG-PET imaging in our institution is defined as covering the patient from head to toe. Partial-body scans include multiple contiguous axial field of views (AFOVs) typically covering the patient from the head to the pelvic floor. The position of the table cradle defines the body area of the patient to be scanned. Thus, with an AFOV of 15 cm, repeated movement of the table cradle by this distance will result in a contiguous series of sections of the patient; this is the way in which whole- or partial-body scans are obtained. Six cradle positions covering approximately 90 cm of the patient’s body are usually sufficient to obtain a tomographic PET data set covering the patient from head to pelvic floor in PET and PET-CT imaging.

Patient Positioning: PET Alone
For PET-alone imaging, positioning includes placement of the patient in a supine position with the head in a headholder to restrict movement, comfortable support of the legs, and fixation of the arms alongside of the body to restrain them from movement.

Patient Positioning: PET-CT
For PET-CT imaging, as in diagnostic CT examinations, the patient has to remove all removable metallic parts, such as rings and artificial dentures, prior to scanning. As in PET-alone imaging, the patient is positioned supine with head first on the table, except when PET-CT data are used for radiation therapy planning (see Chapter 57). For optimal coregistration in the head region, the head is placed in a headholder, but, otherwise, comfortable positioning of the patient is achieved using cushions and fixing stripes. Positioning of the arms is strongly dependent upon the suspected diagnosis. For ENT tumor or other head-and-neck imaging, the arms of the patient should be alongside the body to prevent beam-hardening artifacts at the level of the neck. For all other oncology imaging procedures, the arms are placed above the head whenever possible. Some groups advocate splitting data acquisition into two parts, one covering the head and neck region with the arms down, the other the torso region with the arms up. Positioning of a patient in the radiation treatment position can also be performed without restraints (see Chapter 57).

Oral Contrast Application in FDG-PET-CT Imaging
In FDG-PET-CT imaging, oral contrast (e.g., Micropaque Scanner, Guerbet AG, Aulnay-sous-Bois, France) is administered routinely up to 30 minutes prior to FDG injection, since adequate distribution of contrast in the bowel is achieved typically after 60 minutes. The application of barium sulfate containing oral contrast agents is a safe procedure and mostly used for outpatient imaging. In postoperative patients, iodinated oral contrast agents (e.g., Gastrografin, Schering AG, Berlin, Germany) are used for safety reasons, since these agents do not induce peritonitis when leaking into the peritoneum. The volume of oral contrast agent given (1 liter of solution) is identical to that given in diagnostic CT imaging. Just prior to patient positioning on the table, an additional volume of 1.5 dL oral contrast is given to optimize the contrast between gastric and duodenal structures and their surroundings (3). A contrast enema is not given routinely. No significant artifacts are seen in PET emission imaging due to prior application of oral contrast agent (10,11) (see Chapter 7).

Emission Data Acquisition: PET and PET-CT
Independent of whether a PET-alone or PET-CT scan is acquired, 2-D or 3-D emission data acquisition is started from the level of the pelvis to minimize artifacts from FDG accumulation in the bladder. The scan direction is toward the head. Depending on the hardware used, an axial FOV of round 15 cm is acquired per cradle position. For 2-D imaging, a single slice overlap, at least among adjacent cradle positions, should be assured. For emission data acquisition, a 3-minute scan time per cradle position is adequate with the newer, more sensitive PET scanners, but the scan time should be adapted to patient weight, since in heavy patients self-absorption of gamma rays is more relevant, and longer emission scanning improves count statistics and therefore image quality (see Chapter 3). Frequently, semiquantitative analysis of FDG-PET images and thus SUV-corrected images are made available.

Transmission Data Acquisition: PET Alone
In PET-alone systems, a duration of 1.5 minutes per cradle position is sufficient for transmission scanning in accordance with the rule that, in standard PET imaging, transmission scanning takes about 50% of the time of emission scanning. Transmission scanning is routinely performed by using rotating germanium-68 pin sources and can be done after measuring emission at each cradle position or after completion of the acquisition of emission scanning cradle positions (12). Whenever patient height exceeds the total scan length, patient repositioning and scanning of the legs are necessary. Most institutions do emission scanning only for the legs in whole-body scans, which results in considerable time savings due to the omission of transmission scanning.

Transmission Data Acquisition: PET-CT
In PET-CT imaging, CT data used for attenuation correction are acquired prior to PET emission scanning. If CT data are available prior to PET data, reconstruction of the
PET data can be started while the PET scan of consecutive body areas is still ongoing. CT data are acquired during breath-hold. A study by our group shows that the non-forced end-expiratory position is the optimal position for image coregistration, since PET data are acquired during shallow breathing, and a normally breathing individual spends most of the respiratory cycle in this position. In order to minimize breath-hold time during this breath-hold position, which becomes uncomfortable after 10 seconds or so, some breathing exercises are done with the patient prior to scanning (13). The breath-hold command is given only when the CT data acquisition reaches the thoracic inlet and is cancelled when CT data acquisition reaches the midabdomen. Alternatively, in uncooperative patients free breathing is permitted and yields reasonable results, particularly with the 8 and higher multi-slice CTs, where data acquisition is so fast that free breathing does not interfere with scanning.

The following optimized parameters for whole-body low-dose CT data acquisition in PET-CT represent a good compromise between CT image quality and patient radiation exposure for a normal size individual:

- Tube rotation time 0.5 seconds per evolution;
- 140 kV for all scans;
- 80 mA, resulting in a 40-mAs product, with an effective radiation dose of ~4 mSv (see Chapter 9);
- Table advancement 22.5 mm per rotation;
- Slice pitch 6 (high-speed mode);
- Reconstructed slice thickness 5 mm;
- Scan length 867 to 1,300 mm (corresponding to 6 to 9 PET cradle positions); and
- Acquisition time 22.5 to 33.8 seconds per CT scan.

With the full flexibility of the CT scanner, CT data can be acquired using different acquisition parameters whenever a different CT image quality is necessary. For attenuation correction only, CT scans can be run at a much lower milliampere x second product, with a typical lower limit on CT scanners available of 5 mAs. Tube currents of 20 to 40 mAs are sufficient for anatomic imaging in the context of PET-CT (14). PET-CT data of restricted areas like the head can also be obtained. At the end of the CT data acquisition, the data obtained are transferred to the PET console computer system to be used for attenuation correction and also directly transferred to the combined PET-CT data viewing system for coregistered image viewing.

**Image Data Reconstruction for PET and PET-CT Imaging**

Data are reconstructed using iterative reconstruction with two iterations. The reconstructed slice thickness in state-of-the-art PET scanners is around 4 to 5 mm. The in-plane image reconstruction matrix is usually 64 x 64 but preferably 128 x 128 and depends on the intrinsic spatial resolution of the system. The typical transaxial field of view reconstructed is 55 cm. Semiquantitative FDG-PET data are desirable, and thus SUV-corrected images have to be available, as mentioned above.

**Total Data Acquisition Time in PET and PET-CT**

Routine, 860 to 1,010 mm coverage (corresponding to six to seven cradle positions in the described system) is sufficient for imaging patients from the top of the head to the pelvic floor. Therefore, total acquisition time sums up to 18 to 21 minutes (6 x 3 minutes emission scanning plus 23 seconds for CT data acquisition in high-end integrated PET-CT systems). Since a standard PET scanner uses about half the emission scanning time for attenuation correction, or about 1.5 minutes per cradle position, a standard PET scan would require 27 to 31 minutes for the same scanning procedure. With the configuration of the above-described system, a maximum of 9 contiguous cradle position covering 1,300 mm can be acquired in less than 28 minutes of total imaging time, compared with 42 minutes for a standard PET scan. The time savings in imaging time achieved is thus ~30%.

**HEART FDG-PET AND FDG-PET-CT IMAGING**

FDG-PET and FDG-PET-CT of the heart are performed to determine the viability of the heart muscle. This examination always has to be performed in combination with a perfusion study at rest, which identifies the areas of poor perfusion. The perfusion information can be obtained by, for example, NH3-PET or by conventional 99mTc-based perfusion SPECT imaging.

**Glucose Clamping Procedure**

Most importantly, the patient has to be fasting for at least 8 hours prior to the FDG injection to deplete the glucose stores in the heart muscle. Sixty to 90 minutes prior to the FDG injection, the blood glucose level is measured to determine the dose of oral glucose to be administered to activate myocardial glucose uptake. In patients with a significantly elevated fasting blood glucose level (above 13 mmol/L), no additional oral glucose is given. In patients with a blood glucose level below 13 mmol/L, a maximum of 50 g glucose is given orally. Fifteen minutes prior to the FDG injection, the blood glucose level is measured again. Whenever the level is below 6 mmol/L, no intervention is required. If the level is above 6 mmol/L, intravenous application of insulin using the following formula is given:

\[ \text{Insulin dose in IU} = (\text{blood glucose level in mmol/L} - 6) \times 2 \]

In these patients, a rigid control of the blood glucose level has to be achieved during and after the examination (every 20 minutes until the blood glucose level has stabilized). After the FDG injection of a standard dose of 250 MBq, the patient is transferred to the scanner (15).
Emission data should be acquired at least 30 minutes after the FDG injection. In PET-alone systems, transmission data acquisition can be initiated just after the injection. The patient is placed in a “feet first” and “arms above the head” position on the table. Since missing landmarks impede the exact localization of the patient’s heart, a short transmission scan (1 minute) can be helpful for exact localization. Usually, the entire heart can be covered within a single axial FOV. After the patient has been placed correctly, a transmission scan is acquired over 20 minutes with PET-alone systems and with a low-dose CT in PET-CT systems. No cardiac or respiratory gating is required. After completion of the transmission scan, acquisition of 2-D or 3-D emission data for 30 minutes is started. In PET-CT systems, the handling of data acquisition is somehow easier. The acquisition of CT data for transmission correction is done just before the emission data acquisition and takes less than 10 seconds. Image reconstruction can be performed by using filtered back-projection or iterative reconstruction. Reformatted images for viewing and printouts include short as well as horizontal and vertical long axis cuts.

HEART AMMONIA ([13N]AMMONIA) PET AND PET-CT IMAGING

For the quantitative determination of myocardial perfusion, [13N]ammonia is the most widely used radiopharmaceutical. Imaging during rest and pharmacological stress is preferred (16). Since the half-life of [13N] is around 9 minutes, imaging at rest and imaging during stress can be performed within 30 or so minutes of each other, and thus the patient can be left on the scanner table during that time. Obviously, ammonia imaging requires an in-house cyclotron and radiopharmacy.

Patient Preparation

Depending on the clinical requirements, part or all of the cardiac medications of the patient have to be discontinued at an appropriate time prior to scanning. This has to be coordinated with the physician responsible for the patient’s cardiac therapy. It is unnecessary to discontinue oral anticoagulation therapy for a PET scan. However, for safety reasons (not for better uptake, as in cardiac FDG studies) fasting of the patient is required due to possible side effects of pharmacologic stress medication (adenosine or dipyridamole), which can produce nausea and vomiting (17,18). No caffeine-containing food is allowed, as caffeine is an antagonist of these pharmaceutical compounds.

The patient is placed in a “feet first” and “arms above the head” position on the table. To prevent dead-time correction corruption by signal overflow, the injection site of the radiopharmaceutical is chosen (preferably in a foot vein). ECG and blood pressure cuff are installed (19).

A standard dose of 750 MBq [13N]ammonia is injected simultaneously with the start of a dynamic emission data acquisition protocol, which lasts for 20 minutes. Transmission data acquisition is performed for an additional 20 minutes on a PET-alone scanner or by using a short-acquisition, low-dose CT on PET-CT systems. At the end of transmission data acquisition, pharmacological stress under ECG and blood pressure monitoring is started. The use of adenosine (0.14 mg/kg body weight/min for 7 minutes) is preferred over dipyridamole due to its shorter biological half-life. Thus, if the patient has an untoward reaction, discontinuation of adenosine will result in almost immediate cessation of the reaction, while dipyridamole may require the use of theophylline as an antidote (17,18). The injection of a standard dose of 750 MBq is started 4 minutes after the start of the pharmacological stress. No additional transmission scanning is needed since the patient has been kept in the same position throughout the examination. However, should the patient have moved, an additional transmission scan for 20 minutes or a low-dose CT has to be performed. The entire data acquisition time for the rest and stress examination together is less than 60 minutes.

Image data reconstruction for images obtained at rest and during pharmacological stress is done by using filtered back-projection or iterative reconstruction, and images are reformatted in the same manner as in FDG heart studies. Meticulous alignment of the main cardiac axes for both the rest study and the stress study should be obtained to optimize the diagnostic values of the images.

For certain types of examination, the use of water instead of ammonia for the measurement of heart perfusion may be advantageous, but clinically ammonia is easier to handle, since postprocessing is less involved (19). In a satellite PET environment, a rubidium-82 (82Rb) generator can be used for quantitative myocardial perfusion imaging (4). The protocols using 82Rb PET perfusion imaging are basically identical to those using ammonia. The examination time may be somewhat shorter, because the half-life of 82Rb (a little over 60 minutes) permits a shorter interval between the rest study and the stress study.

New strategies include contrast-enhanced multi-slice CT of the coronary arteries in the same imaging session (20) (see Chapter 32). However, the clinical relevance of this strategy has not been determined yet.

BRAIN FDG-PET AND PET-CT IMAGING

Patient preparation is similar to whole- or partial-body FDG imaging. Uptake should be in a quiet, darkened environment during the entire uptake phase, as the brain is the organ that is most sensitive to external stimuli, which will result in areas of increased cerebral FDG uptake, particularly in the visual cortex. Careful positioning of the head in the headholder is necessary. Comfortable positioning of the patient helps to reduce body movements. Alignment of the orbitomeatal line with the scan plane, with fixation by stripes, is preferred. In contrast to the data acquisition in whole- and partial-body PET scanning, 3-D data acquisition is clearly
superior to 2-D acquisition. In PET-alone scanners, the emission scan duration is around 10 minutes, followed by 5 minutes of transmission scanning. On PET-CT machines, the same emission times is used; however, low-dose CT data are used for attenuation correction. Iterative reconstruction and filtered back-projection algorithms are available for image reconstruction. The reconstructed FOV is optimized corresponding to the diameter of the head.

For FDG brain imaging under general anesthesia (as in the case of children or patients with claustrophobia), the FDG injection is performed in the conscious patient. The induction of general anesthesia can only be started after a minimum uptake time of 30 minutes so that the anesthetic medications do not influence the uptake pattern in the brain.

**BRAIN WATER ([15O]H2O) PET AND PET-CT IMAGING**

In patients with cerebro-vascular disease, [15O]H2O is used for the determination of regional cerebral perfusion and the perfusion reserve (2). Therefore a baseline exam is followed by a “stress” perfusion exam. The agent causing pharmacologic stress is acetazolamide (21).

**Patient Preparation and Positioning**

Emptying of the bladder prior to starting the examination is necessary to avoid patient discomfort due to excessive filling, because acetazolamide is a diuretic. Informing the patient of these side effects improves cooperation and therefore image quality. Separate placement of catheters in the radial artery for blood sampling in one arm and the cubital vein for injection in the other one precedes the procedure. The sampling of blood is most easily performed with a continuous sampling device (Fig. 19.1). Head positioning and fixation by using the headholder helps to avoid artifacts from head movements. The arms have to be kept out of the scanner gantry to prevent dead-time correction errors due to excessive counts from the vascular injection site in the arms.

**Data Acquisition**

For both rest and “stress” studies, 700 MBq of [15O]H2O is injected. Although the injection can be performed manually, it is advantageous to use an automatic injection device. Data acquisition for one scan is over 60 seconds, starting with the arrival of the bolus (50 kcps) in the brain. Simultaneously, continuous blood sampling with a special sampling device, which is individually calibrated to the PET scanner, is initiated. After dynamic emission data acquisition, a 10-minute transmission scan for photon attenuation correction is performed. At the beginning of the transmission scan, 1 g acetazolamide is injected as a slow bolus over 2 minutes intravenously. Thirteen minutes following the start of the acetazolamide injection, the second scan (same parameters as above), with injection of 700 MBq, is initiated. The whole procedure lasts approximately 30 minutes. In PET-CT systems, instead of the transmission scan, a low-dose CT is used for transmission correction.

**OTHER TRACERS**

Other examinations with PET tracers are performed, but they are mainly used in research protocols and to our knowledge are not reimbursable. Protocols for substances like FET, FLT, and F-choline are similar to those for FDG whole- or partial-body scans, while specific tracers for the heart and brain require organ scans comparable to those listed above. A detailed discussion is beyond the scope of this book, although F-choline use in prostate cancer is discussed in Chapter 49 and 68Ga DOTATOC is discussed in Chapter 43.

**INTRAVENOUS CONTRAST-ENHANCED CT IN PET-CT IMAGING**

Although most PET-CT users consistently give dilute oral CT contrast agent for the examination, things are not as clear with intravenous contrast agents. Intravenous contrast in CT is used for two purposes: lesion characterization and vessel delineation. FDG is frequently much better for characterizing a lesion than intravenous contrast involving tumor imaging, and hence the main reason for giving intravenous contrast agent during the CT examination part is a better delineation of vessels. The CT portion of a PET-CT in tumor staging is typically run as a
head-to-pelvic-floor examination, but the contrast-enhanced study may be relevant only in a subregion (i.e., CT contrast enhancement in the head and neck region of a patient with a head or neck tumor). Once PET-CT data have been obtained, lesions identified on PET are localized in the anatomic CT reference frame. A mental coregistration of anatomic imaging studies done at a different session than PET-CT is simple due to the anatomic details available. Basically, if any knowledge regarding vascular structures, including tumor-related thrombosis, is needed, a contrast-enhanced CT is required as part of the combined PET-CT exam. Contrast enhancement can also be helpful in the exact localization of FDG uptake in certain anatomical structures, like the mediastinum or the retroperitoneum. Also, in tumors with only mild FDG uptake, contrast-enhanced CT might be necessary.

From a clinical point of view, an important issue is whether FDG-PET-CT is used for initial staging or for follow-up after treatment. After treatment, information regarding FDG uptake of the primary tumor and its metastases is crucial, and contrast enhancement possibly can be omitted. Whenever the PET-CT study is used to evaluate a certain disease for the presence or absence of distant metastases, a routine whole-body contrast-enhanced CT study has to be acquired. In a certain number of cases, however, intravenous contrast enhancement will probably not be needed in patient follow-up. Since the CT systems used in many of the new PET-CT scanners are high-end, any desired CT application can be performed without constraints (22, 23). Intravenous contrast is injected preferably by an automated injector (Fig. 19.2).

### DATA TRANSFER AND ARCHIVING

As in a state-of-the-art PET-CT system, all image data, once reconstructed, are stored in DICOM format, they can be viewed on any standard image viewer having imaging-rendering capabilities suitable for coregistered image data viewing (Chapter 10). Furthermore, they can be archived in any desired commercially available archiving system (PACS). However, it has to be pointed out that to date no DICOM format for dual-modality images rendered in coregistered form exists; thus PET and CT data are always stored as separate data sets. If particularly rendered image data combining both modalities have to be stored, they have to be stored as “screen capture” images using standard formats such as jpg or tiff files.

### REFERENCES


INTRODUCTION

Conventional nuclear medicine imaging has proven to be a functional imaging modality, but most nuclear images contain little anatomic information. CT, on the other hand, has demonstrated that it provides excellent anatomic information, but it contains little to no functional information. Image coregistration with various morphologic imaging modalities (CT or MRI) with dedicated software has substantial merit, as it results in significantly improved image interpretation, reducing the amount of uncertainty regarding the location of a lesion observed in a nuclear scan. The disadvantage of using software coregistration is that exactly coregistered patient positioning in both imaging modalities is difficult to guarantee. Extrinsic markers and mattresses providing “cast-like” forms increase the exactness of patient positioning during imaging with the two modalities intended for coregistration but are cumbersome logistically. In bone scans, this is not necessary, as there are sufficient anatomical landmarks on SPECT for later image fusion with coregistration software. Postprocessing to integrate the two data sets from different imaging devices can be time consuming. The breakthrough is achieved with integration of anatomic and functional imaging in one imaging device, a SPECT-CT gamma camera or a PET-CT camera (1,2).

SPECT-CT cameras have the advantage that all conventional nuclear medicine imaging can be performed with them, and when required, integrated anatomic and functional imaging can be done without the need for patient repositioning or rescanning elsewhere. No postprocessing is needed for image coregistration with such a system. Additionally or alternatively, when required, the CT data can be used for attenuation correction to improve SPECT image quality (3–5).
There is one key difference between SPECT-CT and PET-CT. The cost of the integrated device parts is heavily weighted toward CT if a high-end CT is used in a SPECT-CT system, and SPECT data acquisition is substantially slower than PET data acquisition. As a result, it may be much less attractive financially to own a SPECT-CT system with a high-end CT, as the expensive CT idles much of the time when the combined system is used for an examination, and billable examination costs for SPECT-CT are typically lower than for PET-CT.

SPECT-CT HARDWARE

Several systems are commercially available that integrate dual-head gamma cameras with different CT systems (e.g., the Siemens Symbia T, T2, and T6; the Philips Precedence 6 and 16 slice; and the GE Healthcare Infinia and Hawkeye). These systems have all-energy digital detectors with 5/8- or 1-inch special crystals, with an energy range from thallium to fluorodeoxyglucose (FDG). The axial scan length is 40 cm, with an effective field of view of 540 × 400 mm. In certain low-dose CT systems (like the Hawkeye system), the x-ray tube is mounted on the same slip-ring gantry as the two gamma camera heads. In these systems, the tube voltage is 140 kV, and a fixed current of 2.5 mA is used. The acquisition time for one slice is approximately 15 to 20 seconds, using data from a half scan to reconstruct one slice with a standard thickness of 10 mm and a maximum in-plane resolution of 256 × 256. CT data can be used for attenuation correction and anatomic information. No additional postprocessing is necessary for image coregistration. A typical acquisition time for a SPECT-CT on the Hawkeye with a 40-cm axial field of view is 40 to 60 minutes, depending on the type of radiopharmaceutical used and the field of view covered. In other systems, the CT system operates independently and is mounted in line with the center of the SPECT gantry, very much as in PET-CT systems. The CT systems used are medium to high-end and have up to 16-slice CT scanners. The major advantage of such systems is that, like PET-CT systems, they are able to acquire fully diagnostic, intravenous contrast–enhanced CT images in the region of interest.

Figure 20.1  Indium 111 [111In]octreotide scan in a 75-year-old male patient with known liver metastases of an intestinal carcinoid tumor. Whole-body anteroposterior and posteroanterior planar images 5 hours after injection (A) reveal multiple metastases in the liver and an unclear uptake in the dorsal aspect of the thorax. In the maximal intensity projection image (B) of the SPECT acquisition of the chest, uptake is seen in the midthorax. SPECT-CT images clearly locate the radiotracer uptake in a vertebral body in the thoracic spine, representing an osseous metastasis. C: SPECT image. D: CT image. E: SPECT-CT image.
As mentioned, SPECT in bone scans with technetium 99m [99mTc]phosphonates can be followed by a CT scan on a stand-alone machine. For bone scans, attenuation correction is not necessary, and images can be fused after completion of the examination with coregistration software.

QUALITY ASSURANCE AND CONTROL

Quality control consists of daily, weekly, and trimonthly tests. On a daily basis, we always reset the gantry parameters and test the pressure-sensitive detector control for patient safety. Daily quality control for the CT simply involves performing a blank scan. A pulse height analysis acquisition, energy peak position, and energy resolution for the gamma camera are obtained by acquiring data from an extrinsic flood source and applying energy, linearity, and sensitivity corrections. The flood uniformity is calculated by using National Electrical Manufacturers Association (NEMA) standards. A sealed cobalt 57 (57Co) source is preferred to a 99mTc flood source because it is easier to handle and avoids possible contamination. This quality control test confirms the stability of the system performance characteristics.

Weekly quality control involves removing the collimators and performing an intrinsic flood source acquisition with a technetium point source with the recommended dose, distance, and height given by the manufacturer for a specific number of total counts per detector head at a given count rate per second. This weekly intrinsic quality control test calculates the pulse height analysis acquisition, energy peak position, and energy resolution for the gamma camera. A trimonthly center-of-rotation quality control test should also be performed.

PATIENT SCHEDULING

Optimization of patient throughput in a conventional nuclear medicine unit is highly dependent on the radioisotopes used, the imaging protocols, proper patient preparation, and punctual arrival of patients for their examinations. The critical factor for throughput is the decision when to use SPECT-CT clinically. In systems where the CT is relatively slow, the prudent use of CT for attenuation correction for quantification or image fusion for localization of abnormal uptake will determine how many studies can be performed on the camera during the hours of operation.

Therefore, our standard work schedule includes cardiac imaging in the morning and tumor, skeletal, and lung imaging in the afternoon. The critical factor in camera use is the unpredictability of what additional views are needed after planar image acquisition in the latter examination types, a problem not encountered in cardiac imaging. Therefore, tumor, skeletal, and lung SPECT or SPECT-CT imaging is reserved for the afternoons.

PATIENT PREPARATION IN SPECT-CT APPLICATIONS

For adult patient imaging, no premedication is given for most studies at our institution. The patient preparation requirements for SPECT-CT imaging are no different from those for conventional nuclear imaging. If on the basis of a planar scan SPECT or SPECT-CT imaging is required, the field of view can be limited to the area of interest in order to keep the scanning time at a minimum. Although in FDG studies the patient must fast for at least 4 hours prior to injection of the radiopharmaceutical, this is not necessary in standard nuclear medicine and SPECT studies. All other requirements are identical to those for PET patient preparation (see Chapter 19). With children, adequate fixation and/or sedation is necessary to avoid the need for repeat studies due to motion.

IMAGING PROTOCOLS

Protocols for Tumor and Infection Imaging

Four main examination types initially require extended planar imaging but may eventually require SPECT or SPECT-CT images: whole-body iodine 131 [131I] imaging for the staging of thyroid cancer, iodine 123 [123I]MIBG tumor imaging, indium 111 [111In]octreotide tumor imaging, and [99mTc]DPD whole-body bone imaging. In infection imaging performed with 111In-labeled leukocytes or with 99mTc-labeled monoclonal antibodies against granulocytes, the imaging is usually focused on a particular body region.

Whole-body 131I imaging after radioiodine therapy for staging and follow-up of thyroid cancer is performed if the radiation dose emanating from the patient is less than 5 mSv per hour at 100 cm. In this type of scanning, bowel cleansing is the only special preparation. First, a planar whole-body scan is obtained. If an area of uptake suggestive of malignancy is detected, we now directly perform a SPECT-CT of the area in question and no longer acquire additional planar static views.

The average dose, time of image after injection or oral administration, matrix size, collimator used, and speed of scan are all important factors. In short, when it is mandatory to know the exact location of increased radiotracer uptake in the diagnostic workup, the next imaging step is SPECT in combination with low-dose CT transmission imaging, which allows morphologic coregistration. The acquisition parameters are summarized in Tables 20.1 and 20.2. In addition to being used for image coregistration, the CT data also can be used for attenuation correction, but this is typically not necessary.

Whole-body [123I]MIBG is performed on the first day, 5 hours after an intravenous injection of 370 MBq (10 mCi) of [123I]MIBG (or a reduced weight-adjusted dose in children). It is preferable to perform SPECT-CT imaging of the
region of interest demonstrated on the whole-body planar scan directly after the planar acquisition because of the short half-life of \(^{123}\text{I}\) (12.9 hours). The method of choice for \(^{123}\text{I}\)MIBG imaging is SPECT-CT rather than SPECT only, because it adds the missing anatomic landmarks.

Whole-body \(^{111}\text{In}\)octreotide imaging requires a thorough cleansing of the bowel before the intravenous application of the radiotracer and imaging. Bowel preparation prevents increased uptake in the bowel. However, despite this precaution, it is still very valuable to perform routinely SPECT-CT, which helps to distinguish remaining bowel activity from tumor activity. The bowel-cleansing agent is taken by the patient the evening before the first scan and then once again after all first-day imaging is completed.

SPECT-CT imaging in dual-peak parathyroid imaging is performed with \(^{123}\text{I}\) (sodium iodide) and \(^{99m}\text{Tc}\)MIBI for computerized image subtraction. Approximately 2 hours after application of 7.5 to 22 MBq of \(^{123}\text{I}\), 740 to 1,100 MBq of \(^{99m}\text{Tc}\)MIBI are injected intravenously. No special patient preparation is necessary. SPECT of the neck and chest is performed in dual-peak mode in order not to miss any possible ectopic parathyroid adenomas. After completing the examination, images can be subtracted to clearly show parathyroid adenomas. Results should be correlated with ultrasound findings.

For localizing sentinel nodes in ENT and breast cancer as well as in melanoma, SPECT-CT shows increased sensitivity over planar images. After injection of \(^{99m}\text{Tc}\)Nanocoll into the tumor in ENT tumors or in the peritumoral tissue in breast cancer and melanoma, SPECT-CT is performed over the region of interest.

Lung perfusion studies with \(^{99m}\text{Tc}\)MAA can be performed as SPECT studies. SPECT is performed at steps of 3 and 20 seconds per step, with the camera heads at 180°. Using this data, planar images in the usual planes (anterior, posterior, right anterior oblique, left anterior oblique, right posterior oblique, left posterior oblique) can be calculated, as well as cross-sectional images in different planes. SPECT data can be fused with diagnostic CT data, as in angio-CT for the pulmonary vasculature (contrast-enhanced perfusion CT).

In bone scanning, SPECT or SPECT-CT imaging is performed only when the planar whole-body \(^{99m}\text{Tc}\)phosphate bone scan cannot determine the nature of the decreased
or increased activity uptake (Fig. 20.2). Because in bone scanning, reasonable anatomic landmarks are provided by the skeleton, the use of SPECT-CT in such examinations may be less indicated. The use of a stand-alone CT scanner for image fusion, however, will provide much more anatomical information and can be helpful (Fig. 20.3; see also Fig. 6.7B).

In infection imaging, planar imaging of the area of suspected disease (e.g., the lower leg) is performed. If a lesion is detected, then SPECT-CT is added very much as SPECT would be added if only a SPECT system was available.

Protocols for Cardiac Imaging
Cardiac imaging is performed to identify myocardial ischemia and scar, and we use \[^{99mTc}\text{tetrofosmin}\] or \[^{99mTc}\text{MIBI}\] as the imaging agent. A 1-day protocol with an
initial stress test with a pharmacologic substance is used. Adenosine (0.14 mg/kg body weight/min for 7 minutes) is preferred to dipyridamole because of its shorter biologic half-life. In patients with a history of asthma, dobutamine is used to ensure a safer examination. Three minutes after the start of infusion of the pharmacologic stress agent (under continuous ECG control), 300 MBq (8.1 mCi) of \([\text{Tc}^{99m}]\)tetrofosmin or \([\text{Tc}^{99m}]\)MIBI are administered intravenously. Stress gated, attenuation-corrected SPECT-CT images are acquired 30 to 60 minutes after the stress test. To determine perfusion at rest after initial stress imaging is completed, a dose of 750 to 900 MBq (20 to 25 mCi) of \([\text{Tc}^{99m}]\)tetrofosmin or \([\text{Tc}^{99m}]\)MIBI is administered. After 30 to 60 minutes after injection, a resting gated, attenuation-corrected SPECT image is acquired. Although attenuation correction must be acquired twice (stress and rest, 2- to 3-minute duration for the limited cardiac field of view), attenuation correction is necessary to rule out artificial perfusion defects of the posterior cardiac wall, which occur especially in the stress images because of the relatively low dose injected (Fig. 20.4) (6). To date, available systems using a SPECT camera and a high-end CT machine use up to 16-slice technology. Imaging of the coronary arteries using these CT machines is possible, but currently it is thought that at least 64-slice CT scanners are needed to reliably obtain CT coronary angiograms of good quality (see Chapter 32).

CONCLUSION

Whereas nuclear medicine examinations frequently are excellent for lesion detection, localization in the context of sparse anatomy may be problematic. The introduction of SPECT-CT has changed this substantially. It is now possible to have the “best of both worlds,” providing functional information on lesions within a state-of-the-art anatomic context. Although PET-CT applications are relatively well defined at this point, this is not the case for SPECT-CT. The applications are being extended continually with the advent of more sophisticated SPECT-CT systems. It will be necessary to find out how much anatomical information is really needed, since the spatial resolution of SPECT currently is still poor—hardly better than 1.5 cm in most instances. With SPECT-CT, both functional and morphologic information can be obtained in a single imaging session. For optimal workflow, viewing of planar images, and making decisions based on the information provided in them, knowing where to look in more detail with SPECT-CT is useful. Although performing the additional CT data acquisition requires additional imaging time, the time penalty is low for high-end CT systems, but the cost penalty increases with the quality of the CT scanner used in the integrated system. The cost may currently be the most serious obstacle to the rapid development of SPECT-CT.

REFERENCES

Clinical PET-CT and SPECT-CT of the Brain

Clinical positron emission tomography (PET) and single-photon emission computed tomography (SPECT) and integrated imaging of the brain combining PET or SPECT with magnetic resonance imaging (MRI) or computed tomography (CT) by software-based image fusion have been around for a long time, and one of the early successes of PET imaging was in imaging of the brain. That integration was possible in the brain is due to the relatively simple operations needed to coregister molecular and anatomic data. Some of the basic advantages of PET over other methods have initially been understood in the brain, notably that fluorodeoxyglucose (FDG) frequently shows the highest accumulation in areas where a tumor is most malignant. Many quantitative concepts have also been developed in brain PET and are still best applied when imaging the brain. In addition, PET is an excellent imaging modality for studying various brain functions relatively noninvasively and quantitatively, and some of these research applications, such as quantitative brain perfusion imaging, have gained clinical importance as well.

A major drawback of brain PET imaging with FDG is that the brain is an obligatory user of glucose. As a result, the lesion-to-background ratio in FDG brain PET is not as desirably high as it is in PET imaging in the body. As a result, interesting new radiopharmaceuticals have been evaluated in recent years and may compensate for this disadvantage of FDG brain PET. For example, imaging with amino acids such as fluoroethyl tyrosine or carbon 11 methionine may be of relevance in the brain, as...
amino acids are not strongly taken up by the cerebral cortex, resulting in a high lesion-to-background ratio.

PET-CT and SPECT-CT are likely not to be as relevant in brain imaging as in body imaging for two reasons. First, the prime morphological imaging modality in the brain is not CT but MRI, which also yields some function information; second, image coregistration in the brain is much easier than in the body, since it requires the coregistration of a rigid object imaged with two modalities rather than the coregistration of “flexible” and variable body structures (see Chapter 10). Thus, in the brain the CT portion of PET- and SPECT-CT is primarily used to obtain attenuation correction data.

Despite some disadvantages of PET imaging in the brain and the lesser importance of hardware coregistered anatomomolecular imaging, brain PET remains important, and these clinical indications are discussed in this part of this book.
The Normal Brain Scan

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In order to interpret clinical brain positron emission tomography (PET) scans, it is important to know the appearance of the tracer distribution in the normal brain. For clinical purposes, the most commonly used tracer is fluorodeoxyglucose (FDG). An example of a normal FDG distribution is shown in Figure 21.2. In healthy tissue, the FDG distribution reflects cerebral glucose metabolism, which is most prominent in gray matter. The brain is the organ with the highest glucose consumption in the body. Consequently, there is high physiological FDG uptake in gray matter. FDG uptake in the brain is heavily dependent on the plasma glucose level, and with increasing plasma glucose levels, cerebral FDG accumulation decreases. This can be a problem in PET scans of diabetics. The high physiological FDG uptake in gray matter is a problem if lesions close to or within gray matter structures have to be identified or evaluated, especially if they demonstrate FDG uptake similar to that of gray matter. In such cases, it is mandatory to compare the FDG scan with an MR scan, which ideally should be available in digital format for image coregistration.

Cerebral perfusion can be measured with H$_2^{15}$O and PET; because of the tight coupling of glucose metabolism and blood flow in the brain, FDG and H$_2^{15}$O have the same qualitative appearance. With SPECT, there is no tracer to visualize glucose metabolism; however, blood flow imaging using technetium 99m [$^{99m}$Tc]HMPAO or [$^{99m}$Tc]ECD is very common.

In tumor imaging, amino acid analogs and choline derivates open interesting perspectives.

SPECIFIC TRACERS

FDG

The great majority of the clinical brain scans are performed with fluorodeoxyglucose (FDG). It is important to bear in mind that FDG traces glucose metabolism and that all structures with high glucose demand will demonstrate high FDG uptake. In the head, not only the brain but also muscles, glands, and lymphatic tissue may display high FDG accumulation (see Fig. 33.21). An example of increased FDG uptake in the eye muscles is shown in Figure 21.1, and when searching for tumor metastases, the high uptake of FDG may be an imaging pitfall. In a healthy brain, it is actually possible to determine glucose metabolism quantitatively. The method was introduced by Sokoloff et al. (1). However, quantification of glucose metabolism is complex and usually not required for clinical purposes. Luckily, simple FDG uptake after a certain period is sufficient for clinical diagnosis. Typically, scanning is initiated 40 minutes following injection of FDG. In 3-D mode, enough counts are acquired during a 10-minute scanning period if the injected activity was on the order of 100 to 200 MBq. With lower activity, the scanning duration has to be extended accordingly.

Although the mass of the brain is only a small fraction of the mass of the whole human body, it utilizes about 25% of the total metabolic energy. Most of the energy demand is believed to be necessary for the maintenance of intraextracellular ionic gradients by active sodium–potassium pumps. Moreover, the highest glucose consumption is believed to be localized around the pre- and postsynaptic zone. An excellent introduction on brain energy metabolism is given by Magistretti (2). Only in particular circumstances can substrates other than glucose be utilized by the brain.

A typical normal brain scan, together with a T1-weighted MR image, is shown in Figure 21.2. The resolution of the PET scanner used was around 6 mm (full width
at half maximum [FWHM]), while the cortex is approximately 2 to 4 mm thick. As a result, the actual concentration of FDG in the cortex is somewhat underestimated. Nevertheless, there is reasonable delineation of anatomic structures. It is easy to identify the cortex, the putamen, the head of the caudate, the thalamus, the cerebellum, and the brain stem. The high physiological FDG uptake in the brain is ideal for the study of brain metabolism.

For instance, cerebral activation during and shortly after injection of the tracer will lead to increased FDG uptake. An example is shown in the left panel of Figure 21.3, where right half-field visual stimulation was applied (inverting...
concentric rings). The exposure started immediately before the injection and lasted for 10 minutes. On the scan, it is evident that the stimulation led to an activation primarily of the left visual cortex. In contrast, the subject on the right side of Figure 21.3 had eyes closed during and after injection. Under these conditions, the visual cortex demonstrates a similar FDG uptake as the rest of the cortex. The visual cortex is one of the structures with the highest increase in glucose metabolism during stimulation. If one exposes subjects to a stroboscopic light, the increase may reach 30%. In contrast, cognitive performance leads to an increase on the order of 2% to 5%. For brain scanning, it is reasonable to inject the patients under standardized conditions, which normally include injection in a darkened room. Figure 21.4 shows that it is the first period following injection that drives FDG uptake. Fifty percent of FDG uptake at 60 minutes is already accumulated after 10 minutes. Although the bulk of energy demand is located in gray matter, white matter also increases its glucose metabolism in conjunction with increased neural activity.

Fluoroethyl Tyrosine

For clinical diagnosis, it is important that physiologically increased FDG uptake is not mistaken for a pathology. This is rarely a problem. More of a problem is the high gray

Figure 21.3 FDG uptake pattern in a subject who was visually stimulated during the uptake phase (left panel). Because the stimulation was limited to the right visual field, there is increased FDG uptake predominantly in the left side of the visual cortex (arrow). The subject on the right kept eyes closed during the uptake phase, and consequently the uptake in the visual cortex is similar to that in the rest of the gray matter.

Figure 21.4 Time course of FDG concentration in gray matter (open circles) and plasma (solid line) following an intravenous bolus injection. In plasma, the maximum tracer concentration is reached at 90 seconds following a rapid increase. The FDG concentration in gray matter is continuously rising until the end of the study, at 60 minutes. Roughly 50% of FDG uptake at 60 minutes is already taken up at 10 minutes.

Figure 21.5 Normal distribution of three different tracers. A: A T1-weighted MR. B: The blood flow as measured with $\text{H}_2^{15}\text{O}$. C: A SPECT scan following injection of $\text{Tc}^{99m}$ECD, a common blood flow tracer. D: The normal distribution of $\text{F}^{18}$fluorocholine (FCH), a tracer used in tumor patients. The normal uptake of FCH is very low.
matter uptake of FDG itself. Sometimes it is difficult or impossible to identify smaller lesions that are within or close to gray matter, especially if their FDG accumulation is similar to that of gray matter. A solution to this problem is offered by other tracers. For instance, the amino acid analog $^{18}$F-fluoroethyl tyrosine (FET) has been shown to accumulate in tumors. Since the uptake in normal gray matter is low, the tumor is very often better delineated than with FDG. Another advantage of FET is that it does not accumulate in inflammatory cells (3). On the other hand, uptake of this tracer is high in most tumors, and therefore a grading does not seem possible. An excellent application of this tracer is in the differentiation of radiation necrosis from recurring tumor.

**Water**

Another clinically used tracer is $^{15}$O water for the evaluation of cerebral blood flow. An example of a $^{15}$O water scan is demonstrated in Figure 21.5. Due to the tight coupling of glucose metabolism and blood flow in the brain, FDG and $^{15}$O water images have a similar qualitative appearance. Because of the shorter acquisition time (1 minute) the $^{15}$O water images look noisier.

**Other Tracers**

With SPECT, cerebral blood flow can be imaged using $^{99m}$Tc-HMPAO or $^{99m}$Tc-ECD. An example is shown in Figure 21.5. In tumor imaging, there are multiple new tracers targeting different aspects of tumor biology. At our center, we use FET to measure amino acid transport and $[^{18}$F$]$Fluorocholine (FCH) to identify tumors. Because FCH uptake in normal brain tissue is very low (Fig. 21.5), the tumor-to-background ratio is usually very high.

**REFERENCES**


Brain Tumors: 
Astrocytoma, 
Oligodendroglioma, and 
Glioblastoma 
Images with PET and SPECT

Lutz W. Kracht  Karl Herholz  Stefan Vollmar  Andreas H. Jacobs

Primary brain tumors arise from different types of brain cells: glial cells, neurons, neuroglial precursor cells, pinealocytes, the meninges, choroids plexus, pericytes of the vessels, hypophysis, and lymphocytes. The most common primary brain tumors in adults are gliomas and meningiomas. The grading of brain tumors is based on histopathological changes according to the World Health Organization (WHO), the most common and also most fatal being the glioblastomas, corresponding to WHO grade IV. A better understanding of glial tumorigenesis is crucial for the development of specific molecular therapeutic targets to overcome current therapeutic limitations. Molecular alterations have been identified that indicate the therapeutic response of patients and thus are prognostically relevant. All therapeutic interventions are palliative and therefore must preserve or improve brain function rather than sacrifice it for some tumor treatment of limited efficacy. On the other hand, tumor treatment should be as aggressive and effective as possible to save years of life. Current therapeutic strategies in the treatment of brain tumors, such as stereotactic radiation therapy, stereotactic brachytherapy, and neuronavigation in open surgery, rely on preoperative imaging data. As therapeutic strategies improve in the coming years and patient therapy becomes more and more individually adapted, it will be of utmost importance to gather full information from the different anatomic, metabolic, and functional imaging modalities for therapy planning.

INTRODUCTION

Primary brain tumors arise from different cell types of the brain: glial cells, neurons, neuroglial precursor cells, pinealocytes, the meninges, choroids plexus, pericytes of the vessels, hypophysis, and lymphocytes. The incidence of primary brain tumors varies between the different subtypes. The most common primary brain tumors in adults are gliomas and meningiomas. For gliomas, the incidence is 6 to 8 in 100,000, with approximately 50% belonging to
malignant subtypes. Lower-grade tumors tend to occur in younger patients, whereas higher-grade tumors are more frequent in older patients. Gliomas are divided histologically into astrocytomas, oligodendrogliomas, mixed oligoastrocytomas, ependymal tumors, and tumors of the choroid plexus. Grading is based on histopathological changes according to the World Health Organization (WHO). The most common and also most fatal primary brain tumors are the glioblastomas, corresponding to WHO grade IV (1).

Together with all intracranial neoplasms, the glioblastoma is the second most common cause of death due to an intracranial disease after stroke. Despite aggressive multimodal treatment strategies (surgery, radiation, chemotherapy), the median survival of patients with gliomas is limited, depending on the grade and age at diagnosis; it varies from 1 year for glioblastoma to 2 to 3 years for a grade III glioma and 5 to 10 years for a grade II glioma.

A better understanding of glial tumorigenesis is crucial for the development of specific molecular therapeutic targets to overcome current therapeutic limitations. A complex series of molecular changes occurs that results in dysregulation of the cell cycle, in alterations of apoptosis and cell differentiation, and in neovascularization as well as tumor cell migration and invasion into the brain parenchyma. During progression from low-grade astrocytoma (WHO grade II) to anaplastic astrocytoma (WHO grade III) and to glioblastoma multiforme (WHO grade IV), a stepwise accumulation of genetic alterations occurs. Whereas TP53 mutation and PDGF and PDGFR overexpression represent early changes during low-grade glioma development, progression to anaplastic astrocytoma is associated with pRB alteration and loss of heterozygocity (LOH) of 19q and further malignant progression to glioblastoma, including LOH 10q and mutations of the PTEN gene (1,2). These secondary glioblastomas, which develop from better differentiated astrocytomas, can be distinguished from primary de novo glioblastomas on the basis of molecular genetic findings, with amplification and/or overexpression of the EGFR, p16 deletion, PTEN mutation, pRB alteration, and LOH 10p and 10q associated with primary glioblastoma (1,2).

Most importantly, molecular alterations have been identified that indicate the therapeutic response of patients and thus are prognostically relevant: anaplastic oligodendrogliomas with LOH 1p and/or LOH 19q are characteristically sensitive to PCV (procarbazine, lomustine [CCNU], and vincristine) chemotherapy, and patient survival can be significantly prolonged (3).

In the treatment of brain tumors, the interaction and balance between tumor and brain function is particularly delicate, especially in gliomas, because of their invasive growth and the lack of curative treatment for most of them. Thus, all therapeutic interventions are palliative and therefore must preserve or improve brain function rather than sacrifice it for some tumor treatment of limited efficacy. On the other hand, tumor treatment should be as aggressive and effective as possible to save years of life. Current therapeutic strategies in the treatment of brain tumors, such as stereotactic radiation therapy, stereotactic brachytherapy, and neuronavigation in open surgery, rely on preoperative imaging data. As therapeutic strategies improve in the coming years and patient therapy becomes more and more individually adapted, it will be of utmost importance to gather full information from the different anatomic, metabolic, and functional imaging modalities for therapy planning.

PET AND SPECT TRACERS

Several PET and SPECT tracers have been used in patients with brain tumors in the past decades, with some success. We will not review all of these tracers but focus on the three tracers that have been shown to be most useful in gliomas.

2-[18F]Fluoro-2-Deoxy-d-Glucose

Glucose consumption measured by 2-[18F]fluoro-2-deoxy-d-glucose (18F-FDG)-PET is increased in most malignant gliomas. Although 18F-FDG uptake correlates with the degree of malignancy, there are concerns about the use of the 18F-FDG model to calculate the cerebral metabolic rate of glucose (CMRGlc) in brain tumors. The lumped constant used in the model to estimate glucose consumption from 18F-FDG uptake seems to be higher in tumors and therefore overestimates the glucose consumption if the value for the normal brain is used. Changes in the lumped constant in tumors compared with normal brain may be due to increased expression of hexokinase II in tumors. Hexokinase II has a higher affinity for 18F-FDG than does hexokinase I, which is expressed in the normal brain (4). Increased transport may also play a role, together with increased glycolysis compared with the oxidative metabolism of glucose.

In clinical routine, 18F-FDG images are analyzed visually or the relative 18F-FDG uptake compared with normal brain structures unaffected by the tumor is calculated. Preferably, uptake in the cerebral cortex or the deep white matter and average uptake in the regions of interest are used to calculate relative uptake ratios.

PET studies at the Max Planck Institute are performed either on an HRRT or ECAT EXACT HR (Siemens CTI, Knoxville, TN) (5,6). For an 18F-FDG investigation, the patient is asked to fast on the day of the exam and is encouraged to drink water to facilitate clearance of the FDG from the body. The standard dose of administered 18F-FDG is 10 mCi for adults. In our institute, a 6- to 10-minute transmission scan (depending on scanner) is performed prior to injection of the tracer. The patient is instructed to keep eyes shut, especially when the tumor is located next to or in the occipital lobe. The tracer accumulation is recorded in 3-D mode over 60 minutes in 47 transaxial slices from the entire brain.
from 20 to 60 minutes after tracer injection is used for image reconstruction. Images are reconstructed using Fourier rebinning and filtered back-projection with a ramp filter. Images are corrected for scatter, attenuation, and random coincidences.

**Amino Acid Tracers**

Several studies using different amino acids tracers demonstrate that increased amino acid uptake in gliomas is not a direct measure of protein synthesis but rather seems to be due to increased transport mediated by type L amino acid carriers (7–9). Miyagawa et al. demonstrated in a rat tumor model that facilitated transport of amino acids is up-regulated and suggested that tumors can influence transporter expression in their vasculature (9). At the normal blood–brain barrier, the sodium-independent L-transporter system in the luminal membrane of endothelial cells is the main mechanism of methionine and tyrosine transport into brain tissue (10–13). Movement of an amino acid across sodium-independent transporter systems is driven by its extra- to intracellular concentration gradient, but it is frequently associated with countertransport of a second amino acid. The gradient of this second amino acid can be established by one of the sodium-dependent carriers, like the A system that is located in the abluminal endothelial cell membrane at the blood–brain barrier and transports amino acids with short polar side chains (11–13). Transport system A has been shown to be overexpressed in neoplastic cells and seems to be positively correlated with the tumor cell growth rate (14). This increased growth rate requires an efficient and increased supply of nutrients for protein synthesis, energy metabolism, and proliferation. Therefore, elevated transport of amino acids not only is a result of increased protein synthesis but also reflects the increased demand for the different metabolic activities in the tumor cell. It is well known that tumors can influence the growth of their vasculature and therefore can regulate their increased nutrient supply, including the supply of amino acids (15).

Amino acid uptake in the normal cortex is higher than in white matter, but relatively low compared with the high background activity of the normal cortex in $^{18}$F-FDG-PET (Figs. 22.1 and 22.2).

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**Figure 22.1** MRI (A,D), $^{18}$F-FDG- (B,E) and $^{11}$C-MET-PET (C,F) in low-grade (A,B,C) and high-grade (D,E,F) gliomas. $^{18}$F-FDG clearly distinguishes between the low-grade and high-grade tumors, in contrast to MRI. $^{11}$C-MET shows higher uptake in the malignant tumor, but a clear differentiation is not possible in these examples. (See also Cases 81 and 82). (Reproduced with permission from Jacobs AH. PET in gliomas. In: Schlegel U, Weller M, Westphal M, eds. Neuroonkologie. Stuttgart: Thieme Verlag; 2003:72–76.)
Methyl-[11C]-L-Methionine

The most frequently used radiolabeled amino acid is methyl-[11C]-l-methionine (11C-MET). Radiochemical synthesis is not difficult and provides high levels of radiochemical without the need for complex purification steps (16). Other amino acid tracers, like O-(2-[18F]fluoroethyl)-L-tyrosine (18FET) or (18F)fluoro-Dopa (18F-Dopa), are transported in the brain and tumor, but no further metabolization takes place; thus they reflect transport only. 11C-MET, in contrast, is used in different metabolic pathways: (a) incorporated into proteins, (b) used for methylation, and (c) is needed for DNA translation.

The ratio of 11C-MET uptake to background activity in tumors is in the range of 1.2 to 6.0 in gliomas. Uptake correlates to cell proliferation in cell culture (17), Ki-67 expression (18), proliferating cell nuclear antigen expression (19), and microvessel density (20), indicating its role as a marker for active tumor proliferation and angiogenesis. The highest uptake in gliomas is observed in anaplastic oligodendrogliomas WHO grade III.

L-3-[123I]Iodo-Alpha-Methyl Tyrosine

L-3-[123I]Iodo-alpha-methyl tyrosine (123I-MT) is a transport-only SPECT tracer. It is specifically transported via the L-transporter system, but as an artificial amino acid it does not undergo further metabolization or deiodination (21–23). In comparison with PET amino acid tracers, the main uptake of 123I-MT arises within the first 30 minutes after tracer injection, and the tracer is slowly washed out of tumor tissue (22,23). Tumor-to-background ratios in brain tumors are in the range of 1.5 to 2.5 (24). A study by Langen et al. (25) showed comparable results for 123I-MT and 11C-MET in patients with brain tumors.

Other Amino Acid Tracers

Various amino acids have been labeled for tumor imaging, especially with PET. As carbon 11 (11C)-labeled tracers can only be used in centers with an on-site cyclotron, there were several attempts to label amino acids with 18F-fluorine to facilitate a wider use of amino acid tracers. Clinically relevant findings have been obtained mainly with two of them: (a) 18FET showed results similar to those for 11C-MET and (b) 18F-Dopa, a very interesting amino acid tracer that has been successfully used in movement disorders for several years, also showed results comparable to those for 11C-MET in an initial study by Becherer et al. (26,27).

Data Acquisition of Amino Acid Tracers

Images in amino acid studies are usually acquired within the first hour after tracer injection. The main uptake in the tumor arises within the first 20 to 30 minutes after tracer injection, and a steady state is reached within the first 45 minutes (24). Patients should be studied under fasting conditions or should be on a protein-free diet on the day of the investigation, because extracellular amino acid concentrations clearly influence transport. Transport is concentration dependent, and the labeled tracer competes against the unlabeled amino acids at the transporter molecule (10,13).
In our institution, we use the following protocol for $^{11}$C-MET: After a 10-minute transmission scan, 740 MBq (20 mCi) are injected intravenously. Tracer accumulation is recorded in 3-D mode over 60 minutes from the entire brain. Summed activity from 20 to 60 minutes after tracer injection is used in our institution for image reconstruction. Images are reconstructed using Fourier rebinning and filtered back-projection with a ramp filter. Images are corrected for scatter, attenuation, and random coincidences. Other protocols use acquisition times from 0 to 20 minutes or from 20 to 40 minutes. For the implementation of $^{11}$C-MET images in the neuronavigation system or the stereotactic planning system, excellent image quality is necessary. To minimize influence from blood activity and to optimize imaging statistics, the later and longer acquisition protocol is preferable.

**IMAGE COREGISTRATION**

Image registration is extremely important for the accurate correlation of abnormalities on the MRI with the findings on the PET or SPECT scan (see also Chapter 10). Different modalities, such as $^{11}$C-MET and $^{18}$F-FDG, can be coregistered with MRI in glioma patients (see Fig. 22.2). Because we have established a common procedure with the different departments of the University Hospital of the University of Cologne involved in the treatment of patients with gliomas, most of the patients receive a precontrast T1-weighted MR scan, an axial T1-weighted postgadolinium MR scan, and a T2-weighted MR scan with an isotropic voxel size of 1 mm. This procedure not only allows coregistration of the different image modalities but also helps when PET images are used for biopsy planning, neuronavigation-guided surgery, and target volume planning in stereotactic brachytherapy using $^{125}$I iodine seeds. For coregistration and conversion of the different file formats, we use an in-house-developed software called VINCI (28). A fully automated coregistration tool is implemented within this software that allows very fast and robust coregistration of different modalities. The coregistration is based on a mutual information algorithm and is optimized for brain imaging (28). All coregistered images can be stored in different file formats, such as the Stryker-Leibinger format for use in the stereotactic planning system or the DICOM format for use in the BrainLAB neuronavigation system (Fig. 22.3). Other features include a fusion of four different image modalities in the same

**Figure 22.3** Integration of $^{11}$C-MET uptake above a threshold of 1.3 compared with a corresponding contralateral region (normalized $^{11}$C-MET-PET, light blue area on the screen) into a neuronavigation system to optimize extent of surgery. The position of the tip of the pointer is visualized on the screen (green line).
display and a semiautomated calculation of areas of increased $^{11}$C-MET uptake above a certain threshold.

If the images are not registered, the determination of the location of a small abnormality on the MR images cannot be accurately identified on the PET and SPECT scans. The registration with MRI permits the accurate characterization of even small MRI lesions. The image registration permits the interpreting physician to be more accurate and confident in the diagnosis.

**APPLICATIONS**

**Imaging for Primary Diagnosis**

At the point of first diagnosis, brain tumor patients most often have first-time generalized or focal seizures or demonstrate focal neurological symptoms. They are referred to CT or MRI very rapidly, and in most of the patients the diagnosis of a primary brain tumor can be made from MRI alone. But sometimes other differential diagnoses, like acute inflammatory lesions or ischemic or hemorrhagic stroke, cannot be excluded by MRI findings. Differentiating tumors from nontumorous lesions with $^{18}$F-FDG is difficult because of the high $^{18}$F-FDG uptake in the normal cortex (Figs. 22.1 and 22.4). Low $^{18}$F-FDG uptake is frequently seen in brain tumors, and low-grade gliomas in particular show $^{18}$F-FDG levels comparable to those of white matter and cannot be distinguished from nontumorous lesions, like inflammation or acute stroke (see Fig. 22.3). On the other hand, high $^{18}$F-FDG uptake is not specific for brain tumors but may also be seen in inflammatory lesions (e.g., sarcoidosis, acute demyelinating encephalomyelitis), focal epilepsy, and recent ischemic infarcts with nonoxidative glycolysis. In $^{18}$F-FDG-PET,

![Figure 22.4](image-url)  
*Figure 22.4. $^{18}$F-FDG uptake patterns of different glial tumors. Low-grade tumors (All, OII) show an uptake in the range of that of white matter and clearly below that of gray matter, with the exception of an oligodendroglioma WHO grade II (2 row, 2 line). Differentiation between tumor and inactivated cortex is impossible. All malignant tumors (All, OII, GB) show an $^{18}$F-FDG uptake comparable to that of gray matter. Only an astrocytoma WHO III appears to have an uptake in the range of that of white matter (All, astrocytoma WHO grade II; All, astrocytoma WHO grade III; OII, oligodendroglioma WHO grade II; OIII, oligodendroglioma WHO grade III; GB, glioblastoma WHO grade IV).*
Chapter 22: Brain Tumors: Astrocytoma, Oligodendroglioma, and Glioblastoma Images

IMAGING FOR INTERVENTION PLANNING

Delineation of Tumor Extent

In general, the tumor margins are defined by MRI or CT. The contrast-enhancing lesion in standard T1-weighted MR or CT reflects regions of blood–brain barrier breakdown and is taken as a marker for active tumor tissue. Yet, contrast enhancement is an inaccurate indicator of active tumor. It is false negative in viable tumor parts that do not yet show anaplasia and blood–brain barrier breakdown, and it is false positive in necrotic areas with blood–brain barrier disruption. Serial biopsies of patients undergoing craniotomy for malignant gliomas reveal tumor cells more than 3 cm from the CT contrast-enhancing margin (38,39). Moreover, MRI spectroscopy data also suggest that standard T1-weighted enhanced MRI may inadequately represent the volumes of metabolically active tumor (40), and T2-weighted MRI abnormalities, historically believed to represent edema, are known to include microscopic disease extension, as verified by biopsy studies by Kelly et al. (39). Thus, advanced therapeutic strategies such as neuronavigation in open surgery, stereotactic brachytherapy, radiosurgery, and conventional radiotherapy need a more accurate definition of tumor extent for target volume planning than is provided by standard MRI or CT (see Fig. 22.3).

Many studies have shown that the margins of tumors in 11C-MET and 123I-MT are frequently wider than they appear in MRI or CT (41). This phenomenon is even more pronounced in low-grade tumors and in diffuse gliomatoses because of often missing contrast enhancement in MRI (42). 11C-MET-PET is superior to 18F-FDG-PET in the assessment of tumor extent (43–45) (Figs. 22.1 and 22.3).

Bergstrom et al. described a patient with an anaplastic astrocytoma who was examined with CT and PET using [68Ga]EDTA, [18C]glucose, and 11C-MET (43). The patient died 15 days after the 11C-MET-PET, and histological evaluation at autopsy showed excellent agreement between tumor extent and 11C-MET uptake. More than 50% of the tumor would not have been detected without the 11C-MET-PET (43). Studies integrating 11C-MET-PET images in radiation therapy planning procedures confirm the discrepancies between MRI, CT,

|TABLE 22.1| 11C-MET UPTAKE RATIOS OF GLIOMAS |
|---|---|---|---|---|
|Histological Type| I| II| III| IV|
|Astrocytoma| 2.0 ± 0.6| 1.7 ± 0.7| 2.9 ± 0.9| 2.9 ± 0.7|
|Oligoastrocytoma| 1.8 ± 0.4| 3.5 ± 2.4| 4.5 ± 1.7|
|Oligodendroglioma| 2.5 ± 0.5| 4.5 ± 1.7|

tumors often demonstrate a wide rim of reduced 18F-FDG uptake, which might be also due to functional inactivation by the infiltrating tumor growth or edema formation (see Figs. 22.1, 22.3, and 22.4).

For amino acid tracers, Herholz et al. (29), in a study of 89 patients, found a sensitivity of 76% and specificity 87% for the discrimination of brain tumors from nontumoral brain lesions with 11C-MET. Similar results were observed for 123I-MT (23). Low-grade tumors in particular are better detected by amino acid tracers because of the low background activity of normal brain (see Fig. 22.1). On the other hand, a small percentage of low-grade astrocytomas demonstrate only low amino acid tracer uptake, and again acute inflammation or ischemic stroke might present with increased amino acid uptake (30,31). Brain lesions that show hypo- or isometabolism on 18F-FDG PET can be detected and differentiated with high sensitivity and good contrast using 11C-MET. 11C-MET can provide additional information when used in combination with 18F-FDG-PET in the evaluation of these patients (18).

The level of accumulation of 18F-FDG in a primary brain tumor correlates with the tumor grade and tumor cell density (32–34). Low-grade tumors have 18F-FDG uptake levels similar to or less than that of normal white matter, whereas high-grade tumors have 18F-FDG uptake levels equal to or exceeding that of normal gray matter (see Figs. 22.1 and 22.3). In a study of 58 patients tumor-to-white matter (T/WM) and tumor-to-gray matter (T/GM) ratios were able to distinguish benign tumors (grades I and II) from malignant tumors (grades III and IV) (35). T/WM ratios greater than 1.5 and T/GM ratios greater than 0.6 showed a sensitivity of 94% and a specificity of 77% for the detection of malignant tumors (35).

Although there is a good correlation between amino acid uptake and histological tumor grade, there are overlaps in tracer uptake in the different histological tumor types and grades (Table 22.1), and amino acid tracers might not be suitable for noninvasive grading (29,36). Other studies found good differentiation properties between high- and low-grade tumors (37). Generally, our experience indicates it is very difficult to determine the histological grade from 11C-MET PET without knowing the histological subtype or without additional information from MRI or CT (see Fig. 22.1).
and ¹¹C-MET-PET (46,47). ¹¹C-MET-PET detects solid parts of brain tumors as well as infiltration zones with high sensitivity and specificity (48). Therefore, ¹¹C-MET uptake is an excellent method for defining tumor extent for further therapy planning (see Fig. 22.3), although the extent of WHO grade II astrocytomas is underestimated by ¹¹C-MET-PET in 20% of patients (48).

**Biopsy Planning**

Gliomas are characteristically heterogeneous and may present with areas of different histological grade when they progress to a more malignant subtype. The part of the tumor that has already progressed to a more malignant grade might not show contrast enhancement in MRI or CT. Therefore, MRI- or CT-guided biopsies may be associated with significant sampling error and potential mis-staging. Trajectory planning in stereotactic biopsy based on ¹¹C-MET or ¹⁸F-FDG-PET improves the detection of tumor tissue compared with anatomical imaging alone (37,49–52).

**IMAGING OF TREATMENT EFFECTS AND DIFFERENTIATION OF TUMOR FROM NECROSIS**

After tumor resection, normal postsurgical changes do not show increased FDG uptake. Therefore, hypermetabolic activity after surgery is highly suspicious for residual tumor, and ¹⁸F-FDG-PET can be performed within a few days after surgery (53).

One of the most important applications of PET and SPECT tracers after the treatment of gliomas is in the differentiation of radiation-induced changes such as necrosis and recurrent or residual tumor after radiation therapy. Generally, the question “tumor or necrosis?” is an oversimplification, as in most cases both tumor and necrotic tissue can be found next to each other.

Some studies found that ¹⁸F-FDG-PET is not suitable for detecting residual tumor soon after therapy (54,55). Several weeks after treatment, the therapeutic effects of radiotherapy can be visualized. ¹⁸F-FDG shows a transient increase of uptake in the initial phase caused by infiltrating macrophages consuming ¹⁸F-FDG (56–58). A newly detected hypermetabolism weeks after therapy indicates a recurrent tumor and progression from low-grade to high-grade glioma (53,59). The sensitivity of ¹⁸F-FDG-PET was 75% and the specificity 81% for the detection of recurrent tumor versus radiation necrosis in a study by Chao et al. (60,61). Another study, by Leveiller et al. (62), showed that there is a certain overlap in ¹⁸F-FDG uptake in recurrent tumor and radiation necrosis. The disadvantages of ¹⁸F-FDG-PET include accumulation of ¹⁸F-FDG in macrophages that may infiltrate the sites that received radiation therapy. Therefore, radiation necrosis may be indistinguishable from recurrent tumor. It should be noted that in patients receiving corticosteroids as
symptomatic treatment, evaluation of $^{18}$F-FDG-PET may be hampered by a reduced cortex-to-white matter ratio (63). Roelcke et al. (64) found that patients with brain tumors have decreased glucose metabolism in the contralateral cortex, and the degree of decrease correlates with tumor size. This phenomenon might also be caused by corticosteroids, but a functional inactivation of the contralateral hemisphere by deafferentiation of the input from the ipsilateral hemisphere cannot be excluded (64). In $^{18}$F-FDG-PET, tumors often demonstrate a wide rim of reduced $^{18}$F-FDG uptake, which might also be due to functional inactivation by the infiltrating tumor and the edema formation (see Figs. 22.1, 22.2, and 22.4).

Amino acid tracers seem to be more useful in the differentiation between postradiation changes and recurrent tumor. Necrosis and glioses after therapy show a reduction of amino acid uptake, in contrast to recurrent or residual tumor growth. Therefore, $^{11}$C-MET-PET and $^{123}$I-MT-SPECT successfully differentiate between recurrent tumor and radiation necrosis, with the detection of recurrent tumor at high sensitivity and high specificity (48,65–68) (Figs. 22.5 and 22.6). Wurker et al. (55) found a dose-dependent reduction in uptake in low-grade gliomas up to 1 year after brachytherapy, whereas $^{18}$F-FDG-uptake was unchanged.

**MONITORING CHEMOTHERAPY**

As with other malignancies, it is very important to detect responders and nonresponders as early as possible during chemotherapy treatment. It is crucial not to forfeit bone marrow reserve and quality of life to an ineffective treatment.

Early evaluation of tumor metabolic response was performed by using $^{18}$F-FDG-PET in recurrent high-grade brain tumors.

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**Figure 22.6** Chemotherapy monitoring. Follow-up of a patient with a recurrent glioblastoma in the right temporal pole. During months 0 to 14, a clear decrease of $^{11}$C-MET uptake can be observed, in contrast to the lack of change in signal abnormalities in contrast-enhanced MRI. The patient stayed in complete remission until month 36. A small contrast enhancement appeared next to the head of the right caudate nucleus and showed rapid growth within 3 months, with infiltration of the left hemisphere. The patient died a few months later.
glia in brain tumor patients are promising (73–74).

CONCLUSION

PET and SPECT have a multitude of applications in the management of brain tumors. In most instances, close correlation of the images with MRI or CT is mandatory. The major applications are in tumor grading, intervention planning and guidance, and distinguishing between tumor recurrence and necrosis. The use of the various tracers available for the different indications is summarized in Table 22.2.

REFERENCES


Chapter 22: Brain Tumors: Astrocytoma, Oligodendroglioma, and Glioblastoma Images


Approximately half of all malignancies in the brain are gliomas, and the other half are metastases, primarily intracranial lymphomas and nongliomatous primary brain tumors, the most frequent ones being meningiomas, pituitary adenomas, and schwannomas. Smaller studies have evaluated the use of PET in patients with intracranial metastases and primary intracerebral lymphoma in acquired immunodeficiency syndrome (AIDS) patients, but no extensive systematic series are available, including none with image coregistration between PET and CT or PET and MRI.

Fluorodeoxyglucose PET (FDG-PET) lacks sensitivity for the detection of brain metastases, as metastases may show both hyper- and hypometabolism of FDG, even among metastases in the same patient. Other and new radiopharmaceuticals such as carbon 11 (¹¹C) methionine (MET), [¹⁸F]methyltyrosine or ethyltyrosine, and ¹³C- or ¹⁸F-labeled thymidine or choline may be useful, especially in combination with MRI or CT in individual patients in whom precise delineation of metastases is mandatory before stereotactic therapy.

In AIDS patients, FDG-PET has the ability to discriminate between primary central nervous system (CNS) lymphoma (Fig. 23.1) with high uptake and infectious lesions with lower FDG uptake. For primary CNS lymphoma in non-AIDS patients, brain FDG-PET seems useful in combination with MRI or CT for stereotactic biopsies. An alternative is thallium 201 (²⁰¹Tl) SPECT.

Nongliomatous primary brain tumors show variable FDG uptake. The choline-based tracers seem to be promising in these patients. However, no larger patient series are available. Individually designed protocols for diagnosis and follow-up in patients with these infrequent brain tumors may evolve with the use of coregistered PET and MRI.

In conclusion, CT and particularly MRI, with the administration of intravenous contrast agents for evaluation of the integrity of the blood–brain barrier, are the methods of choice for evaluating nongliomatous brain tumors. FDG-PET and ²⁰¹Tl SPECT can be used to differentiate recurrent tumor from radiation injury. Coregistration to MRI should be applied whenever possible to characterize the underlying anatomical structures. If suspicious lesions on MRI show FDG uptake at or above that of intact gray matter, tumor recurrence should be suspected.
For the diagnosis of malignancies, imaging methods with high contrast between the malignancy and the surrounding tissue are attractive. Classically normal and abnormal brain anatomy is mapped with CT. In the last two decades, MRI has superseded CT in the evaluation of most patients with brain disease, yielding detailed anatomical and also some functional information. The highest degree of functional information is, however, obtained with the use of radiotracers, and here PET imaging and SPECT imaging have a predominant role. Using compounds labeled with positron-emitting or gamma ray-emitting short-lived radioisotopes, it is possible to gain information on flow, metabolism, and receptor systems with tracer doses down to picomolar concentrations in a tissue.

**Figure 23.1** Primary B-cell lymphoma. A: A solitary focus in the left caudate nucleus close to the wall of the lateral ventricle on CT suggested possible ependymoma (red arrow). B: On FDG-PET one week later, there is a markedly increased uptake in the tumor extending outside the CT-defined lesion. Additional uptake in the fourth ventricle is indicative of spread into the cerebrospinal fluid. Frontal and occipital cortex is suppressed. At the time of diagnosis, lymphomas are usually solitary (in 70% of cases) and supratentorial. The site of origin is often the basal ganglia, the corpus callosum, or the periventricular subependymal regions. This accounts for the frequent liquoral spread of neoplastic cells and the multi-focality of lesions at later phases of the disease.
The use of fluorodeoxyglucose PET (FDG-PET) in the diagnosis of intracranial malignancies has been less successful than PET diagnosis and staging of malignancies in other organs. The healthy brain accounts for approximately 20% to 25% of the total body glucose consumed. Thus, the lesion-to-background ratio is particularly unfavorable in this organ when using FDG to delineate a tumor.

The uptake and concentration of a radiolabeled compound in the tissue will depend on several factors. These include blood flow, which determines how much tracer enters the organ, and the rate of transport from the blood to the tissue, which in the brain often will be limited by the impermeability of the blood–brain barrier to most hydrophilic substances. Further, the volume of distribution and possible binding in the tissue (e.g., metabolic trapping of FDG or binding of ligands to specific receptors) are relevant factors. All these variables form a complex mosaic, and it is not always obvious which mechanism is responsible for a high concentration of a radiotracer in a malignancy. An example is the trapping of the natural amino acid [14C]methionine (MET) in a cerebral malignancy. Although the uptake of this tracer might be assumed to represent increased tumor protein synthesis, the correlation between uptake and synthesis remains poor (1). In fact, the MET uptake primarily represents amino acid transport across the blood–brain barrier through an overexpressed L system. Further, a blood–brain barrier rupture, which is characteristic of high-grade tumors and radiation necrosis, will increase the uptake of MET, other amino acids, and amino acids analogs dependent on this transport. For diagnostic purposes, it is important to have a high contrast between diseased and normal tissue and less important whether this is due to one or another pathophysiological mechanism. However, understanding the basic pathophysiology is of utmost importance for understanding the nature of current diagnostic procedures and for guiding future developments.

For the use of PET and SPECT in the diagnosis of intracranial nongliomatous malignancies and radiation necrosis, the literature is relatively sparse; is dominated by short communications, small patient series, and retrospective investigations; and exhibits the associated limitations and biases.

**PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL)**

Primary central nervous system lymphoma (PCNSL) is a rare form of extranodal non-Hodgkin lymphoma (NHL) confined to the brain. The majority of PCNSLs are histologically indistinguishable from NHLs elsewhere in the body, are usually high grade, and show the B phenotype. PCNSL accounts for 1% to 6% of all intracranial tumors (2). A recent dramatic increase in the incidence has been shown in both immunocompetent and immunosuppressed patients and in patients with congenital or acquired immunodeficiencies. The latter include transplant patients and HIV-infected patients, who have a risk of 1% to 5% and 2% to 6%, respectively (3). The absolute risk of PCNSL in immunocompetent patients, however, is still very low. No larger systematic studies are available on the use of PET or SPECT for grading these patients or for assessing their response to treatment. Most immunocompetent patients receive intensive chemotherapy combined with radiotherapy, which increases survival but also usually affects cognitive performance. Overall survival is considered poor, 25% to 42%, compared with the survival rates for other high-grade extranodal lymphomas (4).

In Hodgkin and non-Hodgkin lymphomas outside the CNS, it is well established that FDG-PET has an important role in staging, monitoring of recurrence, and evaluation of treatment effects (5). In PCNSL, however, the use of FDG-PET for these indications remains to be established in larger prospective patient series (6). PCNSLs are highly proliferative tumors and usually show very high levels of FDG uptake (Fig. 23.1). In reading a PET scan, it should be kept in mind that some PCNSLs are very sensitive to dexamethasone treatment, which can lead to a marked reduction in the FDG uptake (7). Due to the lack of specificity of FDG for lymphoma, histology therefore remains mandatory for establishing the diagnosis for PCNSL as well as the diagnosis for extracerebral lymphoma (5,6). As for the gliomatous brain tumors (see Chapter 22), FDG-PET can probably be used to optimize the diagnostic quality of a stereotactic biopsy. Of the other PET tracers, only few have been applied. In a study of 10 subjects with biopsy-proven PCNSL, MET-PET was found useful for lesion delineation and for monitoring the therapeutic effect of irradiation (8).

In HIV-infected or AIDS patients with contrast-enhancing brain tumors on CT or MRI, studies suggest that FDG-PET may help to discriminate CNS lymphoma from inflammatory lesions (e.g., toxoplasmosis) with an accuracy of 80% to 95% (9–11). O’Doherty et al. (11) reported that the standardized uptake value (SUV; see Chapter 11) in cerebral lesions of toxoplasmosis was in the range of 0.14 to 3.7 (N = 13) and in cerebral lesions of lymphoma was in the range of 3.9 to 8.7 (N = 6). Three additional patients with progressive multifocal leukoencephalopathy had SUVs in the range of 1.0 to 1.5 in the lesions (11). FDG-PET therefore seems useful for differentiating between lymphomas and infectious lesions in AIDS patients, as also reported in two previously cited studies (9,10).

Thallium 201 (201TI) SPECT is thought to represent blood flow and blood–brain barrier permeability on early images, whereas delayed images are thought to represent viable tumor tissue. This technique has been used to solve the same differential diagnostic problem, and most studies have reported moderate to high sensitivities (83% to 100%) and specificities (83% to 100%) (12–17). However, direct pathological confirmation was performed in fewer than 50% of the cases, and some patients were on steroid treatment. In studies with pathology performed on steroid-naive patients, the sensitivity (60%) and specificity (55%) were found to be too small to endorse the use of the
method (18), probably reflecting the diverse mechanisms of tracer uptake. The limitations of using $^{201}$Tl SPECT reside in the low energy peak, which leads to significant soft-tissue attenuation, unfavorable dosimetry (15 to 20 mSv per scan), and limited spatial resolution.

Although the use of FDG-PET and $^{201}$Tl SPECT scans seems promising, the effective antiviral therapies for AIDS introduced in recent years have reduced the prominence of the diagnostic problem of determining whether an intracerebral mass is due to infection or lymphoma in AIDS patients. For patients suspected of PCNSL with inconclusive biopsies or cerebrospinal fluid (CSF) cytologies or patients who cannot undergo surgery due to involvement of deep vital structures, a diagnosis based on radiological MR criteria may be acceptable for routine clinical practice. Confirmatory FDG-PET and $^{201}$Tl SPECT scans can be recommended, a very high uptake being suggestive of PCNSL, but these investigation are not mandatory (4). It should be noted that FDG-PET cannot differentiate PCNSL from metastasis or glioblastoma multiforme (6).

**NONGLIOMATOURS PRIMARY BRAIN TUMORS**

The most common nongliomatous primary brain tumors are meningioma (15% to 20%); tumors of the nerve sheet cell, including neurinoma, schwannoma, and neurofibroma (6% to 8%); and pituitary adenoma (6% to 8%). For these tumors, no larger series document the use of PET for diagnosis, recurrence monitoring, or treatment monitoring. MRI and CT scanning with intravenous contrast enhancement are the methods of choice for diagnosis and follow-up. However, studies of small patient series show that meningioma and schwannoma have increased FDG uptake (Fig. 23.2), and they even indicate that the degree of FDG uptake could be used as a prognostic factor (19,20). About 4% to 5% of patients with neurofibromatosis type 1 (NF-1) develop malignant peripheral nerve sheath tumors, which arise within plexiform neurofibromas and often carry a poor prognosis. In extracranial neurofibromas, FDG-PET allows discrimination of benign neurofibromas from malignant neurogenic peripheral nerve sheath tumors (MPNSTs). FDG-PET also seems to be able to monitor intracranial malignant degeneration of unidentified bright objects (OBSs) on MRI (Fig. 23.3). Pituitary adenomas are generally benign tumors, but they may show marked uptake on FDG (Fig. 23.4) (21).

The use of MET has been investigated in smaller patient series in patients with meningioma. Iuchi et al. (22) found that the proliferative activity of meningioma varied from tumor to tumor and even from tumor region to tumor region in individual patients. They reported that MET uptake correlated significantly with the Ki-67 proliferation index. MET uptake is low in benign lesions and in radiation necrosis. However, high uptake has been described in acute infarctions and acute inflammatory processes (23).

In a recent study by Chung et al. (24) on the use of MET-PET in the evaluation of brain lesions that are hypo- or isometabolic on FDG-PET for patients with meningioma,
these meningiomas had variable but significant MET uptake. MET-PET scans can be brought into stereotactic radiation treatment planning and have been found to improve the target volume definition of meningioma (25).

The membrane proliferation tracer [11C]choline was examined in a recent study of 22 patients suspected of having brain tumors (26). One patient with a meningioma, two patients with schwannoma, one patient with cranio- pharyngioma, and one patient with malignant lymphoma all showed markedly increased [11C]choline uptake in their brain lesions, with images displayed as PET-MRI coregistered images. Areas of [11C]choline accumulation on the PET scans were generally larger than the corresponding areas on the MRI scans (26).

The use of PET for biopsy guidance is not documented for nongliomatous tumors. However, in high metabolism areas of the tumor on FDG-PET, MET-PET, or [11C]choline PET and high blood flow visualized by H215O PET, the chance of finding viable tissue is naturally high. Oppositely, areas of necrosis show low tracer uptake. PET-MRI image coregistration with these tracers is therefore of great interest for stereotactic biopsies.

If PET is considered for monitoring recurrence, a pretherapeutic PET is necessary. If a tumor in the pretreatment phase reveals either FDG hyper- or hypometabolism or an increased uptake of an amino acid tracer like MET, the PET scan may show the same increased uptake if a recurrence occurs at a later stage. Again, no large patient series documents this strategy for monitoring recurrence, but it is used clinically in some centers. In a study from Uppsala, MET was used to evaluate the effect of high-energy proton irradiation treatment on meningioma. A reduced MET uptake rate after treatment was used as sign of beneficial effect of proton irradiation (27). For guiding brachytherapy, PET-MRI or PET-CT image coregistration with a tracer showing tumor hypermetabolism should be more beneficial than anatomical scans alone.

Brain activation studies prior to neurosurgery to localize important brain areas, such as the language and motor areas, should be used according to the same principles that apply to gliomatous tumors.

Future diagnosis and therapy monitoring in brain tumor patients may develop into more individually designed diagnostic protocols as a result of PET-MRI image coregistration and the variety of new tracers now becoming available. At present, the use of FDG is widespread, but tracers like MET, [18F]tyrosine, [11C]choline may soon become more readily available. This, combined with international efforts to perform larger multicenter studies on the use of PET with image coregistration in patients with less common cancers, will hopefully lead to more evidence-based data on the use of PET for nongliomatous brain lesions.

**BRAIN METASTASES**

The percentage of cancer patients in whom cerebral metastases are detected has increased over the last decades, presumably because of better diagnostic techniques and increased patient survival. Autopsy studies have revealed
intracranial metastases in approximately 25% of patients who die from cancer. The metastases are widely distributed, with approximately 80% occurring in the cerebral hemispheres and 20% in the posterior fossa, roughly corresponding to size and the distribution of regional cerebral blood flow. The most frequent metastases are from carcinomas reaching the brain, predominantly through hematogenous spread. In a series of 729 patients with brain metastases, the primary tumors, in descending order of frequency, were NSCLC, breast cancer, melanoma, renal cell cancer, and
gastrointestinal tract cancer (28). Thus, a priori, the most common origin is a pulmonary tumor, which occurs with reported frequencies from 45% to 73%.

The discovery of brain metastases is clinically important, as their presence can affect the therapeutic approach decisively. Whole-body FDG-PET is a very sensitive method for identifying metastases from most malignancies outside the brain but is inadequate inside the brain. Thus, contrast-enhanced MRI remains the principal imaging tool for localizing brain metastases. The inadequacy of FDG-PET for separating metastasis from normal cortex is a consequence of its often poor lesion-to-background ratio. Intracranial metastases are often small, challenging the spatial resolution of PET; are located in the junction between gray and white matter; and have limited edema. Edema can cause a low activity "halo" effect and thus emphasize a metabolically active lesion against the equally active cortical mantel. Furthermore, several studies have shown that the FDG uptake of intracranial metastases is variable (Fig. 23.5), even among metastases in the same patient (29,30). Thus, in an early FDG-PET study, only 68% of the brain lesions were detected, although four lesions were above 1 cm in diameter (31).

Figure 23.5  Brain metastases evaluated by FDG-PET. A-C: MRI showing a 6-mm-diameter contrast-enhancing metastasis from a pulmonary adenocarcinoma in the left mesial parietal lobe. On coregistered FDG-PET, the most obvious pathology is decreased uptake in the adjacent white matter and overlying cortical gray matter secondary to the peritumoral edema. The lesion itself is presumably hypermetabolic but cannot be clearly discerned from normal cortex. D-F: Right frontal lobe metastasis from a distal esophagus cancer found unexpectedly during routine whole-body FDG-PET-CT scanning. This origin rarely metastasizes to the brain. The metastasis is contrast enhancing on CT (left) and shows moderately increased FDG uptake relative to gray matter values (right). Note the slight head displacement between PET and CT. In more severe cases, attenuation artifacts are seen, but not in this case.
Two large studies have evaluated the benefit of including the brain in the field of view for routine clinical FDG-PET scans in patients with a broad range of malignancies in order to identify cerebral metastases. The clinical impact, however, was rather small, with identification of unexpected cerebral lesions or skull metastases in only 0.4% to 0.7% of scans (32,33). At our institution, screening is usually only included in the case of malignancies with a high a priori affinity for spreading to the brain, such as primaries originating in lungs, breast, and skin (melanoma).

Attempts have been made to deal with the contrast-to-background limitations of FDG by using amino acid tracers and analogs, such as MET, $^{18}$F]methyltyrosine or $^{18}$F]ethyltyrosine, and the nucleotides that probe the DNA synthesis or tumor proliferation rate, such as $^{11}$C]thymidine. All have low uptake in normal gray matter and may be useful for diagnosis and follow-up in patients with brain metastases, as evidenced in recent promising reports (24,34,35). MET-PET showed high sensitivity and good contrast in the evaluation of brain lesions with hypometabolism on FDG-PET. In a series of 45 patients with brain lesions, Chung et al. (24) compared MET-PET with FDG-PET. Of the 45 patients, 5 had metastatic brain tumors, and on FDG-PET they were described as being hypometabolic or with only faint peripheral uptake. With MET-PET, metastases were identified in 4 of the 5 patients.

$^{18}$F]choline is a tracer of the essential building block of the phospholipids in the cell membrane. Malignant tumors may show high proliferation and increased metabolism of cell-membrane components, leading to increased uptake of choline. $^{11}$C]choline uptake is very low in the normal brain, with some uptake in the choroid plexus and pituitary gland, as those regions do not have a blood–brain barrier. Brain tumors and metastases are characterized by increased cell membrane synthesis, with a very fast uptake of the tracer, making it possible to start the PET scan 5 minutes after tracer injection. In a recent pivotal study comparing $^{11}$C]choline and $^{18}$F-FDG in lung cancer, 3 of 17 patients were reported to have brain metastases, with 23 lesions in total. $^{11}$C]choline detected all 23 lesions, whereas $^{18}$F-FDG detected only three (36).

The therapeutic possibilities are restricted in patients with brain metastases. Depending on the number of lesions and their accessibility, surgical resection or stereotactic irradiation with a multi-cobalt unit (“Gamma knife,” “radiosurgery”) can be offered. The precise role that FDG-PET and MET-PET might have in treatment planning and evaluation has not been established, but as for radiotherapy planning in other parts of the body, FDG-PET combined with structural images (MRI) has been found useful for optimizing the target volume, particularly in ill-defined or infiltrating lesions (37). There are indications that, during follow-up, FDG-PET is superior to CT and MRI for the differentiation of radiation injury from recurrence in patients with tumor growth after stereotactically irradiated brain metastases (38,39). In particular, coregistration with MRI improved the diagnostic value, increasing the sensitivity from 65% to 86% (39). The additional clinical value of FDG-PET is especially prominent when MRI is either positive or inconclusive for the presence of viable tumor, as the FDG uptake pattern will increase the diagnostic accuracy significantly (40).

In the few investigations using $^{201}$TI and $^{99}$mTc-MIBI SPECT, only limited sensitivity for cerebral metastases has been demonstrated (41).

It is not unusual for the primary manifestation of a systemic malignancy to be a cerebral metastasis. The diagnostic strategy for locating an unknown primary tumor will be directed by the clinical history and findings. Given the high a priori probability of a pulmonary tumor, a chest x-ray will often be included. In directing the search further, whole-body FDG-PET is an excellent diagnostic option. Several studies have shown that PET is able to identify the unknown primary tumor in 82% to 100% of patients (30,42–44) and may identify unsuspected distant metastases in 30% of patients (44). Further, in clear-cut cases, PET may help direct the biopsy to extracerebral sites for a less traumatic diagnostic procedure. Finally, applying the criteria of evidence-based medicine, no studies document the usefulness of FDG-PET or PET with other tracers for the evaluation of treatment effects in patients with brain metastases.

**TUMOR RECURRENCE VERSUS RADIATION INJURY**

Radiation therapy is frequently used, often in combination with surgery and chemotherapy, in the primary treatment of high-grade brain tumors. Other sources of high-dose radiation exposure to the brain are radiosurgery, brachytherapy in the form of radioactive seed implantations, and radiation therapy for head and neck cancer, particularly nasopharyngeal carcinoma (temporal lobe) (45) and ocular and maxillary cancer (frontal lobe). A major dose-limiting complication of brain irradiation is late radiation injury, and differentiating this condition from recurrent tumor is a key challenge. Cerebral radiation injury can be classified by the time of symptom appearance after therapy (Table 23.1). The incidence of late radiation injury is difficult to estimate, but biopsy-proven necrosis has been found in up to 25% of patients treated for malignant glioma (46). “Radiation necrosis” is the term loosely used to denote all appearances of this condition, but it should be reserved for late radiation injury. The severity increases dependent on the administered dose and the mode of application—radiotherapy, radiosurgery, or brachytherapy (47). The exact pathological processes are still under investigation (direct oligodendrocyte damage, ischemic necrosis, and autoimmune vasculitis), but the outcome is primary damage of the vascular endothelium leading to white matter necrosis (48,49). The disrupted blood–brain barrier will lead to vasogenic edema and contrast enhancement on MR and CT and will imitate the appearance often seen in tumor recurrence.
The rationale for using FDG-PET is that increased uptake is observed in tumor recurrence (Fig. 23.6), whereas radiation injury results in decreased uptake. However, the literature points in diverse directions. The initial reports contained very encouraging results, including sensitivities and specificities of 100% (50–52), but later studies showed sensitivities ranging from 43% to 88% and specificities from 22% to 100% (39,53–57). However, the criteria used have been diverse—uptake was evaluated purely visually or with reference to white matter, gray matter, or “adjacent” tissue—or a contralateral homologous region prevented computation of reasonable pooled estimates of the diagnostic value.

There are a further number of noteworthy methodological limitations in some of these studies that pertain to histological confirmation. Histological confirmation is not always present, raising the possibility of patient selection bias directed by findings on MRI or PET or the clinical presentation (56,58). Furthermore, recurrent tumor is often nodular. Thus, biopsy should be optimized by focal uptake on FDG-PET coregistered with MRI to avoid sampling error. Even with all this in place, apparently viable tumor cells from an irradiated resected specimen can appear morphologically intact on histology but have little metabolic or clinical activity (53). Thus, the clinical outcome can be that of tumor recurrence or radiation injury,

<table>
<thead>
<tr>
<th>Type of Injury</th>
<th>Time Interval after Irradiation</th>
<th>Pathology</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Hours to weeks</td>
<td>Tumor swelling Edema of the surrounding brain</td>
<td>Good (transient and reversible symptoms)</td>
</tr>
<tr>
<td>Early delayed</td>
<td>Weeks to months</td>
<td>Demyelination</td>
<td>Good (transient and reversible symptoms)</td>
</tr>
<tr>
<td>Late</td>
<td>Months to years</td>
<td>Liquefactive or coagulative necrosis</td>
<td>Usually progressive and irreversible</td>
</tr>
</tbody>
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Figure 23.6  Recurrence versus radiation injury? Resection and radiotherapy for left frontal grade III astrocytoma. Clinical deterioration with progressive frontal lobe symptoms. Initial PET scanning (PET 1) showed reduced metabolism in residual cortical gray matter but lacked convincing signs of recurrence. After three months (PET 2), there appeared an irregular area of increased uptake in the depth of the resection cavity (red arrows) close to the left caudate nucleus that was indicative of tumor recurrence.
causing uncertainty about what predictions can be made from the pathology.

On the whole, FDG-PET does seem to add valuable clinical information for the management of these patients. Coregistration to MRI should be done whenever possible to characterize the underlying anatomical structures further. If suspicious lesions on MRI show FDG uptake at or above the level of intact gray matter, tumor recurrence must be suspected. This threshold may not always apply after brachytherapy (59). The use of MET has shown promise in a few smaller studies and could be particularly helpful after radiation therapy for low-grade tumors (60,61). However, as the radiolabeled amino acids and analogs reflect blood-brain barrier transport characteristics, the value in areas of contrast enhancement may be limited. With 201Tl SPECT, the results have been quite encouraging, with relatively high sensitivities of 69% to 94% and specificities from 40% to 76% (35,61–65). The more recent studies are in the higher parts of the ranges. One issue is the recommended cutoff retention indexes comparing tumor uptake to reference region. They seem to be dependent on the institute-specific methodology and underlying histology (range, 1.25 to 5.0). This can limit the spread of the technique (64). Further, high physiological uptake in the hypophysis, the veins and sinus, the choroidal plexus of the lateral ventricles, and the fossa posterior can hamper adequate analysis (63); 201Tl can also be taken up in radiation injury (61,66); and uptake can also be confounded by blood-brain barrier disruption. One other SPECT tracer, 99mTc-MIBI, has also been applied to this problem, but it is of only limited diagnostic value (67,68).

In conclusion, there is clearly no best diagnostic test at the present time. However, combined with clinical and methodological insight, both FDG-PET and 201Tl SPECT can provide useful information.

FUTURE PERSPECTIVES

MR continues to be the primary diagnostic neuroimaging tool for evaluation of brain tumors. This review of the literature illustrates the present uncertainty regarding the use of PET in the diagnosis of nongliomatous intracranial malignancies. In general, few larger series have given evidence-based documentation supporting the use of PET. However, several studies have shown results that are promising for the future development of PET and clarification of its indications in the diagnosis of intracranial malignancies. The evolution in the coming years of this decade will probably include the use of new radiolabeled tracers and possibly even tracers that are specific for receptors unique to the malignancy. These developments might very well link to molecular biology and genomic research. SPECT represents the less costly alternative, with easier handling of isotopes and better spatial resolution. However, given the availability of a broader range of tracers, improved resolution, and a rapidly increasing range of PET-CT scanners, PET is likely to be the most frequently employed modality of the two.

REFERENCES


Imaging of Cerebral Infection with PET

Alfred Buck Ehab Kamel

There are a few clear indications for fluorine 18 (18F) fluorodeoxyglucose (FDG)-PET in infectious brain diseases. With MRI and CT, it is sometimes difficult to distinguish between a brain abscess and tumor, especially if the latter is necrotic. FDG-PET may be helpful in this area. Usually the FDG accumulation in the abscess wall is between the level in white matter and the level in gray matter. Unfortunately, this is also the range of the accumulation in some tumors, which limits the usefulness of FDG. If, however, the FDG uptake exceeds that in gray matter, a tumor is much more likely. A promising tracer for differentiating abscess from tumor is [18F]ethyltyrosine, which is not taken up by inflammatory cells.

FDG-PET is very useful for distinguishing between toxoplasmosis and lymphoma in HIV patients. In lymphoma, FDG uptake is above, in toxoplasmosis below, cortex FDG uptake. An example is shown in Figure 24.5.

INTRODUCTION

Cross-sectional neuroimaging techniques are very sensitive to any intracerebral alterations. With the clinical history, physical examination, laboratory results, and appearance on CT or MR images, the differential diagnosis between the different disease entities can usually be narrowed down. Because epidural and subdural infections usually do not produce problems in differentiating them from other non-infectious diseases, only intraparenchymal lesions will be discussed in this chapter.

The major point of interest is the differential diagnosis between a primary intracerebral neoplasm and an inflammatory or infectious lesion, mainly an abscess. High-grade tumors (WHO grades III and IV) usually are separated from other intracerebral lesions by their high uptake of fluorine 18 (18F) fluorodeoxyglucose (FDG) when compared with cortical gray matter. This is specially true for anaplastic astrocytomas grade III, glioblastomas, meningiomas, lymphomas, some metastases, and juvenile primary brain tumors. However, difficulties have been described in differentiating even high-grade lesions from granulomatous tissue, especially in ongoing radiation-induced necrosis. It is known from experimental studies (1–3) that inflammatory cells do accumulate FDG to a higher degree; therefore, some sort of quantification is usually recommended to help in the differential diagnosis. Another problem is making a differential diagnosis between low-grade tumors and inflammatory or infectious lesions by FDG-PET, since all these lesions exhibit a similar level of FDG uptake. As discussed below, a new promising tracer is [18F]ethyltyrosine, which does accumulate in tumors but not infectious tissue (3).

PYOGENIC BRAIN ABSCESS

A pyogenic brain abscess is formed through hematogenous dissemination of a primary site. It occurs most often in patients with pulmonary or cardiac infections, patients with infections from the paranasal sinuses, septic patients, and patients with intravenous drug abuse. The brain abscess favors the frontal and parietal lobes along the supplied territory of the middle cerebral artery. It is usually located at the junction of gray and white matter and may occur as a single lesion or as multiple lesions.

Neuroimaging with CT and MRI

Using experimental CT imaging, four stages of abscess formation have been described: (a) early cerebritis (1 to
3 days), (b) late cerebritis (4 to 9 days), (c) early capsule formation (10 to 13 days), and (d) late capsule formation (14 days and later) (4). In the cerebritis phase, a lesion of low density and patchy enhancement may be seen. In the late cerebritis phase, a necrotic center is formed within the infectious lesion and surrounded by a granulation tissue. Therefore, ring-like enhancement is often present. The mature abscess appears of low density, with considerable edema surrounding the lesion.

On magnetic resonance (MR) imaging, the lesion is of low intensity on T1-weighted images and of high signal on T2-weighted images in the early cerebritis phase. After 2 to 3 weeks, the mature abscess appears, as a well demarcated mass of low intensity on T1-weighted sequences, with edema beyond the lesion. On T2-weighted images, high intensity is seen in the cavity. As ring-like enhancement is seen in the mature abscess on both CT and MR imaging, several differential diagnoses have to be considered, including infarction, fungal or parasitic infection, primary or metastatic brain tumor, tuberculosis, granuloma, multiple sclerosis, and subacute hematoma. In this clinical setting, FDG-PET, in conjunction with conventional neuroimaging, might help in narrowing down the differential diagnosis.

PET with FDG and [18F]Ethyltyrosine

As pyogenic abscesses are surrounded by granulomatous tissue in the late phase of cerebritis, ring-like FDG uptake might be observed (Fig. 24.1). However, this FDG uptake in the granulomatous tissue is inconsistent, and can be missing altogether. This feature is probably dependent on the time of scanning, the amount and the characteristics of the inflammatory cells. It is therefore often difficult to separate tumor and abscess. Glioblastomas are often necrotic and there may be only little tumorous tissue at the edge. In these cases the actual FDG uptake may be underestimated due to the limited resolution of the PET scanner. In such cases an additional PET using an amino acid analogue such as [18F]ethyltyrosine (FET) may be helpful. We demonstrated, that FET is not taken up in experimental abscesses induced in rat muscle (3). Based on this result one can hypothesize that lacking FET uptake would also characterize a brain abscess. In contrast, there is high FET accumulation in brain tumors, as is demonstrated in Figure 24.2.

CREUTZFELDT-JAKOB DISEASE

Creutzfeldt-Jakob disease (CJD) is an invariably fatal illness with no effective treatment. However, early detection is clinically warranted to control the transmission of the disease (5). CJD is believed to be caused by proteinaceous infectious particles (prions). Clinically, it is characterized by rapidly progressive dementia, myoclonic jerks, ataxia, visual disturbances, extrapyramidal and pyramidal manifestations, and akinetic mutism (6,7).

In the early stage of the disease, the electroencephalogram (EEG) is characterized by nonspecific background slowing; later, in the terminal phase, periodic triphasic wave complexes appear. Cerebrospinal fluid examination for the presence of brain protein 14-3-3, a marker of progressive neuronal destruction, supports the clinical suspicion of CJD, but a definite diagnosis can only be achieved by neuropathological examination, which usually reveals histopathologic evidence of neuronal loss, gliosis, and spongiosis in addition to identification of the pathologic prion protein by means of immunohistochemistry (8–10).
Neuroimaging with CT and MR

MRI and CT have not been found to be useful modalities for early diagnosis of CJD. Nevertheless, in the advanced disease stage (and apart from the occasionally detected brain atrophy), several MRI reports have shown striatal and thalamic signal abnormalities in a considerable proportion of CJD cases. The most frequent signal abnormalities are in the form of mild to moderate symmetric signal hyperintensity on proton-density and T2-weighted images. Less frequently, mild signal abnormalities are also noticed in cerebral cortex, globi pallidi, cerebellar cortex, and medial temporal structures (11–13).

FDG-PET

Functional studies such as PET and SPECT can provide useful biophysiologic information regarding blood flow and

![Figure 24.2](image-url)
Figure 24.3  Creutzfeldt-Jakob disease. The T2-weighted images demonstrate frontal atrophy. Hyperintensities are found in the basal ganglia bilaterally. The quality of the proton-weighted images in the second row is impaired due to severe motion artifacts. The FDG-PET images in the third row were acquired at the same time as the presented MR images. The PET scans at the bottom were performed 46 days later. The initial scans demonstrate reduced FDG uptake frontally and in the basal ganglia, in line with the MR abnormalities. These changes are even more pronounced 46 days later, indicating the rapid deterioration of the patient.
metabolism that may precede the appearance of parenchymal abnormalities on morphological imaging. Dramatic reduction of regional glucose metabolic rates down to 48% of the values obtained from age-matched healthy subjects was reported in CJD. The pattern of diminished FDG uptake does not appear to display a specific regional predilection, unlike in other dementias. Diffuse brain involvement was the main finding in the majority of the studied cases (14,15). Perfusion also appears to be reduced (16). An example of a FDG-PET of a patient with CJD is shown in Figure 24.3.

**DIFERENTIATION OF TOXOPLASMOSIS AND LYMPHOMA IN HIV PATIENTS**

The differentiation of toxoplasmosis and lymphoma is a clear indication for FDG-PET. The correct diagnosis is sometimes difficult to establish on MRI or CT, and it is important for the proper treatment. In FDG-PET, lymphomas display an FDG uptake exceeding that of gray matter. In toxoplasmosis, the FDG accumulation ranges between the levels for white and gray matter. An example of toxoplasmosis is shown in Figure 24.4, and a cerebral lymphoma is shown in Figure 24.5.

**Figure 24.4** Contrast-enhanced CT and FDG-PET of an HIV patient with toxoplasmosis. The CT demonstrates the contrast enhancement at the edge of the lesion (arrows). FDG uptake in this area ranges between white and gray matter (see also Case 83).

**Figure 24.5** T1-weighted MRI (A,B) and FDG-PET (C,D) images of a HIV patient. The highly increased FDG uptake in the lesion demonstrates that the patient suffers from lymphoma and not toxoplasmosis. In PET, there is the typical high FDG uptake, which exceeds the one in cortex. This high uptake reliably separates lymphoma from toxoplasmosis (see Fig. 24.5).
REFERENCES

Epilepsy Imaged with PET and SPECT

Alfred Buck Heinz-Gregor Wieser

Positron emission tomography (PET) scans are indicated in the presurgical evaluation of epilepsy patients. Most of these patients suffer from temporal lobe epilepsy (TLE), where the major pathology is found in the medial temporal lobe. One of the operations performed to cure such epilepsy is selective amygdalohippocampectomy. A prerequisite for deciding on such surgery is that the disease is unilateral, since a bilateral operation would lead to intolerable neuropsychological deficits. The most commonly used tracer in PET epilepsy imaging is fluorodeoxyglucose (FDG), and the typical finding in TLE is illustrated in Figure 25.1. The reduction of FDG uptake is not restricted to the medial temporal lobe but extends to the lateral temporal lobe. The important information FDG PET can provide is that the pathology is unilateral. There are indications that carbon 11 [11C]flumazenil, which binds to the benzodiazepine receptors, shows the pathology in a somewhat better circumscribed way. This is illustrated in the bottom panel of Figure 25.1. However, [11C]flumazenil requires an on-site cyclotron, which renders the tracer less available.

Another important application of PET in epilepsy concerns ictal studies. These are usually done with perfusion tracers, and the tracers need to be injected within minutes of the onset of a seizure. This puts a challenging demand on the imaging infrastructure. Most of these studies are performed with single-photon emission computed tomography (SPECT) and a technetium 99m (99mTc)–labeled flow tracer. Due to the relatively long half-life of 99mTc, one can prepare the tracer and wait for a seizure to occur. After the seizure and the concomitant tracer injection, the patient can be stabilized and images acquired hours after injection. If seizures can be triggered reproducibly, ictal studies can also be performed with PET. An example is shown in Figure 25.2.

INTRODUCTION

Epilepsy represents a considerable health care problem, and in the United States the prevalence is 500 to 800 cases per 100,000. The classification of epilepsies, seizures, and epileptic syndromes uses these categories: primary, generalized, and partial. It is the partial epilepsies where functional neuroimaging is of special interest. Partial seizures originate from one focus. The epileptic discharge may remain localized or may spread over the whole brain. In the latter case, one talks of “secondary generalization.” If partial seizures involve consciousness, they are referred to as “complex partial seizures.” In general, these originate in the medial temporal lobe. Although most epileptic patients are adequately treated with medication, a considerable number are medically intractable.

A major subgroup of these patients suffer from temporal lobe epilepsy (TLE), which is commonly associated with hippocampal sclerosis. Surgical treatment in these cases has proven to be an effective means of eliminating seizures. There exist various surgical strategies. The standard procedure initially consisted of removing the anterior two thirds of the affected temporal lobe, so-called Falconer's en bloc anterior temporal lobe resection. In Zurich, the standard operation since 1975 has been selective amygdalohippocampectomy, a procedure pioneered by Wieser and Yasargil (1). For extratemporal refractory epilepsy, surgical therapy is less often performed, although this is changing with improved methods for presurgical evaluation. In general, positron emission tomography (PET) imaging has proven to be useful in candidates for epilepsy surgery.
TEMPORAL LOBE EPILEPSY

Preoperative Evaluation

The aim of preoperative evaluation in temporal lobe epilepsy is to maximize the chances for the patient to be free of postsurgical seizures (or at least have a substantial reduction in seizure frequency) and minimize postsurgical deficits. A prerequisite for surgery is that the seizures always originate from a stable focus. Patients displaying bilateral disease must be excluded from operative treatment since the neuropsychological deficits following a bilateral operation would be prohibitive. The preoperative workup of patients with TLE differs somewhat among centers. At our institution, it includes noninvasive as well as invasive electroencephalographic recording of interictal and ictal events (EEG), long-term video monitoring, magnetic resonance imaging (MRI), and FDG PET. All these modalities yield complementary information.

FDG PET

The typical interictal finding in TLE is reduced FDG uptake in the affected temporal lobe. The area of hypometabolism usually extends beyond the medial temporal lobe and often includes the lateral temporal cortex, as is illustrated in Figures 25.1 to 25.5. A likely reason for this phenomenon is deafferentation of the cortex functionally connected with the epileptogenic focus. Besides the abnormality in the medial temporal lobe, hypometabolic regions in TLE are also reported: the thalamus, the basal ganglia, and parts of the frontal lobe (2). These examples illustrate that FDG PET is not suitable for localizing the seizure onset zone per se. The important PET information is the lateralization and the exclusion of a pathology on the contralateral side. The incidence of an ipsilateral temporal lobe hypometabolism in patients with TLE is in the range of 60% to 90% (3–10).

Flumazenil PET

Flumazenil (FMZ) is a benzodiazepine receptor antagonist. Labeled with carbon 11 ($^{11}$C), it is an excellent PET marker for cerebral benzodiazepine receptor density. Since the receptors are located on the neurons, reduction in receptor density may indicate neuronal loss, as is typical in a sclerotic region. Examples of FMZ PET images in patients with TLE are shown in Figures 25.1 through 25.5. Whereas glucose metabolism is depressed well beyond the sclerotic medial temporal lobe, FMZ demonstrates a circumscribed defect limited to the affected medial temporal lobe. An interesting case is shown in Figure 25.4. This patient was not seizure free following selective amygdalohippocampectomy. Besides a lack of uptake in the operated area, there is also reduced FDG uptake PET in almost the whole lateral temporal lobe. Although extended reduction in FDG uptake is typical in TLE, the degree and area of reduction in this patient exceeded the usual pattern. The question therefore arose whether there might be neuronal damage in the lateral temporal lobe. Structural damage in this area was excluded on MRI (Fig. 25.4B). The normal FMZ uptake in the lateral temporal lobe clearly demonstrates neuronal integrity. That reduction of FMZ uptake is restricted to the abnormal tissue, was demonstrated in several studies (11,12) and confirmed using the more objective method of statistical parametric mapping (13). In another study, it was shown that by correcting for resolution effects, the sensitivity for detection of unilateral hippocampal sclerosis could be increased to 100% (14). Abnormalities on the contralateral side were present in 30% of cases.

Magnetic Resonance Imaging

The main rationale for MRI in epilepsy patients is to identify or exclude underlying pathologies such as tumors,
vascular lesions, and migrational disorders. In TLE, the most common pathology is hippocampal sclerosis, which resisted reliable evaluation with MRI until the early 1990s. This has changed with the advance of MRI technology. There exist qualitative and quantitative approaches to assess hippocampal sclerosis; the latter are more accurate and measure the hippocampal volume. In a study with 41 patients, it was shown that hippocampal volume ratios yielded the correct lateralization of the seizure focus in 76% of cases (15). Although useful, the technique of hippocampal volumetry is rather laborious and therefore not suitable in a clinical setting. Nevertheless, new methods like voxel-based morphometry seem to ameliorate subjective bias (16,17). In addition MRI studies revealed that other structures, such as the parahippocampal area, the entorhinal cortex, and the thalamus, seem to be involved in temporal lobe epilepsy (18,19).

**EXTRATEMPORAL EPILEPSIES**

**FDG PET**

Outside the temporal lobe, malformations of cortical development are a common cause of refractory epilepsy in adults (20). The pathology observed on FDG PET is often more extensive than the one identified on MRI (21). In frontal lobe epilepsy, the area of hypometabolism may also exceed structural abnormalities. However it is not uncommon for the hypometabolic zone to be restricted to an underlying structural pathology (22,23). Hypometabolic areas are found in approximately 60% of patients with frontal lobe epilepsy, most of which also demonstrate a structural abnormality on MRI. In general, it seems that the epileptogenic focus is contained within the hypometabolic area, if one exists. Given the high incidence of positive MRI scans, the value of FDG PET in frontal lobe epilepsy seems mainly to lie in its ability to exclude other pathologic areas.

Most malformations of cortical development are identified with MRI, and the additional value of FDG PET seems limited to special cases. For instance, metabolic abnormalities in the contralateral hemisphere of patients with hemimegalencephaly have been associated with a poorer prognosis following surgery (24).

**Flumazenil PET**

There are indications that FMZ may also be of high clinical value in the evaluation of extratemporal epilepsies. In a preliminary series of six patients with frontal lobe epilepsy, FMZ demonstrated circumscribed lesions consistent with clinical and EEG data (25). In two out of four patients who were also scanned with FDG, the area of reduced FDG uptake was more extensive than the one delineated with FMZ. The MRI scan was read as normal in five patients, underlining the usefulness of FMZ PET. In malformations of cortical development, the abnormalities on FMZ PET also seem to be spatially more spread out than the lesions seen on MRI (26,27).

**MRI**

As in temporal lobe epilepsy, MRI is the method of choice for delineating structural abnormalities. Interesting entities often leading to seizures are the malformations of cortical
development (MCDs). These include schizencephaly, agyria, diffuse and focal macrogyria, focal polymicrogyria, minor gyral abnormalities, subependymal gray matter heterotopias, bilateral subcortical laminar heterotopias, tuberous sclerosis, focal cortical dysplasias, and dysembryoblastic neuroepithelial tumors. Such malformations were found in more than 4% of 303 patients with epileptic seizures referred for MRI (28). Malformations of cortical development can also be found in the temporal lobe. In a series of 222 patients with seizures originating from the temporal lobe, such malformations were diagnosed in 7% of cases (29). These included focal cortical dysplasia, nodular

**Figure 25.3**  $T_1$-weighted (top) and $T_2$ weighted (bottom) MR images of a patient with right-sided temporal lobe epilepsy (A). The original transaxial images are shown on the left. The images on the right are reoriented parallel to the long axis of the temporal lobes. There is no evident abnormality on visual inspection. The FDG and flumazenil (FMZ) PET images are shown in panel B. Images on the left represent transaxial sections; those on the right are oriented parallel to the long axis of the temporal lobes. The patient displays the typical findings of temporal lobe epilepsy with hippocampal sclerosis. Hypometabolism extends beyond the hippocampal region into the lateral temporal lobe. In contrast, the reduction in FMZ uptake is restricted to a small area in the medial temporal lobe, corresponding to the sclerotic tissue.

**Figure 25.4**  Temporal lobe epilepsy patient who was not seizure free following selective amygdalohippocampectomy. A: A $T_1$-weighted (TR 500 ms, TE 14 ms) gadolinium-enhanced MR image. The gadolinium enhancement of the dura along the area of resection corresponds to normal postoperative changes. The artifact on the right corresponds to a susceptibility effect caused by the reservoir of a shunt. B: A proton-weighted (TR 3500 ms, TE 15 ms) MR image above the area of resection shows no pathology within white matter and cortex of the left temporal lobe. C: Co-registered transaxial FDG-PET and FMZ-PET slices aligned along the long axis of the temporal lobe. For explanations, see text.
heterotopia, abnormal gyration, limited schizencephaly, and hippocampal malformations.

**OTHER TRACERS USED IN THE INVESTIGATION OF EPILEPSY**

All tracers mentioned here are helping to shed new light on the pathophysiology of epilepsies, but their clinical usefulness has yet to be demonstrated. Using [11C]carfentanil, it has been shown that the μ-opioid receptors are increased in the ipsilateral temporal lobe of patients with TLE (30). It has been speculated that up-regulation of the μ-opioid receptors serves to limit the spread of the seizures. Other opioid receptor subtypes have been studied with [18C]diprenorphine and fluorine 18 [18F]cyclofoxy. These studies demonstrated that the various subtypes of opioid receptors are differentially affected in TLE.

A few studies have investigated the distribution of the enzyme MAO B. This enzyme is mainly located on glial cells. Since these are increased in sclerotic tissue, the demonstration of elevated MAO B concentration may positively identify epileptogenic foci in patients with TLE. Studies using [11C]deuterium deprenyl indeed demonstrated increased binding in the medial temporal lobe of patients with TLE (31). This finding was confirmed in a single-photon emission computed tomography (SPECT) study with the ligand iodine 123 [123I] Ro 43-0463 that binds reversibly to MAO B. This study furthermore revealed increased MAO B in the ipsilateral putamen (32).

**ICTAL STUDIES**

Whereas interictal studies commonly show decreased metabolism, blood flow, or receptor densities in the
Figure 25.6  A: Transaxial T₁-weighted (TR 600 ms, TE 20 ms) MR image of a patient with epileptic seizures due to Rasmussen encephalitis. Cortex and subcortical white matter are indistinguishable due to hypointensity of the right frontal subcortical white matter. B: The corresponding transaxial T₂-weighted (TR 3800 ms, TE 80 ms) MR image delineates more clearly the pathology caused by Rasmussen encephalitis. There is cortical and subcortical increase in signal intensity that affects the right frontal and insular region, putamen, caudate, external capsule, and anterior limb of the internal capsule. The cortical–subcortical border is partly erased along the superior temporal gyrus (arrow), showing an additional region of involvement. The Sylvian fissure is slightly widened, indicating atrophy adjacent to the pathologic signal. Coregistered transaxial FDG-PET (C) and [¹⁵N]NH₃-PET (D) scans. The increased FDG uptake in the right frontal lobe, the caudate, and parts of the lateral temporal lobe corresponds to practically continuous epileptic discharges. [¹⁵N]NH₃ may be used to trace cerebral perfusion. The uptake pattern shows increased perfusion in the active epileptogenic zones. The important information in this case is the absence of epileptogenic activity in the contralateral hemisphere. The patient was scheduled for left hemispherectomy. Evidence of contralateral epileptogenic activity would have been a clear contraindication for the surgical procedure. The increased perfusion and metabolism in the contralateral cerebellum most probably correspond to activations via crossed cerebrocerebellar pathways.
epileptogenic tissue, ictal studies demonstrate increased blood flow early after the onset of a seizure. This can be demonstrated using SPECT technology and tracers such as 99mTc-labeled HMPAO and ECD (ethylcysteinate dimer). SPECT is superior to PET in this regard, because the tracers can be injected in the neurology ward while the patient is being monitored. Imaging can then be performed hours later after the patient has been stabilized. This is possible because HMPAO and ECD get trapped in the brain within 2 minutes following injection, and the activity distribution hours later still reflects the distribution at the time of injection. Ictal SPECT has established itself as a highly accurate method for identifying seizure foci, especially when combined with interictal studies. In TLE, the identification of the seizure focus was possible in up to 90% of cases (33–38). Ictal SPECT has also proven its value in the evaluation of extratemporal epilepsies, where 92% of foci were correctly identified (39). Ictal SPECT may be of special value in patients with no MRI findings. Good surgical outcomes were reported if the resected area was concordant with the ictal SPECT findings (40,41). The method also helped to localize the area to be resected in patients with malformations of cortical development (42).

Ictal studies with PET are more difficult to perform. The half-life of oxygen 15 (15O) is so short that imaging would have to be performed immediately after injection. In most cases, this is clinically impractical, since the patient would have to remain positioned in the PET scanner until a seizure occurred. However, it is possible to perform ictal PET scans in selected cases, as shown in Figure 25.6. These patients suffered from Rasmussen encephalitis. The pathophysiology of this rare disease is not clear. One hypothesis assumes the involvement of autoantibodies against a subpopulation of the glutamate receptors, in particular GluR3. Normally such antibodies cannot penetrate the blood–brain barrier (BBB). However, if the BBB is disturbed, such antibodies may enter brain tissue and cause inflammation, which itself causes further damage to the BBB, thus continuously worsening the disease. Sometimes the only effective therapy is hemispherectomy. Patients with Rasmussen encephalitis suffer from intractable epileptic seizures. In our patients, the seizures occurred almost continuously (epilepsia partialis continua). It was therefore easy to perform ictal scanning. In the first patient (Fig. 25.2), H-15O was used to delineate the epileptogenic area. In the second patient (Fig. 25.6), the FDG and NH3 scans showed increased metabolism and blood flow in the affected areas, namely, the right frontal lobe. Of interest is the additional activation of the contralateral cerebellum. This is most probably due to crossed cerebrocerebellar pathways. If these pathways are interrupted, such as is the case in a brain tumor, one often observes a deactivation of the contralateral cerebellum. For this patient, the clinical value of PET lay in its ability to confirm the existence of a unilateral neocortical disease, which is a prerequisite for surgical therapy.

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188  Molecular Anatomic Imaging


PET Imaging in Dementias and Extrapyramidal Disorders

Alfred Buck  Ehab Kamel  Klaus Tatsch

Some types of dementia display a distinct metabolic signature. The hallmark of Alzheimer disease is bilateral parietal hypometabolism, although the pathology can be more extended at later stages. Not affected are the motor and visual cortex, the basal ganglia, and the cerebellum. Pick disease is located more frontally, and multi-infarct dementia shows a patchy pathology. The main clinical indication for positron emission tomography (PET) scanning in dementia is the confirmation of Alzheimer disease (AD). This has become increasingly important with the introduction of cholinergic therapies. Before using an expensive medication, one would like to have a clear diagnosis. The tracer most often used is fluorodeoxyglucose (FDG). A typical example of an FDG-PET scan of an Alzheimer patient is shown in Figure 26.1.

Extrapyramidal disorders include idiopathic Parkinson disease (PD), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD), and DOPA-responsive dystonia. In most cases, the diagnosis is established clinically; however, sometimes the situation is not clear, and PET imaging can be helpful. All the extrapyramidal disorders are characterized by a disturbance of the dopaminergic system, which can be evaluated with various PET and single-photon emission computed tomography (SPECT) tracers. A summary of findings is presented in Table 26.1. In PSP, MSA, and CBD, the pre- and postsynaptic sides degenerate; in PD, the presynaptic side mainly is affected. This pattern allows separation of PD from the other extrapyramidal disorders.

Electrolyte imbalance, nutritional deficiency, Parkinson disease, Huntington disease, normal-pressure hydrocephalus). Because of its effect on the patient’s ability to function in society, dementia affects not only the patient but also the people in his or her environment. The prevalence of dementias increases with age (3% of the population older than 65 years, 10% of the people older than 75 years) (1), and dementing diseases will thus become a growing sociologic health problem in the aging society of developed countries. The number of affected elderly people is thought to have doubled between 1981 and 2001 (2).

**POSITIVE EMISSION TOMOGRAPHY IMAGING IN DEMENTIAS**

Dementia is defined as a chronic, acquired, global, and progressive impairment of the intellect, memory, and personality without impairment of consciousness. The dementing diseases can be classified in two main categories: (a) diseases in which dementia is the only symptom (Alzheimer disease, Pick disease, multi-infarct dementia) and (b) diseases in which dementia is associated with other clinical or laboratory signs (infection, subdural hematoma, brain tumor, metabolic disorder,
Figure 26.1  A 60-year-old man with progressive cortical dementia. **A**: Cortical atrophy is shown by MRI. **B**: FDG-PET shows the typical bilateral temporoparietal hypometabolism seen in Alzheimer dementia.

**TABLE 26.1**

<table>
<thead>
<tr>
<th>PET AND SPECT TRACERS FOR THE EVALUATION OF THE DOPAMINERGIC SYSTEM</th>
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<td><strong>Presynaptic</strong></td>
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<td><strong>PET</strong></td>
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<td>$[^{18}F]$fluorodopa</td>
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MSA, multiple system atrophy; PD, idiopathic Parkinson disease; PSP, progressive supranuclear palsy; +, increased binding; –, decreased binding.
Chapter 26: PET Imaging in Dementias and Extrapyramidal Disorders

Indication for Positron Emission Tomography Studies

The diagnostic assessment in dementia includes a detailed history, a physical (especially neurologic) examination, blood and cerebrospinal fluid (CSF) screening, and computed tomography (CT) or magnetic resonance imaging (MRI). These tools are very useful in detecting most of the treatable causes of disorientation and loss of memory. For the remaining dementing diseases, such as neurodegenerative disorders and some cerebrovascular diseases, the definitive diagnosis is often based on biopsy or postmortem histopathologic findings. Functional imaging, such as positron emission tomography (PET), in combination with morphologic imaging, such as CT or MRI, helps in identifying the cause of dementia and in determining the neurophysiologic mechanisms underlying the disorder.

Normal Aging

Histopathologic findings show that the brain undergoes a number of age-related changes, which include neuron loss, ventricular enlargement, and cortical sulcal atrophy. CT and MRI are valuable techniques for identifying brain volume loss and ventricular enlargement. In an MRI study of 76 normal subjects, it was shown that the volumes of the cerebral hemispheres, of the frontal and temporal lobes, and of the amygdala-hippocampal complex decrease with age, whereas the ventricular volumes increase (3). The FDG-PET findings show a reduced metabolic rate in the elderly brain compared with that of young controls (4). However, when corrected for brain atrophy with CT or MRI, this age-related effect disappears (5). Effects due to atrophy should therefore always be taken into account when interpreting FDG-PET scans of elderly patients.

Alzheimer Disease

Alzheimer disease (AD) is the most common cause of dementia. The clinical diagnostic criteria require progressive, chronic cognitive deficits in patients aged 40 to 90 years without an identifiable underlying cause (6). Although these criteria permit accurate identification of AD patients with severe disease, it is very difficult to diagnose patients with early disease and to differentiate them from patients with other forms of neurodegenerative disorders.

Although the diagnosis is done on microscopic criteria, the brain of AD patients often shows characteristic changes on gross examination, such as cortical atrophy in the frontal, temporal, and parietal cortices, as well as frequent enlargement of the lateral and third ventricles (7,8). Analyzing the atrophy pattern in CT or MRI helps in distinguishing AD from normal age-related atrophy. With appropriate scan angles, it is possible to evaluate the temporal lobe and the hippocampus. The sizes of the sylvian fissures, the temporal horns, the temporal sulci, and the suprasellar cisterns characterize the temporal lobe atrophy and aid in differentiating brains affected with AD from normal brains (9). Furthermore, atrophy of the hippocampus present in AD patients is detected by an enlargement of the choroids–hippocampal fissure (10). Atrophy analysis by hand-drawn regions of interest, such as the hippocampus and the temporal role, helps in identifying AD, but this method is observer dependent (11,12).

Different FDG-PET studies that compared AD patients with age-matched normal controls showed a 20% to 30% decrease in whole-brain FDG uptake, with prominent hypometabolism in the bilateral parietal and temporal lobes (13–15) (Fig. 26.1). The visual and motor cortices appear to be spared this reduced FDG uptake. Studies of the cerebral blood flow with H2O-PET or with technetium 99m [99mTc]hexamethylpropyleneamineoxime (HMPAO)-SPECT (single-photon emission computed tomography) show a similar picture, with relative hypoperfusion in the parietal and temporal lobes (16,17). The biparietal pattern is highly predictive for AD, but it is not always present. In a study involving 129 patients with dementia, Salmon et al. (18) found that 97% of clinically or pathologically diagnosed AD subjects had an abnormal FDG distribution, with 66% showing the typical bilateral pattern. After repeated scans, the patients with atypical patterns tended to evolve to the characteristic FDG distribution. With disease progression, the hypometabolism and the hypoperfusion extended to the frontal regions (15) (Fig. 26.2). The magnitude and extent of the hypometabolism has been shown to correlate with the severity of the dementia symptoms (19).

Different investigators showed that PET appears to be a valuable tool in predicting AD in patients with mild dementia (20). This clearly shows the utility and advantage of PET in the assessment of demented patients. Since the introduction of new therapies for AD, such as with cholinesterase inhibitors, early diagnosis may be of importance for the success of the treatment. PET also appears to be a good modality for assessing the effect of these new treatments. When treated with cholinesterase inhibitors, AD patients showed an increase in the impaired cerebral glucose metabolism (21).

Neuroreceptor imaging is a promising tool in the diagnosis of AD. Different studies have identified alterations of the neurotransmission of the cholinergic, the serotonergic, and the γ-aminobutyric acid (GABA)-ergic systems (22–24). However, these types of PET examinations are not yet part of the clinical routine.

Multi-Infarct Dementia

After AD, multi-infarct dementia (MID) is the second most common cause of dementia, accounting for about 13% to 24% of cases. MID is caused by multiple infarcts that are usually distributed asymmetrically throughout the cortex. Clinically, the symptoms tend to progress stepwise, in contrast to the constant disease progression in AD. CT and
MRI have been shown to be sensitive in detecting MID. Vascular dementia is supported by the demonstration of vascular lesions by T1-weighted MRI or CT (25–27). The absence of vascular lesions in these imaging modalities is sufficient to exclude a vascular etiology for the dementia. FDG-PET studies of patients with MID show multiple scattered focal areas of hypometabolism corresponding to the lesions seen on MRI (26,28) (Fig. 26.3). The severity of the dementia was found to correlate with the total volume of hypometabolic brain tissue. The lesions seen in PET appear to be greater than the corresponding MRI lesions and thus can be of help in early diagnosis. MID and AD commonly coexist, which makes it necessary to combine FDG-PET and MRI findings to establish the diagnosis (26).

Frontotemporal Dementia

Frontotemporal dementia (FTD) defines a group of dementing diseases characterized by atrophy of the frontal and the temporal lobes. Pick disease, the best known
member of this group, is a neurodegenerative disease associated with atrophy, neuronal loss, gliosis, and the presence of Pick bodies on histopathologic examination. These alterations affect predominantly the frontal and temporal lobe of patients in middle to late adulthood.

Clinically, the distinction between Pick disease and AD is difficult. Frontal or temporal atrophy, as well as widening of the interhemispheric fissure frontally, with compensatory enlargement of the frontal horn, can be seen in MRI or CT (29). Differentiation between AD and FTD can be difficult on the basis of these findings. In PET studies, subjects with Pick disease show a symmetric reduction of glucose metabolism in both frontal and anterior temporal lobes (30) (Fig. 26.4). These same regions appear also to have a reduced perfusion (31). This pattern aids in distinguishing this disease from AD, which is important because AD patients could benefit from specific treatment, in contrast to subjects with Pick disease. Other disorders, such as schizophrenia, also have bilateral frontal hypometabolism but are not difficult to differentiate clinically from Pick disease.

**Normal-Pressure Hydrocephalus**

Normal-pressure hydrocephalus (NPH) is an important cause of dementia because it is potentially treatable. Clinically, the triad of dementia, ataxia, and urinary incontinence characterizes this disease. Although there is a dilation of the ventricles, the cerebrospinal pressure appears to be normal. Although the clinical and radiologic diagnostic criteria are clear, in some cases, identification of NPH can be difficult. Making the correct diagnosis is important because the patient may benefit from a CSF shunt. The success of shunting is highest for patients with a history of meningitis or subarachnoid hemorrhage. MRI and CT findings in patients with NPH show variable grades of ventricular enlargement with rounding of the anterior third ventricle and increases in the size of the temporal horns and the sylvian fissures (32). A good parameter for hydrocephalus is the increased ratio of the maximum ventricular horn width to the transverse inner diameter of the calvaria. A CSF flow void within the aqueduct and the third ventricle can be seen in MRI (33). PET studies done on NPH patients yield a diffuse cortical reduction of perfusion and metabolism without any regional predilection (34,35) (Fig. 26.5). The ventricular dilation, when massive, also can be identified with PET. The selection of patients for shunting is based on clinical, CSF, and imaging findings combined with response to spinal tap and removal of CSF.

**Alcohol-Related Dementia**

In patients with a long-term history of alcoholism, dementia can develop, along with impairment of orientation. In PET studies done on alcoholic patients, investigators found a decrease in metabolism in the whole brain but especially in the cortical and subcortical brain regions (36). Other studies reported more pronounced hypometabolism in the left hemisphere. Chronic alcoholic patients with cerebellar degeneration show hypometabolism in the superior vermis when compared with age-related control subjects. A study that compared the effects of administering alcohol to chronic alcoholics and normal subjects found that the former exhibited reduced glucose metabolism in the occipital, prefrontal, and cerebellar cortices, which are the regions with highest density of the GABA<sub>A</sub> receptors (37).

**Creutzfeldt-Jakob Disease**

Creutzfeldt-Jakob disease (CJD) is caused by a transmissible prion. The disease is characterized by a subacute spongiform encephalopathy in which a rapidly increasing dementia develops; the patients die shortly after diagnosis. Because this disease was not consistently recognized until recently, only a few PET studies with proven autopic or biopic diagnosis have been carried out. CJD patients show decreased FDG uptake, but the pattern is not yet clear. Perfusion also appears to be reduced (38).

**AIDS-Related Dementia**

Different neurologic dysfunctions can arise in patients infected with the human immunodeficiency virus (HIV). These conditions can be caused by the virus directly; by a secondary opportunistic infection, such as toxoplasmosis; or by acquired immunodeficiency syndrome (AIDS)–associated neoplasms. AIDS-related dementia is thought to be directly caused by HIV, and its occurrence is one of the criteria that define AIDS. It can occur as the only symptom or in association with other clinical manifestations of AIDS. The prevalence of dementia in AIDS patients is thought to be at least 5%. PET findings in patients with AIDS-related dementia show decreased glucose metabolism and perfusion in the cerebral cortex (39).
Clinical Consequences

In summary, when combined with morphologic neuroimaging techniques such as CT or MRI, PET is a useful tool in the diagnosis of dementing diseases. Comparing MRI and PET findings allows the estimation of the physiologic effects of morphologically identifiable brain lesions. For some diseases, such as Pick disease, PET seems to be a superior means of differentiating the disorder from other causes of dementia (31). Abnormal findings in PET often precede the alterations that can be found in CT or MRI, thus leading to an earlier diagnosis (21,40,41).

Unfortunately, most of the dementias discussed are untreatable. Nevertheless, for some dementing diseases, newer treatments appear to be able to increase the quality of life. AD patients profit from therapy with drugs that enhance cerebral cholinergic activity, such as cholinesterase inhibitors. Early diagnosis in these patients can lead to an early start of treatment. In MID patients, in whom lesions appear to be greater and thus easier to identify with PET than with MRI or CT, early diagnosis leads to improved control of risk factors such as hypertension and diabetes mellitus. This permits slowing or even stopping the disease progression. In NPH, PET may help in choosing patients who could benefit from a shunting operation (34).

If the diagnosis is not clear, PET findings often help to direct the subsequent investigation. Hypometabolism in the striatum, especially the caudate, for example, is suggestive of Huntington disease, which can be proven by genetic tests. Diagnosis of Huntington disease is very important because genetic counseling is mandatory.

PET seems to be a useful tool in understanding the pathophysiologic mechanisms of the underlying disease, and this could be helpful in developing new treatment strategies. Moreover, PET appears to be a valuable method for monitoring drug effects in dementing diseases. An increase in glucose metabolism has been observed after the administration of tacrine, a cholinesterase inhibitor, and piracetam in patients with AD (21,40).

Neuroreceptor imaging is a promising modality. For the time being, much neuroreceptor imaging is based on carbon 11 PET radiopharmaceuticals, which are inherently less useful in clinical routine than fluorine 18 (18F) PET radiopharmaceuticals, and data analysis is still time consuming and clinically practical in only a few cases. However, neuroreceptor imaging is of great interest among researchers attempting to understand the pathophysiology of many diseases.

PET AND SPECT IN EXTRAPYRAMIDAL DISEASES

Among extrapyramidal diseases, Parkinson disease (PD) and atypical parkinsonian syndromes, such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD), are the clinically most relevant diagnoses. In patients suffering from these illnesses, establishment of an early and accurate diagnosis can have impact on their management, help to avoid wrong treatment decisions, and aid in the selection of patients for therapeutic trials with newly developed drugs. Clinically,
extrapyramidal disorders are characterized by disturbances in motor function, such as tremor, rigidity, bradykinesia, and postural abnormalities (42,43). Structural imaging, such as CT and MRI, has limited value in the early diagnosis of extrapyramidal disorders, as in most instances structural abnormalities can be seen only when the disease is far advanced, if at all (44). Conversely, in other approaches, such as the assessment of perfusion or metabolism, PET and SPECT allow the evaluation of various aspects of dopaminergic neurotransmission, which is helpful in the differential diagnosis of extrapyramidal disorders (42,43). A summary of the tracers currently more often used for this purpose is provided in Table 26.1. It is important to realize that PET and SPECT permit the evaluation of the integrity of the pre- and postsynaptic sides of the striatal dopaminergic system, where the different extrapyramidal disorders might show distinct changes. However, before the differential diagnosis of extrapyramidal disorders becomes an issue, parkinsonism and tremor conditions that are not associated with dopamine terminal dysfunction but may mimic “true” parkinsonism have to be ruled out (e.g., drug-induced parkinsonism, psychogenic parkinsonism, essential tremor, drug-induced tremor, and psychogenic tremor).

### Parkinson Disease

The predominant pathology in PD, which accounts of about 70% to 80% of extrapyramidal disorders, is the loss of dopaminergic neurons that project from the substantia nigra pars compacta in the midbrain to the striatum (the putamen and caudate nucleus) in the forebrain. Typically, the projections to the posterior putamen are earlier and more affected than the projections to the caudate (42). The loss of neurons results in a dopaminergic deficit that is believed to provoke most of the symptoms, which include hypokinesia, tremor, and rigidity. Dementia is present in 23% to 30% of PD patients (point prevalence) (45) and will develop in more than 70% during the course of the illness (46). The diagnosis of PD is most often established clinically based on the criteria of the UK Parkinson’s Disease Society Brain Bank criteria, including positive response on dopaminergic medication as an important criterion. However, since PD shares some of the main features with several other disorders, there is evidence that clinically established diagnoses may be wrong in early- and even late-stage disease (47,48). When the diagnosis is unclear, PET or SPECT neuroimaging protocols may help to clarify it (43,49).

Whether changes in glucose metabolism and perfusion may be helpful in establishing the diagnosis of PD is still controversial, even though distinct pathologic observations have been reported. In early PD, studies have shown increased regional metabolic rates of glucose in the lentiform nucleus and thalamus (50,51), and this finding has been attributed to increased firing in the basal ganglia neurons as a direct consequence of dopamine deficiency (43). Similar observations have been reported for cerebral blood flow (50). In more advanced stages of PD, decreased caudate nucleus and cortical metabolic activity (parietal, temporal, frontal) has been reported in patients with and without associated dementia (52–55). Modern processing tools like anatomical standardization with pixelwise evaluation or discriminant and network analyses have shown promising results in discriminating PD patients from controls and patients with atypical PS. However, due to significant individual subject overlap, the clinical utility of these tools is still uncertain (56–58).

The biochemical hallmark of PD is the degeneration of the presynaptic nigrostriatal nerve fibers, whereas the postsynaptic side bearing the receptors remains intact. This is also the reason for the positive treatment response of PD to dopaminergic drugs that act exactly at this location. The presynaptic system can be assessed with [18F]fluorodopa (Fig. 26.6), which traces dopamine synthesis, or PET and SPECT ligands that bind to the vesicular monoamine transporter or the plasma membrane dopamine transporter and are thus considered a measure of presynaptic neuronal density. A commercially available SPECT ligand for measuring the presynaptic transporter density is iodine 123 [123I]FP-CIT. An example is shown in Figure 26.7. Functional PET and SPECT imaging with all these three types of presynaptic terminal measures show reduced radioligand uptake in the striatum of PD patients, with more a pronounced decrease in the putamen than in the caudate, and usually an asymmetry, with more severe affection of the striatum contralateral to the side with the predominant clinical symptoms. Significant correlations between disease severity and the reduction of the pertinent presynaptic terminal measures have been reported (59,60).

The postsynaptic dopaminergic system can be evaluated by using radioligands targeted to the dopamine receptors (see Table 26.1) (43). In PET studies carbon 11 [11C]raclopride and in SPECT studies [123I]IBZM, both D2-receptor

![Figure 26.6](image) **Figure 26.6** [18F]fluorodopa PET in a patient with Parkinson disease (PD). The tracer is primarily taken up in the striatum and traces the degeneration of the presynaptic side. A reduction of fluorodopa uptake is noted mainly in the right putamen. The left putamen and the caudate on both sides are relatively spared. This is the typical finding in PD, showing asymmetry and normal caudate nuclei.
tic density of the D2 receptor density is typically increased, as which are severely reduced in PD. On the contrary, the postsynaptic sures the dopaminergic transporters on the presynaptic side, patient with idiopathic Parkinson disease (PD). [123I]FP-CIT mea-

sures the dopaminergic transporters on the presynaptic side, which allows the two disorders to be distinguished. 

The major difference between MSA and PD, therefore, is postsynaptic tracers show reduced binding (60,69–71). 

ing in the striatum, in particular, might help to distinguish cortical structures (56–58,65–68). Thus, the reduced bind-

ing in the striatum, in particular, might help to distinguish MSA from PD patients. With respect to neurotransmission, MSA is characterized by degeneration of the pre- and postsynaptic dopaminergic system. Consequently, PET and SPECT investigations with all the pertinent pre- and postsynaptic tracers show reduced binding (60,69–71). 

The major difference between MSA and PD, therefore, is the presence of pathologic findings on the postsynaptic level, which allows the two disorders to be distinguished.

**Multiple System Atrophy**

MSA is a sporadic progressive neurodegenerative disorder that up to 10% of patients with extrapyramidal disorders may suffer from (63). Clinically, MSA is characterized by varying degrees of parkinsonism, cerebellar ataxia, and autonomic dysfunction. Depending on the predominant phenotype of the motor disorder, MSA is mainly classified into a parkinsonian type (MSA-P) and a cerebellar type (MSA-C). Pathologic studies exhibit neuronal degeneration and gliosis in the basal ganglia, brainstem, cerebellum, and spinal cord (64). In MSA, glucose metabolism and regional cerebral blood flow have been reported to be reduced in the lentiform nuclei, the cerebellum, and some cortical structures (56–58,65–68). Thus, the reduced binding in the striatum, in particular, might help to distinguish MSA from PD patients. With respect to neurotransmission, MSA is characterized by degeneration of the pre- and postsynaptic dopaminergic system. Consequently, PET and SPECT investigations with all the pertinent pre- and postsynaptic tracers show reduced binding (60,69–71).

The major difference between MSA and PD, therefore, is the presence of pathologic findings on the postsynaptic level, which allows the two disorders to be distinguished.

On the presynaptic level, a reliable differential diagnosis is not possible (72), even though a pattern of signal loss with more uniform affection of the caudate and putamen in MSA than in PD has been reported.

**Progressive Supranuclear Palsy**

PSP is a rapidly progressing degenerative disease belonging to the family of tauopathies. Clinically, it is characterized by parkinsonism with bradykinesia, rigidity, postural instability, and a pseudobulbar syndrome that includes dysarthria and dysphagia. The key feature of PSP, supranuclear palsy of the vertical gaze, is rarely present at the onset of the disease and usually appears later. Subcortical-type dementia is often present. Histopathologic findings show cell loss, gliosis, and accumulation of tau proteins in different brain regions, such as the brainstem and basal ganglia (pallidum, substantia nigra, subthalamic nucleus), with the cortex usually spared. The midbrain atrophy, particularly of the tectum, and the enlargement of the aqueduct of Sylvius, quadrigeminal cistern, and posterior third ventricle observed in MRI reflect the neuropathologic changes (73). 

Decrement of glucose metabolism in the midline frontal regions and in the brainstem have been postulated as the main distinguishing features of PSP versus MSA and PD. Hypometabolism in the superior frontal cortex, insula, and caudate nucleus, together with relative hypermetabolism in cortical motor areas, the parietal cortex, and the thalamus, has also been reported. According to this pattern, PSP patients could be differentiated from MSA and PD patients with an accuracy between 85% and 92% (66) and also from subjects with AD. Similar patterns have been reported for changes in regional cerebral blood flow (74,75). Since neurodegeneration in PSP affects both the pre- and postsynaptic dopaminergic systems, the PET and SPECT findings are similar to those in MSA subjects, showing a marked reduction in both levels (71,76,77). Therefore, PSP patients cannot be reliably distinguished from those with MSA using either pre- or postsynaptic tracers. However, as in MSA, the presence of pathologic PET and SPECT findings on the postsynaptic level allow discrimination between PSP and PD.

**Corticobasal Degeneration**

CBD is an asymmetric progressive neurodegenerative disease characterized by cortical and subcortical involvement, with both motor and cognitive dysfunction. CBD patients often initially present with apraxia and a parkinsonian picture of an akinetic rigid type, which usually does not respond to dopaminergic therapy (78). Dystonia and alien limb phenomena are also frequently present. Pathology reveals asymmetric frontoparietal neuronal loss and gliosis, nigral degeneration, and variable subcortical involvement. This results in markedly asymmetric cortical hypometabolism of glucose in PET studies affecting the primary sensorimotor (frontoparietal) cortex, insula,
striatum, and thalamus (66,79). A similar distribution of reduction in regional cerebral blood flow has been observed (75,80). Since corticobasal ganglionic degeneration involves the striatal presynaptic and possibly also the postsynaptic dopaminergic system, PET and SPECT studies of the latter should present with pathologic results. Concordantly, reduction in striatal fluorodopa uptake down to 25% of normal values was described (81), and SPECT studies have also revealed a marked decrease in dopamine transporter binding (82,83). Generally, a clear asymmetry was noted, with predominant affection of the striatum contralateral to clinical symptoms. Both the caudate and putamen seem to be similarly affected (84,85). Reports on the postsynaptic receptor status in CBD are rare and somewhat controversial, describing preserved (83) as well as diminished striatal binding (78). Large-scale systematic evaluations of the integrity of the dopamine receptors with PET and SPECT are still lacking.

Huntington Disease

This genetic disorder, in which an autosomal dominant defect occurs on chromosome 4, is characterized by progressive motor dysfunction (including chorea and akinetic rigidity), behavioral disturbances, and progressive cognitive deterioration, with an onset in the third or fourth decade. Although chorea is the hallmark of this disease, intellectual deterioration can precede the development of this motor abnormality. Histopathologically, there is a neuronal loss and a gliosis in the striatum of patients with Huntington disease (HD). Accordingly, PET studies show a substantial decrease of perfusion and glucose metabolism in the caudate nucleus and in the putamen (Fig. 26.8). These findings often precede the striatal atrophy seen in CT and MRI. The hypometabolism is not confined to the striatum but can also affect various cortical regions, and the degree of dementia was found to correlate with decreased FDG uptake in the frontal, parietal, and temporal lobes.

Exclusion of Neurodegenerative Extrapyramidal Disorders

One important question for clinicians is whether patients with equivocal or unclear symptoms suffer from extrapyramidal disorders or have other disorders not associated with neurodegeneration. Sometimes clinical symptoms indicative of parkinsonism or tremor conditions mimic “true” parkinsonism but are not associated with dopamine terminal dysfunction. Although the assessment of glucose metabolism or regional cerebral blood flow is of little help in this context, imaging of presynaptic terminal function with PET and SPECT has been shown to be a highly accurate means of confirming or excluding nigrostriatal degeneration. With these techniques, for example, patients with PD and atypical parkinsonian syndromes have been clearly distinguished from healthy controls, patients with...
drug-induced or psychogenic parkinsonism, patients with essential tremor and other tremor syndromes, and patients with dopa-responsive dystonia. Since dopamine terminals are not involved in the latter groups, normal presymptomatic terminal function has been reported in those cases (60).

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Cerebrovascular disease can be chronic or acute. A typical example of the latter is stroke. The clinical value of PET in the diagnostic workup of stroke patients is small, mainly due to its limited availability and high cost. Magnetic resonance imaging (MRI) has established itself as the method of choice in this field. Chronic cerebrovascular disease (CVD) is another matter. Symptoms such as transient ischemic attacks (TIAs) are often caused by severe stenoses in the larger arteries feeding the brain. In most cases, the treatment will be conservative. However, selected patients may benefit from surgical revascularization procedures. In these patients, a thorough diagnostic workup, including PET, is indicated. A special vascular pathology is moyamoya disease, which has the highest prevalence in Japan. At present, PET is the only method that allows a fully quantitative assessment of cerebral perfusion.

The physiological parameters of interest are blood flow (rCBF), blood volume (rCBV), and cerebral perfusion reserve, which can be evaluated with oxygen 15 \(^{15}\text{O}\)H\(_2\)O for perfusion and \(^{15}\text{O}\)CO for blood volume. An important parameter is the perfusion reserve, which is the ratio of rCBF at rest to that during vasodilation. The latter is induced by hypercapnia achieved by inhalation of CO\(_2\)-enriched air or the intravenous administration of acetazolamide (Diamox). In compromised areas, blood vessels are normally dilated, and the effect of hypercapnia is minimal. Thus, the perfusion reserve in such areas is reduced. For the assessment of perfusion reserve, two injections of \(^{15}\text{O}\)H\(_2\)O are needed, one at rest and one during hypercapnia. In between the two scans, it is possible to acquire the transmission scan for the correction of photon attenuation. The duration of the whole examination is 30 minutes. An example of a patient with a severe stenosis of the right internal carotid artery is shown in Figure 27.1.

The major indication for PET is the hemodynamic evaluation of cerebral perfusion before surgical revascularization. The most common tracer used to evaluate cerebral perfusion is \(^{15}\text{O}\)H\(_2\)O, which most often is intravenously injected as a bolus. Some groups use \(^{15}\text{O}\)CO\(_2\) which is inhaled through special delivery systems. In the body, \(^{15}\text{O}\)CO\(_2\) is almost immediately converted to \(^{15}\text{O}\)H\(_2\)O. Another PET perfusion tracer is \(^{15}\text{O}\)butanol. Cerebral blood volume (CBV) is typically altered in chronic cerebrovascular disease. It can be measured with \(^{15}\text{O}\)CO. Recent studies demonstrated that the density of benzodiazepine receptors is a good predictor for potentially salvageable tissue following stroke. It can be assessed with carbon 11 \(^{11}\text{C}\)flumazenil. Another crucial measure for the survival of tissue is oxygen metabolism, which is evaluated using \(^{15}\text{O}\).
CEREBROVASCULAR DISEASE–IMAGING METHODOLOGY

Perfusion

The kinetic behavior of diffusible perfusion tracers such as oxygen 15 \[^{15}\text{O}\]H\_2\text{O}\ is crucially different from tracers that get trapped, such as the SPECT agent technetium 99m \[^{99}\text{mTc}\]HMPAO. This difference warrants a completely different acquisition protocol. Since \[^{99}\text{mTc}\]HMPAO uptake does not change following injection, imaging can be performed as a single scan from minutes to hours following injection. In contrast, \[^{15}\text{O}\]H\_2\text{O}\ is washed in and out of the tissue within minutes. Together with the short physical half-life of \[^{15}\text{O}\], this requires imaging to be performed within minutes following injection if one uses a bolus injection. An interesting alternative method for certain applications is the use of a constant infusion protocol, which allows the continuous monitoring of blood flow (1). A detailed description of the methods used for \[^{15}\text{O}\]H\_2\text{O}\ imaging is given in the appendix at the end of the chapter.

Cerebral Blood Volume

Following inhalation as a bolus, \[^{15}\text{O}\]CO is irreversibly bound to hemoglobin. Its distribution is therefore restricted to intravascular space. Thus, the ratio of the \[^{15}\text{O}\]CO concentration in the brain and in blood directly yields the CBV.

CHRONIC CEREBROVASCULAR DISEASE

PET Imaging in Chronic Cerebrovascular Disease

Stenoses of the larger arteries feeding the brain are common. An important clinical aspect in this regard concerns the hemodynamic significance. There are two mechanisms by which atherosclerotic plaques may lead to symptoms such as transient ischemic attacks (TIAs) or stroke. Emboli may break lose from the plaques and cause the symptoms. Another possibility is that the stenosis is severe enough to lead to compromised cerebral perfusion in areas fed by the affected artery. The cerebral vascular response to reduced perfusion is complex. As a first response to decreased perfusion, the brain increases the oxygen extraction fraction. Another response is the dilatation of the vessels in an attempt to reduce vascular resistance and counteract reductions in perfusion. When the potential of these mechanisms is fully exploited and the perfusion still decreases, the patient becomes symptomatic. For instance, if the perfusion is just sufficient with maximum oxygen extraction and fully dilated vessels, any further stress will lead to decapensation. Such patients may benefit from a revascularization procedure such as endarterectomy or extracranial to intracranial (EC-IC) bypass surgery. The improvement of cerebral perfusion following revascularization has been demonstrated in several studies (2–7). An example of a patient with a severe stenosis of the right internal carotid artery is shown in Figure 27.1.

There exist several methods and parameters for evaluating patients with chronic cerebrovascular disease. Based on the physiological regulation of cerebral blood flow, the assessment of blood volume and perfusion is useful. This is illustrated in Figure 27.2A. The images on the left sketch the vascular autoregulation that occurs in cerebrovascular disease. The most common site for stenoses is the carotid bifurcation. The regulatory steps include increase of the oxygen extraction and dilatation of the vessels to reduce vascular resistance. The latter step is equivalent to an increase in cerebral blood volume (CBV). One method of evaluating the hemodynamic situation is indeed based on the measurement of CBV. The CBV/CBF ratio is an especially useful measure. The critical situation is reached when the vessels are fully dilated and CBF continuous to decrease. This situation is reflected by an increasing CBV/CBF ratio. Alternatively, one can measure hemodynamic behavior during induced vasodilatation. A strong stimulus for vasodilatation is an increase in arterial CO\(_2\) (PaCO\(_2\)). Hypercapnia can be induced by inhalation of an CO\(_2\)-enriched air mixture or by the administration of acetazolamide (Diamox).

In healthy subjects, the reduced vascular resistance due to induced vasodilatation leads to an increase in CBF. The ratio of CBF during hypercapnia and at baseline is often referred to as the cerebral perfusion reserve. The situation with a stenosis is illustrated at the bottom of Figure 27.2A. rCBF is normal at baseline due to chronic vasodilatation on the compromised side. Blood flow images will reveal symmetric perfusion in both hemispheres. Inducing hypercapnia will now dilate the vessels on the healthy side but not on the affected side or to a lesser degree, as they are already dilated. Blood flow will therefore predominantly increase on the healthy side, leading to a marked asymmetry in rCBF.

Blood flow imaging with SPECT primarily allows the qualitative assessment of CBF. The assessment of the hemodynamic situation with that modality most often relies on the evaluation of the CBV/CBF ratio or the asymmetry index during baseline and induced hypercapnia. A common problem arises if there is bilateral or even more extended disease. In that case, the hypercapnia-induced blood flow increase may be uniformly impaired and not lead to marked asymmetries. In these situations, the CBV/CBF ratio may be a more reliable measure for the hemodynamic situation. The most accurate evaluation is the quantitative assessment of the hemodynamics, as is possible with PET. A disadvantage in the clinical setting is that the accurate full quantification of cerebral blood flow requires the placement of an arterial catheter for the measurement of the tracer concentration in arterial blood. However, in a recent publication we showed that a simplified method may be sufficient for clinical purposes. The method is based on injected activity and does not require arterial blood sampling (8). Another important issue is the reproducibility of a method. We did an evaluation in 42 subjects who underwent quantitative perfusion scanning on two
consecutive days. On each day, three scans were performed 10 minutes apart. It was then assumed that the actual flow values during the same session were identical. So the difference between scan 2 – scan 1 and scan 3 – scan 2 in the same session is a measure of reproducibility. The results are shown in Figure 27.2B as a Bland-Altman plot (9) for gray and white matter. To determine gray matter flow, the flow values in all gray matter voxels were averaged. The range between the bottom and top horizontal line is defined by mean ± 2 SD. In gray matter, 2 SD was 17.2%. This means that a change in mean gray matter flow has to be larger than 17% in order to be considered significant with a 95% probability. In white matter, the corresponding value is 20.5%.

Examples of cerebrovascular evaluations are shown in Figures 27.3 to 27.5. The benefit of surgical treatment of occlusive cerebrovascular disease is still inconclusive. One large international trial failed to demonstrate the effectiveness of EC-IC bypass surgery for preventing cerebral ischemia in patients with arteriosclerotic cerebrovascular disease (10). However, one criticism of that study is that the patients preoperative hemodynamic status was not
fully assessed. It is possible that a quantitative evaluation of the hemodynamic situation may better select those patients who can potentially benefit from bypass surgery. A more recent study involving 12 patients demonstrated hemodynamic improvement following bypass surgery using quantitative $^{[15\text{O}]}\text{H}_2\text{O}$ PET (11). A Japanese trial involving patients with low rCBF demonstrated no benefit from EC-IC bypass surgery in terms of stroke prevention, although a significant improvement of rCBF was found in the surgical group (12). It is obvious that larger studies are needed to resolve the issue.

**SPECT Imaging in Chronic Cerebrovascular Disease**

SPECT allows the qualitative assessment of the hemodynamics using tracers like $[^{99\text{Tc}}]\text{HMPAO}$ or $[^{99\text{Tc}}]\text{ECD}$. The major advantage of SPECT is its wide availability. Differences in the uptake pattern at baseline and during hypercapnia allow conclusions regarding the perfusion reserve. The cerebral blood volume can be assessed using $^{99\text{Tc}}$-labeled erythrocytes. The disadvantages of SPECT compared with PET are as follows:

- It is qualitative, although attempts at quantification have been published.
- Under physiological conditions, the SPECT perfusion tracers are only 60% to 70% extracted, and the intracellular trapping requires an intact metabolism. In pathological situations, the extraction and the intracellular trapping may be changed. Thus, altered uptake may reflect not just changed blood flow. In this regard, $^{[15\text{O}]}\text{H}_2\text{O}$ is ideal: it does not require intact metabolism, and its extraction fraction is high.
Figure 27.3  

A: The axial T₂-weighted image shows enhanced signal in the right caudate, indicating infarction.  
B: The preoperative angiogram shows the stenosis of the right middle carotid artery (arrow 1).  
C: Preoperative quantitative evaluation of cerebral blood flow with [¹⁵O]H₂O PET. The difference between blood flow during hypercapnia (Diamox) and baseline is depicted in the bottom row. Note the reduced baseline flow and the lack of increase during hypercapnia in most of the right MCA territory.  
D: Quantitative evaluation of cerebral blood flow with [¹⁵O]H₂O PET following EC-IC bypass from the superficial temporal artery to the middle carotid artery. There is a marked improvement in the hemodynamic situation, best appreciated on the difference images (bottom row). Although there is still an impaired perfusion reserve in the posterior part of the MCA territory, the situation has clearly improved in the anterior part.
Figure 27.4  A: The preoperative angiograms in this patient show a stenosis of the left internal carotid artery (1) and the right vertebral artery (2) and a complete occlusion of the left vertebral artery (3). B: Preoperative quantitative evaluation of cerebral blood flow with $[^{15}O]$H$_2$O PET. The difference between blood flow during hypercapnia (Diamox) and baseline is depicted in the bottom row. Note the lack of increase of blood flow during hypercapnia in parts of the left cerebellum (arrows). C: Angiogram following EC-IC bypass from the occipital artery to the posterior inferior cerebellar artery. The arrow points to the anastomosis at the occipital artery. D: Quantitative evaluation of cerebral blood flow with $[^{15}O]$H$_2$O PET following EC-IC bypass from the occipital artery to the posterior inferior cerebellar artery. The hemodynamic situation has completely normalized.
Assessment of the perfusion reserve relies on two scans, one at baseline and one during hypercapnia. With SPECT, these scans have to be acquired on separate days, due to the relatively long half-life of $^{99m}$Tc-based tracers. With $^{[15O]}$H$_2$O PET, injections can follow at 15-minute intervals, resulting in a total procedure duration of only 30 minutes.

Figure 27.5  A: In this patient, the T$_2$-weighted MRI shows the infarction in the left frontal lobe. B: Preoperative quantitative evaluation of cerebral blood flow with $^{[15O]}$H$_2$O PET. The difference between blood flow during hypercapnia (Acetazolamide) and baseline is depicted in the bottom row. Note the actual decrease of blood flow during hypercapnia in the anterior left frontal cortex (steal phenomenon), indicating a severely compromised hemodynamic situation. C: The postoperative angiogram shows adequate blood supply from the bypass (superficial temporal artery–MCA) to the left MCA territory (arrows). D: Quantitative evaluation of cerebral blood flow with $^{[15O]}$H$_2$O PET following endarterectomy, demonstrating a complete normalization of the hemodynamics in the posterior part of the right MCA territory and residual impairment in the anterior part.

Other Imaging Modalities
Computed tomography (CT) and magnetic resonance imaging (MRI) are used to assess possible manifestations of chronic CVD. Angiography is used to assess the morphology of the vessels and identify the location and degree of stenoses. Quantitative perfusion measurements can be
performed with xenon-enhanced CT. However, this method is less validated than \[^{15}O\]H\(_2\)O PET. Only with the newest 64-row detector scanners can a large portion of the brain be assessed simultaneously, but at the penalty of a very high radiation dose.

**Examples**

**Case A**
The case of a 23-year-old woman is illustrated in Figure 27.3. The T\(_2\)-weighted MRI of the brain demonstrates an infarct in the right caudate (Fig. 27.3A). Angiography revealed a stenosis of the right middle carotid artery (MCA) (Fig. 27.3B). The result of the hemodynamic PET evaluation is shown in Figure 27.3C. Already the baseline examination reveals a reduced CBF in the greater part of the right MCA territory. Following acetazolamide, there is no CBF increase in that area, indicating a severely compromised hemodynamic situation. Following EC-IC bypass surgery from the superficial temporal artery to the MCA, the hemodynamic situation improved, as illustrated by the postoperative PET evaluation (Fig. 27.3D). The improvement is best appreciated on the difference images. Although there is still an impaired perfusion reserve in the posterior part of the MCA territory, the situation has clearly improved in the anterior part.

**Case B**
Figure 27.4 shows the case of a 78-year-old woman with complete occlusion of the left vertebral artery and a stenosed right vertebral artery (angiograms in Fig. 27.4A). There was another stenosis in the internal carotid artery. The preoperative PET evaluation demonstrated a normal perfusion pattern at baseline but a severely decreased perfusion reserve in parts of the cerebellum (Fig. 27.4B). The hemodynamic situation normalized completely following bypass surgery from the occipital artery to the posterior inferior cerebellar artery (Fig. 27.4C). The postoperative PET assessment showed a normal perfusion pattern and perfusion reserve (Fig. 27.4D).

**Case C**
This example demonstrates the usefulness of a fully quantitative assessment of blood flow. The patient was a 67-year-old woman who suffered from syncope and episodes of motoric aphasia. Angiography revealed an occlusion of the left internal carotid artery and a 50% stenosis of the right internal carotid artery. MRI demonstrated an infarction in the left frontal lobe (Fig. 27.5A). The preoperative PET examinations (Fig. 27.5B) showed an almost normal perfusion at baseline and severely pathological behavior during hypercapnia in the territory of the left MCA. The red areas in the subtraction images indicate that blood flow even decreased during hypercapnia (steal phenomenon), demonstrating a severely compromised hemodynamic situation. The demonstration of an actual decrease requires some sort of quantification. A qualitative assessment would only have demonstrated an asymmetry during hypercapnia. The patient's symptoms disappeared following bypass surgery from the superficial temporal artery to the left middle cerebral artery. The postoperative angiography reveals good blood supply from the bypass to the left MCA territory (Fig. 27.5C). The postoperative PET assessment (Fig. 27.5D) demonstrated a normalization of the hemodynamics in the posterior left MCA territory. As expected, no changes occurred in the left frontal infarction area.

**MOYAMOYA DISEASE**
The name for this disease was coined by J. Suzuki. It is characterized by abnormal vascular networks at the base of the brain. “Moyamoya” means “something hazy just like a puff of cigarette smoke drifting in the air” (13). The abnormal vessels are thought to function as collaterals in the presence of stenotic or occlusive lesions at the terminal parts of the internal carotid arteries. The clinical hallmarks of the disease depend on the patient’s age. Younger patients most often suffer from the consequences of hemodynamic insufficiency, such as transient ischemic attacks. These are characteristically triggered by hyperventilation leading to hypocapnia, a vasoconstrictive stimulus. Older patients often present with intracranial bleeding.

**Imaging**

**CT**
Forty percent of cases presenting with cerebral ischemia have been reported to demonstrate abnormal finding on CT, including
- Low density areas in the cortex and/or white matter, usually not in the basal ganglia;
- Dilatation of the convolutions and sulci;
- Mild ventricular dilatation; and
- High-density areas corresponding to hemorrhage in the basal ganglia, thalamus, ventricle, subcortical areas, and cortex (in order of frequency).

**MRI and MRA**
MRI may detect infarcts not seen on CT. MRI and magnetic resonance angiography (MRA) are increasingly used instead of angiography, especially in children. The clear advantage is the noninvasiveness.

**Cerebral Angiography**
Angiography is still the most common method for diagnosing the disease. In addition to the cardinal finding of stenosis or occlusion at the terminal parts of the internal carotid arteries and abnormal vascular networks, the following may also be observed in typical and advanced cases, indicating the presence of a transdural collateral circulation:
- Ethmoidal moyamoya, abnormal vessels at the base of the brain anteriorly, and
Vault moyamoya, transdural anastomoses at the cranial vault originating from these arteries: anterior facial artery, middle meningeal artery, ethmoidal artery, occipital artery, tentorial artery, superficial temporal artery. In addition, cerebral aneurysms are detected in 4% to 14% of cases.

\[ ^{15}O \text{H}_2\text{O PET} \]

A typical example of a 25-year-old woman is illustrated in Figure 27.6. The abnormal vascular network is clearly seen in the angiography shown in Figure 27.6A. The gadolinium-enhanced, T₁-weighted (TE 14 ms, TR 500 ms) MRI in Figure 27.6B shows flow visualized within numerous dilated thalamoperforating and lenticulostriate branches. The hemodynamic PET evaluation is shown in Figure 27.6C. The baseline scan demonstrates a lack of perfusion in temporolateral, frontal, and parietal areas of the left hemisphere, corresponding to infarction. Following the administration of acetazolamide, perfusion does not appropriately increase in most of the brain except the cerebellum thalamus and striatum. There is even a decrease of perfusion in a right frontal area, which is best appreciated on the difference images. D: The images show the hemodynamic evaluation, but in contrast to part C, the qualitative count images (accumulated over 60 seconds following arrival of the bolus in the brain) are shown.

Figure 27.6  Moyamoya disease A: Lateral projections of common carotid (left panel) and vertebral (right panel) angiography. The late arterial phase reveals an occlusion of the internal carotid artery (1) distal to the origin of the ophthalmic artery. A collateral network is present supplied by meningo cortical branches (2) and thalamoperforating arteries (3). In conjunction with dilated lenticulostriate branches, the collateral network gives rise to the typical “puff of smoke” appearance of moyamoya disease. B: The gadolinium-enhanced, T₁-weighted (TE 14 ms, TR 500 ms) MRI shows flow visualized within numerous dilated thalamoperforating and lenticulostriate branches. C: Hemodynamic evaluation with PET. The baseline scan shows lack of perfusion in temporolateral, frontal, and parietal areas of the left hemisphere, corresponding to infarction. Following the administration of acetazolamide, perfusion does not appropriately increase in most of the brain except the cerebellum thalamus and striatum. There is even a decrease of perfusion in a right frontal area, which is best appreciated on the difference images. D: The images show the hemodynamic evaluation, but in contrast to part C, the qualitative count images (accumulated over 60 seconds following arrival of the bolus in the brain) are shown.
superiority of quantitative perfusion imaging. The images in Figure 27.6D represent the counts accumulated over 60 seconds following the arrival of the bolus in the brain. The images are scaled to the maximum of each image. Although they demonstrate relatively decreased tracer uptake in large frontal, temporal, and parietal areas, the absolute decrease in the right frontal cortex and the normal increase in the cerebellum, thalamus, and striatum are not appreciated.

**ACUTE ISCHEMIC STROKE**

Acute stroke is a common complication of cerebrovascular disease that often leads to death or severe handicap. In contrast to heart attacks, the therapeutic window for treatment is much shorter, due to the higher vulnerability of neurons for hypoxia. However, double-blind trials with thrombolytic therapies have lately shown promise (14). These positive findings are explained by experimental results and also PET experiments that demonstrated that larger areas with vital tissue could potentially be salvaged by some kind of reperfusion therapy. In this regard MRI, CT, and PET can be used to identify the tissue at risk. MRI with diffusion-weighted imaging (DWI) and contrast-enhanced CT have lately made substantial progress in this area. PET will be limited to specialized centers and is not as useful because of the need for acute availability.

**PET and SPECT Imaging in Acute Stroke**

However, PET imaging has contributed valuable insights into the pathophysiology of stroke. In acute ischemic stroke, the evaluation of perfusion and oxygen metabolism is of special interest. The affected tissue in stroke consists of various zones. If no reperfusion occurs within a short period of time, the most hypoperfused tissue will become necrotic. This zone is often surrounded by a region of tissue at risk, called the “penumbra.” This tissue may survive depending on the postinfarction course of the cerebral perfusion status of the patient. PET measurements have shown that perfusion values below 12 mL/min/100 g lead to irreversible damage. Values between 12 and 25 mL/min/100 g are typical for the penumbra and can be tolerated for hours (15). One of the most important parameters regarding tissue vitality is the rate of oxygen metabolism. Values below 65 μmol/min/100 g lead to irreversible damage. Serial studies in stroke patients demonstrated that the oxygen metabolic rate may deteriorate during 2 weeks following the onset of the stroke, especially in the penumbra (16,17). Another promising approach to detecting viable tissue in stroke relies on the evaluation of benzodiazepine receptors with [11C]flumazenil. It was shown that the pattern of flumazenil uptake could separate vital from irreversibly damaged tissue (18). These results underline the importance of the penumbra. It is this zone that draws most attention in newer thrombolytic approaches.

Perfusion SPECT also allows the exact delineation of the stroke area at very early stages. However, if the choice exists between CT or MRI (including DWI) and SPECT, the former are superior because they deliver morphological and angiographic information in the same session.

**Other Imaging Modalities**

In the diagnostic workup of acute stroke, CT scanning is used to exclude hemorrhage. This is important because bleeding may affect management of the patient. Ischemic stroke may evade detection in the very early stages. Angiography is necessary if intra-arterial thrombolysis is considered as a treatment. With the newest multi-row CT scanners, protocols have been developed that seem to be able to distinguish necrotic areas from the penumbra, which is critical for the start of thrombolytic therapy.

Also, standard MRI fails to detect early ischemic lesions. In later stages, MRI is the method of choice to investigate the number and extent of infarct areas. Structural MRI is more sensitive than CT, especially in the cerebellum, brainstem, and deep white matter (19–21). Where available, MRI combined with MRA is ideal for delineating infarction beyond 12 hours of infarction onset. Recent progress in functional MR methods now allow the investigation of early infarction. DWI is sensitive to the self-diffusion of water and can detect ischemic lesions at the earliest periods studied (22–24). These methods are especially useful in stroke centers where new methods of treatment are developed.

A detailed discussion of the use of CT and MRI in the workup of acute stroke is beyond the scope of this chapter.

**CEREBROVASCULAR DISEASE: SAMPLE PROTOCOLS**

**Quantitative Evaluation of Perfusion**

The following is a protocol we use at our institution to assess the cerebral perfusion reserve. It is based on the autoradiographic method.

**Patient Preparation**

Place catheters in the radial artery for blood sampling and a cubital vein for injection.

The sampling of blood is most easily performed with an automatic injection device.

*Injection of 700 MBq of [15O]H2O. Although the injection can be performed manually, it is advantageous to use an automatic injection device.*
Molecular Anatomic Imaging

Acquisition of one 60-second scan following the arrival of the bolus in the brain.
Continuous blood sampling with a special sampling device.
Acquisition of a 10-minute transmission scan for photon attenuation correction.
At the beginning of the transmission scan, injection of 1 g of acetazolamide as a slow bolus over 2 minutes.
Thirteen minutes following the start of the acetazolamide injection, initiation of the second scan.

The whole procedure lasts approximately 20 minutes.

Data Analysis
Following reconstruction, the data are exported and processed in a flexible analysis tool (www.pmod.com) (25,26). In a preprocessing step, delay and dispersion of the arterial input curve are corrected using the method described by Meyer (27). The parametric flow maps are then smoothed with a Gaussian filter and subtraction images calculated (flowdiamox – flowbaseline).

Quantitative Measurement of Blood Volume

Patient Preparation
Placement of a catheter in a cubital vein for continuous blood sampling.

Data Acquisition
Acquisition of a 10-minute transmission scan for photon attenuation correction.
Inhalation of 1000 MBq of $[^{15}O]$CO as a bolus.
Acquisition of five 60-second scans immediately following inhalation.
Drawing of continuous venous blood samples with a continuous sampling device 3 to 5 minutes following inhalation.

The whole procedure lasts approximately 20 minutes.

Data Analysis
Following reconstruction, the time course of the activity in the brain is assessed by defining a region of interest, which can encompass a whole transaxial slice. The purpose is to find the timepoint after which full equilibrium is achieved and the activity remains constant. This point is usually reached after 2 to 3 minutes. Then all scans acquired after this timepoint can be summed. The division this of summation image and the mean radioactivity in blood during the equilibrium period yields the blood flow directly. Depending on the required accuracy, it must be considered that the hematocrit in arterial blood and the hematocrit venous blood are slightly different. The easiest way to correct for the difference is to use a fixed correction factor. Alternatively, arterial or arterialized blood could be sampled.

APPENDIX: DETAILED METHODOLOGY FOR QUANTITATIVE PERFUSION IMAGING

Methods Using Bolus Injection
Diffusible tracers display typical time–activity curves (TACs) following injection. An example for $[^{15}O]$H$_2$O is shown at the bottom of Figure 27.7. Displayed are the TACs in arterial plasma and tissue in a simulated situation. The arterial TAC shows a relatively sharp peak. The tissue TACs follow the arterial curve with dispersion. At the higher flow rate, the initial increase is steeper, the peak higher, and the subsequent decline (washout) faster than at the lower blood flow. Based on these kinetics, there exist several possibilities for assessing perfusion. It can easily be shown that the area below the TAC during the initial increase is closely related to perfusion. Due to back-perfusion, this area will underestimate true perfusion, and this effect is more pronounced the longer the integration time. Nevertheless, the integration of activity during the first 60 seconds following the arrival of the bolus in the brain is a reasonable measure for perfusion.

Full quantification requires the application of a mathematical model. An example for $[^{15}O]$H$_2$O is shown at the top of Figure 27.7. The model consists of an arterial input, a tissue compartment, and the venous outflow. It is assumed that the tracer distribution in the accessible part of the tissue compartment is homogeneous and that the concentration is equal to the venous outflow. The partition coefficient $p$ is the fraction of tissue space that is actually permeated by the tracer. For water, it is in the 80% to 90% range. The kinetics is then described by a single differential equation that contains only one unknown, flow $F$. The solution for the differential equation can be written as a convolution with the arterial input curve. If one measures the tissue TAC and the arterial input curve, flow $F$ can be calculated by some standard method of parameter estimation. Probably the simplest is the autoradiographic method, which requires only one static scan besides arterial blood sampling. $F$ is then adjusted by a fitting routine so that the model value fits the measured value.

Somewhat more complex are the methods that use a series of scans. The advantage of such methods is that they allow an estimation of the partition coefficient along with flow. This may be advantageous in situations where the partition coefficient is altered. For all methods that make use of an arterial input curve, it is important to note that this curve is being measured at a place distant from the brain, often the radial artery. Therefore, the delay and shape of the measured input curve may differ from the true input curve in the brain. Further distortions occur if an automatic sampling device is used. The main disadvantage of the described method is the need for an arterial catheter to determine the arterial tracer concentration.
This is somewhat impractical in a clinical setting. To circumvent this disadvantage, we developed a method that does not require arterial blood sampling (8).

### Imaging at Equilibrium Using a Constant Infusion Protocol

An interesting alternative to bolus injection is the use of a constant infusion protocol (1). Imaging is performed when tissue and intravascular $^{15}$O$\text{H}_2\text{O}$ are at equilibrium, which takes around 10 to 15 minutes after the start of the infusion. Crucial for this method is the short half life of $^{15}$O. If the half-life of the isotope is on the order of the transit time in tissue, a considerable amount will decay during the passage of the tracer through the tissue. The lower the perfusion, the longer the transit time and the greater the decay. Areas of decreased perfusion will therefore demonstrate a decreased $^{15}$O$\text{H}_2\text{O}$ concentration. In addition, the ratio of $^{15}$O$\text{H}_2\text{O}$ in tissue to plasma allows an absolute quantification of perfusion according to the following equation:

$$\text{CBF} = \frac{\alpha}{1 - \alpha/p}$$

where $\alpha$ is the ratio $^{15}$O$\text{H}_2\text{O}$ tissue/$^{15}$O$\text{H}_2\text{O}$ plasma, $\lambda$ is the decay constant of $^{15}$O (0.376 min$^{-1}$), and $p$ is the partition coefficient. The advantage of a constant infusion protocol is that the time course of a perfusion change following an intervention (e.g., acetazolamide) can be monitored continuously. An example is shown in Figure 27.6.

### REFERENCES

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Clinical PET and Integrated Modality Imaging of the Heart

Cardiac imaging is extremely important because of the high prevalence and morbidity of cardiovascular disease. Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) have been the methods of choice for imaging myocardial perfusion. Myocardial perfusion imaging is probably almost as relevant as the morphologic depiction of the coronaries, because a morphologic stenosis does not necessarily result in distal myocardial hypoperfusion, as collateralization may be present. Thus, treatment of a morphologic coronary abnormality always requires unequivocal proof that ischemia is present in the patient, whether on the basis of clear clinical signs and symptoms or perfusion imaging.

Myocardial perfusion imaging, now most frequently done with SPECT, is one of the most relevant imaging examinations in daily nuclear medicine practice, while PET has an important role to play because of its unique quantitative features. PET is able to quantify perfusion and thus permits the determination of coronary reserve, a parameter with high sensitivity and predictive value for coronary artery disease. Furthermore, it remains the gold standard for the identification of hibernating myocardium. Transmission correction in myocardial PET, but also in myocardial SPECT, is important because, particularly in somewhat obese people, the inferoposterior wall can exhibit an artificial decrease in perfusion, which leads to misinterpretation. Transmission correction is especially simple with the use of SPECT-CT and PET-CT cameras, and because such cameras are currently being widely introduced, transmission correction of such images will likely soon become state of the art in myocardial perfusion imaging.
The Normal Heart
Scan: PET and SPECT

Philipp A. Kaufmann

This chapter provides a short summary of the commonly used tracers and techniques for assessing viability and perfusion by positron emission tomography (PET), along with examples of normal heart scans. The most commonly used tracer for clinical assessment of myocardial blood flow by PET is ammonia. The heart is displayed in short-axis sections beginning from the apex and ending at the base, as well as in vertical and horizontal long-axis sections. Liver accumulation of nitrogen 13 \(^{13}\text{N}\)ammonia is often prominent. For viability, fluorine 18 fluorodeoxyglucose (\(^{18}\text{F-FDG}\)) is actually the best-accepted PET tracer (see Fig. 28.2). The heart can be visualized by \(^{18}\text{F-FDG}\) only when the patient is not in a fasting state. Cardiac PET studies with this tracer are performed after a glucose load before scanning. Images are acquired 40 to 60 minutes after injection. For both ammonia and FDG, there is no tracer uptake into the membranous septum, very weak accumulation in the right ventricle, and frequently decreased uptake at the apex of the left ventricle.

Myocardial perfusion SPECT images look similar to myocardial perfusion PET images. Also, in the case of SPECT myocardial images, there is an increasing tendency to perform attenuation correction. This is facilitated by the new SPECT-CT imaging systems, which are currently gaining more and more acceptance.

MYOCARDIAL PET PERFUSION TRACERS

Various radionuclides are available for cardiac perfusion studies using PET (see Table 3.1). The positron-emitting radionuclides used in PET studies typically have short physical half-lives. These should be compared with the half-lives of radionuclides routinely used in diagnostic nuclear medicine, such as technetium 99m \(^{99}\text{mTc}\) and thallium 201 \(^{201}\text{Tl}\), which have half-lives of 6.0 and 73.5 hours. The short half-lives of positron-emitting radionuclides provide a number of practical advantages, in particular, the reduction of the radiation dose to the patient and the acquisition of repeated myocardial blood flow (MBF) measurements in the same patient in the same scanning session within a reasonable time (1 to 2 hours).

None of the tracers tested thus far have all the characteristics required for optimal quantification: short physical half-life, minimal radiation dose, uptake directly related to flow and independent of metabolic conditions, and availability without a cyclotron. At present, quantification requires sophisticated mathematical analysis, rapid data acquisition free of detector saturation, and, depending on the technique, concomitant administration of a blood pool tracer.

The three most common tracers are nitrogen 13 \(^{13}\text{N}\)ammonia, rubidium 82 \(^{82}\text{Rb}\), and oxygen 15 \(^{15}\text{O}\)water; these tracers are discussed from a radiopharmaceutical point of view in Chapter 16. They have been selected for their physical and biochemical properties. Their physiologic characteristics show remarkable differences. \(^{15}\text{O}\)water is metabolically inert and freely diffuses across all capillary membranes, including those of the myocardium, rapidly equilibrating between the vascular and extravascular spaces. There is only minimal effect of flow on \(^{15}\text{O}\)water uptake and nearly 100% extraction (1). The 2-minute half-life of the \(^{15}\text{O}\) isotope allows repetitive MBF measurements at 10-minute intervals. However, \(^{15}\text{O}\)water also remains in the blood pool, contaminating the image with uptake within the ventricular chambers.
and surrounding structures. Therefore, a traditional short-
coming of the \[^{15}\text{O}]\text{water} technique used to be its need for additional \[^{15}\text{O}]\text{carbon} monoxide blood pool scans to define the regions of interest and correct for the high \(^{15}\text{O}\) activity in the blood pool. Recently, a new technique was proposed for generating myocardial images directly from the dynamic \[^{15}\text{O}]\text{water} scans, eliminating the need for additional carbon (C) \(^{15}\text{O}\) blood pool scans (2) while allowing serial \[^{15}\text{O}]\text{water} PET measurements of MBF (Fig. 28.1). This technique was validated against microspheres in experimental animals (3), and we have extensively documented its reproducibility in humans (4–6).

By contrast, \[^{13}\text{N}]\text{ammonia} provides high image contrast because it is rapidly cleared from blood and is avidly retained in myocardial tissue. Because of its tissue solubility, it diffuses readily into cells, where most is trapped as glutamate. At physiologic pH, ammonia is found primarily in the form of \(\text{NH}_4^+\). Its concentration in the myocardium depends not only on flow but also on the amount of \[^{13}\text{N}]\text{ammonia} administered as a function of time (input function), its extraction at the instantaneous flow, and the metabolic state. The normal myocardial uptake pattern for PET using ammonia tagged with \(^{13}\text{N}\) is comparable to that obtained using fluorine 18 fluorodeoxyglucose (\(^{18}\text{F-FDG}\)) (Fig. 28.2). However, it is obviously independent of the fasting state of the patient. There is often prominent liver accumulation of \[^{13}\text{N}]\text{ammonia} (Fig. 28.3).

The potassium analog \(^{82}\text{Rb}\) can be eluted from a strontium 82 generator system (see Chapter 16), avoiding the need for an on-site cyclotron. The extraction is flow related at high flow rates, and therefore a correction of \(^{82}\text{Rb}\) uptake for extraction is needed. The mean positron energy emitted by \(^{82}\text{Rb}\) is higher than that in \[^{13}\text{N}]\text{ammonia}. Thus the distance traversed by \(^{82}\text{Rb}\) positrons in tissue is longer, resulting in a somewhat lower spatial resolution. In addition to the lower count rate due to the shorter half-life, image quality is reduced compared with that obtained with \[^{13}\text{N}]\text{ammonia}. At present, the application of \(^{82}\text{Rb}\) must be considered immature because of these technical limitations, at least for the purpose of myocardial perfusion quantification, and it is very costly.

**Figure 28.1** Midventricular short-axis raw image (A–C). After intravenous application of \(^{15}\text{O}\)-labeled water, the activity is first seen in the blood pool of the right ventricle (A) and subsequently of the left ventricle (B). Thereafter, activity is seen in blood pool and myocardial tissue, resulting in low-quality images (C) and preventing the drawing of regions of interest. By contrast, after applying factor analysis, the resulting pictures well depict blood pool (D) in the right ventricle (RV) and left ventricle (LV) as well as the left ventricle myocardial tissue (E).
Tomographic imaging, by displaying data in the format of slices with discrete thickness, allows better separation of myocardial and other nonmyocardial structures and individual coronary artery beds, and tomographic PET imaging is inherently quantitative. A standardized nomenclature for tomographic views (short axis, vertical long axis, and horizontal long axis) and image displays has been developed for different tomographic imaging techniques, including SPECT, PET, computed tomography (CT), and magnetic resonance imaging (MRI), by the Committee on Advanced Cardiac Imaging and Technology, the Council on Clinical Cardiology, and the American Heart Association in collaboration with the Cardiovascular Imaging Committee of the American College of Cardiology and the Board of Directors of the Cardiovascular Council of the Society of Nuclear Medicine (7).

**QUANTIFICATION OF MYOCARDIAL PERFUSION IN PET**

Several techniques are available for measuring coronary blood flow or MBF in humans, including Doppler catheterization, quantitative coronary arteriography, thermodilution, and measurement of inert tracer clearance. However, most methods are invasive and have serious limitations (8). Noninvasive assessment of MBF may be performed with either SPECT or PET, and early clinical data suggest that MRI also may be used for this purpose. The physical limitations of SPECT do not permit absolute quantification of MBF. By contrast, PET overcomes some of these limitations by providing superior resolution, accurate attenuation correction, and partial volume correction, thus allowing reproducible absolute quantification of regional MBF. The advances in myocardial perfusion techniques over the past several years with PET led to the development of methods that are suitable for clinical use. Techniques have been established for the tracers mentioned in which diffusible tracers ([15O]water) must be distinguished from the nondiffusible tracers ([13N]ammonia). For quantification with [15O]water, a one-compartment model is widely used, whereas for [13N]ammonia, either a two- or a three-compartment model has been proposed (see Chapter 13). The specific details of the development and validation of these methods are beyond the scope of this chapter.

We recently studied absolute baseline and hyperemic MBF in a large group of normal volunteers (131 men and 38 women; age range, 21 to 86 years) by using PET with [15O]water (9). The mean resting MBF was 0.99 ± 0.23 mL/min/g (range, 0.59 to 2.05 mL/min/g), and the mean hyperemic flow was 3.54 ± 1.01 mL/min/g (range, 1.11 to

![Figure 28.2](image_url) **Figure 28.2** Normal uptake pattern of [18F-FDG] into the heart, late phase at 40 to 60 minutes. Short-axis cuts of the left ventricle starting at the apex (A). Vertical cuts along the long heart axis (B) and horizontal cuts parallel to the long axis (C). Note the absence of [18F-FDG] uptake in the membranous septum (top right, section closest to the cardiac base) and the very weak accumulation of [18F-FDG] in the right ventricle. Furthermore, there is decreased [18F-FDG] uptake at the apex of the left ventricle, which is frequently noted and normal.

![Figure 28.3](image_url) **Figure 28.3** Normal uptake pattern of [13N]ammonia scans of the heart. Two top rows: Eight short-axis scans starting at the apex and ending at the base. Third and fourth row: Four horizontal and four vertical long-axis cuts, respectively. Note the lower activity in the thinner right ventricular wall. Liver accumulation of [13N]ammonia is prominent.
5.99 mL/min/g). In agreement with previous studies, we found that hyperemic MBF declines with increasing age; therefore, in subjects older than 65 years, the combination of the increase in baseline and the reduction in hyperemic MBF leads to an even larger decrease in coronary flow reserve. These changes are likely to result from the combination of a number of mechanical and neurohumoral factors associated with aging, including increased arterial impedance, thickening of left ventricular myocardium, reduced lusitropism (impaired diastolic relaxation), reduced catecholamine responsiveness, endothelial dysfunction, and deficient neuroendocrine regulation. Although there are no firm data on whether aging modulates the pharmacologic effects of dipyridamole and adenosine, it is conceivable that peak vasodilation could occur at different times in younger and older individuals, which might contribute to these findings.

**IMAGING MYOCARDIAL VIABILITY WITH FDG**

The heart is able to use a variety of substrates, usually fatty acids and glucose, to support oxidative metabolism, but under most normal conditions fatty acids are the preferred energy source. With 18F-FDG, the heart can be consistently visualized only when the patient is not in a fasting state. When fasting, 80% or more of individuals show low myocardial 18F-FDG uptake. Thus cardiac PET studies with 18F-FDG require patients to receive a glucose load before scanning, typically 50 g of sugar (10,11).

The appearance of the heart is affected by the time elapsed between 18F-FDG injections and scanning. Because 18F-FDG uptake is relatively slow, occurring over a period of 20 to 60 minutes, substantial intraventricular activity is noted in the early phases, up to around 20 minutes (Fig. 28.4). As time progresses, the ventricular wall activity becomes dominant, and intraventricular activity recedes. After the typical uptake time of 30 to 40 minutes, intraventricular activity is minimal. Uptake in the left ventricular wall is homogeneous, with typically a slightly lower uptake at the apex of the left ventricle (the so-called apical dip is thought to be due to the increased motility of the heart in this region and therefore to physiologic partial-volume averaging when scanning is not gated to the cardiac cycle). Transmission correction is always applied for proper heart scanning to correct for decreased photon-attenuation penetration from the inferoposterior and lateral wall segments. Strongly inhomogeneous uptake can be noted in diabetic patients. This is a result of inadequate glucose uptake due to insulin resistance in diabetes mellitus type II patients or to inadequate insulin blood levels in diabetes mellitus type I patients. It can be so detrimental to image quality that PET scans in diabetes become uninterpretable unless the patient is examined under a glucose clamp (12,13). The right ventricular wall is commonly not seen, and if visualized in the FDG scan, it indicates a right ventricular hyper-trophy, usually due to pressure overload of the right heart in pulmonary hypertension or to volume overload in congenital heart disease with shunt.

Because there is a considerable amount of blood pool activity in the field of view during cardiac scanning, quantitative uptake measurements can be done by using the arterial input function from a region of interest taken from the left intraventricular region (14). Only a venous sample is needed for the quantification of data in this case.

**MYOCARDIAL PERFUSION IMAGING WITH SPECT**

The three commercially available SPECT perfusion tracers have equal accuracy for the detection of coronary artery disease (15). 201Tl has better uptake characteristics and, in theory, provides defects with greater contrast, but 99mTc-labeled sestamibi and tetrofosmin images are superior in terms of resolution and susceptibility to attenuation artifacts. The net effect of these technical differences in clinical practice is negligible, but the technetium tracers are preferred in obese patients or when ECG-gating is required. In fact, ECG-gating can aid the distinction between artifact and perfusion defect and can increase confidence in reporting (16). Most centers now represent their myocardial perfusion data as so-called polar maps, in which the short-axis sections of the imaging studies are displayed in concentric circles, with the cardiac apex in the center and the more basal sections of the heart at the periphery. This representation is convenient, because the perfusion territories of the main coronary arteries are represented by sectors on the polar maps (Fig. 28.5).
REFERENCES


Figure 28.5 Vertical long axis (A), short axis (B) and polar map (C) of a stress perfusion scan without x-ray tomography–based attenuation correction (upper row) and with such correction (lower row). Without correction, there is a large inferior soft-tissue attenuation artifact (arrowheads), which disappears after correction (arrows) in a patient without coronary artery disease.
Coronary Artery Disease: Perfusion with PET and SPECT

Philipp A. Kaufmann

This chapter presents an overview of the impact of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) myocardial perfusion imaging on the evaluation of patients with coronary artery disease (CAD). SPECT and PET are accurate tools for the noninvasive detection of CAD (see Fig. 29.1) in symptomatic and asymptomatic patients. PET is particularly useful in those patients with balanced three-vessel disease. PET also is often used in the assessment of physiologic stenosis severity to identify the culprit lesion as a target for revascularization strategy in patients with documented CAD. SPECT and PET permit assessment of the response to anti-ischemic and thrombolytic treatment as well as percutaneous transluminal angioplasty and surgical interventions designed to augment perfusion and improve function. Recently PET has been used for the detection of preclinical coronary endothelial dysfunction and the follow-up of progression or regression of CAD during risk factor modification.

INTRODUCTION

With the development of positron emission tomography (PET) technology, accuracy in diagnosis and prognosis has improved. In addition, PET provides an elegant tool for assessing metabolic processes in myocardial cells. In particular, it allows the distinction of viable myocardium from nonviable left ventricular segments after myocardial infarction. Accurate assessment of the extent of dysfunctional but viable myocardium (hibernating myocardium) is important in patients with large myocardial infarction and left ventricular dysfunction. With combined information from PET and coronary angiography, the best revascularization strategy can be found. For the detection of viable myocardium, PET offers positive and negative predictive values of 85% to 90% and 70% to 75%, respectively.

Coronary artery disease (CAD) detection and risk assessment continue to be mainstays of modern cardiology. They have gained in importance because of the broad range of therapeutic options now available to patients with CAD. These options range from cardiac surgery and catheter revascularization to modern pharmacologic treatment.

Basically, there are two possibilities for describing stenosis severity: anatomic determinants and physiologic determinants. The gold standard for the evaluation of CAD remains coronary angiography, which provides exact information on the location and anatomic severity of epicardial coronary artery stenoses. However, the interpretation of coronary angiographic images is affected by a considerable interobserver variability (1). This is underlined by the poor agreement of angiographic results in vivo with those after death (2,3). Furthermore, the physiologic significance of any lesion may be difficult to assess from angiographic images alone, and perfusion abnormalities may occur in the absence of arteriographically assessable stenoses. Angiographic evidence of stenosis severity is reported to show no or poor correlation
with clinical or physiologic parameters such as coronary flow reserve (CFR) and reactive hyperemia. Even the introduction of quantitative coronary angiography did not improve the predictive value of angiography. This explains the increasing importance of cardiac perfusion imaging in cardiovascular medicine. PET is the most advanced scintigraphic technique, allowing accurate qualitative and quantitative assessment of regional myocardial tracer distribution (4). PET has gained increasing clinical acceptance in cardiology.

Two specific clinical applications of PET have been proposed for the evaluation of patients with CAD by the joint task force of the American College of Cardiology and the American Heart Association (5). The first is the noninvasive detection of CAD and estimation of the severity of the disease. This is dealt with in this chapter. The second clinical application of PET is the assessment of myocardial viability in patients with CAD and left ventricular dysfunction (see Chapter 30).

EVALUATION OF CORONARY ARTERY DISEASE WITH PET

In a large number of studies, several primary clinical applications of PET perfusion imaging in CAD have been established:

- Accurate noninvasive diagnosis of CAD in symptomatic or asymptomatic patients, including those with balanced three-vessel disease;
- Assessment of physiologic stenosis severity for identification of the culprit lesion as a target for revascularization procedures in patients with documented CAD;
- Assessment of response to anti-ischemic and thrombolytic treatment as well as percutaneous transluminal angioplasty and surgical interventions designed to augment perfusion and improve function;
- Follow-up of progression or regression of CAD during risk factor modification; and
- Assessment of microcirculatory dysfunction.

In daily clinical routine (5), diagnostic visual qualitative evaluation of nitrogen 13 \[^{13}\text{N}\]\] ammonia or rubidium 82 \(^{82}\text{Rb}\) PET perfusion images has proven feasible and accurate with a subjective scoring method of flow quantification rather than absolute flow quantification (6). The procedure is performed by using a PET perfusion agent at rest and during pharmacologic vasodilatation. The short half-lives of such agents permit rapid sequential examinations, such as rest dipyridamole studies, within a short time frame (1 to 2 hours). After intravenous administration, both \[^{13}\text{N}\]\] ammonia and \(^{82}\text{Rb}\) distribute in proportion to regional blood flow. Images of the heart show deficits in regions where blood flow is relatively reduced and in zones of nonviable myocardium (e.g., previous myocardial infarction). The term “ischemia” is used loosely to denote impaired regional myocardial flow reserve during stimulation. Myocardial perfusion tracers indicate flow disparity between myocardial regions supplied by normal vessels and regions supplied by hemodynamically impaired vessels. Pharmacologically induced myocardial hyperemia is commonly used to cause such regional inhomogeneities in the perfusion pattern related to coronary stenoses, as illustrated in Figures 29.1 and 29.2. Physical exercise is less feasible in PET studies and has therefore only rarely been used.

Figure 29.1  A: Short-axis projection of NH\textsubscript{3} perfusion scan at rest (top) and after dipyridamole stress (bottom) of a patient with a lateral myocardial infarction. A matched lateral defect with additional adjacent stress-induced defects was found. B: Coronary angiogram of the left coronary circulation showing a high-grade stenosis of the circumflex coronary artery.
Figure 29.2  Cardiac horizontal long-axis view of a patient who had a large anterior myocardial infarction. A: PET imaging shows a matched large anterior defect with no perfusion (NH3 scan, top) and no glucose uptake (FDG scan, bottom), indicating a scar. B: Comparison of end-diastolic (left) and end-systolic (right) left ventricular angiography (RAO projection) shows massive dyskinesia of the anterior wall, whereas the lower panels show a proximal left anterior descending artery stenosis.
Pharmacologic Stress

The common drugs used as substitutes for exercise stress testing are dipyridamole (Persantine), adenosine (Adenocard), and dobutamine (Dobutrex). Since the introduction of dipyridamole-induced coronary vasodilatation as an adjunct of thallium 201 (201Tl) myocardial perfusion imaging, pharmacologic interventions have become important in the noninvasive diagnosis of CAD. Excellent reproducibility of hyperemic flow response has been documented using PET for vasodilator (7) as well as for dobutamine (8).

Intravenous dipyridamole induces coronary vasodilatation indirectly by inhibiting cellular uptake of adenosine. This subsequently causes an increase in blood and tissue levels of adenosine, which is a potent direct coronary vasodilator and markedly increases coronary blood flow. Pharmacologically induced flow increase is of lesser magnitude through stenotic arteries, thus creating heterogeneous myocardial perfusion that can be visualized with a perfusion tracer. This mechanism may exist independent of myocardial ischemia, but in some patients true myocardial ischemia can occur with either dipyridamole or adenosine because of a coronary steal phenomenon. The accuracy of myocardial perfusion imaging with pharmacologic and physical stress has been found to be equal (9). Left bundle branch block may lead to false-positive septal defects with physical stress but not as much with pharmacologic stress (10). Before using dipyridamole or adenosine, patients must fast for 4 to 8 hours because of potential side effects of the stressors, such as nausea, vomiting, and hypotension. In addition, they must refrain from intake of caffeine-containing foods and beverages or aminophylline-containing drugs within 24 hours before the imaging study to prevent interference with the hyperemic effect.

High doses of dobutamine (20 to 40 μg/kg/min) elicit a secondary increase in myocardial blood flow (MBF) by increasing the three main determinants of myocardial oxygen demand: heart rate, systolic blood pressure, and myocardial contractility. Although the achieved flow increase (two- to threefold above baseline) is less than that elicited by the direct vasodilators mentioned earlier, it is sufficient to cause heterogeneous perfusion with radionuclide imaging. Overall, the accuracy is in the same range as that attainable with exercise, dipyridamole, or adenosine tests. Despite frequent side effects, high doses of dobutamine appear to be relatively safe.

Bicycle Exercise Stress

Adenosine or dipyridamole is commonly used as a hyperemic stimulus, although little is known about the interaction with drugs studied in pharmacologic interventions. Furthermore, the use of a pharmacologic stimulus may be of limited value in the assessment of the physiologic importance of any cardiovascular disease. Physical exercise is a physiologic stimulus that reflects the natural response of the coronary arteries to physical activities better than any isolated pharmacologic stimulation (11–14).

Nevertheless, only a few reports in the literature deal with the use of physical exercise in PET (15–18). Just recently we evaluated the feasibility and reproducibility of hyperemic MBF induced by supine bicycle exercise stress in the PET scanner and compared it with adenosine-induced hyperemic MBF. The mean CFR value for exercise stress was 1.9 ± 0.4, whereas the value for adenosine-induced flow reserve was 3.5 ± 1.0. Despite these differences, both stimuli revealed excellent reproducibility, as indicated by the mean difference of 3% for both stimuli (19). Thus we found that the assessment of CFR with oxygen 15 [15O]H2O and PET using bicycle exercise stress in the PET scanner is feasible and at least as reproducible as using adenosine stress. Our results seem to support the use of bicycle exercise stress in PET as a physiologic stimulus to induce hyperemic flow.

Accuracy

Several studies using 82Rb or [13N]ammonia indicated their high diagnostic accuracy for the detection of CAD. After animal studies indicated that this technique is sensitive for the detection of regional coronary artery lesions, the first clinical study by Schelbert et al. (20) confirmed these observations, demonstrating the high sensitivity and specificity of this approach in a selected patient population. A similar diagnostic performance was found with 82Rb and [13N]ammonia in a larger patient population (6). These promising results have been reproduced in several groups with either [13N]ammonia or 82Rb (21,22). From these studies, an average sensitivity of 92% and specificity of 88% can be derived.

Although these data indicate the diagnostic superiority of PET over single-photon emission computed tomography (SPECT) imaging, one must interpret these data with caution for several reasons. Most reports on the diagnostic accuracy of myocardial perfusion imaging have used sensitivity and specificity values requiring binary (positive or negative) classification of both perfusion imaging and coronary angiographic results. This approach, however, has several inherent limitations:

- Coronary disease is not an all-or-none condition but shows a continuous spectrum of severity by both of these imaging methods.
- It has been shown that percentage diameter narrowing is not an adequate standard for quantifying stenosis severity because of the hemodynamic importance of the absolute diameter, integrated length effects, shape, and functional integrity of the endothelium (14,23).
- As with any test in medicine, positive and negative predictive values are determined by the prevalence and (in perfusion imaging) the severity of the disease in the study population (24).
Furthermore, it is very difficult to perform a true comparative study between clinically established diagnostic tests and new imaging modalities. The results of the established tests are most likely used in the clinical decision-making process (e.g., as an indication for coronary angiography). This has been referred to as “verification” or “post-test” bias, and it affects the apparent accuracy of a test (25). Verification bias results when a newly introduced technology is evaluated after physicians have begun to rely on its results and no longer require verification of them. Thus, patients with positive tests are more likely to have their results verified (in this case, by undergoing angiography), whereas those with negative tests are rarely referred for subsequent studies. This practice will increase the apparent sensitivity, because false-negative results are unlikely to be discovered. Conversely, the specificity will decrease, because true-negative results will be less likely to be confirmed and therefore will be underrepresented. An elegant possibility for overcoming some of these problems is to compare directly PET with SPECT imaging in the same patient population. However, only few such studies exist. The first study, of 51 patients with a prevalence for CAD of more than 90%, reported on a sensitivity of 96% for $^{201}$TI SPECT and 98% for $^{82}$Rb PET (26). The lack of difference between the two techniques could be explained by the magnitude of the defects, which were large enough to be detected equally, even by the inferior technique (27). A global specificity for this study is not available because of the few patients without CAD (only three patients). In a study from the Cleveland Clinic, $^{82}$Rb PET imaging proved to be significantly more sensitive than $^{201}$TI SPECT imaging (95% vs. 79%), with coronary angiography as gold standard (28). In a study from the University of Michigan, there was a significant improvement in specificity when $^{201}$TI SPECT imaging (53%) and $^{82}$Rb PET imaging (85%) were compared (22).

Based on available results of PET studies, a joint task force of the American College of Cardiology and the American Heart Association, together with the Society of Nuclear Medicine, have found a sensitivity of 87% to 97% and a specificity of 78% to 100% for PET, compared with a sensitivity of 89% and a specificity of 76% for SPECT (4). Although it is clear that PET provides valuable diagnostic information, larger, more definitive comparative studies with comparable expertise in both PET and SPECT imaging are required to determine the relative diagnostic efficacy of the two techniques. Thus, at present PET is a competitive tool for the evaluation of CAD. Its replacement potential will depend mainly on its cost-effectiveness compared with SPECT.

**PET AND PRECLINICAL CORONARY ARTERY DISEASE**

PET has been shown to allow noninvasive and accurate quantitative measurements of regional MBF if suitable tracers are used and appropriate mathematical models are applied. Baseline MBF measurement and hyperemic MBF measurement allow the assessment of CFR, an integrated parameter of endothelial function and vascular smooth muscle relaxation. PET has been widely used to assess CFR in healthy volunteers and patients with CAD, coronary risk factors, and other cardiac diseases (29,30). In the past years, remarkable advances have been achieved in vascular biology. Critical mechanisms in the evolution of CAD have been unraveled, along with the fundamentals of combating the disease or, if already present, preventing its progression or even reversing it. In this area, PET can play a potentially pivotal role in risk stratification, disease management, and monitoring the effects of different interventions. Initial findings have been promising.

Until quite recently, many of the most important forms of cardiovascular disease were considered to involve primarily large vessels, particularly the conduit coronary arteries. However, recent advances have highlighted the crucial involvement of the microcirculation in many cardiovascular conditions. A new concept has emerged: “microvascular disease” is viewed as a well-defined condition that often precedes the development of full-blown diseases and may have independent prognostic value.

Measurement of CFR with PET has been used to assess the effect of pharmacologic interventions such as alpha- and beta-blockade (31), lipid lowering (32), and cardiovascular conditioning. PET-based measurements of MBF offer a means of probing coronary vasomotion and, even more important, of testing for early, evolving, but preclinical atherosclerosis. For example, we have found impaired coronary microcirculatory function due to oxidative stress in otherwise healthy and asymptomatic smokers (33). This microcirculatory dysfunction was normalized after administration of the antioxidant vitamin C. Similarly we reported on low-density lipoprotein (LDL)–dependent coronary microcirculatory dysfunction in hypercholesterolemic yet asymptomatic subjects (29).

In the past decade, a number of PET studies have demonstrated that in hypertrophic cardiomyopathy (HCM) patients the vasodilator response to dipyridamole and hence CFR are markedly impaired not only in the hypertrophied septum but also in the least hypertrophied left ventricular free wall (34). This inadequate hyperemic MBF response to demand in patients with HCM is clinically relevant in that it predisposes them to myocardial ischemia, which in turn has been implicated in the pathogenesis of syncope, abnormal blood pressure response to exercise, left ventricular systolic dysfunction, and sudden death. A recent PET study proved that myectomy exerts its beneficial effect on CFR by reducing extravascular compressive forces as a result of improved diastolic relaxation, reduced force of contraction, and thus reduced compression of the coronary arteries (35). The severity of coronary microvascular dysfunction assessed by PET has been found to be the strongest independent predictor of long-term clinical deterioration and death from cardiovascular causes in patients with hypertrophic cardiomyopathy (36). Similarly, in patients...
with dilated cardiomyopathy, impaired myocardial perfusion reserve has been shown to be an independent predictor of subsequent cardiac events and to be associated with an increased relative risk of death and further progression of heart failure (37).

Although direct visualization of the coronary microcirculation has been achieved in experimental animal preparations using intravital microscopy and stroboscopic epifluorescence imaging of the heart, there is no technique which enables the direct visualization of the coronary microcirculation in man in vivo. The resistive vessels in the coronary circulation are not generally visible on angiography and are too small to be amenable to selective catheterization. Therefore, study of the human coronary microcirculation is indirect and relies on assessing parameters, which reflect its functional status, such as MBF and CFR. These are principally regulated by the coronary microcirculation and thus, in the absence of coronary stenoses, their measurement provides an index of microvascular function.

**ASSESSMENT OF CORONARY ARTERY DISEASE WITH SPECT**

Typical angina is a good indicator of myocardial ischemia, and the abolition of symptoms is the primary aim of treatment. The symptoms, however, can be indeterminate, and they do not indicate the site or extent of underlying ischemia. It is therefore often helpful to proceed to further investigations to aid in the diagnosis and guide future management. Myocardial perfusion SPECT is a robust, noninvasive, and widely available method of assessing regional myocardial perfusion, and it has an obvious role in the clinical setting. Many studies have assessed the sensitivity and specificity of this technique for the detection of CAD, with coronary arteriography typically used as the standard by which the accuracy of scintigraphy is judged.

Reported numbers for the sensitivity and specificity of MPS vary widely and depend on the characteristics of the population studied (gender, presenting symptoms, medication, previous infarction, etc), the imaging technique used (planar or SPECT, qualitative or semiquantitative analysis), and the experience of the center. By using modern techniques with tomographic imaging, good accuracy can be achieved, with a sensitivity and a specificity as high as 91% and 89%, respectively, which is significantly better than exercise electrocardiography. Gated myocardial perfusion SPECT imaging has several strengths that explain its increased and sustained widespread clinical use. The assessment of motion aids the distinction between attenuation artefact and true perfusion abnormality, because infarcted myocardium is unlikely to move or thicken normally, and hence reporting confidence is increased and additional prognostic information is obtained (Fig. 29.3).

With a technical success rate of approximately 100%, SPECT perfusion imaging has become a highly standardized method, providing objective and reproducible assessment of perfusion and function as well as risk stratification. However, SPECT does not provide information regarding early atherosclerotic disease. In addition, the procedures are relatively slow and require prolonged imaging times. Due to its “relative” nature, SPECT frequently fails to identify patients as having “high-risk” coronary artery disease, resulting in occasional false-negative studies in patients with balanced reduction in flow due to three-vessel disease.

Cardiac PET has the advantage of routine, robust attenuation correction and higher resolution than SPECT. Because of these factors, PET is likely to result in a higher accuracy for CAD detection than SPECT. A further advantage of PET is the potential to quantify absolute myocardial blood flow and flow reserve, which may avoid the above-mentioned drawbacks of relative quantification. On the other hand, there is a large body of solid data documenting the value of SPECT for risk stratification, whereas only limited data exist for PET perfusion scanning. Furthermore, assessment of the extent of ischemia with SPECT has recently been shown to provide information regarding the likely benefit from revascularization (38). Finally, PET is substantially more costly than SPECT; thus in clinical routine, SPECT is the mainstay for myocardial ischemia imaging.

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Molecular Anatomic Imaging


Coronary Artery Disease: Tissue Viability and Perfusion

Markus Schwaiger  Stephan G. Nekolla

Diagnosis of reversible left ventricular dysfunction in patients with heart failure remains an important clinical challenge. Single-photon emission computed tomography (SPECT) in combination with myocardial flow tracers plays an important role in the identification of reversible or irreversible perfusion defects as markers of tissue viability in segments with exercise included ischemia. Several positron emission tomography (PET) tracers of cardiac energy metabolism allow the semiquantitative or quantitative assessment of physiologic processes such as myocardial oxygen consumption, metabolic rate of glucose utilization, and myocardial blood flow. Metabolic imaging with PET offers a sophisticated means of assessing regional tissue viability in patients with advanced coronary artery disease (CAD) and impaired left ventricular function, as demonstrated in several clinical investigations. The assessment of relative and regional uptake covering the complete left ventricular volume with SPECT and PET represents an advantage over competing modalities. The classification of myocardial tissue into viable, hibernating, or scarred can be performed with high sensitivity, specificity, and reproducibility (see Fig. 30.8 and Table 30.2). The identification of hibernating and viable myocardium that will profit from revascularization (as proven by recovery of regional function) results in the high clinical utility of these tests. In addition, the combination of PET and SPECT with computed x-ray tomography (CT) allows the assessment of coronary anatomy and calcification, which, together with functional measurements by scintigraphic techniques, provides an important means of stratifying risk in patients with heart failure.

INTRODUCTION

The incidence of heart failure is increasing in industrialized nations, and the associated morbidity is consuming considerable national health care system resources. More than 50% of patients with impaired left ventricular function have coronary artery disease (CAD), as shown in large multicenter trials evaluating new drugs for the treatment of heart failure. It remains a diagnostic challenge to identify patients with significant CAD, because the extent and severity of ischemia as well as the degree of dysfunction determine the prognosis of patients with ischemic heart failure. Therefore, diagnostic tests are needed that not only address the quantification of left ventricular function and coronary anatomy but also provide indices of ischemic injury in this patient population. Because many of these patients had previous myocardial infarctions, the extent of remaining viable tissue is of clinical interest and also has been related to prognosis (1).

Several clinical studies have shown that myocardial dysfunction in patients with CAD may be reversible (2). Revascularization with either bypass grafting or percutaneous coronary intervention (PCI) may be beneficial in these patients in terms of relief of symptoms as well as
long-term survival. First results demonstrating the benefit of revascularization in patients with impaired left ventricular function used pharmacologic interventions in the catheter laboratory to demonstrate reversibility of regional wall motion before revascularization (2). Infusion of catecholamines identifies contractile reserve in the presence of resting myocardial dysfunction. Rahimtoola et al. introduced the term "hibernating myocardium" to refer to persistent left ventricular dysfunction in the presence of severe CAD that is reversible after revascularization (3). The pathophysiology underlying these phenomena is thought to reflect the down-regulation of function in the presence of reduced blood flow and oxygen supply (3,4). There is ongoing discussion of whether the left ventricular dysfunction is associated with the reduced myocardial resting blood flow or whether it represents repetitive ischemia in the presence of reduced coronary flow reserve (2). Independent of this academic discussion, the important clinical issue is the identification of reversibly injured myocardium. A number of noninvasive tests have emerged in recent years to address this issue. These tests for detecting viable myocardium can be divided into several groups: (a) assessment of contractile reserve during the infusion of catecholamine analogs or exercise by echocardiography or MRI; (b) the regional evaluation of perfusion and tracer retention using tracers such as technetium 99m [99mTc]sestamibi or thallium 201 (201Tl) in combination with SPECT; (c) the measurement of myocardial energy metabolism using PET, and (d) the identification of scar by delayed regional Gd-DTPA washout evaluated by MRI (late enhancement).

This chapter reviews the role of PET and SPECT in assessing regional tissue viability in patients with advanced CAD and impaired left ventricular function. Tracers of flow and cardiac energy metabolism are addressed, followed by a discussion of the available clinical results.

### FLOW TRACERS

#### SPECT Flow Tracers

Several flow tracers have been introduced to assess myocardial perfusion under rest and stress conditions (Table 30.1). Potassium 43 (43K) and 201Tl were introduced because of their attractive physiological characteristics: high first-pass extraction, rapid blood clearance, and slow tissue washout (5). 201Tl became a very successful clinical flow tracer, but its low photon energy (80 to 90 KeV) and long physical half-life (73 hours) affect the image quality and limit the applicable dose with tolerable radiation exposure. Pohost et al. first described the use of 201Tl redistribution as marker of viable tissue (6). Based on the tissue kinetics of 201Tl, the myocardium can be characterized as normal (normal uptake, normal washout), ischemic (low uptake, delayed washout), or scar (low uptake, fast washout). Comparing early tracer retention at 15 to 30 minutes after injection with that of later timepoints (3 to 4 hours) allows for the separation of left ventricular segments with and without tracer redistribution. Some investigators proposed to monitor the redistribution process over prolonged time periods. Gutman et al. reported that in the presence of severe stenoses, defects that appeared fixed at 3 to 5 hours often displayed redistribution after 24 hours (7). Kiat et al. demonstrated subsequently that the redistribution pattern at 24 hours is more predictive for tissue recovery after revascularization than 3- to 4-hour data (8).

Although the presence of redistribution has been shown to serve as specific marker of viability, the absence of redistribution at 3 to 4 hours after tracer injection does not rule out tissue viability (8–10). In order to accelerate the redistribution of relative activity in the myocardium, a second 201Tl injection has been proposed (11). An injection of 201Tl at peak exercise with early imaging is followed by an injection

#### TABLE 30.1

<table>
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<th>PROPERTY</th>
<th>15O</th>
<th>13N</th>
<th>82Rb</th>
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at rest and imaging after 3 to 4 hours. Based on this protocol, 201Tl scintigraphy has gained wide clinical acceptance as the most appropriate viability test using SPECT imaging. The 99mTc flow tracers have more suitable physical characteristics than 201Tl. A photon energy of 140 KeV and a half-life of 6 hours provide better count statistics because of less attenuation and higher allowable dose application. However, the first-pass extraction fraction of 99mTc-sestamibi and 99mTc-tetrofosmin is lower than that of 201Tl (12–14). This may be a limitation for the assessment of perfusion at high flow rates but does not affect resting tracer distribution necessary for viability studies. Both 99mTc-labeled tracers are retained in viable myocardium for prolonged time periods. [99mTc]sestamibi is taken up in the mitochondria and retained by an electrochemical gradient. The relative distribution of both tracers at rest reflect perfusion and tissue viability (15).

**PET Flow Tracers**

Blood flow tracers can be classified based on their physiological behavior (see Table 30.1). Oxygen 15 \[^{15}O\]water, for example, represents a freely diffusible tracer that washes in and out of myocardial tissue as a function of blood flow. The first-pass extraction of \[^{15}O\]water in the heart is not diffusion limited, nor is \[^{15}O\]water tissue extraction affected by any metabolic pathways (Fig. 30.1) (16–18). The second group of flow markers are radiotracers retained in myocardial tissue proportional to myocardial blood flow. For these radiopharmaceuticals, the initial tracer extraction (first-pass extraction) and their tissue retention are important factors defining their suitability as blood flow tracers. Nitrogen 13 \[^{13}N\]ammonia is highly extracted by myocardial tissue in the form of \[^{13}N\]ammonia (19–21). Within the tissue, the tracer can either back-diffuse into the vascular space or be trapped in the form of \[^{13}N\]glutamine (Fig. 30.1). Ionic tracers such as rubidium 82 (\(^{82}\)Rb), rubidium 81 (\(^{81}\)Rb), and potassium 38 (\(^{38}\)K) display tracer kinetics similar to those of 201Tl (12,22,23). Initial extraction of these compounds ranges from 50% to 70%. For both \[^{13}N\]ammonia retention and ionic tracer extraction, a nonlinear relationship exists between blood flow and tissue tracer extraction (22,24). For methodological details of myocardial flow measurements by PET, please refer to an excellent recent review by Kaufmann and Camici (25).

**METABOLIC TRACERS**

Several PET radiopharmaceuticals have been developed to investigate the myocardial energy metabolism that depends on the oxidation of various substrates (Fig. 30.2). Under fasting conditions, the majority of cardiac adenosine triphosphate (ATP) production relies on the oxidation of free fatty acids (26,27).

Free fatty acids are avidly extracted by the myocardium where long-chain acyl-coenzyme A (CoA) is rapidly formed. Activated fatty acids are used in the synthesis of triglycerides or phospholipids. The majority of acyl-CoA, however, is transported via the carnitine shuttle into the mitochondria, where \(\beta\)-oxidation takes place. The end product of \(\beta\)-oxidation is acetyl-CoA, which enters the tricarboxylic acid (TCA) cycle, the final pathway of oxidative metabolism of all substrates. In the presence of high free fatty acid as well as low insulin plasma levels, only a small amount of glucose is extracted by the myocardium. However, in the postprandial state, glucose transport into the cell is enhanced, and the glycolytic rate increased. Even after carbohydrate loading, only about 30% to 50% of overall cardiac substrate metabolism depends on oxidative metabolism of glucose (28). During physical exercise, plasma lactate levels increase and contribute to myocardial energy metabolism (29).

Aside from the physiologic increase of glycolysis in the postprandial state, glycolysis plays an important role during and after myocardial ischemia. Experimental studies have shown that myocardial glucose transport and metabolism are up-regulated during myocardial ischemia with the production and release of lactate (30–33). However, after ischemic episodes, glycolysis remains enhanced, with evidence of oxidative and nonoxidative utilization of endogenous glucose (34,35). There is evidence that enhanced myocardial oxidative glucose metabolism persists after ischemic episodes (36,37). Biopsy studies in patients with severe CAD and chronic dysfunction of left ventricular segments have shown increased glycogen storage, evidence of
chronic alterations of glucose metabolism in hibernating myocardium (38). Such a metabolic pattern may reflect cell dedifferentiation with altered gene expression in repetitively ischemic myocardium with predominant glycolytic metabolism (39,40).

**Fatty Acid Metabolism**

The first radiopharmaceutical used in combination with PET for the assessment of regional cardiac metabolism was carbon 11 [$^{11}$C]palmitate. [$^{11}$C]palmitate is avidly taken up by the myocardium, with an extraction fraction of about 50%. The myocardial $^{13}$C activity clears in a biexponential pattern, including a rapid early and slow late phase. Experimental studies changing cardiac workload or cardiac substrate availability demonstrated changes in the relative contribution of the early and late phase of [$^{11}$C]palmitate kinetics (41). Based on these studies, a relation was established between the early clearance phase and the relative contribution of long-chain fatty acid metabolism (42,43). The early clearance phase was correlated with myocardial oxygen consumption (41,43). Myocardial ischemia leads to impaired [$^{13}$C]palmitate oxidation, as demonstrated by tracer kinetics (44,45). Experimental work correlating [$^{13}$C]palmitate kinetics with ultrastructural tissue analysis in animals with ischemic injury revealed good correlation between lipid droplets and increased deposition of [$^{13}$C]palmitate into a slow turnover pool (27). Quantification of mitochondrial function using [$^{13}$C]palmitate is limited because of the influence of plasma substrate levels on the metabolic fate of exogenous fatty acids in terms of their incorporation into triglycerides or immediate oxidation. To avoid the complexity of substrate interaction defining the relative contribution of long-chain fatty acids and carbohydrates to overall oxidative metabolism, [$^{11}$C]acetate has been proposed as an alternative probe to describe oxidative metabolism. [$^{11}$C]acetate is converted to [$^{13}$C]acetyl-CoA in the mitochondria and enters the TCA cycle. $^{13}$C activity equilibrates within TCA cycle intermediates, and $^{13}$C activity clears from myocardium in the form of [$^{13}$C]CO$_2$ (Fig. 30.3). Several studies have indicated that [$^{13}$C]acetate kinetics, as assessed by dynamic PET imaging,
correlate closely with myocardial oxygen consumption, as assessed directly in the animal laboratory or by hemodynamic parameters in the clinical setting. Kinetics of [11C]acetate are only sparsely affected by substrate interactions and thus allow quantification of myocardial oxygen consumption (46–50). Tracer kinetic models have been introduced to quantitate [11C]acetate kinetics (51,52). However, most clinical studies use simple determination of clearance rates by using monoeponential curve fitting of regional myocardial 11C myocardial time–activity curves (47).

The use of [11C]palmitate and [11C]acetate in healthy volunteers indicates homogeneous uptake of these tracers within the normal left ventricular myocardium (47,53,54). The high initial extraction of [11C]palmitate and [11C]acetate allows the qualitative assessment of regional myocardial perfusion (41,55,56). The comparison of [11C]acetate uptake and [11C]ammonia blood flow measurements also indicates close correlation of results in patients with CAD, which points to the opportunity to assess flow and metabolism with a single tracer injection (see Fig. 30.3).

Glucose Metabolism

Fluorine 18 deoxyglucose (FDG) traces transmembranous transport as well as phosphorylation of exogenous glucose (57,58). FDG does not enter any further metabolic pathways but accumulates in myocardium proportional to glucose transport and phosphorylation (59,60). Very little dephosphorylation of FDG occurs in the myocardium. Experimental studies in isolated rabbit septum as well as canine models demonstrated a close relation of FDG uptake and exogenous glucose metabolism, measured by the Fick principle (60,61). However, FDG molecules display a different affinity for glucose transport and phosphorylation than does the glucose molecule itself (62). To correct for this discrepancy, a correction term is necessary for the quantification of exogenous glucose utilization of the myocardium by FDG. This correction term (lumped constant) is assumed to be constant under physiologic and most pathophysiologic conditions (63,64). Recent data, however, indicate that under rapidly changing conditions, the lumped constant may actually change as a function of altered affinities for glucose transport as well as for the hexokinase reaction (65,66). Exogenous glucose utilization can be quantified by using a simple fitting procedure of FDG myocardial kinetics and parametric display of regional metabolic data (67–69) (see Chapter 13).

The comparison of [11C]acetate uptake and clearance with regional FDG kinetics in normal volunteers demonstrated an inhomogeneity of regional glucose utilization in the heart (70). Regional FDG uptake is increased in the lateral wall of the left ventricle and slightly decreased in the area of intraventricular septum (71). Combined [11C]acetate and FDA myocardial substrate metabolism can be used for the quantification and determination of the relative contribution of glucose to overall oxidative metabolism (70,72). Such measurements have been performed to evaluate cardiac glucose metabolism in patients with insulin-dependent and non-insulin-dependent diabetes mellitus. In patients with a history of insulin-dependent diabetes, there was no significant difference in overall glucose utilization as compared with a control population if insulin was replaced by a euglycemic insulin clamp (73–75).

CLINICAL APPLICATION OF SPECT FLOW TRACERS

201Thallium Imaging

There are numerous methods proposed to assess myocardial viability with 201Tl. The most commonly used imaging protocol with 201Tl includes stress injection of the tracer followed by re-injection and redistribution imaging 3 to 4 after tracer application. Bax et al. analyzed 33 studies with over 800 patients in a meta-analysis and found that 201Tl imaging using rest and stress protocols had a sensitivity of 86% and a specificity of 59% in predicting functional recovery following revascularization (76). The relatively low specificity may reflect the criteria used to classify viability as well as the protocol of data acquisition. Several investigators observed that the redistribution process following 201Tl injection may be prolonged in patients with severe coronary stenosis (7,8). Gutman et al. reported that in the presence of severe stenosis perfusion defects that appeared fixed at 3 to 6 hours after injection often showed redistribution at 24 hrs (7). Kiat et al. supported the observation that late imaging can be used to identify 201Tl redistribution in areas that were labeled fixed at 4 hours after injection (8). The investigation of Liu et al. following patients with single-vessel disease before and after coronary angioplasty confirm the notion that a fixed 201Tl defect does not exclude tissue viability (9). In this cohort of patients, 72% of patients with fixed defects also had evidence of myocardial viability after revascularization. This is further supported by studies comparing 201Tl kinetics with FDG-PET images. Brunken et al. demonstrated that patients who had fixed 201Tl defects displayed 18F-FDG uptake in the area of fixed defects (10). In this cohort, 58% of fixed 201Tl defects had evidence of viability based on metabolic imaging. Subsequently 201Tl re-injection was introduced to enhance the redistribution process. Dilisizian et al. reported that in patients with a fixed 201Tl defect on redistribution images, re-injection caused normalization of the defect in 49% of cases (77). Further studies by the same group indicated that 201Tl re-injection imaging has a much greater concordance with FDG-PET imaging than does conventional 201Tl redistribution, indicating a higher sensitivity for tissue viability by the re-injection procedure. In this study, 88% of viable segments by 201Tl re-injection protocols were also viable based on the FDG-PET studies (78).
Stress perfusion imaging may not be necessary in patients with known coronary artery disease who are scheduled for viability studies. Therefore, a number of investigators evaluated the value of rest-delayed $^{201}$Tl imaging as the preferred method for assessing regional tissue viability. In a group of 26 patients, Iskandrian found that 12 of 16 patients with normal or transient $^{201}$Tl defects showed improved ventricular function after surgery, whereas 2 out of 10 patients with fixed defects demonstrated some degree of functional recovery (79).

Besides the predictive value of $^{201}$Tl imaging for tissue recovery after revascularization, the prognostic value of this imaging approach for long-term clinical outcome was investigated by Pagley et al. (80). Seventy patients with multi-vessel coronary artery disease and severe left ventricular dysfunction (ejection fraction less than 40%) were imaged prior to bypass surgery. Following surgery, event-free survival was compared in patients with viable versus nonviable revascularized tissue. Patients with a myocardium at least about two thirds viable as measured by a semiquantitative index had significantly improved 3-year event-free survival as compared with patients who had less viable tissue (80,81).

$^{99m}$Technetium Flow Tracers

Hybrid Protocol

As discussed above, $^{99m}$Tc flow tracers have physical characteristics that provide better SPECT image quality. In order to combine the better image quality of $^{99m}$Tc flow tracers with the established value of $^{201}$Tl imaging for the assessment of tissue viability, a number of laboratories employ a hybrid protocol consisting of a $^{201}$Tl rest injection followed by a stress $^{99m}$Tc flow tracer application. The combination of both tracers exploits the favorable physiologic and physical characteristics of each tracer (82,83). In this protocol, $^{201}$Tl is injected under resting conditions, and imaging is performed 15 to 30 minutes after injection. In the case of advanced CAD and severe left ventricular dysfunction, the waiting period can be prolonged up to 3 to 4 hours to optimize the viability information. Due to the higher photon energy of $^{99m}$Tc and the higher dose used, the $^{201}$Tl background activity does not interfere with data interpretation in the hybrid protocol.

$^{99m}$Tc Protocols

Several studies have shown a relatively good agreement between stress–rest imaging with $^{99m}$Tc flow tracers and $^{201}$Tl imaging in the same patients. The $^{99m}$Tc flow tracers sestamibi and tetrofosmin are avidly taken up and retained in myocytes. Retention of these tracers exploits the favorable physiologic and physical characteristics of each tracer. Increased uptake of $^{99m}$Tc sestamibi as compared with $^{201}$Tl imaging yielded a sensitivity of 60% (76). The likelihood of tissue viability was inversely related to the defect severity of both tracers. In comparison to FDG-PET imaging, a threshold of above 50% tracer retention revealed the best agreement for the identification of viable tissue. Medrano et al. compared regional $^{99m}$Tc sestamibi distribution in myopathic heart removed during heart transplantation (87). Comparison of in vitro determined $^{99m}$Tc sestamibi uptake by autoradiography and histology showed good agreement between tracer uptake and tissue viability. $^{99m}$Tc tetrofosmin has been evaluated by several groups, who documented good agreement between resting SPECT perfusion imaging and $^{201}$Tl kinetics and FDG-PET (88,89). Siebelink et al. performed a prospective, randomized study in 103 patients comparing $^{99m}$Tc sestamibi SPECT and F18FDG/NH$_3$PET for the management of advanced CAD. The imaging resulted in comparable patient management and event-free survival after revascularization independently of the use of PET and SPECT (90). However, the left ventricular ejection fraction was less than 30% in only one third of the patients.

Bax et al. summarized 20 viability studies using $^{99m}$Tc flow tracers in almost 500 patients and reported an average sensitivity of 81% and an average specificity of 66%, resulting in a positive and negative predictive value of 71% and 76%, respectively. Most of these studies used a semiquantitative threshold of $^{99m}$Tc tracer uptake between 50% and 60% (76).

Attenuation correction is expected to decrease the incidence of false-negative defects for viability, especially in the inferior wall of the left ventricle. First studies by Matsumari et al. comparing attenuation-corrected SPECT and F18FDG-PET indicate that an underestimation of viable tissue remains a limitation (88).

More recently, investigations proposed the use of nitrates prior the injection of $^{99m}$Tc flow tracers in order to enhance viability information. Nitrates may affect the blood flow pattern by improving trans-stenotic and collateral blood flow to hypoperfused segments (84). The use of this pharmaceutical intervention results in smaller $^{99m}$Tc sestamibi perfusion defects, increasing the sensitivity for detecting viable myocardium. Bisi et al. demonstrated that left ventricular segments, which improved after revascularization, had a 37% decrease of $^{99m}$Tc rest perfusion defect size following nitrate application (91). Sciagra et al., from the same group, demonstrated an improved correlation of $^{99m}$Tc sestamibi defect with $^{201}$Tl redistribution data as well as postrevascularization function (92). In the above cited meta-analysis by Bax et al., nitrate-enhanced $^{99m}$Tc sestamibi imaging yielded a sensitivity of 86% in predicting viability (76). More recently, Giorgetti et al. compared nitrate-enhanced $^{99m}$Tc tetrofosmin SPECT...
with contrast-enhanced magnetic resonance imaging (MRI) (93). The correlation of nitrate-enhanced SPECT images with contrast-enhanced MRI was significantly better than without nitrates, supporting the notion that resting imaging with \(^{99m}\)Tc flow tracer underestimates tissue viability but that this limitation can be overcome by nitrate application. Several protocols of nitrate administration (s.l., oral, infusion of nitrates) have been proposed, and these have yielded results similar to those achieved with \(^{201}\)Tl viability imaging.

With the advent of ECG-gated SPECT acquisition, regional function and perfusion can be combined to improve viability information. Stollfuss et al. showed that the sensitivity for predicting functional recovery after revascularization assessed by MRI by \(^{99m}\)Tc tetrofosmin SPECT can be improved to 86%, including functional information (94). Iskandrian et al. added low-dose dobutamine stress to SPECT imaging to evaluate tracer distribution and regional wall thickening as two independent markers of tissue viability (95). However, such ambitious imaging protocols may have limited acceptance by the imaging community.

**CLINICAL APPLICATION OF METABOLIC IMAGING**

**Metabolic Standardization**

As outlined earlier, the myocardium relies on several substrates as energy sources. The metabolic profile of the heart is defined by plasma substrate availability; thus it is of utmost importance to standardize the metabolic state when applying metabolic tracers to study regional tissue viability. The first studies using FDG were performed in the fasting state. During fasting conditions, the normal myocardium takes up primarily fatty acids and very little glucose. Therefore, the image quality after intravenous injection of FDG is poor. FDG imaging in the fasting state has been applied to CAD patients after exercise to detect segments that were rendered ischemic during physical exercise (35,96). Such an imaging protocol produces high contrast between normal and ischemically compromised myocardium. However, the additional use of blood flow tracers is needed to delineate the integrity of myocardium, which does not use glucose at the time of FDG injection.
To assess tissue viability, most laboratories use interventions that stimulate glucose utilization. Oral glucose loading leads to a rapid increase of insulin levels and reduces plasma fatty acid levels. This is associated with a metabolic switch toward glucose utilization, resulting in high myocardial FDG uptake (97). However, many patients scheduled for tissue viability studies have diabetes mellitus, which is associated with an altered glucose tolerance. Because high plasma levels of glucose interfere with the uptake of FDG, hyperglycemia must be avoided during the injection of FDG (98). At our institute, we do not recommend intravenous application of FDG if the blood glucose level exceeds 150 mg/dL.

Several imaging laboratories advocate the use of hyperinsulinemic–euglycemic clamping procedures to standardize the metabolic state of the patient (99,100). The clamping procedure involves the simultaneous infusion of insulin and glucose to guarantee maximal stimulation of myocardial glucose utilization in the presence of normal plasma glucose concentrations. With such an approach, most patients demonstrate high glucose uptake, allowing diagnostic evaluation of regional tissue viability (75). An alternative approach has been introduced by applying acipimox to standardize myocardial glucose utilization (101). Acipimox lowers the free fatty acid plasma levels, resulting in enhanced myocardial glucose utilization. This method provides satisfying results in most patients with normal cardiac metabolism; it is, however, of limited utility in patients with advanced diabetes mellitus or decreased insulin sensitivity.

The use of [11C]acetate does not require standardization of the metabolic state, because this tracer is taken up by the myocardium independently of the overall metabolic state. [11C]acetate is a preferred substrate that bypasses the glycolysis or β-oxidation (see earlier). Therefore, this tracer offers distinct advantages over metabolic tracers such as ^18F-FDG or ^11C-palmitate. However, the relatively short half-life of ^11C compounds limits their clinical utility, especially in satellite PET programs. In addition, [11C]acetate requires dynamic data acquisition to separate myocardial blood flow from myocardial glucose uptake.

Figure 30.5 Three different patterns of tracer distribution in PET flow and metabolism imaging can be observed, as shown in three representative short- and long-axis images of patients with severely reduced left ventricular function. Within the panels, the NH₃ study is shown on the left and the FDG study on the right. The distinct patterns are maintained NH₃ and FDG uptake (viable), concordant reduction of NH₃ and FDG (scar; here, in the inferolateral wall), and decreased flow with maintained FDG uptake (hibernation; here, in the anterolateral wall). Image acquisition for the NH₃ study began 5 minutes after intravenous injection of 740 MBq NH₃, and data were acquired over 15 minutes. For the FDG study, image acquisition began 10 minutes after intravenous injection of 370 MBq, and the measurement period lasted for 20 minutes under insulin clamp conditions.
flow from metabolic function, which is associated with more demanding data analysis (see Fig. 30.3).

**Image Acquisition**

Initial experience with FDG imaging involved the direct comparison of regional FDG uptake and myocardial blood flow by using [13N]ammonia or oxygen 15 [15O]water as blood flow markers. By comparing the distribution of myocardial blood flow with regional FDG uptake, different patterns were described (Fig. 30.5). Matching of flow and FDG uptake is considered a marker of normal viable myocardium, whereas decreased perfusion and metabolism are indicative of irreversibility tissue injury. Reduced myocardial blood flow in the presence of increased FDG uptake is considered a mismatch pattern. This mismatch between perfusion and metabolism identifies viable but ischemically compromised myocardium (97). Most PET blood flow tracers have a very short physical half-life, requiring an on-site cyclotron for their production. Therefore, several groups proposed the use of 99mTc-labeled flow tracers as substitutes for the PET tracers (102).

Most cardiac FDG studies are acquired 40 to 60 minutes after injection of the tracer. This time period is required to reduce the FDG plasma concentration to ensure high contrast between blood pool and myocardium. In patients with diabetes mellitus, a longer waiting period is advised to enhance myocardium-to-blood contrast (103).

More recently, gated data acquisition has been proposed in order to combine the evaluation of perfusion metabolism with the assessment of myocardial function. According to protocols developed for SPECT imaging, gated data acquisition provides an accurate and automated calculation of left ventricular ejection fraction by using automated programs. Several studies have shown good agreement between these measurements with independent measures of left ventricular function (Fig. 30.6) (104,105).

**Data Analysis**

Most FDG images are analyzed visually by evaluating the homogeneity of tracer distribution within the myocardium in comparison with the blood flow information. Parallel to the visual analysis, semiquantitative approaches have been advocated to quantify the tracer distribution based on circumferential profile analysis (106,107). Various thresholds of FDG uptake as markers of tissue viability have been proposed, averaging between 60% and 50% of tracer retention normalized to the maximal myocardial activity (102,108). Because normalization processes are involved, the standardization of metabolic conditions becomes even more important. Figure 30.7 shows an example of such semiquantitative data analysis relating the relative uptake of FDG to myocardial perfusion, as assessed with [13N]ammonia. Quantitative criteria have been developed to identify areas of reduced perfusion by using the normal [13N]ammonia database (106). In areas with reduced perfusion, the FDG uptake is compared with the [13N]ammonia data. If there is a concordant decrease of perfusion and metabolism, the area is labeled scar tissue. In contrast, if FDG uptake is greater than [13N]ammonia uptake (more than 15% higher), the area is identified as having a mismatch pattern. To relate the FDG uptake to the [13N]ammonia distribution, the FDG data are normalized to the area of “normal” (highest) [13N]ammonia uptake. This means that the region of interest placed in the area of “normal” resting [13N]ammonia uptake is copied to the FDG data. Regional FDG data are subsequently normalized to this area. After applying this technique to a polar map representation of the entire left ventricular myocardium, the extent of normal, mismatch, and scar tissue can be related to the left ventricular surface and expressed as a percentage of left ventricular (Fig. 30.6).

A more comprehensive evaluation with PET allows the quantitative evaluation of myocardial blood flow metabolism and function. However, this approach requires dynamic data acquisition for [13N]ammonia and FDG as well as subsequent gated data acquisition. Such protocols are attractive for clinical research but are not appropriate for most clinical issues in patients with heart failure. Several studies have tried to develop quantitative criteria for the metabolic rate of glucose uptake (MRGU) for the assessment of tissue viability (75). However, there is a large interindividual variation of regional glucose utilization depending on the metabolic state, yielding low specificity for “absolute” quantitative thresholds of glucose uptake. Therefore, most laboratories use relative uptake values as threshold values for identifying areas with or without tissue viability.
Clinical Application in Heart Failure

Animal and clinical studies using FDG as metabolic tracer have shown that reversible left ventricular dysfunction (stunned, hibernating myocardium) is associated with maintained or even increased tissue FDG uptake (27,34,97,109). Experimental data support the notion that reversible chronic left ventricular dysfunction in patients with advanced CAD represents not ongoing ischemia but down-regulation of function. Two experimental conditions may serve as a model for the clinical presentation of reversible dysfunction in ischemic heart disease. First, transient ischemia with restoration of blood flow leads to slow functional recovery on the basis of "stunning" (110,111). Second, chronic reduction of blood flow in the animal model is associated with metabolic adaptive changes that minimize the imbalance of oxygen supply and demand, limiting the development of irreversible cell injury (hibernation) (112,113).

There is increasing evidence that similar mechanisms are involved in the pathophysiology of reversible chronic dysfunction in patients with advanced CAD (114,115). Rahimtoola first described this condition as "hibernating myocardium" (114). His definition included chronic reduction of blood flow as the culprit in the observed dysfunction, implying chronic ischemia. However, subsequent studies with PET have shown that blood flow can be either normal or only slightly decreased in dysfunctioning viable myocardium. Vanoverschelde et al. found near-normal perfusion in collateral, dependent, viable but dysfunctioning myocardium distal to an occluded coronary artery (109). Sophisticated measurements of blood flow corrected for tissue loss (perfused tissue fraction) also indicate that dysfunctioning myocardium may not be limited by oxygen supply under resting conditions. Based on these results, there is ongoing discussion as to whether reversible left ventricular dysfunction in severe ischemic heart disease reflects "repetitive stunning" or "hibernation" (2,3). The clinical situation in most patients is characterized by a heterogeneous ischemic injury consisting of necrosis or scar in the subendocardium surrounded by viable but...
compromised tissue. The dynamic nature of ischemic heart disease renders these segments ischemic during daily life activities that may lead to repetitive stunning. Conversely, severe flow restriction may result in chronic hypoperfusion, fulfilling the original criteria of hibernation. One can speculate that both conditions coexist in most patients with advanced CAD and impairment of left ventricular function.

From a clinical point of view, the pathophysiologic discussion is less important, because many studies have shown that revascularization results in functional improvement of both stunned and hibernating myocardium. Therefore, differentiation between reversible and irreversible dysfunction in patients with severe impairment of left ventricular function has become a major clinical issue for the decision-making process concerning revascularization. Qualitative evaluation of PET flow studies demonstrated decreased $^{13}$N-ammonia and increased FDG uptake (mismatch) in viable myocardium, which has been considered the scintigraphic hallmark of hibernation (see Fig. 30.7) (97). Although such a pattern suggests reduced blood flow, the intensity of tracer uptake depends not only on flow but also on left ventricular wall thickness (partial volume effect) (116). Therefore reduction of $^{13}$N-ammonia uptake may

**Figure 30.8** After normalization of the polar maps, a comparison to a NH$_3$ normal database is applied. Then, the difference to the normalized FDG polar map is calculated, which allows the subsequent application of a set of empirical rules (see Table 30.1). Using these rules, the extent of normal, mismatch, and scar tissue in relation to the left ventricular surface area is determined. This result can be visualized in 3-D, eliminating the geometrical distortion introduced by the polar map display.

**TABLE 30.2**

<table>
<thead>
<tr>
<th>NH$_3$</th>
<th>Diff ≤ 15%</th>
<th>Diff &gt; 15%</th>
</tr>
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<tr>
<td>≤ −4.5</td>
<td>Scar</td>
<td>Scar</td>
</tr>
<tr>
<td>−4.5 &lt; NH$_3$ ≤ −2.5</td>
<td>Scar</td>
<td>Hibernation</td>
</tr>
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<td>Hibernation</td>
</tr>
<tr>
<td>NH$_3$ &gt; −1</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
reflect wall thinning or an admixture of viable and scarred myocardium (117). In contrast, the FDG signal indicates a relatively higher extraction of FDG in comparison with $[^{13}\text{N}]$ammonia.

**Diagnostic Value**

By using information on both blood flow and glucose metabolism, sensitive specific identification of viable myocardium can be performed. This was first shown by Tillisch et al., who compared relative FDG uptake in patients with advanced CAD and impaired regional and global function before and after revascularization (97). Their study demonstrated that maintained FDG uptake in dysfunctioning segments with reduced flow is associated with functional recovery after revascularization, whereas segments with concordantly decreased flow and metabolism do not recover after restoration of blood flow. Subsequently a large number of similar studies confirmed the predictive value of FDG imaging. Table 30.3 summarizes clinical PET results that were collected from several laboratories documenting the high predictive value of PET metabolic imaging for tissue recovery after revascularization. In all studies, recovery of regional function after revascularization served as the gold standard for tissue viability. However, the criteria of viability have not yet been standardized and vary from study to study. Bax et al. recently compared the diagnostic performance of various viability tests. PET proved to be the most sensitive method, whereas methods assessing contractile performance displayed greater specificity for wall motion recovery (118). This finding is not surprising, because the gold standard for functional recovery may underestimate the presence of viable myocardium, especially in the epicardium. Revascularized segments with subendocardial infarction may show only little functional recovery but may benefit from improved oxygen supply, especially during stress to viable epicardial layers.

It has been shown that functional recovery of hibernating myocardium may require several months; therefore, the timepoint of functional follow-up may affect the predictive value of the test (106,119). Only one study included coronary and bypass angiography after surgery to ensure completeness of revascularization (117). More recently, Haas et al. compared the PET data before revascularization with functional recovery assessed by serial echocardiography after revascularization (106). The data indicate that areas of left ventricular dysfunction but maintained perfusion and metabolism under resting conditions show very rapid functional recovery, whereas areas with mismatch display prolonged functional recovery. Although most segments, hibernating and stunned, appear to recover most dramatically within the first few weeks after revascularization, continued recovery occurs for up to 1 year. In the absence of a “true” gold standard of tissue viability, clinical results depending on functional recovery of segmental wall motion assessed several months after revascularization must be interpreted carefully, with recognition of the limitations not only of the diagnostic test but also of the gold standard.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Journal and Year</th>
<th>Patients</th>
<th>Dysfunctional Segments</th>
<th>Predictive Accuracy (%)</th>
<th>Positive Predictive Accuracy (%)</th>
<th>Negative Predictive Accuracy (%)</th>
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<tr>
<td>Tamaki</td>
<td><em>J Nucl Med</em> 1989</td>
<td>22</td>
<td>46</td>
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<td>Marwick</td>
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<td>21</td>
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<td>16</td>
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<td>429</td>
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As aside from the predictive value of FDG for tissue recovery after revascularization, the prognostic information provided by FDG uptake in segments with reduced perfusion as assessed by $[13\text{N}]$ammonia PET has been emphasized by several groups (Table 30.4). Retrospective data analysis revealed a high incidence of cardiovascular complications in patients with decreased blood flow who maintained FDG uptake but did not undergo revascularization (102,120–124). In contrast, the incidence of cardiovascular complications was similar in groups with scintigraphic evidence of scar or normal myocardium regardless of whether they were revascularized.

These data indicate that the mismatch pattern identifies a subgroup of patients at increased risk for cardiovascular complications. The prognostic information appears independent of the traditional markers, such as left ventricular ejection fraction or the New York Heart Association (NYHA) classification, which were not different among the investigated subgroups. Survival was significantly higher in revascularized patients with mismatch (125). Di Carli recently reviewed PET studies comparing both therapy strategies in patients with mismatch (123). As shown in Figure 30.9, this scintigraphic pattern was associated with a significantly better survival in all patient cohorts (123).

The degree of functional recovery of patients after revascularization can be predicted based on scintigraphic pattern as well as on extent of mismatch (117,126). Di Carli et al. reported an 80% likelihood of functional improvement in the presence of mismatch exceeding 18% of the left ventricle (126). Such quantitative measurements associated with an estimated likelihood of beneficial therapy effect make PET a useful clinical tool in assessing patients who have severe left ventricular dysfunction and are considered candidates for revascularization or cardiac transplantation.

Table 30.4

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Viability Assessment</th>
<th>Patients</th>
<th>LVEF (%)</th>
<th>FU(mo)</th>
<th>OR</th>
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<td>PET</td>
<td>50</td>
<td>24 ± 7</td>
<td>13</td>
<td>7.00</td>
</tr>
<tr>
<td>vom Dahl et al.</td>
<td>1997</td>
<td>MIBI/EDG</td>
<td>77</td>
<td>≤ 50</td>
<td>29</td>
<td>1.21</td>
</tr>
<tr>
<td>Rohatgi et al.</td>
<td>2001</td>
<td>PET</td>
<td>58</td>
<td>22 ± 6</td>
<td>25</td>
<td>1.27</td>
</tr>
</tbody>
</table>

Figure 30.9  Relative risk of cardiovascular events (odds ratio) for patients with moderate to severe left ventricular dysfunction and viable (hibernating) myocardium treated with revascularization compared with medical therapy. (Reproduced with permission from Di Carli MF. Assessment of myocardial viability after myocardial infarction. J Nucl Cardiol. 2002;9:229–235.)

Dreyfus et al. recently reported that the assessment of tissue viability in such patients before surgery improves the selection process for revascularization, with low perioperative mortality (127). Haas et al. confirmed this prognostic
As an alternative, [11C]acetate has been proposed for limited in some patients undergoing tissue viability studies oral glucose loading and intravenous injection of FDG is glucose tolerance (130); therefore, the image quality after levels and the hormonal milieu. Many patients with CAD Regional FDG uptake is modulated by plasma substrate [11C]Acetate in the Assessment and without revascularization (7.7% vs. 6.2% annual mortality with ability in dysfunctional segments did not benefit from hibernating myocardium. Patients without evidence of via-

evidence of viability, indirectly indicating the degree of treatment (16% vs. 3.2%). The benefit of revascularization was related to the extent of dysfunction in patients with evidence of viability, indirectly indicating the degree of hibernating myocardium. Patients without evidence of viability in dysfunctional segments did not benefit from revascularization (7.7% vs. 6.2% annual mortality with and without revascularization, respectively).

Allman et al. summarized the available prognostic data for viability tests in a meta-analysis of 24 studies (more than 3,000 patients) (129). In patients with evidence of viability, revascularization was associated with an 80% reduction in annual mortality compared with medical treatment (16% vs. 3.2%). The benefit of revascularization was related to the extent of dysfunction in patients with evidence of viability, indirectly indicating the degree of hibernating myocardium. Patients without evidence of viability in dysfunctional segments did not benefit from revascularization (7.7% vs. 6.2% annual mortality with and without revascularization, respectively).

[11C]Acetate in the Assessment of Tissue Viability

Regional FDG uptake is modulated by plasma substrate levels and the hormonal milieu. Many patients with CAD have diabetes mellitus or prediabetic conditions affecting glucose tolerance (130); therefore, the image quality after oral glucose loading and intravenous injection of FDG is limited in some patients undergoing tissue viability studies (73). As an alternative, [11C]acetate has been proposed for the assessment for residual oxidative metabolism in patients with severe CAD. Gropler et al., by comparing [13C]acetate kinetics and FDG in patients with recent myocardial infarction undergoing revascularization, demonstrated that there was a significant difference between [13C]acetate kinetics in normal, reversible dysfunctioning, and irreversible dysfunctioning myocardium in the subacute phase of myocardial infarction (131). More recent studies by Gropler et al. demonstrated that [15C]acetate may also be useful in the assessment of tissue viability in patients with chronic, stable CAD (132). [13C]acetate serves as alternative to FDG imaging. However, the assessment of [13C]acetate kinetics requires dynamic data acquisition and sophisticated image processing, limiting widespread clinical use.

82Rb as Marker of Tissue Viability

As stated earlier, the generator-produced tracer 82Rb is considered a potassium analog. As previously demonstrated for 201Tl, Goldstein reported that the use of 82Rb kinetics permits differentiation between reversible and irreversible ischemic injury (133). The clearance half-time of 82Rb activity in ischemically injured canine myocardium was significantly shorter in necrotic cell populations than in reversible injured myocardium. Based on these promising results, Gould et al. compared two static PET images describing early and late 82Rb distribution after tracer administration in patients with CAD and compared the results with FDG imaging (134). There was a close relation between the infarct size determined by FDG imaging and the size based on the washout pattern of 82Rb. The results of this study were confirmed subsequently by vom Dahl et al., who determined the washout rates for rubidium activity from myocardial segments by using regional time–activity curves (135,136). Further studies are required in order to compare 82Rb tissue kinetics with functional recovery after revascularization. However, Yoshida and Gould demonstrated that 82Rb may be useful in the prognostic evaluation of patients considered for revascularization and may improve the selection of patients for high-risk interventions (137).

SUMMARY

Tracer techniques provide the sensitive and specific delineation of tissue viability in patients with advanced CAD and impaired left ventricular function. SPECT imaging with flow tracers characterizes the severity and extent of stress-induced ischemia as well as viability. However, these measurements are limited because of alternation artifacts and the tracer kinetics. Due to delayed redistribution (201Tl) or impaired delivery (99mTc flow tracers), the viability may be underestimated. In contrast, assessment and metabolism by PET allow sensitive and specific detection of tissue viability based on the integrity of cardiac substrate metabolism. The quantitative nature of the measurement and the combination of various physiologic signals, such as flow and contractile function, make this method very competitive in comparison with alternative approaches.

The increased FDG uptake in hibernating myocardium is an independent prognostic parameter that can identify ischemically compromised myocardium, a high-risk clinical condition. This metabolic signal of jeopardized myocardium is especially helpful in patients with advanced ischemic heart failure, because revascularization is associated with higher risk. With the increasing clinical acceptance of PET in oncology, it is expected that this technology will be more widely available for clinical use in cardiology. The combination of PET and CT will allow the correlation of coronary anatomy and metabolic imaging, further
improving the noninvasive assessment of patients with ischemic heart failure.

ACKNOWLEDGMENT

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PET and SPECT in Other Cardiac Diseases

Frank M. Bengel  Markus Schwaiger

In several noncoronary cardiac diseases, nuclear imaging has been used for the noninvasive assessment of myocardial metabolism, microvascular reactivity, and autonomic innervation. The application of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) has substantially contributed to our understanding of pathophysiologic relationships. In addition to their value as research tools, PET and SPECT may be helpful in the clinical setting, as some studies in noncoronary heart disease have indicated. In idiopathic dilated cardiomyopathy, prognosis may be determined by the identification of impairments of sympathetic innervation (Fig. 31.1) or microvascular function. The effects of therapeutic approaches on the tissue level can be monitored in cardiomyopathies. In the transplanted heart, nuclear imaging allows early identification of rejection and allograft vasculopathy and assessment of sympathetic reinnervation. Finally, in pediatric cardiology, evaluation of myocardial perfusion and viability may contribute to the workup of children who have Kawasaki disease or have undergone surgical coronary reimplantation due to congenital abnormalities.

INTRODUCTION

Compared to existing evidence in the diagnostic and prognostic workup of coronary artery disease, few data exist on clinical applications of nuclear imaging in noncoronary heart disease. However, imaging of myocardial perfusion, metabolism, innervation, and other molecular targets has substantially contributed to the characterization of specific aspects of the sometimes poorly understood pathophysiology of some noncoronary cardiac diseases. Based on an improved understanding of pathogenetic mechanisms, nuclear imaging approaches hold promise for the future evaluation of therapeutic effects and the prediction of outcome in these patients.

This chapter provides an overview of existing data for single-photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging keyed to different types of noncoronary cardiac disease. Basic pathophysiologic research is outlined, but special emphasis is given to those approaches that have emerged as tools in clinical trials and that may thus contribute to patient workup in the future. Table 31.1 summarizes the different types of noncoronary diseases of the heart treated in this chapter, along with the specific nuclear imaging applications.

IDIOPATHIC DILATED CARDIOMYOPATHY

Idiopathic dilated cardiomyopathy can be separated from ischemic cardiomyopathy as the source of left ventricular dysfunction by use of nuclear imaging. In PET viability imaging, idiopathic cardiomyopathy shows more regional homogeneity and fewer and less severe defects in nitrogen...
13 \[^{13}\text{N} \text{ammonia}\] perfusion and fluorine 18 deoxyglucose (\[^{18}\text{F-FDG}\]) metabolic images (1). Additionally, in gated myocardial perfusion SPECT imaging, the regional heterogeneity of wall motion abnormalities and perfusion is pronounced in ischemic cardiomyopathy (2).

In addition to the relative regional perfusion homogeneity in PET and SPECT qualitative images, quantitative investigations of global myocardial blood flow by PET have revealed abnormalities of microcirculatory function in idiopathic dilated cardiomyopathy. In patients with normal coronaries, overt heart failure, and depressed left ventricular function, Merlet et al. demonstrated substantially reduced hyperemic flow in response to dipyridamole vasodilation compared with normals, which correlated with intracoronary Doppler flow measurements (3). Drzewa et al. additionally observed an impaired flow response to sympathetic stimulation using the cold pressor test (4). Neglia et al. investigated cardiomyopathy patients without overt heart failure, and found impaired blood flow both at rest and during pharmacologic vasodilation, suggesting that abnormalities can be present without severe alterations of hemodynamics. Progression of disease was associated with more severe depression of perfusion in this study (5). Furthermore, the same group identified depressed blood flow during pharmacologic vasodilation as a predictor of adverse outcome in a more recent study (6). It remains unclear, however, whether the observed alterations of myocardial blood flow are part of the still unknown pathophysiology of idiopathic dilated cardiomyopathy or whether they are epiphenomena.

An innovative approach to characterizing heart failure in cardiomyopathy is to combine the assessment of overall oxidative metabolism using carbon 11 \[^{11}\text{C} \text{acetate}\] PET (Fig. 31.2) with noninvasive measures of ventricular function and cardiac work. Myocardial efficiency, which is defined by the amount of oxidative energy required to maintain a given level of cardiac work, can then be estimated by noninvasive means (Fig. 31.3). As might be expected, PET-derived estimates of efficiency are reduced in dilated cardiomyopathy compared with normals (7). More importantly, this approach can be used for a detailed evaluation of therapy effects by taking into account the energy cost of an increase of cardiac output achieved by a therapeutic measure. Beneficial effects of afterload reduction (8), dobutamine (9), \(\beta\)-adrenoceptor blockade (10), and resynchronization therapy (11) on cardiac efficiency have already been demonstrated. Noninvasive estimation of myocardial efficiency thus represents an appealing endpoint in clinical trials and may even serve to optimize individual therapy in the future.

Alterations of the sympathetic nervous system are a common feature of progressive heart failure. Sympathetic

![Figure 31.1](image1)

**Figure 31.1** PET studies of myocardial perfusion with \[^{13}\text{N} \text{ammonia}\] (NH\(_3\)) and of presynaptic sympathetic innervation with \[^{11}\text{C} \text{hydroxyephedrine}\] (HED) in a normal control and a patient with idiopathic dilated cardiomyopathy (DCM). Images and polar maps show normal perfusion in both cases, while there is a marked global reduction of HED retention in the patient with DCM. (SA, short axis; HLA, horizontal long axis; VLA, vertical long axis.)
activation results in elevation of systemic catecholamine levels and subsequent down-regulation of postsynaptic β-adrenoceptors, as demonstrated by Merlet et al. using PET and the β-receptor ligand 3C CGP12177 (12). In addition, presynaptic alterations can be observed, as indicated by globally reduced myocardial uptake of the catecholamine analogs iodine 123 (123I) meta-iodobenzylguanidine (MIBG) imaged by SPECT or 11C hydroxyephedrine (HED) imaged by PET (see Fig. 31.1). In 29 patients, Hartmann et al. observed abnormally low HED retention in 64% ± 32% of the left ventricle despite nearly normal perfusion. The degree of presynaptic alterations was correlated with reduction of ejection fraction and New York Heart Association (NYHA) status (13). In a more recent study, a correlation with impaired metabolic efficiency was also observed (14). These PET-determined alterations of presynaptic sympathetic innervation thus seem to reflect the severity of heart failure in dilated cardiomyopathy and are in line with similar observations using SPECT and 123I-MIBG (15). Further observations in larger groups of patients showed that reduced presynaptic sympathetic activity identified by 123I-MIBG SPECT is associated with impaired outcome and represents an independent prognostic parameter (16). This prognostic value has been confirmed by Pietila et al. using HED PET (17). Finally, measures of presynaptic sympathetic impairment can be used to predict the response to medical therapy, such as β-blockade (18) and ACE inhibition (19).

### HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is a mostly genetically determined disease and results in abnormal hypertrophy of the myocardium, which often is regionally heterogeneous and

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**TABLE 31.1**

**SPECT AND PET IN NONCORONARY HEART DISEASE**

<table>
<thead>
<tr>
<th>Type of Disease</th>
<th>Imaging Approach (Tracer)</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic dilated cardiomyopathy</td>
<td>Imaging of perfusion/function (various SPECT tracers)</td>
<td>Differentiation from ischemic cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>Metabolic imaging, viability (18F-FDG)</td>
<td>Differentiation from ischemic cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>Metabolic imaging, oxidative metabolism/efficiency (11C-acetate)</td>
<td>Assessment of heart failure therapy</td>
</tr>
<tr>
<td></td>
<td>Flow quantification (13N-ammonia)</td>
<td>Assessment of microcirculatory dysfunction</td>
</tr>
<tr>
<td></td>
<td>Imaging of pre-/postsynaptic innervation (various SPECT and PET tracers)</td>
<td>Assessment of disease severity/prognosis</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Metabolic imaging (18F-FDG), flow quantification (13N-ammonia, 15O-water)</td>
<td>Assessment of mechanisms of disease/therapy effects</td>
</tr>
<tr>
<td></td>
<td>Imaging of pre-/postsynaptic innervation (various SPECT and PET tracers)</td>
<td>Assessment of mechanisms of disease</td>
</tr>
<tr>
<td>Arrhythmogenic diseases</td>
<td>Imaging of pre-/postsynaptic innervation (various SPECT and PET tracers)</td>
<td>Definition of pathogenetic role of adrenergic nervous system</td>
</tr>
<tr>
<td>The transplanted heart</td>
<td>Imaging of inflammation (various SPECT tracers)</td>
<td>Detection of transplant rejection</td>
</tr>
<tr>
<td></td>
<td>Imaging of cell death (various SPECT tracers)</td>
<td>Detection of transplant rejection</td>
</tr>
<tr>
<td></td>
<td>Imaging of perfusion/function (various SPECT tracers)</td>
<td>Diagnosis and prognosis of transplant vasculopathy</td>
</tr>
<tr>
<td></td>
<td>Flow quantification (13N-ammonia)</td>
<td>Identification of transplant vasculopathy, characterization of rejection</td>
</tr>
<tr>
<td></td>
<td>Imaging of pre-/postsynaptic innervation (various SPECT and PET tracers)</td>
<td>Identification of denervation/reinnervation</td>
</tr>
<tr>
<td>Pediatric cardiology</td>
<td>Imaging of perfusion/function (various SPECT tracers)</td>
<td>Detection of ischemia, prognosis</td>
</tr>
<tr>
<td></td>
<td>Metabolic imaging (18F-FDG)</td>
<td>Viability assessment after coronary reimplantation</td>
</tr>
<tr>
<td></td>
<td>Flow quantification (13N-ammonia)</td>
<td>Assessment of (early) microcirculatory dysfunction</td>
</tr>
</tbody>
</table>
especially pronounced in the septum. In patients symptomatic for chest pain, Nienaber et al. observed reduced blood flow but normal glucose utilization rates in hypertrophied areas that failed to increase during physical exercise, suggesting the presence of myocardial ischemia (20). Camici et al. found an impaired global flow reserve not only in hypertrophied but also in nonhypertrophied areas (21) and concluded that the observed results were due to primary changes rather than regional hypertrophy. Their results are further supported by studies done by Choudhury et al. and Radvan et al., who observed greater impairment of coronary vasodilatory reserve in patients with hypertrophic cardiomyopathy than in patients with secondary hypertrophy (22) and also observed no alterations in athletes with physiological myocardial hypertrophy (23). Recently, a prognostic value for PET-determined impaired flow reserve has been demonstrated in a long-term study with follow-up from 6 to 10 years (24).

PET has also been used to measure the effects of treatment. Gistri et al. found reduced regional heterogeneity of myocardial blood flow but no changes in absolute flow during therapy with verapamil in 20 patients with hypertrophic cardiomyopathy (25). Additionally, an improvement of endocardial perfusion relative to epicardial perfusion during verapamil treatment in septal hypertrophied areas was reported using oxygen 15 [15O]water PET by Choudhury et al. (26). Kuhn et al. used 18F-FDG metabolic imaging to identify and quantify the necrotic area in the septum after transcoronary ablation of septal hypertrophy in hypertrophic obstructive cardiomyopathy (27).

Finally, alterations of the sympathetic nervous system, which may play a role in the phenotypic expression of hypertrophic cardiomyopathy, have been identified. Schaefers et al. found significant reductions of both presynaptic innervation studied with 11C-HED as well as postsynaptic β-receptor density, studied by 11C-CGP12177 (28). In another study, it was demonstrated that reduced β-receptor density is correlated with the degree of ventricular dysfunction (29). Impaired presynaptic innervation has also been identified by use of 123I-MIBG SPECT (30). Whether these findings of altered innervation are of similar prognostic value as in idiopathic dilated cardiomyopathy has not yet been evaluated in detail.

**ARRHYTHMOGENIC CARDIAC DISEASES**

Nuclear imaging investigations in arrhythmogenic disorders of the heart have mainly focused on the role of the sympathetic nervous system. In patients with sustained ventricular tachycardia, Calkins et al. found a regional...
correlation between ventricular refractoriness and evidence of sympathetic neuronal dysfunction as determined by PET with $^{11}$C-HED, suggesting an involvement of the cardiac adrenergic nervous system in arrhythmogenesis (31). Other studies evaluated the pre- and postsynaptic sympathetic nervous system in several primary arrhythmogenic disorders, including right ventricular outflow tract tachycardia (32), arrhythmogenic right ventricular cardiomyopathy (33), and Brugada syndrome (34), and reported reduced postsynaptic β-receptor density and/or reduction of pre-synaptic catecholamine uptake as part of the pathogenesis. The clinical implications of these observations and their potential impact on prognosis remain to be determined, however.

### THE TRANSPLANTED HEART

The two major complications limiting survival of cardiac transplant recipients are acute allograft rejection in the early phase after transplantation and chronic graft vasculopathy in the later phase. Diagnosis of both is still mainly achieved using invasive procedures, and interest in noninvasive tests has continuously increased. PET studies using dipyridamole-induced vasodilation (35) or physical exercise (36) have indicated that global myocardial flow reserve is within normal limits after orthotopic heart transplantation in the absence of angiographically defined transplant vasculopathy or allograft rejection if the baseline flow is corrected for a higher rate pressure product. Therefore, subnormal exercise performance, which is common in transplant recipients, does not seem to be related to altered vasoreactivity. A transient reduction of hyperemic flow and an increase of resting flow have been observed by Chan et al. during acute allograft rejection (37). In the same study, improvements were found after successful treatment, so the authors concluded that serial PET flow measurements may be useful for guiding immunosuppressive therapy.

The finding of impaired perfusion, however, is not very specific for allograft rejection, so other, more practical approaches to noninvasive detection have been employed. SPECT tracers of inflammation, such as indium $^{111}$In–labeled lymphocytes or $^{111}$In octreotide (which binds to somatostatin receptors on activated lymphocytes), have been tested along with tracers of myocyte death such as $^{32}$P-Pi.
antimyosin and technetium 99m (99mTc) annexin V (38–41). All these tracers were promising and showed good correlation with results of rejection in endomycocardial biopsies, but the studied groups were small, and a clear clinical indication has not yet been derived.

For the detection of chronic graft vasculopathy as an accelerated and diffuse form of coronary artery disease, SPECT techniques have been employed. Abnormality on scans is associated with impaired outcome in a manner similar to observations in non-transplant-associated coronary disease (42,43). Although obtained in a smaller number of patients, these data strongly indicate that noninvasive perfusion SPECT imaging has a clinical and prognostic value in guiding transplant coronary disease therapy that is similar to its value in conventional coronary disease.

Quantitative flow measurements by PET also appear to be useful for early detection of allograft vasculopathy. Zhao et al. found a decrease of myocardial blood flow in cardiac allografts at sequential imaging that was more pronounced in patients with angiographic evidence of transplant vasculopathy, and they concluded that serial PET may be more sensitive in detecting graft vessel disease than angiography (44). Kofod et al. studied 32 patients with diffuse transplant vasculopathy. They found a reduction of the flow response to cold pressor and during dipyridamole vasodilatation. Additionally, a significant correlation between hyperemic blood flow and intimal thickness measured by intravascular ultrasound was observed (45). In another study by the same group using serial intravascular ultrasound measurements, an association between early impairment of PET flow reserve and subsequent reduction of ultrasound vessel area and lumen diameter was found in 19 patients, suggesting that the course of transplant vasculopathy can be predicted by noninvasive PET imaging (46).

One of the consequences of cardiac transplantation is a complete denervation of the allograft due to surgical transection of autonomic nerve fibers. Sympathetic denervation can be demonstrated by use of radiolabeled catecholamine analogs. Denervation is thought to be the major reason for chronotropic incompetence and impaired exercise capacity in transplant recipients. PET studies using 11C-HED have substantially contributed to the identification and characterization of sympathetic reinnervation (47), which occurs frequently and increases with time after transplantation (Fig. 31.4). Reinnervation remains regionally limited, starting in the basal anteroseptal wall and extending toward the apex and lateral wall with time, while the inferior wall remains denervated up to 18 years after transplantation (48). Although regionally incomplete, reinnervation has been shown to improve microvascular reactivity in response to cold (49) and to influence regional substrate utilization by lowering glucose uptake in reinnervated myocardium (50). Most importantly, it has been demonstrated recently that reinnervation also improves chronotropic and inotropic response to exercise and thus overall exercise capacity and daily life activity in transplant recipients (51). Beneficial effects on the patient course long after transplantation and thus on long-term outcome remain to be determined.

**PET VIABILITY IMAGING**

Kawasaki disease is an inflammatory disease of early childhood that frequently affects coronary arteries and may cause lesions such as aneurysm or stenosis. In children with Kawasaki disease in the acute and subacute phase, assessment of myocardial perfusion by SPECT may indicate ischemia and guide further therapy in a manner similar to coronary artery disease in adults (52). Even in the absence of epicardial coronary abnormalities, quantitative PET flow measurements have revealed an impaired global flow reserve long after Kawasaki disease, suggesting residual damage at the microcirculatory level (53). The clinical consequences of such alterations of microvascular reactivity, however, remain to be determined.

Using dynamic [13N]ammonia PET, studies in other patient groups have also suggested impairments of myocardial blood flow despite normal epicardial coronary arteries. In children long after surgical correction of transposition of the great arteries using an arterial switch operation (54) and in patients after repair of anomalous left coronary artery using pulmonary artery (56), microvascular dysfunction was observed, suggesting a pathophysiologic role for altered vascular reactivity after corrective surgery. Again, however, a prognostic value or therapeutic consequences of these observations in otherwise healthy patients have not yet been demonstrated and remain to be evaluated.

When myocardial infarction is suspected after an arterial switch operation, thorough evaluation of viability is necessary to justify revascularization. The feasibility of 18F-FDG PET viability imaging in these children has recently been supported by Rickers et al., who found residual viability in akinetic or hypokinetic regions in two of seven infants with coronary stenosis or occlusion following an arterial switch, indicating the need for revascularization and supporting the usefulness of PET in guiding therapeutic decision-making in this setting (57).

The assessment of myocardial perfusion or viability may be of clinical value in selected pediatric patients, not only because the higher spatial resolution is advantageous for the imaging of smaller hearts. PET also holds promise as a means to enhance our understanding of pathophysiology in congenital heart disease and to identify long-term consequences of surgical therapy. However, ethical constraints due to radiation exposure in childhood have to be considered, and a lack of age-matched normal ranges currently remains as a limitation in the interpretation of quantitative parameters.

**SUMMARY**

Noninvasive SPECT and PET measurements of myocardial metabolism, perfusion, and innervation have substantially contributed to the pathophysiologic understanding of several noncoronary cardiac diseases. In addition to their value as investigative tools, some studies have indicated that nuclear imaging may be helpful in the clinical setting, such as for determining the prognosis in idiopathic dilated
cardiomyopathy, monitoring therapy effects in dilated and hypertrophic cardiomyopathy, identifying acute transplant rejection and chronic graft vasculopathy early in their development, and assessing myocardial perfusion and viability in children who have Kawasaki disease or have undergone surgical coronary reimplantation due to congenital abnormalities.

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Figure 31.4 PET assessment of sympathetic innervation in three cardiac transplant recipients at various timepoints after transplantation (HTX). Perfusion is homogeneous in all three cases. Myocardial retention of 11C-HED is absent early after HTX, indicating complete denervation. Later, after HTX, there is marked retention in the anteroseptal wall, indicating regionally incomplete reinnervation, which increases with time after HTX.


INTRODUCTION

Integrating computed tomography (CT) with single-photon emission computed tomography (SPECT) or positron emission tomography (PET) has different aims in cardiac imaging than in body imaging. In body PET-CT, CT is used to localize the tracer accumulation seen on PET and for attenuation correction. Cardiac coronary anatomy is simpler but more difficult to image with CT, because the speed and spatial resolution requirements are harder to meet. With the new developments in CT technology, coronary anatomy imaging is on the verge of becoming a reality.

The most important application of any cardiac imaging procedure is to evaluate coronary artery disease. Noninvasive approaches exist for assessing myocardial ischemia (see Chapters 29 and 30), which is currently done by using myocardial stress perfusion imaging, mainly with SPECT and PET, or by imaging wall-motion abnormalities due to ischemia, mainly with stress echocardiography and magnetic resonance imaging (MRI). The diagnostic gold standard for establishing the presence of coronary artery disease is still x-ray coronary angiography, with all its drawbacks. A major limitation of this technique is its invasive nature, with high procedure-related morbidity (1.5%) and mortal-
In addition, the physiologic significance of any lesion is frequently difficult to assess from angiographic information alone, and perfusion abnormalities may occur in the absence of arteriographically assessable stenoses. Therefore, patients are often referred to perfusion imaging to determine the clinical relevance of a coronary stenosis after its invasive documentation. Thus, the integration of noninvasive assessment of coronary anatomy by multi-slice CT coronary angiography and of myocardial perfusion or viability by PET or SPECT is potentially useful.

### ATTENUATION CORRECTION WITH CT

The sensitivity and specificity of cardiac SPECT are commonly affected by image artifacts caused by photon attenuation. “Characteristic patterns” of attenuation in female and male patients are rendered unpredictable by the nonuniform attenuation characteristics of the human body, particularly in the chest area, and by the widely variable body habitus of individual patients. Breast and diaphragmatic attenuation are among the most common causes of these artifacts, but lateral wall artifacts also occur because of obesity. One strategy for identifying and correcting attenuation artifacts is to introduce electrocardiogram (ECG)-gated SPECT. Fixed defects in the anterior and inferior walls may be distinguished from infarction by the identification of normal wall motion. However, in 85 women, Taillefer et al. (1) were able to reclassify only five false-positive fixed defects as normal because of the presence of wall-motion information, and Lee et al. (2) found no gains with gating in 68 patients. By contrast, we found in 153 consecutive cases that by reclassifying the condition of patients with fixed defects and normal function as normal, patients with unexplained fixed defects (no clinical myocardial infarction) decreased from 29% to 10% (3). This confirms that gating adds considerable value to SPECT myocardial perfusion imaging in characterizing fixed defects and potentially improves test specificity.

Whereas the accuracy of cardiac PET imaging has long benefited from correction methods for tissue attenuation, in SPECT imaging, commercial methods have only recently been made available. Various techniques with different line sources, such as americium 241 (241Am), gadolinium 153 (153Gd), and technetium 99m (99mTc), have been proposed. Initial reports indicate that some of these methods have achieved significant improvements but that others have created more artifacts than they have remedied. An overview of these methods, which have varied greatly in their clinical success, has been given elsewhere (4).

Certainly the use of CT for attenuation correction could well be an important step forward in solving some of the major attenuation correction problems of the SPECT technique, allowing consistent image reading in male and female patients. Because of the recent introduction of this technique, only limited data are available. Although initial experiences seem promising (5,6), there are some drawbacks that have to be overcome. For example, misalignment in the γ-direction between SPECT and the attenuation map can lead to artifacts in the apical, septal, and anterior walls that will appear as defects. It also can cause overcorrection in the basal inferior and lateral segments. There is evidence that mismatches along the other directions may have a similar effect. The coregistration of SPECT and the attenuation map needs to be verified for every patient, even when using integrated dual-modality imaging devices (7).

In PET the major advantage of using CT for attenuation correction is the short time duration (less than 5 seconds) compared with conventional correction with germanium sources (10 to 20 minutes). This allows the separation of the acquisitions of perfusion and viability PET scans, as the time loss for an additional transmission scan is minimal. Logistically, this is a major issue in daily clinical routine, as otherwise the ammonia scan must precede the fluordeoxyglucose (FDG) scan, a protocol sequence with severe limitations:

- After the production of FDG, the slots for patients scheduled for an FDG scan are very tight, and any delay caused by potential problems during the nitrogen 13 [13N]NH₃ protocol (e.g., unsuccessful [13N]NH₃ production or intravenous delivery, acquisition delay, chest pain, and adenosine side effects) has an unfavorable effect on patient scheduling for the whole day.
- At the end of the [13N]NH₃ protocol, the patient receives a fluorine 18 (18F)-FDG injection and remains in the scanner for uptake for up to 40 minutes before imaging can be started. This dead time can be avoided by performing the scans on different days or at least separated by time, allowing 18F-FDG decay and putting the [13N]NH₃ scans at the end of the protocol, which is favorable from the point of view of cyclotron logistics.

We recently analyzed the feasibility and reproducibility of CT attenuation correction for quantitative PET myocardial perfusion measurements. The results show that myocardial blood flow quantification is independent of CT beam intensity and that ECG gating of the CT beam seems not to be necessary (8). Therefore, an ungated low-dose CT scan with 5 mAs, the lowest possible dose available on our CT and corresponding to approximately 0.4 mSv radiation exposure, was used to document the reproducibility of the measurements. Attenuation correction with CT provided results highly comparable to those obtained by using germanium attenuation correction, as long as the same reconstruction algorithm (filtered back-projection vs. iterative reconstruction) was applied.

The benefit of CT attenuation correction for time-saving issues will be particularly important once the use of oxygen 15 [15O]H₂O is ripe for clinical use in myocardial blood flow (MBF) assessment (see Chapter 29). The relatively short half-life of this tracer (2 minutes) allows repeated measurements within 10 minutes and flow reserve measurements with a total scan duration of approximately 20 minutes (9). Cutting down the additional 20 minutes for attenuation correction to approximately 4 to 5 seconds for CT correction will considerably shorten the protocol and increase patient throughput.
CARDIAC "ONE-STOP SHOPPING" WITH PET-CT

Noninvasive assessment of coronary artery disease is an important task, because more than 1 million invasive diagnostic coronary angiography procedures are performed each year in the United States alone. Coronary angiography is at present the only accepted method for the clinical imaging of coronary artery disease, despite its cost, the inconvenience to patients, and the inherent risk of complications. These limitations have prompted an intensive search for alternative, noninvasive techniques for coronary artery visualization. The major obstacles that must be overcome are the small diameter of the coronary arteries, their tortuous course, their close anatomic relation to the coronary veins, and their continuous motion due to cardiac contractions and respiratory excursions.

Several strategies have been suggested for coronary imaging, such as transthoracic and transesophageal echocardiography, dichromatic synchrotron radiation (10), electron-beam tomography (11), MRI (12,13), and multi-slice spiral CT (MSCT) (14). Since the first preliminary report on MRI of coronary arteries in 1993 (12), many research groups have investigated ways to improve this technique. A recent multicenter trial (13) reported that (in segments that could be evaluated) in 109 patients MRI found 83% of the stenoses identified using x-ray coronary angiography. Several important limitations may document why this initially very promising technique has been disappointing and has not fulfilled its seeming potential. In the multicenter trial reported by Kim et al. (13), only 84% of the vessel segments could be evaluated, even though evaluation was limited to the proximal 3 to 5 cm of the major coronary arteries. The average examination time of 70 minutes is a major drawback for routine clinical practice. In addition, fewer than 16 patients were included for each of the seven sites during a period of more than 1 year, raising doubts as to whether the patients in the study constitute an unbiased representative sample of patients referred for coronary angiography.

For x-ray–based tomographic imaging of the heart, electron-beam CT (EBCT) was thought to represent the reference standard because of its high temporal resolution, but it is available in only a few centers. Quantification of coronary calcium is the most widely recognized use of cardiac imaging with EBCT, a technique that requires no contrast media and provides an accurate assessment of overall calcified plaque burden in the coronary tree. It does, however, not directly identify or localize coronary stenoses. MSCT is a rapidly developing technology that provides diagnostic-quality images of the beating heart under many circumstances and may facilitate the broader application of cardiac and coronary CT in the near future. Contrast-enhanced CT coronary angiography (CTCA) can be performed with EBCT or MSCT to obtain images of the major branches of the coronary tree and to define luminal narrowing. Despite the high accuracy of CTCA in the assessment of obstructive coronary artery disease, it was considered an investigational technique for these applications until recently, because many coronary segments (particularly in the periphery) in many patients were not evaluable. However, using the latest generation of CT scanners (with 64 slices), excellent image quality can be achieved in the vast majority of the patients, with values for sensitivity, specificity, and positive and negative predictive values averaging 88%, 96%, 72%, and 98%, respectively (15–18). With its high negative predictive value, noninvasive angiography may play an important role when the clinical goal is to rule out coronary artery disease in patient populations with low clinical probability for coronary artery disease. As up to 75% of all invasive angiograms in the United States remain purely diagnostic (19), and between 20% and 40% of all diagnostic invasive coronary angiograms reveal no clinically significant disease (20), noninvasive procedures have the potential to play an important role in the future by eliminating a substantial fraction of these invasive angiograms (e.g., in cases of atypical chest pain, equivocal stress test results, and low to intermediate clinical probability of coronary disease).

The noninvasive coronary angiography of the major vessels and side branches, combined with the assessment of myocardial perfusion by PET (Figs. 32.1 and 32.2), put the noninvasive strategy into a new perspective, as it will allow simultaneous and integrative noninvasive judgment of anatomic lesions and their pathophysiologic relevance.

Figure 32.1 Three-dimensional reconstruction of the four-slice CT showing the coronary artery tree and the shape of the heart, superimposed by the color-coded qualitative stress perfusion image obtained by PET. Ammonia has been used as the perfusion tracer; red indicates normal stress perfusion response in the anterior and lateral segments of the left ventricle. (Reprinted by permission of the Society of Nuclear Medicine from Namdar M, Hany TF, Koefli P, et al. Integrated PET/CT for the assessment of coronary artery disease: a feasibility study. J Nucl Med. 2005;46:930–935.)
Chapter 32: Integrated SPECT-CT and PET-CT in Cardiac Imaging

(Fig. 32.3). This is likely to improve the accuracy and the predictive value of the technique and thus allow exclusion of those patients without clinically (symptomatic and prognostic) relevant disease from an unhelpful and potentially harmful invasive angiography. Studies from our group (21) show promising initial results (Fig. 32.4).

Multi-slice CT technology is now being integrated in the daily clinical routine, as it provides consistent diagnostic data for noninvasive coronary angiography, particularly with the latest developments in 64-slice scanners. The improvement of this technology may have major consequences for the diagnostic algorithm for screening and evaluation of coronary artery disease in the near future. Further developments announced by some vendors, such as dual-beam CT, may accelerate the implementation of this technique as a first-line tool in cardiology. Integrated with PET, PET-CT may become the long-awaited "one-stop shop" in cardiology, offering combined information on coronary anatomy, myocardial perfusion, and viability.

As an alternative to hybrid PET-CT, integration of SPECT and CT may provide another interesting combination. At present, most SPECT-CT scanners consist of SPECT and CT. The advantage of PET-CT, as compared with SPECT-CT, is its high spatial resolution, allowing the detection of small lesions. The disadvantage of PET-CT is its higher cost per examination.

![Figure 32.2](image1)

**Figure 32.2** A: Contrast-enhanced CT-angiogram showing a stenotic lesion in the left circumflex coronary artery with faint poststenotic flow (black arrow). B: Coronary angiogram showing the same stenotic lesion in the left circumflex coronary artery of the same patient as in part A (white arrow). C: Combined three-dimensional reconstruction of the four-slice CT providing the coronary artery tree and the shape of the heart, superimposed by the color-coded qualitative stress perfusion image obtained by PET. Blue indicates a reversible perfusion defect (ischemia). The lesion shown in parts A and B is hemodynamically relevant, as documented by the reduced hyperemic response to adenosine stress in the lateral wall (white arrow heads). (Reprinted by permission of the Society of Nuclear Medicine from Namdar M, Hany TF, Koepfli P, et al. Integrated PET/CT for the assessment of coronary artery disease: a feasibility study. *J Nucl Med*. 2005;46:930–935.)

![Figure 32.3](image2)

**Figure 32.3** Diagnostic algorithm for clinical decision-making. Only the combination of angiographically significant stenosis and evidence of ischemia (by PET) leads the decision toward revascularization strategy. (Reprinted by permission of the Society of Nuclear Medicine from Namdar M, Hany TF, Koepfli P, et al. Integrated PET/CT for the assessment of coronary artery disease: a feasibility study. *J Nucl Med*. 2005;46:930–935.)

![Figure 32.4](image3)

**Figure 32.4** Clinical decision-making according to the findings of PET plus angiography (Angio) represents the gold standard. Decisions produced by PET-CT were compared against the gold standard. NPV, negative predictive value; PPV, positive predictive value. (Reprinted by permission of the Society of Nuclear Medicine from Namdar M, Hany TF, Koepfli P, et al. Integrated PET/CT for the assessment of coronary artery disease: a feasibility study. *J Nucl Med*. 2005;46:930–935.)
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integrated low-end CT. The latter may be used for attenuation correction but is otherwise not helpful for cardiac imaging. As myocardial perfusion imaging by SPECT does not require an on-site cyclotron or an expensive rubidium generator, integration of high-end multi-slice CT into SPECT may eventually help the hybrid technique establish a more important role in cardiac imaging. We are currently evaluating the potential of such a hybrid scanner by using a stand-alone 64-slice CT for assessing CT angiograms integrated with perfusion images acquired by SPECT (Fig. 32.5).

The benefits of simultaneous noninvasive assessment of coronary anatomy and myocardial perfusion seem to lie in the greater diagnostic confidence that such assessment allows in deciding on the best therapeutic strategy. Elective interventional therapy can be planned carefully, helping to avoid overuse of angioplasty and stent placement. This is extremely relevant, because overuse of expensive intravascular stents is a key driver of cost in invasive cardiology practice (22). When lesion anatomy appears unsuitable for angioplasty, bypass grafting may be considered directly, without the need for further preoperative diagnostic coronary angiography, provided the noninvasive CT angiography images are of diagnostic quality.

Figure 32.5 Three-dimensional volume-rendered reconstruction of a 64-slice CT showing the normal coronary artery tree and the shape of the heart, superimposed by the color-coded qualitative stress perfusion image obtained by a N\textsuperscript{13}H\textsubscript{3} ammonia PET-stress imaging examination. Well-perfused areas are represented in orange to yellow colors, while blue colors represent hypoperfusion. Although part A shows both cardiac ventricles, in parts B and C the right ventricle has been removed. All images show a hypoperfusion in the territory of the left anterior descending coronary artery (LAD). A stenosis, hidden in part A, is noted in the proximal LAD in part C and less well in part B, confirming that hypoperfusion is a result of a coronary stenosis.
In addition to coronary anatomy, multi-slice CT can assess the coronary calcium burden. Algorithms will be elaborated where assessment of calcium could eliminate those patients with low scores from further testing, whereas patients with a score higher than the cut-off value (23) would undergo combined rest-stress perfusion and intravenous contrast MSCT coronary angiography. However, despite encouraging results, the real role of the calcium score in the cascade of noninvasive investigations of coronary artery disease remains to be determined. Initial hopes were high regarding the use of the calcium score as a motivational tool to change practice. Unfortunately, using coronary calcification to motivate patients to make evidence-based changes in risk factors was not associated with improvement in modifiable cardiovascular risk at 1 year, although the resulting management was superior to usual care in dealing with risk factors (24).

Although it is too early to draw conclusions about the definitive role of integrated PET-CT or SPECT-CT in clinical decision-making, the encouraging results of our investigation (21) seem to justify further efforts to improve the accuracy of hybrid imaging in the detection of coronary artery disease by incorporating higher-performance multi-slice spiral CT scanners into hybrids. Such technical refinements may accelerate the clinical implementation of hybrid scanners. Nevertheless, it has to be cautioned that there is currently no evidence that hardware integration is required for the superimposition of SPECT or PET data onto CT data. In particular, the integration of a relatively low cost SPECT camera with an expensive CT, which might idle for much of the day because the SPECT portion is in use, may not be a financially viable proposition.

REFERENCES


Clinical PET-CT and SPECT-CT in Body Oncology

This part of the book deals mainly with PET-CT and SPECT-CT imaging of tumors for staging and therapy control. Thus, with regard to PET, it is especially concerned with FDG imaging of tumors, which is the most important clinical application of PET. Imaging of tumors is essentially imaging of "hot spots," and the key to success with FDG-PET imaging, as well as some SPECT tumor imaging applications, is that the lesions are conspicuous, stand out in an image, and therefore are frequently well demonstrated (see Fig. 33.2). There are different ways of analyzing a PET scan. In FDG-PET, one way is simply to note the lesions and describe them. The problem with this approach is that lesions vary widely in activity, and the strength of uptake is an indication of the nature of a lesion. For example, relatively weak focal bilateral uptake in the hilar regions of the lung of a patient is likely due to chronic bronchitis, whereas strong uptake suggests hilar nodal involvement by bronchial carcinoma.

Therefore, many PET experts measure the standardized uptake value (SUV) of lesions, as this is a quantitative measure (1). Much literature defines SUV thresholds above which a lesion for a given tumor type is pathological, but unfortunately the discriminatory value of these thresholds is limited. A practical approach is to "window" and "level" body PET scans in a consistent fashion. In this approach, the brain FDG uptake is used as a reference, and the image gray scale is set such that the cortex of the brain is just at that level and black. Since FDG uptake into the brain is pretty constant unless the patient is a diabetic,
this level setting gives an upper reference point for the image gray scale. The lower end is set to zero. Using this approach, lesions can consistently be classified as having very high uptake (comparable to the brain cortex) (grade 4), high uptake (grade 3), moderate uptake (grade 2), and weak uptake (grade 1). Many images shown in Parts V and VI of this book are windowed in this way. Although this approach is excellent for the initial staging of tumors, it may not be adequate when subtler changes in FDG uptake are to be analyzed to evaluate the effects of a therapeutic regimen. Then, SUVs have to be used.

The interpretation of a body FDG-PET-CT scan or a SPECT-CT scan for tumor or infection imaging is most readily carried out in the following fashion. The scan is windowed and leveled in the manner described in the preceding paragraph. In most situations, the coronal sections are viewed first. Depending on need, transaxial sections and more rarely sagittal sections are also viewed. Images are best viewed on a workstation using a movie mode in which the coronal sections are scrolled back and forth. Alternatively, a maximum intensity projection (MIP) image of the patient is analyzed first (see Fig. 33.2). It can be rotated around the long axis of the patient, which is an elegant way to identify the dominant lesions at a glance. It is not advised to start viewing the transaxial sections, because they do not contain the brain as a reference, and thus windowing and leveling become arbitrary. Lesions with weak FDG uptake may appear to be more prominent than they really are, which leads to an overly sensitive reading of the PET scan and the identification of false-positive lesions. If SUV normalized images are used, this is not an issue.

Once the suspicious lesions have been identified on the coronal scans, viewing of the relevant transaxial sections through the lesion may be helpful, particularly for the identification of the anatomic location of the lesion. In PET-CT and SPECT-CT imaging, this latter step includes coregistered viewing of the molecular imaging and the CT data. This usually permits precise anatomic localization and may result in additional certainty that a lesion is there when the corresponding CT section shows an anatomic lesion. It is obviously reasonable to use appropriate CT windows, depending on lesion location, so that a lung lesion, a soft-tissue lesion, or a bone lesion noted on PET can be corroborated anatomically. Further image manipulation is rarely used in clinical practice.

With other radiopharmaceuticals, much less experience has been gained on how to consistently represent the images. In PET, even without extensive experience, consistency can be achieved by using the SUVs, because they can be measured for all radiopharmaceuticals.

REFERENCE

Identifying pathology on images requires knowledge of the normal. In nuclear molecular imaging, issues regarding normal scans can be broadly divided into two categories: technical issues related to the performance of a single imaging system or a combination of systems and physiological and pathophysiological issues related to a specific radiopharmaceutical. By their nature, technical issues can be treated in more general terms, whereas issues related to radiopharmaceuticals are largely radiopharmaceutical specific.

Technical issues in positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are mainly related to attenuation correction and to reconstruction of low photon flux images. Computed tomography (CT) artifacts relevant on a daily basis are mainly due to beam hardening. Both types of imaging systems are influenced by the presence of metallic implants in the body. The introduction of PET-CT and SPECT-CT generates additional technical problems because of the interplay of these two technologies, particularly the use of CT data for attenuation correction. The problems arising are due, for example, to the fact that x-ray contrast agents do not function as such at PET photon energies, which can lead to erroneous corrections. A combination of technical and physiological problems are relevant here as well, because although CT acquires data much faster than the breathing cycle, PET and SPECT average over many breathing cycles. The resulting artifacts in integrated scans have to be recognized and are described in this chapter.

Fluorodeoxyglucose (FDG) is still the primary and most important radiopharmaceutical in PET body imaging (see Fig. 33.2). FDG accumulates in the brain and is excreted through the kidneys and urinary collecting system. FDG uptake into heart and skeletal muscles is variable and related to the fasting state and the exercise level, respectively. Extended bowel uptake is variable and cannot be reduced significantly by drug interventions. There is menstrual cycle–dependent FDG uptake into the female genital organs and breast tissue and usually little uptake into the hemopoietic and lymphatic systems, except thymic uptake in children. Patients, particularly after tumor therapy, may show increased FDG uptake into the axial skeleton and into brown fat, which is located mostly in the posterior neck and shoulder region, the costovertebral joints of the cervicothoracic spine, and around the large organs of the upper abdomen. These normal accumulations are responsible for imaging pitfalls and have to be recognized. Additional pitfalls are related to inflammatory tissue, which also takes up
FDG, uptake in exercised muscle, and urine, which can all mimic tumor foci in oncologic patients. There are many findings on FDG-PET scans that have no clinical significance for scan interpretation, and they are described here as well. An example is FDG joint uptake, which increases with age and is probably related to the increasing prevalence of osteoarthritis in the aging population. CT in PET-CT and SPECT-CT greatly help in avoiding pitfalls. Other PET compounds are starting to be used, and a great variety of SPECT compounds are used in daily clinical practice. For the PET compounds, still little information is available on pitfalls, and the discussion here is brief. The SPECT compounds in daily clinical use are well known, but a detailed discussion of their distribution is beyond the scope of this book. Thus, the reader is referred to other relevant publications.

INTRODUCTION

When interpreting any images of a medical imaging modality, distinguishing the normal from the abnormal is the first step to master (1, 2). Like any other imaging modality, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) have their own artifacts, pitfalls, and lesions of physiological or irrelevant pathological significance (PIPS). This problem is compounded in PET-CT (computed tomography) and SPECT-CT, because the use of CT data for attenuation correction of PET or SPECT data can generate additional findings that require knowledge for proper image interpretation. It is therefore not surprising, that newcomers to the field of PET and SPECT imaging often have difficulty classifying lesions as relevant or irrelevant with respect to the diagnostic questions asked by the clinicians. As a result, newcomers to PET tend to generate a substantial number of false-positive findings. However, the data show that the number of findings that can be classified unequivocally as normal, pitfall, or PIPS lesion has much increased with the use of fluorodeoxyglucose (FDG) PET-CT (3).

Writing on artifacts, pitfalls, and PIPS lesions in PET and SPECT is doubly challenging, because in a sense every radiopharmaceutical generates its own problems. In order to deal with the wealth of diverging information, we need to restrict our focus. Here, only examinations that cover extended fields of view (FOVs) of the body are considered; corresponding remarks on brain- and heart-focused studies are presented in Chapters 21 and 28. Although some of the problems of image interpretation are reiterated in the ensuing chapters, here we focus on problems of image interpretation generated by common radiopharmaceuticals. Some examinations use radiopharmaceuticals that can be used only as PET tracers or only as SPECT tracers, such as $^{18}$F-FDG (used in PET), whereas other examinations are performed with radiopharmaceuticals that are available as both PET and as SPECT tracers. In PET and PET-CT, FDG and $[^{18}F]$choline belong to the first group. We will briefly consider other PET agents as well, notably F-ethyl tyrosine. Compounds used as PET and SPECT tracers are bone-seeking agents and the octreotide imaging agents. In SPECT and SPECT-CT, applications are just emerging. The emphasis will be on iodine, iodine analogs, which are lung and sentinel node agents, along with a few words on SPECT inflammation markers and iodine 123 ($^{123}$I) and $^{131}$I-MIBG. The normal scan appearance for these SPECT examinations will be discussed in later chapters where appropriate.

In this chapter, artifacts are considered to be related to the imaging technologies per se, whereas pitfalls and PIPS lesions are related to the interaction of radiopharmaceuticals with physiologic or pathophysiologic processes. Artifacts, being due to imaging technology issues, are common to all types of examinations. Different radiopharmaceuticals have little or no influence on these artifacts, and thus more general statements can be made on artifacts than on pitfalls and PIPS lesions, which are typically radiopharmaceutical specific.

ARTIFACTS

Artifacts due to system malfunction are partially treated in Chapters 3, 4, and 6. In line with the clinical nature of this chapter, artifacts are discussed here in a clinical context. First artifacts are discussed, which are specific to a modality or appear both in emission and transmission computed tomography. Then artifacts resulting from the integration of PET or SPECT with CT are presented.

PET and SPECT: Photon Attenuation by Body Tissue Artifacts

PET and SPECT are both emission techniques, and the artifacts discussed here are specific to emission techniques. In an emission scan, the photons traveling to the detectors are attenuated more strongly when they are located more centrally in a transaxial section of a patient than when they are located more superficially. The attenuation decreases exponentially with the distance traveled in the tissues (see Chapter 3). Due to differences in the detection technologies, these attenuation artifacts differ somewhat in PET and
SPECT. The result, however, is basically the same: if the images are not corrected for body attenuation, central foci with the same activity appear to be less active than superficial foci, and the foci are distorted (4). This has to be taken into consideration when scans not corrected for attenuation are clinically interpreted.

To eliminate attenuation effects, the PET and SPECT emission images have to be corrected using an attenuation map. This map is obtained either by gamma radiation-emitting sources in PET or SPECT systems rotated around the patient as a second part of the examination. In PET-CT and SPECT-CT systems, the map is obtained by the CT scanner. With the advent of PET-CT, the acquisition of transmission scans to correct for differences in attenuation has become much less time consuming; thus PET images from a PET-CT scanner are nowadays rarely viewed without attenuation correction. The only exception is when body regions containing metallic implants are evaluated (see “Attenuation Artifacts due to Beam Hardening” later). If a PET-only scanner is used for partial- or whole-body scanning, issues of patient throughput may prevent performances of one from carrying out a transmission scan, as it takes about 30% of the entire imaging time. Although not optimal, it may still be appropriate to view non-attenuation-corrected scans. In SPECT, attenuation correction was introduced successfully into myocardial perfusion scanning a few years ago, but the standard in SPECT imaging for other purposes is still to use uncorrected scans. This may change soon, as various manufacturers are now starting to offer SPECT-CT systems, in which acquisition of an attenuation scan is much faster than with conventional SPECT systems.

In SPECT, collimation is done with lead collimators. In this detection process, activity on the surface of the patient is seen more prominently, because there is less body tissue between the radiation source and the detector system to attenuate the emitted gamma rays (Fig. 33.1A). Furthermore, the spatial resolution decreases with increasing distance from the detector; therefore, the radiation detected by an opposing detector in a dual-detector gamma camera will not contribute much to the image. As a result, for the same activity, superficial lesions appear to be of higher activity a focus needs to have to become detectable is two times higher than its surroundings; second, that the minimal activity a focus needs to have to become detectable is two times higher than its surroundings; and third, that the PET has a better central than peripheral spatial resolution (see Chapter 3). Artifacts due to lack of attenuation are seen in Figure 33.1C.

These types of artifacts are not relevant for CT, as attenuation is in fact the physical principle by which CT images (or x-ray images in general) have contrast in them.

**PET and SPECT: Low Photon Flux Artifacts**

PET and SPECT data typically are based on low photon flux, and the images are noisy. When such images are reconstructed with projection reconstruction algorithms, streaks cross the axial section FOV, particularly when there are great differences in contrast in the image. They are noted only when the lower threshold of image display is set very low. Modern PET and SPECT scans are mostly reconstructed using iterative algorithms, which do not lead to these artifacts (see Chapter 3).

**PET and SPECT: Partial-Volume Artifacts**

As discussed in Chapter 3, each real imaging system is not able to depict a point source as a point, but the signal is spread to give rise to the so-called point spread function. There are two situations that are useful to distinguish. In the first situation, the focus is as large as or larger than a single voxel. Particularly when the activity or signal in a focus is much higher than that of the surroundings, some of the activity “spills over.” In the images, activity thus is also seen in neighboring voxels, and the lesion appears larger than it actually is. This effect is frequently noted in PET scans with the ureters, which are typically thin and less than 5 mm in diameter but can contain very high activity (Fig. 33.2E–G). In SPECT, this effect is frequently seen in thyroid SPECT scans of remnant thyroid tissue, where again the activity noted on the SPECT scan extends beyond the morphological confines of the activity focus.

The second situation occurs when the lesion is smaller than the voxel or when the voxel is located at the edge of a lesion. Partial-volume effects occur in all tomographic examinations but have different linear scales, as the spatial resolution of PET is on the order of 5 mm, the spatial resolution of SPECT is on the order of 15 mm, and in the anatomic imaging modalities it may be less than 1 mm. In PET and SPECT, many relevant lesions seen in the body, such as lymph nodes, may be smaller than a single voxel, and they might not be detected due to limited spatial resolution. Nevertheless, in both PET and SPECT, smaller lesions can be detected if their specific activity is high (this is also true for the anatomic imaging modalities, but to a lesser extent, because contrast differences are typically not as high as they are in PET and SPECT). The point spread function smears a focus out over the entire voxel. As an example, let us assume, first, that a voxel in a PET examination has linear dimensions of 10 mm and thus a volume of 1,000 mm³; second, that the minimal activity a focus needs to have to become detectable is two times higher than its surroundings; and third, that the
background activity has a value of 1 (arbitrary unit). If a focus has an activity eight times higher than the background, a focus that is only 5 mm in diameter and has a volume of 125 mm³ will still generate an apparent activity that is $8 \times \frac{125}{1,000} = 1$ above the background activity. The voxel containing that focus will then have an activity twice that of the background, which is readily detectable. Hence, a lesion with a volume only 1/8 of the voxel can be detected when its activity is eight times that of the background. The activity of the focus, however, is artificially reduced to 2. In general, partial-volume effects make very small lesions undetectable, but lesions somewhat smaller than the voxel can still be detected, although they will have an artificially lowered activity. In PET, this effect is particularly relevant in the case of small pulmonary metastases, which either may escape PET detection because of their size or appear to have a low SUV despite the fact that the primary tumor has a high SUV.

Analogous arguments can be made for the detection of a focus in CT, but scaled to the resolution of CT.

**Reconstruction: Beam-Hardening Artifacts**

Beam hardening occurs whenever polychromatic rays are traveling through dense material. In this situation, only the higher-energy photons are transmitted, while the lower-energy photons are absorbed. The spectrum of PET and SPECT gamma rays is close to monochromatic, whereas in CT polychromatic x-rays are used; thus beam hardening does not affect PET and SPECT images much but can severely deteriorate CT images. In CT, images affected by beam hardening show areas of higher and lower density, which is a result of CT spatial resolution insufficient to depict the interface of the high-density and low-density material and the lack of lower-energy photons, which have
been filtered out by the high-density material in the FOV (Figs. 33.3B and 34.15A). Furthermore, high- or low-density streaks, mostly in the left to right patient axis, can be noted even distant from the beam-hardening object in the image (Fig. 33.24D,F). These artifacts are noted frequently at the skull base and in the shoulder region, where the horizontal plane the bony shoulder girdle presents a substantial bulk of high-density absorption material. Any body portion containing a metallic implant, most notably hip prostheses and metallic dental work, will also generate beam-hardening artifacts. With low photon flux, these artifacts tend to be more prominent. As in PET-CT and SPECT-CT, frequently low-dose CT images are acquired, and the issue of image quality versus diagnostic necessity has to be carefully weighed.

As stated, there are many other technical artifacts that can occur. They are related to partial loss of detector function, misalignment of the rotation center of the system, and many other causes. They are not discussed here, as they do not interfere with image interpretation when the system functions properly.

Strong CT beam attenuation by metallic implants will affect the quality of PET or SPECT emission images reconstructed using CT attenuation maps. Thus such attenuation affects not only CT images but also images of the integrated systems.

**Artifacts Due to Integration of PET or SPECT with CT**

The most relevant artifacts occurring as a result of the integration of PET or SPECT and CT are due to a limited axial FOV in CT or to erroneous attenuation values introduced from CT attenuation maps into attenuation-corrected PET and SPECT images. Some of the basic issues concerning these artifacts are covered in Chapters 7 and 8. Here, the clinical implications are emphasized.

**Limited Axial Field-of-View Artifacts**

In a CT scanner, a limited axial FOV can cause linear cranio-caudal streaks, which prominently appear on the lateral edges of the coronal PET sections’ maximum-intensity projection images (Fig. 33.4). In wide patients, particularly in the shoulder region, the most lateral body portions will not be in the CT fan beam when it cuts through
the patient in the anteroposterior and posteroanterior positions. These artifacts have to be recognized but are hardly a problem for image interpretation as long as the pathology evaluated is not located very laterally. This problem is obviously nonexistent when using gamma ray sources in PET- and SPECT-only systems, as the beam coverage for the emission and attenuation-correction scans are the same. Most recent reconstruction algorithms are able to suppress these artifacts.

There are several causes that introduce erroneous attenuation values from CT scans into the algorithm correcting PET or SPECT images for attenuation:

- Use of CT scans with beam-hardening artifacts for attenuation correction,
- Erroneous attenuation in metal-containing regions,
- Erroneous attenuation in regions containing high-concentration x-ray contrast agents, and
- Erroneous attenuation due to physiological movements between CT and PET or SPECT data acquisition.

The errors associated with these causes of improper attenuation correction are discussed in the following paragraphs.

The basic principle for all the causes listed is the same. If the CT data suggest lower attenuation in a certain region than really exists, the PET or SPECT activity in this region will not be adequately enhanced by the attenuation correction algorithm, leading to an apparent photon deficit. Conversely, if the CT data suggest higher attenuation than actually exists, the attenuation correction algorithm will increase the PET or SPECT activity of that region too much, leading to an apparent activity accumulation.

**Attenuation Artifacts Due to Beam Hardening**

As stated earlier, beam hardening occurs when x-rays travel through high-density material such as extended areas of bone (see Fig. 33.24D,F), or, more importantly, prosthetic metallic implants. The artifacts are stronger the higher the density (z-value) of the object. Due to beam hardening, the CT data have either artificially higher or lower Hounsfield unit pixels surrounding the actual object. As a result, CT-corrected PET and SPECT images show artificial activity in these pixels, which depends somewhat on the SPECT or PET reconstruction algorithm used. Because of these artifacts, it is difficult to obtain meaningful diagnostic information from PET-CT or SPECT-CT images in the immediate surrounding of a metallic implant. In daily practice, this problem is mostly seen in patients with metallic implants (5), most notably metal dental work (Figs. 33.5 and 34.15A) (6). The definition of the extent of a floor-of-the-mouth tumor near dental metal work may
be impossible, or activity along the shaft of a hip prosthesis may suggest the presence of an infection. Diagnostic improvement in these situations can be obtained by also examining the emission scans not corrected for attenuation. Artificial lesions will disappear or fade, while real lesions will persist (Fig. 33.5).

**Attenuation Artifacts Due to Metallic Objects**

In the location of a metallic object in the CT image, the Hounsfield units may be properly represented or come out to high or too low (see Fig. 33.3). How an actual metal object is depicted in a PET or SPECT scan is thus somewhat unpredictable, but also irrelevant, because by definition there will be no activity concentration within the metallic object.

**Attenuation Artifacts Due to Extrinsic Contrast Material**

These artifacts, which occur when CT contrast material with high Hounsfield units is present in CT scans, are discussed in Chapter 7. Briefly, the contrast material used in CT is a good contrast agent for distinguishing soft tissues from contrasted structures at CT photon energies of around 100 keV and also for the most frequently used technetium 99m (\(^{99m}\)Tc)-based SPECT agents. However, at PET photon energies of 511 keV, the CT contrast agents provide no contrast to soft tissues: they attenuate no more than water. Areas containing CT contrast material thus look like soft tissue for the PET photons. But on the basis of the CT scan, an overcorrection of the activity in the region in the attenuation correction process of the PET scan makes this region appear to have higher activity than in reality. These effects are only relevant when the contrast focus on CT exceeds around 200 Hounsfield units, as only beyond this CT density do relevant apparent SUV increases above 5% occur in the PET images (7–9). Clinically, the presence of dilute oral contrast agent in the bowel is thus hardly ever a problem, while concentrated bowel contrast remaining from a previous abdominal contrast examination with conventional or CT techniques may cause an artificial focus (Fig. 33.6). We also do not recommend use of CT scans that have been acquired during dynamic intravenous CT contrast infusions, as the Hounsfield units measured in the large arterial vessels may exceed the critical level of 200. Thus, in our institution, dynamic intravenous-enhanced CT scans are always acquired as an add-on after a (low-dose) nonenhanced initial CT attenuation-correction scan and the PET emission scan (see Chapter 19).

**Attenuation Artifacts Due to Physiological Motion**

Physiological misregistration artifacts occur when the PET or SPECT emission scan are displaced relative to the CT scan used for attenuation correction. This is not only relevant when CT attenuation maps are used but can also be relevant when attenuation correction in PET or SPECT systems is done with rotating radioactive sources emitting gamma rays or x-rays. These artifacts can be caused by a misalignment of the PET or SPECT scanner relative to the CT scanner, which represents a technical problem that should be corrected immediately. In everyday scanning, these artifacts are related mostly to physiological motion. One source of physiological motion is patient movement between the examinations. This occurs relatively frequently in the head and neck regions. Fixation of the patient’s head...
is useful for minimizing this type of motion. Artifacts due to such motion are particularly striking around metallic implants (5). There are software tools, such as the PMOD program (www.pmod.com), that can be used to eliminate such artifacts by simply translating or rotating the image sets after the acquisition to counteract the translation or rotation the patient underwent between the CT scan and the PET or SPECT scan. Because oncologic patients are usually cooperative and hold their body still during the 20 or so minutes of image acquisition, this type of physiological motion does not frequently introduce image artifacts.

The major source of misregistration artifacts is involuntary physiological motion. Involuntary movements occur in the trunk of the body and are related to respiration, cardiac contraction, peristalsis, and bladder filling between scan acquisitions. Because in PET-CT, CT data are obtained at a speed much faster than a respiratory cycle, they depict images in a specific phase of the respiratory and the cardiac cycles. The much longer PET and SPECT data acquisition averages over all respiratory and cardiac positions. Note that the early SPECT-CT systems use slow CTs, and so cardiac and respiratory misregistration is no problem in such systems. Peristaltic bowel motions are slower and rarely a problem of misregistration. If necessary, bowel motility–reducing drugs can be given prior to scanning. Bladder filling is a nonissue if CT data acquisition and acquisition of emission data in the bladder region are done right one after the other, because then there will be not much bladder filling between scans. Because the heart is not an organ of diagnostic relevance in partial-body imaging, the only cause of physiological misregistration of major concern is respiration. Respiratory effects are most marked around the diaphragm. The most prominent artifact induced by this motion is an artifact I like to call the “banana artifact” because on coronal PET sections near the central body axis scans it looks like two low-activity bananas overlying the diaphragm (Fig. 33.7A–C). Although PET or SPECT will depict the average tidal breathing position of the diaphragm, in CT the diaphragm may be caudally displaced relative to this position when the CT is acquired with the patient close to end-inspiration or in end-inspiratory breath-hold. Such a CT used for attenuation correction will erroneously place lung tissues in the cranial abdominal regions, where on coregistered PET or SPECT there are soft tissues. As the lung CT pixel values are low and result in a low attenuation correction, this region will appear as having less activity than it actually has. The cranial areas of the liver and the spleen thus appear as if they would be part of the lung on the PET or SPECT scans.

Although misregistration of peridiaphragmatic structures between PET or SPECT scan acquisition and CT scan

![Figure 33.7](image-url)
acquisition can introduce image artifacts, it can also introduce diagnostic errors, because the lesions noted in the emission images do not superimpose onto the correct anatomic structure on CT. Focal activity such as metastases in the cranial portions of the liver or spleen may thus appear as lung foci (Fig. 33.7C). Respiration-related misregistration can be minimized by giving the patient proper breathing instructions. We have found that instructing the patient to hold the breath at end-expiration will minimize the artifact (10). Unfortunately, patient instruction is somewhat time consuming. Also, frequently patients getting the order to hold their breath at end-expiration will take a deep breath due to apprehension, and thus end-inspiration CT images are acquired, resulting in the maximum diaphragmatic discrepancy in the emission scans. As a consequence, we have stopped instructing patients and acquire CT data during tidal breathing. This is acceptable with fast multi-slice CT data acquisition but may still cause problems with the lower-end CTs more frequently used in SPECT-CT systems.

As shown in Figure 33.7, this misregistration is relevant not only for peridiaphragmatic attenuation correction but also for misplacement of lesions on the anatomic CT map. While this may result in problems in the upper abdomen, it hardly causes a difficulty in the chest (11). When a lesion is noted on an emission image, like a lung metastasis on an FDG-PET scan, and no corresponding lesion is found on CT, we know that the lesion is not real. The rule in the lung, which contains mostly air, is simple: if a lesion shown on an emission scan truly exists, it must be present on the CT scan, because the spatial resolution is much better in CT than in emission scans. A search for an anatomic focus in the vicinity of the focus on the emission image will have to demonstrate the anatomic lesion. This rule also applies in a situation that we have noted in very few FDG-PET scans and that could potentially occur in SPECT and with other radiopharmaceuticals as well. Slight problems with the injection of the radiopharmaceutical may result in the formation of a radioactively labeled micro blood clot. If this lodges in the lung as a micro embolus, a very high specific activity lesion may be apparent. Such a clot may fool one into thinking that a pathological focus is present. An inability to find a corresponding anatomic lung lesion will suggest this explanation for the focus (Fig. 33.8).

NORMAL FDG-PET SCANS, PITFALLS, AND LESIONS OF PHYSIOLOGICAL OR IRRELEVANT PATHOLOGICAL SIGNIFICANCE (PIPS LESIONS)

As stated, the appearance of normal scans, pitfalls, and lesions of physiological or irrelevant pathological significance (PIPS) varies with the radiopharmaceutical used,

Figure 33.8  A: Patient with left-sided bronchial carcinoma seen on a MIP-PET scan (arrow). Also noticeable is a focus in the right upper lobe (arrowhead), which is seen on transaxial PET (B) and PET-CT (D) scans as well but is not apparent in the corresponding CT section (C). There was some paravenous FDG injection in this patient, as can be seen in part A (curved arrow). (See Case 76.)
and so general statements are not useful here. Rather, each radiopharmaceutical can be thought of as generating a "new imaging modality." As this book contains much information on FDG-PET, this section deals almost exclusively with FDG. In addition to the information on FDG, there is a short discussion of \(^{18}\text{F}\)choline, which is the pharmaceutical used second most frequently at our institution for partial- or whole-body imaging. There are a few notes on other PET agents as well, notably \(^{18}\text{F}\)ethyl tyrosine, \(^{18}\text{F}\)thymidine, and \(^{18}\text{F}\)Dopa. Compounds available as PET and SPECT radiopharmaceuticals are bone-seeking agents and the octreotide-based imaging agents. In SPECT and SPECT-CT, applications are just emerging. The scans are discussed in the relevant chapters.

As a general remark, FDG tumor and inflammation scanning is done starting no earlier than 45 minutes postinjection, after substantial accumulation in organs and lesions has occurred and FDG has mostly cleared from the blood vessels and been excreted by the kidneys. After 45 minutes there are only small changes in the activity distribution in PET scans, so the qualitative appearance of the scan remains unchanged. Dynamic scans are not described. The appearance of normal brain and heart images is discussed in Chapters 21 and 28, respectively. The focus here is on normal scan appearance, pitfalls, and PIPS lesions in relation to the various organ systems in which they are occurring.

As stated at the outset of this part, we like to grade FDG uptake from 0 to 4 for the sake of simplicity, with 4 equal to or higher than brain uptake (which does not vary much) and 3 between brain and liver uptake. Liver uptake and comparable uptake into other lesions are graded as 2, other general body activity is graded as 1, and the regions surrounding the patient are graded as 0. The grades roughly correspond to the following standard uptake value (SUV) ranges: liver is around 1.5, and brain is above 4. Note that this grading scale applies to sections but not to maximum-intensity projection (MIP) coronal PET images, where the brain as a large bulk of tissue taking up much FDG will appear very dark.

### Heart and Blood Vessels in FDG-PET Scans

The heart can alternatively use glucose or fatty acids as an energy source depending on availability. Therefore, cardiac uptake is determined by the fasting state of the patient. As discussed in Chapter 28, glucose loading prior to FDG-PET scanning yields consistent FDG uptake into the myocardium. In standard body PET imaging, the patient is asked to fast for at least 4 hours, sometimes 12 hours, prior to PET scanning. Despite this, a substantial number of patients (in the range of 20%) show left ventricular myocardial uptake in a whole- or partial-body FDG-PET scan (Figs. 33.7A, 33.9, and 33.10). Note that hospitalized patients are frequently on infusions, and these should not contain glucose if FDG tumor or infection scanning is to be performed! Although left ventricular myocardial uptake can be strong, the right ventricular wall is infrequently seen, as its wall is much thinner and its energy requirements are lower. The right ventricular myocardium can be visible in patients with right ventricular hypertrophy or right ventricular overload. Occasionally, even the atrial walls and the ascending aorta are noticeable (Fig. 33.9).

![Figure 33.9](33.9) Weak FDG activity in the ascending aorta and its arch. Activity is clearly not within the lumen of the aorta but in the vessel wall. There is, however, some general vascular activity, best seen in the pelvic vessels; substantial bilateral activity in the parotids; normal renal and bowel activity; and some increased joint activity in the shoulders and hips, suggesting osteoarthritis.

![Figure 33.10](33.10) Three adjacent 5-mm coronal sections from a patient showing physiologic uptake into the myocardium and the liver. In this patient, weak FDG activity is seen in most major vessels: the neck vessels, the abdominal aorta and inferior vena cava, and the iliac vessels. This finding is likely due to incomplete FDG uptake at the time of scanning and can be reduced by scanning later.
Why they are occasionally seen is not fully clear but is likely related to increased muscular stress (e.g., in hypertension). In uncorrected PET images, there is an artificial decrease of activity in the posterior and lateral left ventricular walls, as they are deeper inside the body (see Chapter 28). On rare occasions, a pericardial effusion is noted, which presents as a low-activity rim around the myocardial perimeter.

The blood vessels can show general vascular activity as a result of early scanning, when there is still sizable FDG blood pool activity (Fig. 33.10). As FDG uptake is a slow process, it is highly recommended not to scan earlier than 45 minutes postinjection (see Chapter 19). Even when such an amount of time has elapsed, occasional vascular uptake is noted in the thigh vessels, which can be related to both arteries and veins (Fig. 33.11). Less frequently, vascular activity can also be seen in the upper extremities and the large thoracoabdominal vessels. Such activity is a definite sign of overly early scanning.

Occasionally, the aorta shows weak to moderate FDG uptake of grades 1 to 2 (see Fig. 33.9). This is noted in the ascending aorta or in the entire thoracic aorta, but we have virtually never seen it in the abdominal aorta. As stated, it is not clear what this represents. Possible explanations include (a) increased vascular tone leading to increased FDG uptake by the muscular layers in the aortic wall and (b) mild inflammation. Some authors suggest that such uptake may represent atherosclerotic plaque or components thereof, such as activated macrophages in the lesion (12), but we do not feel that there is substantiated evidence for this last interpretation, although there is probably an occasional inflamed aortic plaque visible. Mild chronic inflammation as a reaction to a foreign body is the likely explanation in patients who show some FDG uptake into the walls of an aortic graft (see Fig. 59.5). After initial euphoria regarding the clinical significance of this latter finding (which points to a graft infection), we have become more cautious over time and call this pathological only if the uptake is above the liver uptake and thus stronger than grade 3 (i.e., substantially stronger than the liver uptake) and if the SUVs are above 2.5. This finding is a PIPS lesion, which may represent a pitfall to the inexperienced PET reader. Inflammatory vascular uptake is further discussed in Chapter 59.

Distinct venous focal or extended FDG activity is occasionally seen in a section of a superficial thigh vein. This is due to focal inflammation of a venous valve or inflammation of an entire venous segment in patients with varicose veins. Focal uptake in the superior vena cava has been
noted in patients with indwelling central catheters and represents a focal infection of the catheter tip.

**Respiratory System Appearance in FDG-PET Scans**

In scans not corrected for attenuation, the lung shows some activity, which is never greater than grade 1, along with some peripheral enhancement of the lung perimeter. The lungs in such scans are more active than the mediastinum and the surrounding tissues (1) (see Fig. 33.1C). This is due to the lack of attenuation correction of soft-tissue structures surrounding the low-attenuation lungs, as discussed at the beginning of this chapter. In attenuation-corrected scans, there is less lung activity than in corrected scans and there is more activity in the mediastinum and surrounding tissues (see Fig. 33.2A).

PET-CT imaging artifacts around the diaphragm have been discussed above (13). When CT is acquired in end-inspiration, the “banana” artifacts above the diaphragm can be quite apparent on PET and PET-CT images (see Fig. 33.7). This respiratory-induced misregistration can also lead to pathological foci lying just below the diaphragm, thereby mimicking lung foci. An example is shown in Figure 33.7C. Since the lung parenchyma experience not only craniocaudal motion but also anteroposterior and lateral motion during respiration, the activity of a lesion noted on PET and its anatomic correlate noted on CT can also be displaced, but the major offset is in the craniocaudal direction. The erroneous anatomic CT location of a lesion on PET scans is thus primarily supradiaphragmatic rather than subdiaphragmatic. The pitfalls are readily noted when keeping in mind that any PET lesion appearing in the lungs must have an anatomic correlation (see Fig. 33.8). A simple check whether there is any anterior or lateral displacement between PET and CT due to respiration is to see whether the body contours of the PET scan are offset in relation to those of the CT scan.

There are several imaging pitfalls in the chest that we have come across. Perihilar moderate to strong “cauliflower”-like multifocal uptake can correspond to sarcoidosis, a pitfall occasionally seen in patients who are scanned for tumor staging (see Fig. 38.10). Sparser and less active foci are due to chronically inflamed lymph nodes in smoker’s bronchitis. They have to be classified as PIPS lesions and, particularly if bilateral, are unlikely to be tumor manifestations. If unilateral and in a patient with bronchial carcinoma, tumor involvement cannot be ruled out. Identifying such lymph nodes as tumor manifestations rather than PIPS lesions requires considerable experience. An SUV over 2.5 to 3 is helpful in determining that there is tumor involvement. Other pitfalls are peripheral focal manifestations, which on PET alone may impress as peripheral lung metastases. With PET-CT, they are readily identified as rib fractures if the superposition of the PET focus onto rib fractures shows callus formation on CT (Fig. 33.12). If callus formation is absent, the focus might be a bone metastasis.

**Genitourinary System Appearance in FDG-PET Scans**

Most radiopharmaceuticals are excreted through the urine, and FDG is no exception. The appearance of FDG in the urine may be surprising at first sight, because glucose is
quantitatively reabsorbed in the kidney but FDG is not. Due to the renal-concentrating capability, the strongest FDG accumulation outside of the brain is found in the urinary collecting system, be it in the renal pelvis, the ureters, or the bladder (Fig. 33.13; see also Figs. 33.2, 33.7, and 33.9) (1,2). This can lead to unwanted contamination activity in the groin area. Since tomographic scans are acquired, this is less of a potential problem in image interpretation than in planar bone scanning. Except for the rare case of intrarenal obstruction (see Fig. 33.12), by the time the PET scan is acquired, all FDG resides in the renal collecting system. Thus, the renal calices contain much activity in most patients. The activity is typically in the over-range (higher than grade 4). The ureters also frequently contain activity, either focally or in extended parts (see Figs. 33.2 and 33.13A). The bladder exhibits high activity (higher than grade 4) in most cases (see Figs. 33.2, 33.9, 33.12, and 33.13). This can result in image degradation in the pelvic PET sections containing the bladder, although the standard use of iterative reconstruction algorithms (see Chapter 3) by all manufacturers has much alleviated this problem. Nevertheless, it is good practice to send the patient for voiding before partial- or whole-body PET examinations and before starting PET image acquisition from the pelvis up rather than from the head down (see Chapter 19). This is obviously to no avail in patients with urinary retention, and here catheterization, even with rinsing, may be necessary. Measures to reduce this activity are still useful. Occasionally, urine activity is noted in the bladder neck, and this unequivocally points to a status post transurethral resection of prostatic disease.

Pitfalls from imaging the genitourinary system are mainly due to focal urine accumulation in a ureter in a patient who is referred for the evaluation of tumors with potential lymph node disease in the retroperitoneum. Careful image analysis usually prevents the making of this mistake. It is important to look carefully for the linear FDG-filled ureteral structures, which are easily recognized on the MIP images (see Fig. 33.13A). Still, sometimes urine is present only as a focal spot, and then distinguishing it from a tumor focus is difficult. PET-CT solves this problem, as the activity focus will either superimpose onto the ureter or, if indeed pathological, be associated with a globular structure, such as a lymph node, on CT. Other pitfalls are “hot” lesions adjacent to the bladder. Unless anatomic coregistration is obtained, the diagnosis of bladder diverticulum-associated or ovarian-associated FDG activity (see below) cannot be made confidently. Sometimes a vaginal tampon will contain urinary activity, and this also needs to be recognized (see Fig. 33.13B–D). In a patient with a rare cancer of the external female genitalia, care has to be taken to ensure that the patient cleans her groin prior to imaging so that urine contamination does not appear as a lesion. Anatomic variants such as horseshoe kidneys should also be recognized, but being aware of their existence makes the diagnosis easy. Again, PET-CT coregistration leaves no doubt that the structure seen is indeed a horseshoe kidney (Fig. 33.14).
The testicular structures can show moderate FDG uptake (see Fig. 33.7A) comparable to the liver. The significance of this is not known. In the female, the ovaries can show strongly increased FDG uptake (Fig. 33.15), which may also be interpreted as a bladder diverticulum by the inattentive interpreter. Ovarian uptake is related to developing follicles and corpora lutea, with occasionally associated hemorrhage, and is found during the midmenstrual cycle. There is also variable uptake into the endometrium, which occurs in the first few days of the menstrual cycle and during ovulation. This is an important pitfall in premenopausal women with gynecological malignancies, but uptake is not found in postmenopausal women. SUV measurements are of some usefulness in differentiating benign conditions from malignant conditions (a SUV cutoff of 7.9 results in a sensitivity of 57% and a specificity of 95%) (14,15).

Gastrointestinal System Appearance in FDG-PET Scans

The gastrointestinal structures in PET imaging may generate uncertainties in image interpretation (7). This is due to the fact that parts of the bowel, particularly the large intestine, take up FDG to a variable degree, sometimes, though rarely, intensely enough to reach grade 4. FDG-accumulating intestinal structures are usually recognized through their "snake"-like accumulation, suggesting bowel loops, and sometimes the entire colon frames the abdomen by its intense uptake (Fig. 33.16). Whether this uptake is related to muscular peristaltic activity due to the high concentration of white cells in the bowel wall or some secretory cells secreting FDG into the bowel wall or lumen is not known. Some experiments suggest that extra FDG excretion occurs in the cecum with increased distention, which can occur with the application of an oral contrast agent (8). No obvious physiological or pharmacological maneuvers have yet been identified to consistently minimize this accumulation problem (16). The esophagus is usually not visualized in FDG scans, but occasionally, as incidental finding, an esophagitis due to reflux, prior radiation therapy or other causes is identified by FDG activity in the distal esophagus, or more extended esophageal activity is noted, pointing to a more extended esophageal inflammation (Fig. 33.17A,B). The stomach is seen quite frequently (Fig. 33.17D), but whether its visibility is due to peristalsis or muscular activity is not clear.

It is easy to imagine that the bowel activity is a source of many pitfalls and generates diagnostic uncertainty. As stated, no efficient measure exists to suppress this activity, and experience is necessary to separate normal bowel activity from disease. Obviously, the major pitfall to avoid is mistaking normal bowel activity for a lesion. In FDG-PET, the simplest notion is that tumorous lesions are focal (17) and that “normal” bowel activity tends to occur in extended sections of bowel (see Fig. 33.16A). Some patterns are easily distinguished from tumor due to their anatomic appearance. An example is diverticulitis, which will show bead-like activity along the course of the large bowel corresponding to FDG accumulation in infectious foci. Obviously, other abdominal findings, such as a horseshoe kidney (see Fig. 33.14), have to be properly identified and distinguished from bowel activity.

Figure 33.14  A: Patient with bronchial carcinoma, showing some intense bead-like activity in the lower abdomen as well as activity in the colon and the bladder. B: The bead-like activity represents a horseshoe kidney, as can be readily seen on the coregistered transaxial PET-CT image. (See Case 77.)
PET-CT is helpful in distinguishing bowel activity from other abdominal foci, because it allows one to determine whether the activity is associated with the bowel or clearly outside it. Although some air in the large bowel often helps in identifying the bowel without an oral CT contrast agent, we have found it to be very useful to have all patients drink an oral contrast agent, as this will define most parts of the small intestine in addition to the large bowel. A comparison of 30 unenhanced and 30 enhanced bowel scans at our institution showed that the use of abdominal contrast does not alter the image quality of the PET scans; thus, like unenhanced CT scans, CT scans containing a dilute oral contrast agent can be used as attenuation maps (8).

The liver shows homogeneous FDG uptake of a gray shade, which we define as grade 2 (see examples in Figs. 33.2A, 33.7A, 33.9, and 33.10), and in scans not corrected for attenuation it may show a peripheral enhancement in the lateral and anterior portion, corresponding to a “skin” artifact (see Fig. 33.1C; see also “Skin, Connective Tissues, and Fat” later). Since FDG is not excreted through the bile, the biliary collecting system is not seen unless there is pathology. The spleen has less FDG uptake than the liver in normal situations, and comparable activity should make one suspicious of tumorous involvement. The normal pancreas is not seen on PET scans.

As the liver is just adjacent to the lungs, artifacts in PET-CT due to respiration are noted. They correspond mainly to mismatches of PET and CT body contours. If a patient has not been cooperative with breathing during CT, the anterior extension of the anatomic liver confines is larger than that seen on the PET scan. If lesions are seen, this may lead to substantial coregistration inaccuracies (see Fig. 33.7). In order to estimate the mismatch in such cases, it is extremely useful to bring down the upper level of the window to put the liver activity close to the over-range. This will show the PET liver and body contours on transaxial images and make it possible to gauge the extent of the mismatch and thereby

Figure 33.15  Patient who underwent a PET-CT scan as follow-up for melanoma. A: Note the two foci of uptake in the pelvis on the PET-MIP image, the left-sided one potentially mimicking a bladder diverticulum. B,C: The association of both foci with the uterus and anatomic correlation suggest ovarian activity. (See Case 73.)
estimate where the lesion noted on the PET scan should reside on the CT scan.

**Lymphatic and Hematopoietic System Appearance in FDG-PET Scans**

It is well known that FDG accumulates in white blood cells, mainly granulocytes and macrophages (see Chapter 58). These cells reside mainly in the hematopoietic bone marrow and the bowel wall. However, FDG accumulates strongly only in activated cells; thus normal hematopoietic bone marrow shows weak FDG accumulation. Whether the spine is seen to accumulate FDG (typically grade 1) (see Fig. 33.7B) due to white cell activity or cell proliferation in the nonactivated bone marrow or due to incorporation of free fluoride cannot be stated with certainty. Thus, disease located in the bone marrow spaces, such as metastases or infectious foci, can be spotted easily in FDG-PET even in bones containing hematopoietic marrow. Whether the bowel activity frequently noted is due to FDG accumulation in activated inflammatory cells in the bowel wall is not known (18). We have noted increased FDG uptake into bone marrow in patients shortly after chemotherapy, where presumably the hematopoietic bone marrow is proliferating rapidly to replenish the chemotherapy-depleted cell pool (Fig. 33.18). An additional lymphatic structure frequently noted in children and adolescents is the thymus. This has to be recognized (Fig. 33.19A). Normal lymph nodes do not accumulate FDG, and hence FDG accumulation in lymph nodes is either pathological (due to tumor involvement or inflammation) or a result of paravenous injection (Fig. 33.20). An area frequently showing FDG accumulation probably due to inflammation is the lymphatic tonsillar tissue of Waldeyer (Figs. 33.13 and 33.21). Accumulations have to be considered to be normal in this region, but sometimes differentiation from tumor involvement is difficult. This problem is partly alleviated by noting that the tonsillar tissue is typically symmetrical.

PET-CT is not more helpful than PET in locating activity in the hematopoietic marrow, as the outlines of the spine are well recognized on an FDG-PET scan alone. The thymus has a typical V-shaped appearance on transaxial

![Figure 33.16](image_url)
Chapter 33: PET-CT and SPECT-CT Body Scans

**Figure 33.17** MIP images of patients showing FDG uptake in the distal esophagus as a result of reflux esophagitis (A) along the entire course of the esophagus (B; sagittal midline section).

**Figure 33.18** Increased bone marrow activity in a patient after chemotherapy because of lymphoma. Note the increased bone marrow activity in the axial skeleton and the ribs. This patient also shows moderately increased uptake into the parotid glands and greater increased uptake into the sublingual glands bilaterally and the tonsillar tissue of the pharynx.

**Figure 33.19** A: MIP image of a 3-month-old infant showing prominent thymic activity. B,C: PET-CT images show the colocalization of anatomic and functional images. Also note the increased FDG uptake into epiphyseal plates and hemopoietic bone marrow as zones of increased cellular proliferation and metabolism (A). (See Case 78.)
images, which is also readily recognized without the anatomic reference provided by CT (see Fig. 33.19B–D). PET-CT is helpful in localizing FDG activity in lymphatic tissue in general and specifically in lymphatic tissue in the head and neck region (see Chapter 34).

**Endocrine Organs in FDG-PET Scans**

Notable FDG uptake into endocrine organs is either absent, infrequent, or weak, except for the ovaries (see Fig. 33.15). The thyroid gland occasionally exhibits some FDG uptake, and uptake can be stronger than grade 2 (19). If asymmetrical, pathology has to be considered. Paralaryngeal FDG uptake of grade 2 to 3 is noted frequently and associated with the use of muscles of phonation (tell the patient to shut up during the uptake phase!). Exact analysis of the shape of the uptake on transaxial images will mostly distinguish thyroid from laryngeal muscular uptake, as the former is located anterior and lateral to the trachea, while the laryngeal musculature is located posteriorly and anteriorly, but very closely apposed to the trachea. Although distinguishing thyroid from laryngeal uptake on PET is sometimes difficult, thyroid uptake is infrequent, and thus if uptake is observed, it is unlikely associated with the thyroid. On PET-CT, the anatomic correlation makes distinguishing between the two structures potentially containing FDG easy.

No normal FDG uptake beyond grade 1 is noted in the adrenals. Thus, identification of adrenal metastases is easy. Testicular uptake may reach a grade 2, and ovarian uptake can even be 3, as discussed in “Genitourinary System Appearance in FDG-PET Scans” above.

There is occasional FDG accumulation in the buccal exocrine glands. The parotid glands may show relatively strong FDG uptake, up to grade 3, without being pathological (see Fig. 33.21). Distinguishing such uptake from a parotid tumor depends on the fact that in normal uptake the entire gland appears symmetrically, which is highly

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**Figure 33.20** Patient with bronchial carcinoma. The right-sided axillary focus (A; arrow) shows uptake into a lymph node, which on CT is normal (B). FDG activity superimposes onto the node (C). There is right paravenous injection of FDG, as noted in the right arm (A; arrowhead).
unlikely in the presence of a tumor. The sublingual glands may also be noted (see Fig. 33.21).

**Muscles, Bones, and Joints in FDG-PET Scans**

**Muscles**

FDG activity in muscles (1) and joints (20) is frequent, but little activity is usually seen in bone. Exceptions are mentioned above (see Fig. 33.18). FDG accumulates in muscles because muscles, including the myocardium, use FDG when exercised. Although normal muscles accumulate little FDG, uptake of grade 1 or less, muscles exercised just prior to or around the time of FDG injection can exhibit FDG uptake of grade 3 to 4. Being aware of this fact makes it usually simple to qualify an area of FDG as muscle uptake, but some subtle observations have been made that suggest that muscular uptake is another major source of pitfalls in PET image interpretation. Diffuse muscular uptake in patients is rare and most frequently related to hyperglycemia in diabetic patients. This is why it is important to control blood sugars prior to FDG injection when the patient is a known diabetic (Fig. 33.22A). A bodybuilder who has just strenuously exercised will show up for a PET scan and show FDG uptake in extensive parts of his musculature (Fig. 33.22B), and so will a late patient running to a PET appointment (see Fig. 33.1C). Finally, patients should be kept comfortably warm during injection so that they do not shiver during the FDG uptake phase, as this can also lead to intense whole-body muscular FDG activity. Note that a patient with hiccups during FDG uptake will show activity in the diaphragm due to its muscular exercise (Fig. 33.22C).

Starting from the head, a first muscle group frequently noted to contain substantial amounts of FDG are the ocular muscles, as the constant eye movements make them continuously use glucose. They have to be recognized as such to avoid misdiagnosis as tumor tissue, particularly if the patient suffers from a sinus tumor or ocular melanoma. Other muscles in the head frequently activated are the muscles in the floor of the mouth, particularly the mylohyoid muscles, which are needed to prevent the tongue from falling back in the supine patient (see Fig. 33.21G). Accumulation of FDG in the neck musculature is relatively frequent and must be related to various tension states in the examined patients. Identification of such muscles is often easy, as the FDG accumulation involves the entire muscle, with its characteristic anatomic shape. However, this is not a foolproof rule, as sometimes muscular activity is located only in one part of a muscle. Most frequently, the sternocleidomastoids are seen uni- or bilaterally (see Fig. 33.2), but the interspinosus muscles and the scalenes may show, particularly in patients with COPD. Other muscles are small and more globular. One important area is the larynx. If the patient is not kept quiet during the post–FDG injection phase, the laryngeal muscles used for phonation may show. They are located posterolaterally and extend anterolaterally and are closely apposed to the trachea (see Figs. 33.21F and 33.22). There is infrequent accumulation in the muscles of the chest...
and the diaphragm (Fig. 33.22C). Accumulation in the muscles of the abdominal and pelvic area is rarely seen. FDG in the extremity musculature is frequently noted and depends on the patient’s physical activity just prior FDG injection (Fig. 33.21B).

PET-CT is helpful in identifying muscular activity, as PET activity has to superimpose on the anatomic confines of a muscle (Fig. 33.2). Thus PET-CT helps in avoiding pitfalls. One such pitfall is a focal activity in the paralaryngeal area localized to one of the posterior crycoarytenoid muscles, which is often mistakenly taken to be a pathological lymph node. In these patients, a palsy of the recurrent laryngeal nerve is present, which leads to overuse of the contralateral posterior crycoarytenoid and consequent increased use of FDG (Fig. 33.23) (21).

**Bones and Joints**

There is generally little accumulation of FDG in bone (1). FDG uptake into the bone marrow of the normal hematopoietic system residing in the axial skeleton is weak and not higher than grade 1. Exceptions to this are discussed in "Lymphatic and Hematopoietic System Appearance in FDG-PET Scans" above (see Fig. 33.18). If there is a high level of free fluoride, the skeleton starts to appear very much like it does in a bone scan, and some authors have in fact suggested that adding some fluoride to the injection gives an anatomic reference frame that may be useful in image interpretation (22). Cortical bone is virtually free of activity (grade 0), but even in bone marrow of the appendicular skeleton containing fatty marrow only weak grade 1 activity may be seen.

PET-CT is helpful in assigning focal lesions seen on PET either to bone or the surrounding soft tissue. This can be important in many settings, particularly when biopsy is planned, as precise anatomic location is needed. Obviously, it is important to evaluate the CT scans using a bone window when PET suggests a lesion in the bone, but an FDG-accumulating metastasis may be present in the bone marrow without structural alterations of the bone on CT.

Joints accumulate FDG to a variable degree, and FDG uptake of grade 2 is noted relatively frequently. A review of 350 cases published by us demonstrated that there is a significant positive correlation of joint accumulation of FDG with age, with prominent and most frequent accumulation in the acromioclavicular joints but accumulation in other joints as well (see Fig. 33.4) (20). There is little doubt that this accumulation is due to chronic inflammation in joints affected by osteoarthritis, but this is hard to prove, as histological confirmation cannot be obtained serially. Nevertheless, this hypothesis is consistent with the age dependence.
observed. Patients with strong FDG accumulations were asked whether they had pain related to the affected joints, but no correlation between FDG uptake in joints and symptomatic disease could be established. The artifacts around metallic prostheses may be present in the joint space (5).

It has not been established whether PET-CT is able to clarify the issue of osteoarthritic joint involvement. In principle, joints showing osteoarthritic changes should be noted on CT scanning, and a correlation between severity of anatomic findings and FDG uptake could be established.

### Skin, Connective Tissues, and Fat

The skin is too thin to be seen on PET scans. Skin artifacts in nonattenuated scans are discussed in the first sections of this chapter (see Fig. 33.1C). Connective tissues in the body exhibit mild FDG uptake of grade 1 or less, and stronger uptake is pathological.

### Fatty Tissue

That fat can show strong FDG uptake is an interesting fact, and many reports on this have appeared after our seminal paper (23). Most fat does not take up FDG. However, fat uptake appears to be present in the so-called brown fat of 2% to 4% of individuals (24). It is thought that this fat is used for nonshivering thermoregulation. The location of brown fat is mainly in the neck and shoulder area, but there are uptake sites along the spine and around the upper abdominal organs (Fig. 33.24) (25). The uptake can be extended or focal. PET-CT is extremely helpful, as the FDG uptake colocalizes with fat, easily recognized in CT scans due to its density, which is below that of other soft tissues. Brown fat can exhibit strong uptake, up to grade 3 or even 4, in a symmetrical fashion. Fat uptake is a major pitfall in PET imaging and was only recognized with the advent of PET-CT. It is noted more frequently in patients after chemotherapy, and if not recognized properly, it may be mistaken for a tumor recurrence. The best way to minimize uptake into brown fat is to control the ambient temperature. Thus, seeing brown fat does not necessarily suggest pathology, and positive identification of fat uptake is critical. There are also suggestions that fat uptake requires intact parasympathetic innervation, as radiation therapy to one side of the neck, for example, obliterates uptake in that region (Fig. 33.24B).

### Breasts

Breast tissue shows variable activity. While the mammillae are frequently seen, the entire breast can accumulate FDG.
Figure 33.24 Uptake of FDG into brown fat in a 35-year-old female patient after chemotherapy and a 24-year-old female patient after chemoradiotherapy, the latter with uptake into the left neck (arrows). A,B: The MIP images show extensive and intense symmetric FDG accumulation in the paraspinous region, whereas in the neck region the first patient shows symmetric FDG uptake, the second asymmetric uptake (due to an effect of radiation therapy). Part B also shows a fat focus below the right lobe of the liver, one superomedial to the spleen (C), and possibly one lateral to the spleen. Note that the foci can always be correlated with areas of hypodensity on CT corresponding to fat, as seen in the correlating axial images D and E (corresponding to the MIP in part A) and F, G, and H (corresponding to the coronal MIP and scans in parts B and C). It can readily be understood that, for example, the subhepatic focus could be mistaken for pathology. Key is the correlation to fat on CT. The axial CT sections in D and F show some beam hardening streaks crossing in the left-right direction. (See Case 71.)
during the later phases of the menstrual cycle (see Fig. 33.13A). It is typically low grade and rarely exceeds grade 1. During lactation, the breasts take up substantial amounts of FDG as it enters the milk (Fig. 33.25). Thus, in breast-feeding, radiation protection measures are in order, and breast-feeding should be discontinued for 24 hours. As the uptake is diffuse rather than focal, the chance of misinterpreting this finding as pathology is small. Although we are unaware of a published series of women with inflammatory breast disease, we occasionally note substantial FDG uptake even in asymptomatic women. Activity in the range of grade 2 to 3 suggests some active process, and if the activity is diffuse and symmetrical, inflammation is the likely cause.

Breast implants may result in local uptake surrounding the implant, but this is unusual. Such uptake suggests the presence of a chronic inflammatory reaction (Fig. 33.26). Women showing such periprosthetic uptake are usually asymptomatic.

**NORMAL SCANS OF [18F]CHOLINE, F-ETHYL-TYROSINE AND [18F]THYMIDINE**

Several agents other than FDG have become increasingly available. The clinical use of these compounds is ill defined at this point, and only limited information on normal scan appearance is available. Among these agents is choline, which appears to have some clinical value in the detection of metastases in prostate cancer (see Chapter 49). Gallium 68 (68Ga) octreotide analogs are also in use and seem to well demonstrate metastases of endocrine-active tumors (see Chapter 43). Amino acid analogs like F-ethyl-tyrosine (FET) have also been studied, but their main use is in the characterization of brain tumors. In whole-body imaging, it has been shown that FET is less sensitive than FDG, and thus it is not used in staging applications (26). Finally, 18F-l-thymidine (FLT) and many other F-based tracers, such as tracers for estrogen receptors or hypoxia, have also been studied. They are used at few
sites within the framework of research protocols, and thus a discussion would be beyond the scope of this book. The reader is referred to the literature.

**Choline Analogs**

Several choline PET agents are in use, some are $^{18}$F based and some are carbon 11 based. It is not expected that substantial differences in their normal accumulation occur. Choline is an essential building block of cell membranes and has been found to be useful as a tumor-imaging agent. The most relevant application is in prostate cancer (27,28). As the scans are started almost immediately postinjection, a static distribution can be expected to occur only in the cranial portions of an extended FOV PET scan. The scans start in the pelvis to avoid the interference of bladder activity with pathological findings. Subsequent scans are obtained cranially to this position. Hence, excretion of the choline compounds in the renal collecting system may vary depending on acquisition speed and renal function.

A normal MIP F-choline scan is shown in Fig. 33.27A, and coronal PET and PET-CT sections are shown in Fig. 33.27B,C.

**Figure 33.26** A–B: Young patient with bilateral breast implants for cosmetic reasons. Unlike most patients, who do not show increased FDG uptake around the implant, there is substantial FDG activity present, which suggests chronic inflammation. C: Note the implants on the corresponding CT scan.

**Figure 33.27** A–C: Normal appearance of F-choline, including strong uptake into the liver and the kidneys and less uptake into the bowel and salivary glands. There is some activity remaining at the injection site and in the surrounding vessels (A) MIP F-choline PET (B) F-choline coronal PET and PET-CT (C). D: Normal appearance of F-ethyl-tyrosine (in MIP image), showing no marked activity anywhere except in the renal collecting system and the bladder.
F-choline does not pass the blood–brain barrier, and thus little activity is noted in the brain. The compound is cleared rapidly from the circulation, and thus heart and blood vessels show little F-choline uptake, except for the vessels immediately proximal to the injection site (in Fig. 33.27A, the right arm). The lungs also show no uptake. Excretion through the kidneys starts rapidly, and hence, very much as in FDG scans, the renal collecting system (Fig. 33.27A–C) and the bladder are seen, the latter after 3 to 6 minutes if the scan is not started in this region. The organs taking up most choline are the liver, the spleen, and the stomach. The uptake in these organs is so strong that hot lesions in these organs may escape detection, just as FDG-avid lesions in the brain may escape detection. There is also some bowel uptake and bone marrow uptake, like in FDG scans. There is prominent uptake in the salivary glands.

18F-Ethyl-Tyrosine and Other Agents

FET static scans, like FDG scans, are acquired at around 60 minutes postinjection. Therefore, in essence, a static distribution of activity is seen (Fig. 33.27D). FET does not pass the blood–brain barrier, and thus little activity is noted in the brain. The remainder of the body takes up little FET, although there is slightly more activity in the liver and the spleen than in the other structures.

Other PET tracers are not discussed here. Details are given in later chapters where appropriate.

SPECT and SPECT-CT Imaging Agents

It is beyond the scope of this book to discuss the normal uptake patterns of single-photon imaging agents used in SPECT. These uptake patterns are well known and can be found in any standard nuclear medicine textbook, to which the reader is referred. Specific issues are addressed in the chapters containing SPECT and SPECT-CT information. Notably, SPECT and SPECT-CT are of relevance in brain imaging and cardiac imaging, as discussed in previous chapters. The current state of the art in SPECT and SPECT-CT imaging is very different from that in PET and PET-CT imaging, because the spatial resolution and temporal resolution of SPECT is much inferior to those of PET. Thus, in only a few instances are whole- or partial-body SPECT scans acquired. Rather, whole- or partial-body planar images are obtained, and a body region worthy of further analysis is then subjected to SPECT scanning.

In our practice, the single-photon imaging agents used in body imaging most relevant for SPECT and SPECT-CT are the following. One group contains iodine and iodine analogs, lung and sentinel node agents, and Tc-sestamibi and Tc-thallium for tumor detection, inflammation marking, and MIBG scans. In this group, no clinical PET compound having very similar properties is widely available or could be made available relatively quickly, except for 124I, which cannot be used in human diagnostic applications for radiation safety reasons. The other group most notably contains the Tc-based bone-seeking agents and indium octreotide. These agents could be relatively quickly replaced by fluoride-derived compounds and Ga-octreotide-derived compounds or F-Dopa, respectively.

OUTLOOK

In this chapter, much information has been given on the normal distribution patterns of FDG. FDG is by far the dominant compound in clinical practice in terms of frequency of use in body scanning applications. Its use is probably only paralleled by the use of bone-seeking agents, but most examinations with these agents are not yet performed in a tomographic mode. Although FDG will remain the “PET workhorse” for the next 5 years, other PET compounds are emerging, most notably choline analogs. This is why some information was given on their distribution pattern. It is interesting to speculate on what will happen with the other compounds. My guess is that whenever a costly SPECT compound is replaceable by a PET compound in the foreseeable future, the replacement will occur rather quickly, because of the improved quality of the PET over SPECT imaging. In other situations, like in bone scanning, fluoride is readily available, but the cost of PET bone scanning is so high compared with standard bone scanning that the introduction of fluoride PET scanning on a large scale is not imminent. As SPECT gets a developmental boost from the introduction of higher-performance SPECT-CT cameras, we may yet see a resurgence of SPECT applications not considered so far. Promising clinical applications are discussed in some chapters in this book, and these involve perfusion and sentinel node agents, among others.

In conclusion, a further edition of this book may require substantially more extensive discussions of the normal scan appearance of other agents, but for the time being I believe the information selected for inclusion is appropriate for most daily clinical practice work.

REFERENCES


FDG-PET-CT in Head and Neck Cancer

Christina M. Thuerl  Hugh D. Curtin

Head and neck cancer is an important topic in oncologic imaging, because imaging findings can aid significantly in the detection, staging, and treatment evaluation of these tumors. Positron emission tomography (PET) and PET–computed tomography (CT) have become routine imaging tools for the evaluation of patients with head and neck cancer, with fluorodeoxyglucose (FDG) as the most important tracer. For a correct evaluation of the head and neck region, knowledge about the physiological FDG uptake pattern (see Fig. 34.1), artifacts, and pitfalls is important. With the introduction of PET-CT, a spatially more accurate modality can localize increased FDG uptake in primary tumors with certainty. However, T staging of head and neck tumors seems to offer no advantage over conventional imaging methods. T staging by FDG-PET-CT has limitations in small T1 tumors and tumors with superficial spread. Perineural spread, which is common in adenoid cystic carcinoma, can be completely overlooked by FDG-PET-CT. Detection and staging of small tumors can be impaired in areas with physiological uptake of FDG, especially in areas with lymphoepithelial tissue (nasopharynx, palatine tonsils, tongue base).

The sensitivities and specificities of FDG-PET in detecting primary lymph node involvement range between 71% to 93% and 86% to 100% for PET and 53.1% to 82% and 57% to 87.8% for CT–magnetic resonance imaging (MRI). False-negative FDG-PET studies can occur if there is only a small tumor burden in metastatic nodes and also if necrotic nodes maintain only a small rim of viable tumor tissue, seen frequently in squamous cell carcinoma. These nodes can be completely missed by FDG-PET and unenhanced FDG-PET-CT alone.

A major advantage of whole-body FDG-PET-CT is that it improves the detection of distant metastases, second primary tumors, and local recurrence. As a rule, clinically detectable recurrent disease is extremely unlikely in the setting of an entirely negative PET-CT scan. False-positive findings are related to inflammation, infection, or radiation necrosis. First results suggest that the integration of FDG-PET-CT into the radiation treatment planning process may assist in better differentiating normal tissue from tumor-bearing tissues and in identifying areas of high risk for recurrence. An overview of the anatomy and the tumors of the oral cavity, pharynx, larynx, salivary glands, nasal cavity, and sinuses is provided, along with FDG-PET-CT examples of the different tumors.

INTRODUCTION

Head and neck cancer is the sixth most common cancer in the world, and in the United States it accounts for approximately 3% of all cancers in men and 2% of all cancers in women (1). Squamous cell carcinoma represents more than 90% of all head and neck cancers. The incidence rates are more than twice as high in men as in women and are greatest in men older than 50. The risk of malignancy is 6 times greater for smokers than nonsmokers. The synergistic effect of alcohol and smoking increases the risk of the disease 2.5 times more than the simple additive risk of either risk factor alone. Nasopharyngeal carcinoma is associated with Epstein-Barr virus. Human papillomavirus infection is another factor implicated in the development of oral cavity and oropharyngeal squamous cell carcinoma (2,3). Mutation of the tumor suppression gene p53 is one of the most common genetic alterations in squamous cell
of these tumors. Patients presenting with primary tumors that are confined at the time of initial diagnosis (T1-2N0M0) have an excellent cure rate. Unfortunately, at the time of initial diagnosis many patients already have regional nodal metastases (45%) or even distant metastases (10%) (7). For all stages combined, about 85% of persons with oral cavity and pharynx cancer survive 1 year after diagnosis. The 5-year and 10-year relative survival rates are 59% and 44%, respectively (1). Therefore, the major goals of the evaluation of patients with head and neck cancer is an important topic in oncologic imaging, because imaging findings can aid significantly in the detection, staging, and treatment evaluation of these tumors.

TABLE 34.1
OVERVIEW OF FDG UPTAKE IN THE HEAD AND NECK

<table>
<thead>
<tr>
<th>Overview</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological FDG uptake (9,44)</td>
<td>Variable</td>
</tr>
<tr>
<td>Muscles (tongue, floor of the mouth, palate, masticatory muscle, neck)</td>
<td></td>
</tr>
<tr>
<td>Salivary glands</td>
<td>Variable</td>
</tr>
<tr>
<td>Lymphoepithelial tissue in nasopharynx, palatine, and lingual tonsils</td>
<td></td>
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<tr>
<td>FDG-positive malignant tumors</td>
<td>Most common histology in head and neck tumors Perineural spread can be missed in PET-CT</td>
</tr>
<tr>
<td>Squamous cell carcinoma (45)</td>
<td></td>
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<tr>
<td>Adenoid cystic carcinoma (40)</td>
<td></td>
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<tr>
<td>Single reports</td>
<td></td>
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<tr>
<td>Carcinoma ex pleomorphic adenoma (39)</td>
<td></td>
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<tr>
<td>Mucoepidermoid carcinoma (39)</td>
<td></td>
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<tr>
<td>Acinus cell carcinoma (39)</td>
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<tr>
<td>Esthesioneuroblastoma (43)</td>
<td></td>
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<tr>
<td>Adenocarcinoma of the nasal cavity (own experience)</td>
<td></td>
</tr>
<tr>
<td>FDG-positive benign tumors/lesions</td>
<td>Most common salivary gland tumor Second most common salivary gland tumor Lack of FDG uptake is possible in schwannoma (53). Rim-like FDG uptake of lymphoid tissue can mimic necrotic lymph node metastasis.</td>
</tr>
<tr>
<td>Pleomorphic adenoma (38)</td>
<td></td>
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<tr>
<td>Warthin tumor (37)</td>
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<tr>
<td>Schwannoma (46)</td>
<td></td>
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<tr>
<td>Branchial cleft cyst (own experience)</td>
<td></td>
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<tr>
<td>FDG-negative malignant tumors</td>
<td>Even large high-grade adenocarcinomas are negative. One single report of FDG-positive distant metastases, not histologically proven (39).</td>
</tr>
<tr>
<td>Chondrosarcoma (own experience)</td>
<td></td>
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<tr>
<td>Adenocarcinoma of major salivary glands (own experience)</td>
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<tr>
<td>FDG-uptake in post-therapeutic changes</td>
<td></td>
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<tr>
<td>Inflammatory changes after radiation therapy (47)</td>
<td></td>
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<tr>
<td>Radio-osteonecrosis (48)</td>
<td></td>
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<tr>
<td>FDG-positive lesions of the thyroid gland</td>
<td>Biopsy is recommended in cases with focal FDG uptake, since incidental focal FDG uptake is associated with thyroid cancer in 27% to 80% of the cases (50,51,54).</td>
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<tr>
<td>Hashimoto thyroiditis (49,50)</td>
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<tr>
<td>Papillary thyroid cancer (39,50,51)</td>
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<tr>
<td>Follicular thyroid cancer (39)</td>
<td></td>
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<tr>
<td>Hürthle cell carcinoma (39,50)</td>
<td></td>
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<tr>
<td>Nodal hyperplasia (39)</td>
<td></td>
</tr>
<tr>
<td>Follicular thyroid cancer (39)</td>
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<tr>
<td>Medullary carcinoma (52)</td>
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</table>

carcinomas of the head and neck (4–6). Chewing betel nuts, particularly when mixed with tobacco, serves as a local irritant of oral mucosa and therefore a stimulant to the formation of malignancies. Wood dust and woodcarving have been implicated in the increased incidence of nasopharyngeal malignancies, as has the ingestion of smoked fish, particularly in parts of Asia.

Head and neck cancer is an important topic in oncologic imaging, because imaging findings can aid significantly in the detection, staging, and treatment evaluation of these tumors. Patients presenting with primary tumors that are confined at the time of initial diagnosis (T1-2N0M0) have an excellent cure rate. Unfortunately, at the time of initial diagnosis many patients already have regional nodal metastases (45%) or even distant metastases (10%) (7). For all stages combined, about 85% of persons with oral cavity and pharynx cancer survive 1 year after diagnosis. The 5-year and 10-year relative survival rates are 59% and 44%, respectively (1). Therefore, the major goals of the evaluation of patients with head and
neck cancer are locoregional staging, exclusion of distant metastases, and synchronous second primary tumors. Already in 1988, Minn et al. described increased uptake of fluorodeoxyglucose (FDG) in patients with tumors of the head and neck (8).

**PHYSIOLOGICAL FDG-UPTAKE AND ARTIFACTS IN PET-CT OF THE HEAD AND NECK**

FDG is not specific for neoplastic processes in head and neck. It accumulates physiologically in various regions of head and neck (Table 34.1) (9). Low to strong FDG uptake occurs in the normal lymphoepithelial tissue of the nasopharynx and oropharynx (Fig. 34.1A,B), the palatine tonsils (Fig. 34.1H), and at the base of the tongue (Fig. 34.1I). Variable but usually low FDG uptake is visible in the salivary glands, which physiologically secrete low amounts of glucose (Figs. 33.21 and 34.1D,E). Muscular FDG uptake can be seen in the palate (Fig. 34.1C); in the floor of the mouth (Figs. 33.21G and 34.1E); in the tip of the tongue (Fig. 34.1F); in muscles of the face (Fig. 34.1H); in muscles of the larynx (Fig. 34.1J); in the vocalis muscle (Fig. 34.1K); in nervous patients; and in patients who speak during the FDG-uptake phase. However, physiological uptake in the laryngeal muscles is usually symmetric and can be discriminated from cancer. In patients with laryngeal nerve palsy, glottic muscle uptake on the healthy side can be observed (see Fig. 34.22). If patients do not close their eyes during the study, muscles of the eyes and eyelids will also show increased uptake.

Postsurgical changes that distort the normal anatomy after resection and surgical reconstruction can elicit atypical muscle activity (Fig. 34.2). Other reasons for FDG uptake not related to tumor are inflammation, infection, and radiation necrosis.

In patients with head and neck cancer, dental problems are common. If disease of the dental roots and/or periodontal space is present, the teeth will be surgically removed before starting radiation treatment. This will cause an inflammation reaction in the jaw, which can be visible in FDG-PET-CT for several weeks. Inflammation can mimic a malignant lesion, and it is important to interpret images in the light of adequate clinical information.

Dental metal work also causes artifacts. Nonremovable metal dentures, bridgework, and fillings will produce a defect in the emission image that can also be seen in the final attenuation-corrected image (9,10). However, most malignant lesions avidly take up FDG and therefore are usually identifiable without problems. In addition, attenuation correction by means of a CT scan can be deteriorated due to dental metalwork, which can mimic FDG uptake in the dentition.
uptake in attenuation-corrected images (11). Measurement of SUV values can be influenced by these artifacts. Therefore, measurements of FDG concentrations in areas adjacent to nonremovable dentures may be of limited value. Based on our experience, we feel that additional viewing of the non-attenuation-corrected emission scans can render image interpretation of oral pathologies with PET more reliable.

**IMAGING GOALS**

**T Staging**

The first goal of imaging studies is to determine the extent of the primary tumor, in particular with regard to structures whose involvement may alter the surgical approach. Since anatomical information is lacking, FDG-PET has only very limited value in T staging in head and neck cancer. But the introduction of PET-CT, which is a spatially more accurate modality, has meant that increased FDG uptake can be localized with certainty. However, in our experience T staging of head and neck tumors by FDG-PET-CT seems to offer no advantage over conventional imaging methods. Even in PET-CT, the exact size of the tumor is not demonstrated by the FDG uptake, since the elevated FDG activity appears as a spot with blurring.

Quantitative measurement of FDG uptake by means of the standard uptake value (SUV) or other indices is possible and is performed as part of a routine protocol in some institutions. No diagnostic threshold has been clearly established for distinguishing uptake in malignant tumors from that in benign tissues, and in cancer cases no cutoff has been established for defining subgroups of differing prognoses. Previous clinical series suggest a wide range of cutoff values (3.5 to 10) predicting a worse prognosis (12–17).

T staging of head and neck tumors by FDG-PET-CT has limitations in small T1-tumors and tumors with superficial spread. These tumors can be completely missed in FDG-PET-CT (18). Perineural spread, which is common in adenoid cystic carcinoma, can be completely overlooked by FDG-PET-CT. Detection and staging of small tumors can be impaired in areas with physiological uptake of FDG (see Fig. 34.1), especially in areas with lymphoepithelial tissue (nasopharynx, palatine tonsils, tongue base) (19). FDG-PET-CT has also limited value in defining intracranial extension of tumors because of the lack of contrast between the FDG avid brain and tumor tissue. For preoperative staging, which includes a depiction of the relationship of the tumor to vessels and the correct delineation of infiltrated structures in the complex head and neck region, contrast-enhanced CT or MRI is mandatory.

**N Staging**

An important goal of PET-CT is the assessment of the nodal status in the neck. The presence of nodal metastases is an independent prognostic factor for survival in patients with head and neck cancer. It decreases the overall survival by approximately one half (20). The prognosis worsens additionally with the number of lymph nodes involved (21), with extracapsular spread of nodal disease (22,23), and with metastases located in the lower neck (24). The presence and extent of nodal metastases may affect patient management. Therefore, an accurate nodal staging of the neck is important.

The sensitivities and specificities of FDG-PET in detecting lymph node involvement range between 71% and 93% and 86% and 100% for PET and 53.1% and 82% and 57% and 87.8% for CT and MRI (18,25–27). False-negative FDG-PET studies may occur if there is a small tumor burden in metastatic nodes and if also necrotic nodes maintain only a small rim of viable tumor tissue, which is common in squamous cell carcinoma. These nodes can be completely missed by FDG-PET and unenhanced FDG-PET-CT alone (Fig. 34.3). Therefore, FDG-PET-CT should be performed with contrast material to prevent the missing of small necrotic lymph nodes. In contrast, in patients who present large FDG avid lymph nodes in the neck without any central necrotic area, a differential diagnosis of lymphoma should be considered. Nodal metastases in close proximity to the primary tumor may not be detectable as separate hypermetabolic foci when the primary shows very intense tracer uptake (Fig. 34.4). We have observed that FDG-PET-CT cannot differentiate clearly between necrotic lymph node metastases and branchial cleft cysts, because branchial cleft cyst can contain lymphoid tissue (28), which is FDG avid.
M Staging and Detection of Second Primary Tumors

At the time of initial diagnosis, 10% of the patients already have distant metastases, and there is a 5% annual rate of second primaries, mostly occurring in the upper aerodigestive tract (7). The frequency of distant metastases increases with the T stage and the size and number of tumor-involved lymph nodes. Patients with nodal metastases in the lower neck or supraclavicular region have a higher probability of distant metastases. Therefore, a major advantage of whole-body FDG-PET-CT is that it can detect distant metastases and second primary tumors. In addition, FDG-PET-CT can depict small lung metastases whose size is under the spatial resolution of FDG-PET alone.

Detection of Local Recurrence

The early detection of recurrent head and neck cancer is important for the assessment of the ability to perform salvage surgery, which can improve the clinical outcome for these patients. For instance, patients with recurrent early-stage head and neck squamous cell carcinoma who undergo salvage surgery have a 70% 2-year relapse-free survival rate, whereas those with recurrent advanced-stage head and neck cancer who undergo salvage surgery have a 22% 2-year relapse-free survival rate (29). It is therefore critically important to detect potential recurrences early in the course of events. CT and MRI, which rely on structural changes, are unreliable in this setting because of treatment-related alterations of tissue planes. Often, follow-up scans are necessary to detect tumor growth. However, FDG-PET-CT interpretation may also be complicated because postsurgical changes can involve distortions of the normal anatomy related to resection and surgical reconstruction, along with atypical muscle activity (see Fig. 34.2). Other false-positive findings are related to inflammation, infection, and radiation necrosis. Nonetheless, the overall negative predictive values of all studies are consistently high (30-33). As a rule, clinically detectable recurrent disease is extremely unlikely in the setting of an entirely negative PET-CT scan. Even after a short 6-week period after the end of radiochemotherapy, the sensitivity and specificity of FDG-PET scans were reported to be 90.9% and 93.3%, respectively (34).

Searching for an Unknown Primary Tumor

Unknown primary tumors account for 3% to 15% of all cancer diagnoses and for approximately 1% to 2% of head and neck cancer diagnoses. The entity of an unknown primary tumor should be defined as the combination of no history of previous malignancy, no clinical or laboratory evidence of primary neoplasm, and a neck mass that is...
histologically or cytologically proven to be cancer. The occurrence of nodal metastases in neck levels I–III increases the likelihood of a primary head and neck cancer. PET-CT can be a valuable tool in patients with neck metastases from an unknown primary, provided that patients are appropriately selected. These patients should undergo a thorough head and neck examination by a head and neck surgeon, followed by a FDG-PET-CT scan. In particular, small primaries of the tonsils, tongue base, and the nasopharynx can initially be overlooked in clinical examination. In a review of 16 studies involving a total of 302 patients, FDG-PET detected primary tumors that went undetected by other modalities in approximately 25% of cases and was sensitive in the detection of previously unrecognized regional or distant metastases in 27% of cases (19). (For further discussion, see Chapter 36.)

Radiation Therapy Planning

There are first results hinting at improvements in radiation therapy planning by FDG-PET-CT. It is suggested that the integration of FDG-PET-CT into the radiation treatment planning process may assist in better differentiating normal tissue from tumor-bearing tissues and in identifying of areas of high risk for recurrence (35). In our opinion, the use contrast-enhanced CT in FDG-PET-CT is essential for correct planning as it can prevent the overlooking of necrotic, FDG-inactive lymph node metastases.

FDG-PET-CT OF THE PHARYNX, ORAL CAVITY, LARYNX, SALIVARY GLANDS, AND NASAL CAVITY AND PARANASAL SINUSES

Overview of Head and Neck Anatomy

There is a basic subdivision in the suprathyroid and infrathyroid neck. The suprathyroid neck comprises the nasopharynx, oral cavity, and oropharynx. The larynx and hypopharynx belong to the infrathyroid neck. This subdivision is necessary, since the primary tumors in these areas have different routes of spread, nodal dissemination, and prognosis. The staging schemes promoted by the American Joint Committee on Cancer (AJCC) depend on the space that is involved (36). The localization of lymph nodes is described by levels (Fig. 34.5).

FDG-PET-CT of the Nasopharynx

Anatomy

The boundaries of the nasopharynx are, anteriorly, the posterior nasal cavity and, posterosuperiorly, the lower clivus, upper cervical spine, and prevertebral muscles. Inferiorly, the nasopharynx is divided from the oropharynx by a horizontal line drawn along the hard and soft palates. The mucosa of the nasopharynx contains lymphoepithelial tissue, which shows variable FDG uptake (see Fig. 34.1A,B).
in the Rosenmüller fossa. MRI is the imaging modality of choice for evaluating nasopharyngeal carcinoma, especially for determining the intracranial extension. FDG-PET-CT cannot delineate intracranial tumor extension exactly because of the low contrast between FDG avid brain and tumor tissue. Nasopharyngeal carcinoma can also spread to the oropharynx, anteriorly to the nasal cavity, laterally and posteriorly to the parapharyngeal space, including the carotid region (Fig. 34.6). The lateral retropharyngeal nodes (Rouvière nodes) are the first-order nodes involved in nasopharyngeal cancer, but these nodes cannot be palpated (Fig. 34.7).

Besides nasopharyngeal carcinoma, important differential diagnoses of a nasopharyngeal mass is lymphoid hyperplasia of the adenoids, especially in young patients, and non-Hodgkin lymphoma. FDG-PET-CT cannot differentiate between a malignant nasopharyngeal mass and lymphoid hyperplasia (see Fig. 34.1), whereas lymphoid hyperplasia might be identified by MRI.

**FDG-PET-CT of the Oral Cavity**

**Anatomy**
The oral portion of the upper aerodigestive tract is divided into two major components: the oral cavity and the oropharynx. The borders of the oral portion are the palate and the tip of the epiglottis. The border between the oral cavity and the oropharynx are the anterior tonsillar pillars, the circumvalate papillae, and the junction of the hard and soft palate. The contents of the oral cavity are the oral tongue (anterior two thirds), lips, buccal mucosa, alveolar ridge, retromolar trigone, floor of the mouth, and hard palate. On the palate are located numerous minor salivary glands, but minor salivary glands can be found anywhere in the aerodigestive tract. The floor of the mouth consists of the extrinsic muscles of the tongue (i.e., tongue muscles with bony attachment) and the geniohyoid and mylohyoid muscles. The mylohyoid muscle forms a sling that serves as the main supporting structure. It separates the sublingual space from the submandibular spaces, except along its posterior margin. The contents of the sublingual space are the anterior extension of the hyoglossus muscle, the lingual nerve, the lingual artery and vein, the sublingual gland and ducts, the deep portion of the submandibular gland, and submandibular duct. The nerves and vessels constitute the neurovascular bundle. The contents of the submandibular space are the anterior belly of the digastric muscle, the superficial portion of the submandibular gland, the facial vein and artery and the inferior loop of the hypoglossal nerve (cranial nerve XII), and the submandibular and submental lymph nodes. The submental and submandibular nodes are the first-order nodes of the oral cavity. If the posterior oral cavity is involved, drainage occurs first to the jugulodigastric nodes in level II.

Physiological FDG uptake can be observed in the muscles of the floor of the mouth, in the intrinsic muscles of the tongue, in the tip of the tongue, in the orbicularis oris muscle, and in the salivary glands (see Fig. 34.1). In hyperglycemic patients who have not fasted, diffuse FDG uptake in the tongue may be observed. The lymphatic tissue at the base of the tongue can cause also FDG uptake to a variable extent (Fig. 34.1).

Dental restoration can causes artifacts in this area, with defects in the emission image that can also be seen in the final attenuation-corrected image (9,10). In addition, attenuation correction by means of a CT scan can be distorted due to dental metalwork, which can mimic FDG uptake in the area of the beam-hardening artifacts (11). Based on our experience, additional viewing of non-
attenuation-corrected emission scans can render image interpretation of oral pathologies with PET more reliable.

**Tumors of the Oral Cavity**

The most common carcinoma in the oral cavity is carcinoma of the lips. But these tumors are often small at the time of detection, and imaging is often not required. The second most frequent carcinoma is carcinoma of the tongue, followed by carcinoma of the floor of the mouth, the alveolar ridge and retromolar trigone, the buccal mucosa, and the hard palate. Size is an important criterion for T staging, with inclusion of the adjacent areas involved. However, as mentioned earlier, FDG-PET-CT has no value in T staging small T1 tumors and tumors with superficial spread (18).

The usual site for carcinoma of the tongue is the lateral border of the middle third (Fig. 34.8). Invasion of the tongue base and the floor of the mouth is often clinically occult and can be revealed by FDG-PET-CT (Fig. 34.9). Group I and II lymph nodes are at greatest risk for metastases. It is important to determine if there is extension across the midline, invasion of the floor of the mouth, and secondary mandibular involvement after extension across the floor of the mouth (Fig. 34.10).

Squamous cell carcinoma of the floor of the mouth (Fig. 34.11) is usually located in the anterior half. The relationship of the tumor to the mylohyoid muscle and the involvement of the mandible are important issues in local staging.

Tumors of the alveolar ridge and retromolar trigone (Fig. 34.12) are uncommon. They spread to the mandible and masticator space, where they can invade the cranial nerve V3 with extension to foramen ovale. Maxillary alveolar ridge tumors can invade the maxillary sinus. Buccal tumors spread into the cheeks, bone (Fig. 34.13), and parapharyngeal space. Superficial lesions are often not detected by imaging like PET-CT, MRI, and contrast-enhanced CT.

**Hard palate tumors** are either squamous cell carcinoma (Fig. 34.14) or tumors of the minor salivary glands. Lymphatic metastases occur late due to a paucity of local lymphatics.

**FDG-PET-CT of the Oropharynx**

**Anatomy**

The oropharynx is the region that is visible posteriorly through the open mouth. The contents are the pharyngeal wall, the soft palate, the uvula, the palatine tonsils, the posterior third of the tongue with the tongue base, and the
are second in frequency only to carcinomas of the larynx. The patients often present with lymph node metastases at the time of initial diagnosis. Extension occurs to the base of the tongue, retromolar trigone, parapharyngeal space, and soft palate (Fig. 34.15). An important differential diagnosis is lymphoma (Fig. 34.16). Lymphoma and squamous cell carcinoma cannot be differentiated by FDG uptake. The second most common oropharyngeal carcinoma is carcinoma of the base of the tongue, including the vallecula. In carcinoma of the vallecula, the pre-epiglottic space, which is a clinical blind spot, is at risk for invasion (Fig. 34.17). It can be very difficult or impossible to detect small tumors in the palatine tonsils and in the base of the tongue because of the physiological FDG uptake in these regions (see Fig. 34.1).

Soft-palate tumors (Fig. 34.18) can be difficult to image, even in contrast-enhanced CT and MRI. In FDG-PET, a differential diagnosis is muscle activity (see Fig. 34.1). Therefore, it is important to take clinical information into account if high FDG uptake is observed in the palate. Tumors of the soft palate have a propensity for early metastases, and bilateral metastases may exist at presentation. A clinical symptom is a sore throat.

Oropharyngeal posterior wall tumors are uncommon and spread early laterally to involve parapharyngeal and masticator spaces (Fig. 34.19B). Extension to the tongue base and the floor of the mouth can also occur (Fig. 34.19C). It is important to evaluate the CT scan to detect signs of infiltration of adjacent structures, which are obliteration of fat planes and contrast enhancement of the tissue.

**Oropharyngeal Tumors**

One of the most common carcinomas of the head and neck is carcinoma of the palatine tonsil. These carcinomas

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Figure 34.10  Carcinoma of the tongue with crossing of the midline (yellow arrow) and tongue base infiltration (white arrow). Lymph node metastasis in level II. Activity in the orbicularis oris muscle.

Figure 34.11  Squamous cell carcinoma of the anterior floor of the mouth (A) close to the mylohyoid muscle (arrow in B) and the mandible. (See also Cases 39 and 40.)
FDG-PET-CT of the Hypopharynx

**Anatomy**

There are three subsites of the hypopharynx: the piriform sinus, the postcricoid area, and the posterior hypopharyngeal wall. The superior margin of the hypopharynx is at the level of the pharyngoepiglottic fold.

The apex of the piriform sinus is located at the level of the cricoarytenoid joint. The medial border of the piriform is the aryepiglottic fold, which itself is part of the supraglottis.

The postcricoid area is located behind the cricoid cartilage and permits passage of food into the esophagus. The hypopharynx is provided with a rich lymphatic plexus. Therefore, lymph nodes metastases are common in hypopharyngeal carcinoma.

**Hypopharyngeal Tumors**

The most common subsite of hypopharyngeal carcinoma is the piriform sinus. The hypopharynx is often a clinically
Figure 34.14  Squamous cell carcinoma of the hard palate with osseous destruction (A and B) and infiltration of the maxillary sinus and nasal cavity (C).

Figure 34.15  Squamous cell carcinoma of the palatine tonsil with spread to the retromolar trigone, tongue base, and parapharyngeal space (yellow arrows). A: Unenhanced CT. B: FDG-PET-CT. C: Axial FDG-PET. (See also Cases 37 and 38.)

Figure 34.16  Follicular lymphoma grade III with nodal involvement in level II (arrow in A) and extranodal involvement of both palatine tonsils (A) and the right orbita (B).
silent area. Therefore, tumors are often in an advanced stage at the time of diagnosis, with a high rate of malignant adenopathy at presentation (greater than 50%). Hypopharyngeal carcinomas drain to lymph nodes in levels II–V and to retropharyngeal nodes (Fig. 34.20). The tumors are unresectable if the prevertebral fascia is infiltrated (Fig. 34.21). Postcricoid carcinomas are rare, and women with Plummer-Vinson syndrome (iron-deficiency anemia and dysphagia) have a propensity for these tumors.

**FDG-PET-CT of the Larynx**

**Anatomy**

The larynx belongs to the infrahyoid neck and separates the trachea from the upper aerodigestive tract. It is the voice box and an important regulator of respiration. The larynx is subdivided in three subsites, the supraglottic larynx, the glottis, and the subglottis, and it originates from two different embryological parts. The supraglottis develops from the buccopharyngeal “anlage” and has rich lymphatic pathways. The glottis and the subglottis are derived from the tracheobronchial buds and have fewer lymphatic vessels. Therefore, lymph node metastases are more frequent in the supraglottis than in the glottis and subglottis. The supraglottis comprises the epiglottis, the aryepiglottic fold, the arytenoid cartilages, the false vocal cords, the ventricle, and the pre-epiglottic and paraglottic spaces. The pre-epiglottic and paraglottic spaces contain fat and are clinical blind spots. No fascia confines tumor spread in cases of deep infiltration.

The glottis consists of the true vocal cords, along with the glottic muscles, and includes the anterior and posterior commissures. Patients who have spoken during the uptake phase present with FDG uptake in the glottic muscles (see Fig. 34.1). In cases of a palsy of the recurrent nerve, unilateral
Figure 34.19  A: Large bilateral oropharyngeal squamous cell carcinoma (T4a) with infiltration of the soft palate and the medial pterygoid muscle. B: Obliteration of the fat plane (arrow) in the unenhanced CT scan. C: Infiltration of the tongue base and the floor of the mouth in the same patient, with lymph node metastasis in level II not detected by contrast-enhanced CT.

Figure 34.20  A: Hypopharyngeal tumor of the left sinus and posterior wall clinically fixed to the hemilarynx. B: Slight osteosclerosis of the thyroid cartilage (arrow) as sign of beginning infiltration of thyroid cartilage. C: Lateral retropharyngeal lymph node metastasis (Rouviere node). (See Cases 36 and 53.)

Figure 34.21  Hypopharyngeal carcinoma. A: FDG-PET-CT with contrast-enhanced CT. B: Contrast-enhanced CT with suspicion of infiltration of the prevertebral fascia (arrow).
FDG uptake of the glottic muscles can be observed (Fig. 34.22). The anterior commissure, where the two vocal cords converge, is an important structure. In case of tumor invasion, all neighboring structures are at risk for neoplastic destruction.

The subglottis is the area below the true cords, and it extends to the inferior border of the cricoid cartilage. Normally no tissue can be seen between the cricoid cartilage and the mucosa.

There is an intimate relationship between the larynx and the hypopharynx (Fig. 34.23).

The cartilaginous skeleton consists of the epiglottis, the thyroid cartilage, the arytenoid cartilage, and the cricoid cartilage, which make a complete ring. The epiglottis, as part of the supraglottic larynx, prevents aspiration during swallowing. An early sign of invasion of the cartilaginous skeleton is sclerosis. Later, osteolysis can occur. The larynx is innervated by branches of the vagal nerve (i.e., the superior laryngeal nerve and the recurrent laryngeal nerve).

**Tumors of the Supraglottic Larynx**

Laryngeal carcinoma is the most common head and neck cancer. In epiglottic carcinoma, a side-to-side symmetric enlargement of the epiglottis can often be observed. Tumor spread occurs to the paraglottic and pre-epiglottic spaces (Fig. 34.24). Since FDG uptake can overestimate the extension of the disease, and an unenhanced CT scan is not sufficient, contrast-enhanced scans are necessary to define the extension of the disease (Fig. 34.25).

The aryepiglottic fold is a common site for a supraglottic carcinoma (Fig. 34.26), which can spread posteriorly to the piriform sinus and anteriorly to the false vocal cords, to the base of the epiglottis, and into the paraglottic space.

The false vocal cords are an uncommon site for supralaryngeal tumors (Fig. 34.27). False vocal cord tumors can spread to the true cord level, to the medial wall of the piriform sinus, to the inferior base of the epiglottis, and rarely via the true cord level to the thyroid cartilage.

**Glottic Tumors**

Carcinoma of the true vocal cords is much more common than supraglottic carcinoma (the ratio of glottic to supraglottic tumors is 3:1). The patients present with hoarseness, and the tumors are usually detected earlier than in other locations. Since the risk of nodal spread is low in T1 lesions (less than 5%), FDG-PET-CT imaging is rarely performed in small lesions. In case of tumor invasion of the anterior commissure (Fig. 34.28), all neighboring structures are at risk for infiltration: the contralateral cord, the thyroid cartilage, the subglottis, and the paraglottic space.

**Tumors of the Subglottis**

Approximately 5% of the laryngeal carcinomas are subglottic. The subglottis is a clinically silent area, and lesions become large and invasive prior to discovery (Fig. 34.29).

**FDG-PET-CT of the Salivary Glands**

**Anatomy**

The major salivary glands are paired structures: the parotid, submandibular, and sublingual glands. The minor salivary glands are located in the mucosa of the upper aerodigestive tract. They are located in the soft and hard palate, the oral...
cavity, the nose and paranasal sinuses, and the larynx and hypopharynx. Aberrant locations are the thyroid, mandible, middle ear, and sella turcica.

**Tumors of the Salivary Glands**

FDG-PET does not aid in differentiating between benign and malignant salivary gland tumors (37). Pleomorphic adenoma, the most common benign tumor, is FDG avid (38). The second most common benign tumor of the parotid gland, Warthin tumor (also called adenolymphoma and cystadenolymphoma), also shows high FDG uptake (Fig. 34.30). A Warthin tumor may be unilateral or bilateral, solitary or multiple, and is often observed in smokers.

There is a large variety of histological types in malignant salivary gland tumors, and data are limited regarding the FDG uptake of the different histological types. The most common malignant neoplasms of the salivary glands are mucoepidermoid carcinomas, carcinomas ex pleomorphic adenoma, and adenoid cystic carcinomas. Less common are adenocarcinomas and squamous carcinomas. Duct carcinomas are rare undifferentiated carcinomas. Mucoepidermoid carcinoma, carcinoma ex pleomorphic adenoma, acinic cell carcinoma, and adenoid cystic carcinoma are...
FDG avid (39,40). Adenoid cystic carcinoma is known for its tendency to spread perineurally, along the cranial nerves or along vessels. FDG-PET-CT has limited value in local staging of adenoid cystic carcinoma, because it fails to depict perineural spread due to the low tumor burden per volume, but it may be useful in the detection of distant metastases (Fig. 34.31). Noteworthy is that not all distant metastases present with elevated FDG uptake. In our experience, FDG-PET-CT can be negative in adenocarcinoma of the salivary glands, even in high-grade tumors.

**FDG-PET-CT of the Nasal Cavity and the Sinuses**

**Anatomy**

The nasal cavities are pyramidal structures divided in the sagittal midline by the nasal septum. The apex of the pyramid is limited by the cribriform plate of the ethmoid bone. The floor is the hard palate, and the sides are made up of the lateral nasal walls. The lateral walls contain the superior, middle, and inferior turbinates and air spaces between

![Figure 34.26](image1) **A:** PET-CT showing carcinoma of the aryepiglottic fold. **B:** Unenhanced CT demonstrating thickened aryepiglottic fold (arrow).

![Figure 34.27](image2) **A:** PET-CT of the right false vocal cord. Ipsilateral necrotic lymph node metastasis in level III and rim-like FDG uptake. **B:** Unenhanced CT.
the turbinates, with multiple ostia draining the sinuses. The inferior meatus receives anteriorly the nasolacrimal duct. The sphenopalatine foramen is located in the high posterior lateral wall of the nasal fossae and allows passage of lateral nasal and sphenopalatine nerves and vessels. It is a potential pathway for tumor spread toward the pterygopalatine fossa. However, FDG-PET-CT often fails to reveal perineural tumor spread.

The lymphatics of the posterior half of the nasal fossae drain to retropharyngeal and internal jugular vein nodes. In contrast, drainage of the anterior half of the nasal fossae is to the submandibular lymph nodes.

The paired frontal sinuses are located in the frontal bone. The inferior wall of the frontal sinus is the anterior roof of the orbit. Its posterior wall is the wall of the anterior cranial fossa. The ethmoidal complex is grouped as anterior, middle, and posterior ethmoidal cells. The thin lateral wall separating the ethmoid air cells from the orbit is called the "lamina papyracea." The proximity of the orbital apex and optic nerve can lead to loss of vision in inflammatory lesions or tumors.

The floor of the sphenoid sinus is the roof of the nasopharynx. The sinus roof is in relationship to the anterior cranial fossa, the optic chiasm, and the sella turcica. The lateral wall is related to the orbital apex, the optic nerve, and the cavernous sinus. The clivus is posteriorly situated.

The maxillary sinuses develop, for the most part, symmetrically within the body of the maxillary bone on each side. The roof of the maxillary sinus is the floor of the orbit. The canal for the maxillary nerve lies in its middle third, and the anterior facial wall is perforated, 1 cm below the orbital rim, by the infraorbital foramen. The medial central wall is the inferolateral wall of the nasal cavity. The posterior wall abuts the retromaxillary fat pad and the pterygopalatine fossa.
Cancer of the Nasal Cavity and the Paranasal Sinuses

Cancers in the nasal cavity and paranasal sinuses are uncommon. Most cancers present late, with symptoms such as nasal obstruction and epistaxis. Tumor spread through the sphenopalatine foramen may result in perineural infiltration of cranial nerve V2, resulting in paresthesia over the cheek. In our experience, FDG-PET-CT is limited in its depiction of perineural tumor spread. Squamous cell carcinoma accounts for greater than 80% of all malignant tumors of the nasal cavity and paranasal sinuses (41). The others include adenocarcinomas and carcinomas of the minor salivary glands (see “FDG-PET-CT of the Salivary Glands” above), malignant bone or chondroid tumors, esthesioneuroblastoma (olfactory neuroblastoma), non-Hodgkin lymphoma, and melanoma. Melanoma in the anterior part of the nasal cavity is more difficult to detect by FDG-PET than in the posterior sinonasal complex because of possible interference with nonspecific uptake in muscles of the mouth (42).

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Chapter 34: FDG-PET-CT in Head and Neck Cancer


Sentinel Node Imaging in Head and Neck Tumors

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Sentinel node biopsy for head and neck squamous cell carcinoma seems to be able to accurately stage the cN0 neck and to select patients who benefit from elective neck dissection. The goal of sentinel node biopsy is to avoid unnecessary neck dissections in clinically N0 patients and thus decrease patient morbidity and health care costs. The average rate for detecting a sentinel node with lymphoscintigraphy and the intraoperative use of a handheld gamma probe is 95% to 100%. In the head and neck region, where lymphatic drainage patterns are of greater complexity and the primary sites close to the first-echelon node, integrated single-photon emission computed tomography (SPECT)–computed tomography (CT) imaging is thought to be of value in that it provides the surgeon with a more accurate roadmap by precisely defining the drainage basins and the sentinel node localization. SPECT-CT enhances topographic orientation and diagnostic sensitivity, with more sentinel nodes being detectable than by planar lymphoscintigraphy alone. We suggest that planar imaging should be accompanied by iterative reconstructed SPECT-CT to identify lymph nodes adjacent to the primary lesion. Such nodes are easily overlooked by planar lymphoscintigraphy and intraoperative gamma probes, as the high activity at the injection site can obscure their detection (see Fig. 35.1).

INTRODUCTION

Metastatic involvement of cervical lymph nodes is the most important prognostic factor for patients with head and neck squamous cell carcinoma. With the occurrence of neck metastases, the survival rate drops by 50%. Clinically apparent lymph node metastases have to be treated by surgery or radiation or a combination of both. The management of the cN0 neck is still controversial, although most centers advocate elective neck treatment, as the risk of occult metastases in head and neck squamous cell carcinoma is greater than 20% to 30% (1). Given these figures, as many as 70% of patients with a cN0 neck will undergo an unnecessary neck dissection. Sentinel node biopsy (SNB) has been introduced for the treatment of early oral and oropharyngeal squamous cell carcinoma and has shown promising results (2,3). Sentinel node biopsy seems to be able to accurately stage the cN0 neck and appropriately select patients who will benefit from elective neck dissection. The goal of sentinel node biopsy is to avoid unnecessary neck dissections in clinically N0 patients and thus decrease patient morbidity and health care costs.

Lymphatic mapping for the localization of the sentinel nodes includes preoperative lymphoscintigraphy. Lymphoscintigraphy assesses the individual lymphatic drainage pattern (4,5). In head and neck squamous cell carcinoma, the first successful sentinel node biopsy after lymphoscintigraphy was performed in 1996 (6). Since then, many other
centers have adopted the technique and published promising results (7). The average rate for detecting a sentinel node with lymphoscintigraphy and the intraoperative use of a handheld gamma probe is 95% to 100%. Most authors stress that preoperative lymphoscintigraphy is pivotal in guiding the surgeon to the sentinel nodes and in visualizing unexpected drainage patterns (8). Different authors (9,10) share this opinion in the case of squamous cell carcinoma and melanoma of the head and neck, reporting on unpredictable sentinel lymph node sites that would not have been addressed by routine elective lymph node dissection.

In a recently published report (7), the negative predictive value of a negative sentinel node in oral and oropharyngeal HNSSC was 96%. The same paper analyzed the published literature, from which a negative predictive value of 98% was calculated. The authors conclude that sentinel node biopsy for early oral and oropharyngeal squamous cell carcinoma is technically feasible, accurate, and validated.

**SPECT-CT IN SENTINEL NODE IMAGING**

**Sentinel Node Injection Technique**

For lymphatic mapping of the sentinel node, different tracers and techniques have been used. At our institution, technetium 99m (99mTc)-labeled protein particles (Nanocoll) are used as a radiotracer. The particles are between 20 and 80 nm. Small particles are expected to drain fast through the lymphatic vessels and to accumulate early in the sentinel node. The radiotracer is injected 2 hours prior to surgery in a submucosal fashion around the tumor. In most cases, four injections, each containing 10 to 20 MBq of 99mTc in a volume of 0.1 to 0.2 mL, are sufficient to surround the tumor. The lymphatic drainage is monitored dynamically with a gamma camera until the first echelon appears on the screen. This usually takes only 5 to 10 minutes. Lymphoscintigraphic planar imaging in the anterior and lateral projection is used to detect the sentinel node and to mark its localization on the patient’s skin. Then, the patient is transferred to the single-photon emission computed tomography (SPECT)–computed tomography (CT) scanner.

**Imaging**

Since the images obtained by lymphoscintigraphic planar imaging provide views only in anterior or lateral projection, only basic orientation, with little spatial information on the location of the sentinel nodes, is provided. According to reports, in cases where the sentinel nodes are located in close proximity to the primary tumor site, difficulties in detection occur. The presence of radioactive scatter originating from the injection site can obscure the localization of the radioactive sentinel lymph nodes (11,12). For head and neck squamous cell carcinoma, the floor of mouth, with its close relation to nodes in neck level I, has emerged as a problematic primary site for sentinel node mapping in several studies (13).

SPECT imaging of sentinel lymph nodes has been introduced as a means of improving spatial resolution and orientation (14). However, sentinel nodes detected with this technique still cannot be imaged in relation to anatomical landmarks. In the head and neck region, where lymphatic drainage patterns are of greater complexity and the primary sites are close to the first-echelon node, SPECT-CT imaging is thought to be of value in that it provides the surgeon with a more accurate roadmap by precisely defining the drainage basins and the sentinel node localization. SPECT-CT enhances topographic orientation and diagnostic sensitivity, with more sentinel nodes being detectable than by planar lymphoscintigraphy alone (15) (Fig. 35.1). In a group of patients with cutaneous melanoma and squamous cell carcinoma, SPECT-CT was able to identify sentinel lymph nodes missed on conventional lymphoscintigraphy, adding clinically relevant data for 50% of patients with trunk melanoma and 44% of patients with head and neck carcinoma (16). The literature on SPECT-CT for sentinel node biopsy in head and neck squamous cell carcinoma is still scant, but data from the few published studies show that SPECT-CT improves the accuracy of preoperative assessment, especially for difficult sites like the floor of mouth (15).

At our institution we feel that SPECT-CT in combination with planar lymphoscintigraphy helps the surgeon to identify the sentinel nodes with greater accuracy. We suggest that planar imaging should be accompanied by iterative reconstructed SPECT-CT to identify lymph nodes adjacent to the primary lesion. Such nodes are easily overlooked by planar lymphoscintigraphy and intraoperative gamma probes, as the high activity at the injection site can obscure their detection (15) (see Fig. 35.1A). In addition, the anatomical information provided by SPECT-CT is important for precise detection and accurate localization of sentinel lymph nodes. In the near future, further improvement in anatomical localization will be achieved when the older conventional SPECT-CT cameras with low-dose, nondiagnostic CT are replaced by modern cameras with multidetector CT scanners.

*Figure 35.1* A: Right Lateral planar image of lymphoscintigraphy after injection of 70 MBq of 99mTc(Nanocoll in a patient with squamous cell carcinoma of the floor of the mouth (pT1). No adjacent lymph node is visible. B: Coronal plane of SPECT-CT demonstrates adjacent sentinel node in level I. Sentinel node resection and pathological examination revealed no lymph node metastasis.
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SPECT-CT and PET-CT of Tumors with an Unknown Primary

Gerhard Goerres

In patients with a metastasis from an unknown primary, the diagnostic workup is directed according to the site where the metastasis was found at presentation. Positron emission tomography (PET) and PET–computed tomography (CT) using fluorodeoxyglucose (FDG) can be used to detect an unknown primary, but to date PET has mainly been evaluated in the setting of patients with squamous cell carcinoma involving neck nodes. It is not well defined when FDG-PET should be used during the clinical workup of a patient: at the beginning or when all other clinical and imaging evaluations failed to identify the primary. Therefore, PET cannot yet be recommended as a routine procedure in all patients with a metastasis from an unknown primary. However, in patients with a metastasis in a neck lymph node, whole-body PET can identify the primary not only in the neck area but also at distant sites in the thorax or abdomen, which often is the primary site of an adenocarcinoma (see Fig. 36.3).

CLINICAL BACKGROUND

A metastatic cancer of an unknown primary has been defined as a biopsy-confirmed malignancy for which the site of origin is not identified by routine clinical workup (1). Metastatic cancer of an unknown primary has also been referred to as MUO (metastasis of unknown origin), CUO (cancer of unknown origin), and CUP (cancer of unknown primary) syndrome. Patients with metastatic carcinoma from an unknown primary site represent up to 15% of all patients with cancer who present to medical centers and up to 5% of patients with solid tumors referred to the oncologist (2). The mean survival of patients with an unknown primary has been reported to be less than 6 months (3).

The diagnostic workup has to characterize the biology of the tumor and the site of origin as well as the extent of tumor involvement. The approach used to identify the primary site varies depending on the site of metastasis found at presentation. A workup includes a complete history, a physical examination, routine laboratory tests, and imaging. Most important is the careful pathologic examination of the specimen, including specialized studies, such as immunoperoxidase staining, evaluation of the receptor status, and even electron microscopy. Because the diagnostic workup is directed according to the site of the metastasis found at presentation, if liver metastases are found, for example, further evaluation will center on the search for gastrointestinal tumors. In this case, the workup will include a digital rectal examination with a test for occult blood in the stool, as well as endoscopic evaluation, ultrasonography, or computed tomography (CT), because the patient may suffer from colorectal cancer. In addition, pelvic and breast examinations in women and prostate and testicular examinations in men should always be performed. If, for example, the neck is the site of metastasis, clinical and endoscopic examination of the mouth, nose, paranasal sinuses, pharynx, larynx, and esophagus should be carried out.

In some patients who present with a metastasis, the primary tumor is not unknown, since it is definitively
characterized as a known type of tumor on histopathological grounds. However, the primary site of such an occult tumor is not always detectable. This situation can arise, for example, in women with an axillary metastasis of a breast cancer (4,5) or in patients with melanoma or liver metastases of a neuroendocrine gastrointestinal cancer (6). Another possibility is that the lesion suggested to be a metastasis is in fact the primary site. For example, breast cancer can arise in ectopically localized breast tissue in the axilla, mimicking metastasis. Furthermore, it has been postulated that the primary site may disappear due to an immunologic response of the body, which can occur in patients with melanoma and in patients with a squamous cell cancer of the neck presenting with a lymph node metastasis.

Imaging plays a major role in identifying individuals who are treatable. The search is directed primarily by the site and the histological diagnosis of the metastasis (7). Usually, morphological imaging tests are performed as first-line examinations. Imaging evaluations of the neck, chest, and abdomen using CT, ultrasound, and magnetic resonance imaging (MRI) are used to identify the primary lesion. A chest x-ray is often the first imaging test and can identify a bronchogenic carcinoma as the primary tumor in a patient who presents with a brain metastasis but who has no clinical symptoms pointing to the lung in the first place. Up to 70% of patients presenting with brain metastases from an unknown primary have bronchogenic carcinoma (8). In women with axillary metastasis, mammography with ultrasound and if necessary MR mammography should be performed. In many centers, patients with an unknown primary will undergo CT scanning from the head to the pelvic floor as a first-line "screening" test.

THE ROLE OF CONVENTIONAL NUCLEAR MEDICINE

Although most radiological methods provide structural information on only parts of the body, the molecular imaging tests of nuclear medicine are an ideal adjunct for screening the whole body, which can be relevant for characterizing an unknown primary. For example, whole-body imaging with bone scintigraphy may help to characterize a primary, because a typical pattern of distribution of skeletal involvement, although not specific, may narrow the diagnosis. It has been shown that bone scanning can identify the presence of occult malignancy in patients with musculoskeletal pain, since metastatic cancer is one of the main causes of skeletal pain (9,10). Whole-body imaging with nuclear medicine is often able to identify more lesions than primarily suggested, thus influencing further workup and eventual therapy. Additionally, other nuclear medicine methods, such as gallium 67 scintigraphy, were used to evaluate patients with cancer of unknown origin (11) but have been largely replaced by fluorodeoxyglucose (FDG) positron emission tomography (PET).

Nuclear medicine can provide highly specific information on selected tumors. For example, in a recent study, somatostatin receptor scintigraphy was able to identify the primary site of an unknown neuroendocrine neoplasm in patients with negative results after clinical, radiological, and endoscopic workup (12). In this study, the results of somatostatin receptor scintigraphy lead to relevant changes of patient management and prompted surgical intervention in 17% of the patients (12). The use of single-photon emission computed tomography (SPECT)-CT seems advantageous here, in analogy with the experience with other tumors and PET-CT (see Chapter 43). In patients with suspected recurrent colorectal carcinoma based on tumor marker levels and no clinical and radiological signs of local recurrence or metastases, radioimmunoscintigraphy with monoclonal antibodies has been successfully used. However, to date only a few studies are available that have reported on the use of scintigraphy with radiolabeled antibodies in patients with an unknown or occult primary carcinoma (13). As the sensitivity of radioimmunoscintigraphy is notoriously low and the procedure relatively costly, this method has never gained widespread acceptance.

THE ROLE OF PET AND PET-CT

Many reports suggest that FDG-PET can aid in identifying the primary site in patients with metastasis from an unknown primary cancer. The use of PET in this clinical situation is best documented in patients presenting with a metastasis in the neck (14–30). The primary tumor is most often located in the upper aerodigestive tract. In about one third of the cases with squamous cell carcinoma, the primary is located in the tonsils, but it may also be found in areas that are difficult to inspect clinically, such as the pyriform sinus and the nasopharynx (28,31). Furthermore, the base of the tongue is an area where the identification of small primary tumors can be difficult, since in the lymphatic tissue of the Waldeyer ring there is physiologic low to intermediate FDG uptake (see Figs. 33.13 and 33.21). Because it is possible to miss small primaries with imaging, some authors suggest that tonsillectomy or adenoidectomy is performed routinely in these patients. Others perform panendoscopy with routine biopsies of the base of the tongue, pyriform sinus, and tonsils. Small primaries in areas with physiologically increased FDG uptake, such as the Waldeyer ring, can be missed with PET. PET, like other imaging tests, is not a good tool for detecting small primaries and micrometastases, and therefore primaries with a size of less than 5 mm have rarely been reported in the literature (24). The variability of FDG uptake in the tonsils, adenoid, and salivary glands and also in muscles of the head and neck can
render image analysis difficult and may result in false-positive and false-negative findings.

If the histology of the cervical metastasis shows an adenocarcinoma, the primary can also be located in the thorax, the gastrointestinal tract, or the urogenital tract (32). Therefore, it is important to evaluate the whole body—not only to detect a primary in a distant location but also to find distant metastases or a synchronous secondary tumor. The primary lesion can be found in up to 40% of cases when clinical examination, CT, and MRI are performed together, along with panendoscopy and biopsies (28). However, conventional imaging, ultrasound, CT, MRI, and PET have to be used in an approach tailored to the probable nature of the primary tumor (33).

Many reports on PET imaging for the assessment of patients with cervical metastases from an unknown primary have limitations due to their retrospective design, patient selection, and technical considerations. Usually, patients with various histologies, including squamous cell carcinoma, adenocarcinoma, large cell carcinoma, melanoma, and plasmocytoma, as well as nondefined or undifferentiated cancers, were included in the same study. Dedicated PET cameras and coincidence PET scanners were used for imaging with a wide range of different acquisition protocols (14–30). This hampers the comparability of studies. However, a recent meta-analysis that included 15 studies revealed that FDG-PET has an intermediate sensitivity but a high specificity for the identification of unknown primaries (34). This indicates that only a few false-positive results are obtained, making PET a valuable imaging tool in these patients. Also, in patients with extracervical metastases from an unknown primary, PET has a high positive predictive value for the identification of the primary site (35). The increasing use of combined PET-CT imaging may add a further diagnostic benefit in these patients. Recently, it has been shown that the combined information of PET-CT may further improve the detection of primary cancers (35).

In early studies, the PET scans often covered only a limited field of view of the body, and many of the patients included in these studies underwent a diagnostic workup insufficient for the determination of an unknown primary, which is defined as a biopsy-confirmed malignancy whose site of origin is not identified by routine clinical workup (1). Ideally, a patient with a neck metastasis should undergo clinical evaluation with (pan-)endoscopy and

![Figure 36.1](image-url)  
**Figure 36.1** Coronal PET image (A) of a 76-year-old female patient who had a metastasis in the neck originating from an adenocarcinoma (not visible). There is a focal lesion in the mediastinum (A,B,D). PET-CT was done before endoscopy was performed. The transversal PET (B), CT (C), and coregistered PET-CT (D) images show the primary lesion in the esophagus.
imaging using CT, MRI, or ultrasound before the tumor is called an unknown primary. However, it is not well defined how the routine clinical workup of such patients should be done. If PET is done as the first imaging method in the workup of a patient, the test performance will improve, thus, increasing the likelihood that PET offers a diagnostic benefit. Conversely, in centers where the patients with an unknown primary undergo a comprehensive workup before PET scanning, FDG-PET will likely identify fewer additional primaries. In our hospital, in patients with a neck metastasis from squamous cell carcinoma, panendoscopy with or without biopsy and sometimes tonsillectomy, as well as a contrast-enhanced CT of the neck, will be performed before PET (36).

PET is probably a good additional test if a patient has been examined carefully for a lesion in the head and neck and remains negative. This is especially true for patients with a neck metastasis from an adenocarcinoma, as the primary is often located in the chest or abdomen. An advantage of PET is that it can examine the whole body. Figure 36.1 shows a patient with a metastasis of an adenocarcinoma in the neck and a lesion in the esophagus, which was the primary site as confirmed by endoscopy. In this patient, PET imaging was done rather early in the workup, increasing the likelihood that the diagnostic value of PET scanning would be high. Therefore, it has to be further evaluated if whole-body PET could be beneficial in defined patient subgroups when used as the first imaging test at the beginning of the workup. In patients with a neck metastasis from an unknown primary adenocarcinoma, this approach might even be cost-effective, since the combination of gastrojejunoscopy, colonoscopy, (endoscopic) ultrasound, bowel enema, and contrast-enhanced CT of the thorax and abdomen sum up to be very expensive. PET could be of value as an initial evaluation instrument, reserving extensive workups for patients with negative scans.

In some patients, PET is able to guide further search for the primary, from the chest to the gastrointestinal tract, for example. In patients with a solitary metastasis in the brain, a bronchogenic cancer is frequently detected with chest x-ray or CT. In these patients, PET is usually not performed as a first imaging test. Figure 36.2 shows a case of bronchogenic adenocarcinoma in a patient with a cervical metastasis who underwent PET prior to chest CT. In patients with a melanoma metastasis from an unknown primary, the site of origin on the skin is rarely identified, probably due to the disappearance of the primary tumor. However, FDG-PET can identify further metastases in such patients. Note that not all additional lesions found with PET have clinical consequences. The identification of additional metastases does not necessarily influence the therapeutic approach for a patient who is already slated to undergo systemic treatment.

Another situation is liver metastasis from an unknown primary in the abdomen. Based on our experience, in patients with negative findings in endoscopy, endoscopic ultrasound, CT, and small or large bowel series, the primary tumor is rarely found on PET. Figure 36.3 shows a patient with adenocarcinoma of the stomach and multiple liver metastases. Again, endoscopy was performed after the PET scan in this patient, thus qualifying the effectiveness of PET in this clinical situation. The use of PET in patients with liver metastases from an unknown primary is not well supported by the current literature. However, it is well possible that FDG-PET is of additional benefit in patients not able to undergo CT, MRI, or endoscopy because of individual factors. Therefore, in patients with metastasis from a primary that can be expected to show increased FDG uptake, whole-body imaging with PET is an important adjunct to the common strategies used for the workup (37).

To date, it is not well defined if FDG-PET should be done as a first-line test or be acquired as an additional test in patients with negative results after a standard workup. The relatively high sensitivity and the possibility of whole-body scanning are the strengths of PET. However, other authors suggest that the impact on the therapeutic management of patients scanned using FDG-PET for an unknown primary is small (26,29). Therefore, there is a need for further studies defining the clinical role and the cost-effectiveness of PET in patients with a metastasis from an unknown primary.
CONCLUSION

In patients presenting with a metastasis from an unknown primary, the histology of the metastasis influences the diagnostic workup and should also determine whether a PET scan is planned early or late in the course of the workup. In patients with a neck metastasis from an adenocarcinoma, the likelihood of finding a primary in the thorax or abdomen is relatively higher than in patients with a neck metastasis from a squamous cell carcinoma. However, PET has been incompletely evaluated in settings other than the locating of the primary site in patients with squamous cell carcinoma involving neck nodes, and therefore it cannot yet be recommended as a routine procedure in all clinical situations with unknown primaries. PET scans should be acquired from the head to the pelvic floor to identify not only a primary but also distant metastases. Combined PET-CT seems to further improve the identification of a primary in many patients. However, although the use of PET has been recommended for the evaluation of patients with an unknown primary, to date there are no guidelines available defining when PET is to be performed during the workup and how the histology of a metastasis should influence the role of FDG-PET.

REFERENCES


HISTOLOGIC CLASSIFICATION OF THYROID CANCER

The American College of Surgeons Commission on Cancer conducted a patient care evaluation study of thyroid cancer. This prospective study involved a cohort of thyroid cancer patients admitted to more than 1,500 reporting hospitals in 1996. The histologic classification of thyroid cancers was as follows: 81% were papillary, 10% follicular, 3.6% Hurthle cell, 0.5% familial medullary, 2.7% sporadic medullary, and 1.7% undifferentiated/anaplastic. About 50% of the cohort had ancillary 131I therapy (1). From a nuclear medicine point of view, this breakdown is important because only papillary, follicular, and Hurthle cell cancers are capable of concentrating radioactive iodine. These cancers make up the group of differentiated thyroid cancers.

DIFFERENTIATED THYROID CANCER

Incidence and Prevalence

Differentiated thyroid cancer originates from cells within the thyroid follicle, usually presents as a painless lump in the thyroid gland, and is most often detected at the time of
Molecular Anatomic Imaging

routine physical examination. For reasons that are largely unknown, thyroid cancer incidence is increasing rapidly, and it was predicted there would be 25,690 new cases in the United States during 2005. The total rate of death is not increasing, however, and only 1,490 cases within this cohort were predicted to die (Fig. 37.1). Another interesting feature of this disease is that its course is often relatively long, stretching over many years. For this reason, the prevalence of patients with thyroid cancer is relatively large, and in the United States it is estimated that 327,000 patients are survivors of thyroid cancer; of this group, 47,000 were diagnosed more than 30 years ago. Thyroid cancer is a tumor type that tends to recur (Fig. 37.2). More than 30% of patients will ultimately have recurrent cancer, about 20% by 10 years post-treatment, but with recurrence continuing out to nearly 30 years in some patients.

The concept of low- and high-risk tumors is a useful one in well-differentiated thyroid cancer (Fig. 37.3). The AMES categorization uses age, presence of metastases, extension outside the thyroid gland, and size of tumor greater than 4 cm to differentiate between high and low risk, and the low-risk subpopulation has a survival rate of 98% at 20 years, compared with 54% for the high-risk group (2). Nuclear medicine approaches are most useful in the intermediate- to high-risk group.

Based on the natural history of thyroid cancer, modified by the risk factors described above, the take-home message that can be conveyed to the newly diagnosed and treated thyroid cancer patient is as follows: long-term survival is expected, recurrences do occur until years later, and lifelong follow-up is necessary to detect and properly treat any recurrences that may develop.

A detailed discussion of staging of thyroid cancer according to the AJCC TNM classification is outside the scope of this chapter, but a concise and well-written synopsis is available on the Web at this address: http://www.meb.uni-bonn.de/cancer.gov/CDR0000062913.html#REF_14 (3). For well-differentiated thyroid cancer, age is such a dominant factor in prognosis that patients younger than 45 years can achieve a maximum categorization of stage II, even with metastatic disease. On the other hand, patients older than 45 with extension of cancer locally in the neck obtain a stage IV categorization.

Figure 37.1 A: Thyroid cancer incidence in relationship to the incidence of other common human tumors in the United States in 2005. Thyroid cancer is more common than multiple myeloma and Hodgkin disease, and its incidence is comparable to that of leukemia. B: Thyroid cancer is increasing in incidence for unknown reasons. The increase appears greatest in females. Of interest is the fact that the incidence of death has not increased in the past years and has dropped from about 10% to about 5% of the annual incidence.

Figure 37.2 Risk of recurrence of differentiated thyroid cancer and the effect of thyroid hormone suppression and radioactive iodine 131 (131I) in combination with thyroid hormone replacement therapy (T4 + RRA) is standard therapy in this clinical situation and results in a markedly reduced rate of recurrence.

Figure 37.3 Thyroid cancer risk factors.
Standard Workup in Nuclear Medicine

Thyroid nodules are almost always discovered on physical examination or as an incidental finding on diagnostic imaging for other purposes. The use of radiotracers for evaluating such thyroid nodules is mostly of historical interest in our practice. The reason for this is that fine needle aspiration (FNA) with or without ultrasound guidance provides much more definitive information about the nature of a thyroid nodule.

A certain number of thyroid cancers are incidentally detected as thyroid nodules on positron emission tomography (PET) scanning. In patients being screened for other purposes, particularly within a large oncology practice, it is not uncommon to discover hypermetabolic thyroid nodules on fluorodeoxyglucose (FDG)-PET scans (4). Among 4,136 subjects who had undergone PET scanning for other purposes and whose scans were reviewed for the presence of diffuse or focal FDG uptake, 2.2% had increased thyroid uptake that was incidentally discovered. Of these cases of thyroid uptake, half were focal and half diffuse. Among the patients with diffuse uptake, the majority were shown to have a chronic inflammatory condition of the thyroid. Among those with focal uptake, a neoplasm was diagnosed in the biopsied cases, and half of these masses were malignant. The authors concluded that it is important to follow up with biopsy confirmation for any focal abnormality incidentally discovered in the thyroid during the course of FDG-PET imaging (Fig. 37.4).

Treatment with $^{131}$I

Ablation of Postsurgical Remnant

Patients with intermediate to high risk of well-differentiated thyroid cancer are referred for ablation of thyroid remnant after total thyroidectomy. This practice has been shown to be effective in reducing the probability of recurrence and mortality (5). Outcome was compared in 1,004 patients with well-differentiated thyroid cancer, including a 151 patients who underwent ablation with $^{131}$I. In the $^{131}$I-treated group, tumor recurrence was threefold lower ($p < .001$), and in patients older than 40 years of age at time of diagnosis with primary nodules greater than 1.5 cm, there was a significant reduction in the risk of distant metastases ($p < .002$) and death ($p < .001$). The effective dose of $^{131}$I was examined by separating the $^{131}$I-treated patients into two cohorts: the 43% of patients who received 29 to 50 mCi (mean, 47 mCi) and the 57% who received 51 to 200 mCi (mean, 111 mCi). At mean follow-up of 14.7 years, there was no difference in the rate of recurrence in the patients treated with the two different dose ranges.

General Management and Diagnostic Imaging

Evaluation of the Post–Total Thyroidectomy Patient

In the last 10 years, diagnosis and management of thyroid cancer in the post–total thyroidectomy setting has been modified by several important advances: (a) the widespread use of serum thyroglobulin assays for monitoring treatment response and detecting recurrent disease, (b) the growing use of recombinant TSH as a replacement for induced hypothyroidism prior to $^{131}$I administration, and (c) the use of PET-CT in moderate- to high-risk patients for staging and monitoring treatment response (Fig. 37.5). $^{131}$I continues to be the mainstay of thyroid cancer therapy, as it has been for more than 50 years (6).

There are numerous approaches to the management of the thyroid cancer patient. A practice pattern that has
developed at Memorial Sloan-Kettering Cancer Center is described in Figure 37.5. Typically, the postsurgical patient will be treated with either 100 mCi (no soft-tissue extension or metastatic lymph nodes) or 150 mCi (metastasis or other adverse prognostic features). Once patients have been referred for ablation with $^{131}$I, they are followed for an extended period of time, with more extensive testing at 1 year post-ablation. At the time in their annual testing, if metastatic disease is discovered, they will be re-treated, typically with doses varying from 200 to 500 mCi of $^{131}$I (Fig. 37.6). In order to treat at such high doses safely, we have established a procedure for estimating dosimetry of the whole body and blood and bone marrow. We plan dosing so that the total radiation exposure in any single administration does not exceed 200 cGy to the blood. This dose is approximately equivalent to 80 cGy to the bone marrow. The details of and rationale for this approach have been described (7).

When a patient has extensive metastatic disease, it is important to characterize the localization as a guide to further therapy. Because of the very large dose of $^{131}$I that is administered, there is often excellent diagnostic information to be obtained from a whole-body scan performed 5 to 7 days following the administration. In Figure 37.5B, planar gamma camera images are seen after 250 mCi of $^{131}$I. There is extensive uptake in the thorax, including the lungs, as well as in the axial skeleton and extremities. SPECT is often useful in this situation, as a means of defining the extent of the tumor and in particular its relationship to vital bony structures (Fig. 37.7).

In recent years, an important component of our approach has been to use recombinant TSH for the purpose of preparing patients for treatment, either ablation (7) or therapy (8). We have shown that for diagnosis, ablation, and 1-year outcome of therapy (Fig. 37.8), recombinant TSH is equivalent to hypothyroid preparation for radioiodine therapy. Of course, recombinant TSH is much better tolerated by the patient, and hypothyroid side effects are avoided. It should be noted that these side effects can be severe and may include both somatic and mental dysfunction. For example, hepatic enzyme alteration is common in severe hypothyroidism, and psychotic episodes may be seen. Patients whose jobs require hard physical labor or high mental acuity may be unable to work for several weeks while in the hypothyroid state.

**Integrating PET-CT into Patient Management**

As FDG-PET became more widely utilized, it was recognized that some patients with thyroid cancer had positive PET scans (9–18). There is now no doubt that PET adds significantly to the improvement of thyroid cancer management (19). Patient selection is critical if one is to optimize the use of PET in thyroid cancer. The most common indications for PET are an elevated TG level together with a negative whole-body radioiodine scan (20); a histologic diagnosis of Hürthle cell cancer (21); a restaging of known metastasis (22); adverse risk factors, such as biologically aggressive histology (e.g., tall cell papillary thyroid cancer); and advanced age (23).

Prognostic information from FDG-PET scanning in thyroid cancer (22) is also of interest. One of the most intriguing aspects of FDG-PET scanning is the relationship of uptake to cancer biology. About 15% of patients with well-differentiated thyroid cancer will have metastasis sometime during the course of the disease. Metastasis is an
adverse prognostic indicator according to almost any scheme used for risk assessment. We were interested to know whether there was a way to refine the prognosis using PET-CT once a patient has had metastasis. We already had an indication from a prior pilot study that FDG-PET uptake might correlate with prognosis (24). We studied a group of 400 patients with thyroid cancer who had had FDG-PET scans during the course of their management. About 55% of the scans were FDG positive. Of the patients, with negative PET scans, one third had metastasis documented by other means. All the patients with FDG-positive scans had metastasis. In this cohort of 400 patients, we evaluated the hypothesis that the level of uptake of FDG in metastasis from thyroid cancer would correlate with patient prognosis. PET scans were correlated with overall survival, with a mean follow-up of 7.9 years. We also compared these prognostic indicators: patient age, TG level, AJCC stage, number of FDG-avid lesions, and FDG uptake (maximum standard uptake value [SUVmax]).

Univariate analysis showed all of these factors to correlate with survival. However, multivariate analysis showed only age and FDG uptake were correlated with survival. There was a significant inverse correlation between FDG uptake, both in terms of a number of lesions detected and the SUVmax of the lesions. Figure 37.9A shows a large prognostic difference between patients who had a negative FDG scan and those who had a positive scan. The quantitative relationships between SUVmax and the number of FDG-avid lesions and the distribution of lesions are shown in Figure 37.9A. It is clear that FDG-PET is a powerful indicator of prognosis, even if the biologic basis for the correlation is unknown. Based on these data, we have begun to consider more aggressive therapeutic strategies for those patients who have metastatic thyroid cancer with a high SUVmax.

Role of Thyroglobulin in Patient Management

A common indication for PET in thyroid cancer is the finding of an elevated level of TG, especially in conjunction...
with a negative $^{131}$I whole-body scan. The widespread availability of TG serum assay has greatly influenced the management of patients, particularly after ablation treatment with total thyroidectomy and $^{131}$I. A low level of serum TG during thyroid suppression has generally been considered to be reassuring and to suggest a lack of recurrence. However, this result may be misleading (25). About 21% of 734 patients from combined trials were found to have metastatic thyroid cancer with recombinant TSH stimulation to above 2 ng/mL, even when the suppressed TG was less than 1 ng/mL. In 36% of this patient group, distant metastatic disease was discovered. Another interesting feature of this study was that a whole-body radioiodine scan for diagnostic purposes was positive in only 19% of the metastatic population. Thus it is clear that the serum TG level, in particular a recombinant TSH-stimulated TG test with an increase to greater than 2 ng/mL, is the most sensitive way to detect recurrent tumor, although not its location. Thus, a new guideline proposed by a consensus conference suggests the use of recombinant TSH stimulation testing in patients who after thyroidectomy and $^{131}$I ablation have a baseline serum TG level of less than 1 ng/mL.

To further explore the role that TG may play in detecting residual thyroid cancer and its location, we studied a group of 417 thyroid cancer survivors undergoing evaluation for residual disease with the assistance of recombinant human TSH. A total of 169 patients had metastatic disease. In this group of patients, it was discovered that the basal TG level

![Figure 37.9 Prognostic implications of FDG-positive metastatic lesions in differentiated thyroid cancer. A: FDG uptake is a powerful predictor of poor prognosis. B: SUV$_{max}$ inversely correlates with 5-year survival in patients with metastatic thyroid cancer. C: The larger the number of lesions that are FDG avid on PET scanning, the worse the prognosis for differentiated thyroid cancer. D: The location of FDG-avid lesions also correlates with the prognosis for distant disease, having an ominous implication in terms of 5-year survival.](image-url)
directly correlated with the number of lesions and that the level was highest in the patients with follicular thyroid cancer and lowest in those with papillary thyroid cancer. With recombinant TSH stimulation, we found that the increase appeared to correlate with the thyroid cancer histology and that follicular cancers had the greatest increase, papillary cancers had an intermediate increase, and Hürthle cell cancer the smallest increase. We also found that the basal level of TG was highest in patients with bone metastasis and lowest in those with cervical lymph node metastases. However, the actual levels were influenced by histology, the range was very broad, and thus the level of basal or stimulated TG was not a particularly good predictor of the site of metastatic tumor involvement.

The Whole-Body ¹³¹I-Negative, TG-Positive Patient: The Role of FDG-PET

A negative ¹³¹I whole-body scan is likely in the setting of early recurrence. Also, approximately 20% of well-differentiated, metastatic thyroid cancers will not concentrate radioactive iodine, which poses a difficult diagnostic and therapeutic problem. Often these patients will have a positive TG, but the site will be unknown. We and others (26) have found that in this circumstance FDG-PET can be useful for diagnosing disease that in some instances may be treated by other means (Fig. 37.10). We performed FDG-PET scans on 37 patients with negative ¹³¹I whole-body diagnostic scans and positive TG. FDG-PET detected occult disease in 71% of patients. There was one false positive and five false negatives, predominantly where there was cervical lymph node–only metastatic involvement. In this small cohort, FDG-PET changed management in 41% of patients: some patients had surgical resection, others ¹³¹I treatment, and others redifferentiation therapy. We concluded that FDG-PET is capable of detecting occult disease in patients with negative ¹³¹I whole-body scans and positive TG levels, but it is insufficiently sensitive to detect minimal cervical lymph nodes (20).

FDG-PET imaging should be performed in patients with a high probability of metastatic cancer. In poorly differentiated as well as anaplastic cancer, the uptake is high, and valuable information can be obtained about the extent of the disease, particularly when PET-CT is available.

Hürthle cell cancer is one of the more difficult to stage, in part because only about 40% of tumors take up ¹³¹I.
FDG-PET is particularly useful in the study of Hürthle cell cancer because FDG is often taken up with high SUV

**Role of $^{124}$I-PET in Dosimetry**

Dosimetry in thyroid cancer should ultimately include the individual lesion. This is in part because uptake in individual lesions varies greatly from site to site and also because individual response varies. An excellent response to $^{131}$I is by no means rare, but in metastatic disease it tends to occur primarily in young people and those with good uptake. Also, $^{131}$I therapy is not always benign and in therapeutic doses can damage the salivary glands. Also, $^{131}$I in very high doses may be linked to the induction of myelodysplastic syndromes as well as leukemia. Especially in older patients, the cancer may lose the ability to take up radioactive iodine. In this case, there is a question about whether the potential benefits outweigh the risks of treatment. For this reason, a quantitative imaging methodology such as PET would add greatly to the ability to manage individual patients.

It is now known that whole-body $^{131}$I scanning, at least with doses of 5 mCi or less, is not very sensitive for detecting metastatic disease, and in a recent trial comparing diagnostic and post-therapy $^{131}$I scans, for example, only about 30% of tumors were detected (H. W. Strauss, personal communication, 2005). As $^{124}$I becomes more available, it is likely that this will be useful for improved diagnosis as well. In this regard, PET-CT will be very useful for anatomic localization (27).

**MEDULLARY THYROID CANCER (MTC)**

Medullary thyroid cancer originates from parafollicular cells (C cells) that surround the thyroid follicle and are of neuroendocrine origin. The tumor biology is very different than that of differentiated thyroid cancer in that these cells produce calcitonin, a 32–amino acid peptide hormone involved in calcium and phosphorus metabolism. Calcitonin is a useful marker for monitoring the status of the tumor in many patients. The tumor cells lack the expression of sodium iodide symporter and so do not take up radioactive iodine.

The patient normally presents with a painless lump in the neck, which is subsequently diagnosed by fine needle aspiration. Primary therapy is normally surgical, with total thyroidectomy recommended. Because cancer metastasis is to cervical lymph nodes and 75% of patients at presentation will show such metastasis, a bilateral lymph node dissection is normally performed. If the cancer is confined to the thyroid gland, the prognosis is excellent. The overall survival rate is 85% at 5 years and 65% at 10 years. Adverse risk factors impacting
the prognosis include advanced age, prior neck surgery, stage at diagnosis, and associated multiple endocrine neoplasia (MEN).

Twenty-five percent of cases are familial, and patients with a familial history should be screened for other neoplasms, particularly parathyroid adenoma and pheochromocytoma (MEN 2A).

MTC is associated with a mutation in the RET proto-oncogene. Tyrosine kinase inhibitor drugs are being explored as potential molecular targeting therapeutics for this tumor.

A detailed description of staging is outside the scope of this chapter, but the interested reader is referred to this Web site: http://www.meb.uni-bonn.de/cancer.gov/CDR0000062913.html#REF_14.

Figure 37.13 A 64-year-old woman patient presented with pain in the left hip, which was found on FDG-PET scanning (A) to be markedly FDG avid. Considerable erosion of the cortex of the left ilium and soft-tissue extension were seen on the companion CT (B). Biopsy was inconclusive on the histology of the origin, but an additional lesion was seen just beneath the left lobe of the thyroid (C,D), which was found at the time of surgery to be the primary thyroid cancer (Hürthle cell type). E: Coronal PET scan through the pelvic lesion.

Figure 37.14 Iodine 124 used for dosimetry imaging. A-P (A) and lateral (B) chest x-rays showing the miliary spread of papillary thyroid cancer to the lungs. (C) Iodine 124 whole body scan, shown as a re-projection image, with uptake in cervical mediastinal lymph nodes, lungs.
Role of FDG-PET-CT in the Management of MTC

There have been limited studies that have examined the role of FDG-PET in patients with MTC. The literature is conflicting on whether FDG-PET or CT is a better tool for managing MTC (28).

De Groot et al. showed that in a group of 26 patients with occult MTC lesions, FDG-PET was superior to conventional imaging such as 111In octreotide or bone scintigraphy (29). However, FDG may be less helpful in better differentiated lesions, and some authorities have gone so far as to recommend that FDG-PET be done only after a negative 111In octreotide study has been obtained (30).

In a retrospective German multicenter study by Diehl et al., 181 lesions were identified by one of the imaging techniques in a group of 85 patients with MTC, of whom 82 had had a total thyroidectomy and 3 had not yet undergone surgery. In this group, FDG-PET had a sensitivity of 78%, versus 50% for CT. However, this study did not include patients with occult disease (31) (Fig. 37.16).

S zakall et al. showed that in 40 postoperative patients with elevated plasma calcitonin levels, 270 metastases were detected with PET, compared with 116 with MRI and 141 with CT. 131I-MIBG scintigraphy was positive in only 3 patients. The authors showed that PET is more sensitive than other imaging modalities, like CT and MRI, in localizing metastases in the neck, supraclavicular, and mediastinal lymph nodes (32).

In a study of 11 patients with MTC, Hoegerle et al. showed that F-Dopa PET may have better results than FDG-PET and somatostatin receptor imaging, especially for lymph node staging (33,34).

Radiotracers for SPECT Imaging

Medullary carcinoma can demonstrate MIBG uptake, but the sensitivity is relatively low. Therefore 131I-MIBG scintigraphy is not routinely used in the workup of MTC. However, an occasional patient may have exceptional uptake, leading to the possibility of therapy (Fig. 37.17).

131I and anti-carcinoembryonic antigen (CEA) antibodies have been introduced for imaging and therapy of thyroid cancer, and the post-therapy images have been particularly useful in the staging of medullary thyroid cancer. A surprisingly large fraction of patients were demonstrated to have bone marrow involvement in a recent series of patients with advanced disease being treated with radiolabeled, targeted antibody (35). In the future, it is likely that other antibodies as well as other radiolabels will be introduced that may improve the staging of medullary thyroid cancer in some patients, particularly those with occult disease.

Recommendations for Diagnostic Imaging of Medullary Thyroid Cancer

The ability of diagnostic modalities to detect MTC varies widely, and for this reason the patient’s clinical state must
Figure 37.16  FDG-PET imaging in a patient with medullary thyroid cancer. The rows represent orthogonal views, including PET scans (A) and PET-CT scans (B). There are clear-cut abnormalities within the thoracic vertebrae, probably within the bone marrow space. The anatomic localization provided by PET-CT is helpful in defining the relationship of the patient’s pathology to normal anatomic structures.

Figure 37.17  A: A patient with medullary thyroid cancer. FDG-PET imaging shows uptake into lungs bilaterally. FDG may be useful for identifying the location of medullary cancer in patients in whom the disease extent is not known with precision. B–E: 131I meta-iodobenzylguanidine (MIBG) images. There is diffuse uptake bilaterally in both lungs after 131I-MIBG imaging. In selected patients, there may be sufficient uptake of 131I-MIBG to encourage its use for therapeutic applications.
be considered in selecting a particular modality. In patients with rapidly increasing serum markers, including CEA, FDG-PET may be very helpful, since it is most likely to be positive in the least well differentiated tumors. In patients with more chronic, stable disease, a somatostatin agent like octreotide may be helpful and probably should be employed in the initial workup. Some experts consider technetium-labeled dimercaptosuccinic acid (DMSA) to be the agent of choice in the post-therapy setting (36). Anatomic-based imaging modalities, such as CT and MRI, are being studied in a variety of settings and may be more sensitive than functional imaging techniques. However, in most reported series their specificity has been low. Thus, it is often necessary to do a function of anatomic and imaging, individualizing detection and monitoring so as to optimize patient management (37).

REFERENCES

3. American Joint Committee on Cancer. 

Non-small cell lung cancer (NSCLC) includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinomas typically develop in the periphery of the lung and are more common in women and in nonsmokers. Adenocarcinomas have a high incidence of early metastases and tend to grow more rapidly than squamous cell carcinomas. Bronchioalveolar cell carcinoma is a subtype of adenocarcinoma. It typically grows along the alveolar spaces without invasion of the stroma. It can appear as a solitary pulmonary nodule, a pneumonia-like consolidation, or multiple nodules throughout the lung. Squamous cell carcinomas are strongly associated with smoking. In general, they have the best prognosis because of their slow growth rate and their low incidence of distant metastases. They tend to become large and develop a central necrosis. Metastases to regional lymph nodes are common. Squamous
cell carcinoma is the most common cause of Pancoast tumors. These occur typically at the apex of the lung and are associated with Horner syndrome and local bone destruction. Large cell carcinomas are also strongly associated with smoking. They tend to grow rapidly and metastasize early and are associated with a poor prognosis.

The TNM staging system is widely used to classify NSCLC. The last revision of the staging system was approved by the American Joint Committee on Cancer and the International Union against Cancer in 2002 (1) (Table 38.1). NSCLC is also classified into four stages (1). Stage IV includes those patients with evidence of distant metastasis and those with one or more separate metastatic tumor nodules in the ipsilateral non-primary-tumor lobes of the lung. Stage III is divided in two substages, stage IIIA and stage IIIB. Only stage IIIB tumors are considered unresectable. Tumors with limited invasion of the chest wall and mediastinum are included in the operable stage IIIA (Table 38.2). Stage T4 is used for extensive invasion of the mediastinum or diaphragm (e.g., invasion of the great vessels, heart, trachea, or esophagus). N1 disease encompasses peribronchial and ipsilateral hilar metastases, including direct extension. All N1 nodes lie distal to the mediastinal pleural reflection and within the visceral pleura (2). These patients are considered resectable. However, the presence of ipsilateral hilar lymph node metastases decreases the overall survival rate. N2 disease encompasses ipsilateral paratracheal and/or subcarinal lymph node metastases. These patients have potentially resectable disease. Today, at our institution, most patients with N2 disease receive neoadjuvant chemotherapy for the reduction of the tumor mass before surgery. N3 disease encompasses contralateral mediastinal nodal metastases, contralateral hilar nodal metastases, and ipsilateral or contralateral scalene or

**TABLE 38.1**

**THE TNM STAGING SYSTEM**

<table>
<thead>
<tr>
<th>Primary tumor (T) staging</th>
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<tbody>
<tr>
<td>T1 Tumor 3 cm or less at the greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than a lobar bronchus</td>
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<tr>
<td>T2 Tumor with any of the following features of size and extent:</td>
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</tr>
<tr>
<td>More than 3 cm at the greatest dimension</td>
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</tr>
<tr>
<td>Involves one main bronchus 2 cm or more distal to the carina</td>
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<tr>
<td>Invades the visceral pleura</td>
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<tr>
<td>Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.</td>
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</tr>
<tr>
<td>T3 Tumor of any size that directly invades any of the following:</td>
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<tr>
<td>Chest wall (including superior sulcus tumors)</td>
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<tr>
<td>Diaphragm</td>
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<tr>
<td>Mediastinal pleura</td>
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<tr>
<td>Parietal pericardium</td>
<td></td>
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<tr>
<td>Tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina</td>
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</tr>
<tr>
<td>Associated atelectasis</td>
<td></td>
</tr>
<tr>
<td>Obstructive pneumonitis of the entire lung</td>
<td></td>
</tr>
<tr>
<td>T4 Tumor of any size that invades any of the following:</td>
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</tr>
<tr>
<td>Mediastinum</td>
<td></td>
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<tr>
<td>Heart, great vessels</td>
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<tr>
<td>Trachea</td>
<td></td>
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<tr>
<td>Esophagus</td>
<td></td>
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<tr>
<td>Vertebral body</td>
<td></td>
</tr>
<tr>
<td>Carina</td>
<td></td>
</tr>
<tr>
<td>Tumor with a malignant pleural or pericardial effusion</td>
<td></td>
</tr>
<tr>
<td>Tumor with satellite tumor nodule(s) within the ipsilateral primary tumor-affected lobe of the lung</td>
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<table>
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<tr>
<th>Regional lymph nodes (N)</th>
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<tbody>
<tr>
<td>N0 No regional lymph node metastasis</td>
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</tr>
<tr>
<td>N1 Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes involved by direct extension of the primary tumor.</td>
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</tr>
<tr>
<td>N2 Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)</td>
<td></td>
</tr>
<tr>
<td>N3 Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)</td>
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<table>
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<tr>
<th>Distant metastasis (M)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>M0 No distant metastasis</td>
<td></td>
</tr>
<tr>
<td>M1 Distant metastases and/or separate metastatic tumor nodule(s) in the ipsilateral non-primary-tumor lobe(s) of the lung</td>
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and bronchioloalveolar lung carcinoma (6,7) (Fig. 38.1). PET may show negative results for pulmonary carcinoids following previous lung resection or irradiation (5). However, FDG-malignancy results are indeterminate. In a series of 61 patients, PET had a sensitivity of 93% and a specificity of 88% for detecting malignancy. PET is also effective in detecting recurrence after noninvasive biopsy and has a high specificity for FDG-PET. Lesions are considered malignant, although false-positive results have been reported in cases of inflammatory and infectious processes, such as histoplasmosis, aspergillosis, and active tuberculosis. With integrated PET-CT, additional certainty regarding the presence or absence of FDG uptake in the pulmonary nodule can be achieved because morphologic CT criteria and functional CT criteria are available simultaneously.

**SOLITARY PULMONARY NODULE**

Lung masses have been evaluated traditionally by using planar chest x-rays, computed tomography (CT), and, more recently, magnetic resonance imaging (MRI). Some radiographic parameters such as calcifications and smooth margins of a lesion may indicate a lower likelihood that a solitary nodule is malignant, although a substantial percentage of nodules remain radiographically indeterminate. Factors that increase the probability of malignancy include size, absence of calcification, and irregular margins. Unchanged radiographic appearance of a nodule at follow-up examinations over a 2-year period imply that the lesion is benign. Definite diagnoses are established with invasive techniques such as bronchoscopy, mediastinoscopy, and biopsy. In the case of benign lesions, nondiagnostic biopsy results are not uncommon.

The ability of positron emission tomography (PET) to distinguish between benign and malignant lesions is good but not perfect. For benign lesions, Patz et al. (3) demonstrated a high specificity for specificity for FDG-PET. Gupta et al. (4) showed that FDG-PET is highly accurate in differentiating malignant from benign solitary pulmonary nodules for sizes from 6 to 30 mm when radiographic findings are indeterminate. In a series of 61 patients, PET had a sensitivity of 93% and a specificity of 88% for detecting malignancy. PET is also effective in detecting recurrence after previous lung resection or irradiation (5). However, FDG-PET may show negative results for pulmonary carcinoids and bronchioloalveolar lung carcinoma (6,7) (Fig. 38.1).

PET is clinically useful in patients with a solitary pulmonary nodule less than 3 cm in diameter, especially where biopsy may be risky or where there is a low risk of malignancy based on the history or radiographic findings. Lesions with low FDG uptake can be considered to be benign and can be monitored with chest radiographs. Lesions with increased FDG uptake should be considered malignant, although false-positive results have been reported in cases of inflammatory and infectious processes, such as histoplasmosis, aspergillosis, and active tuberculosis. With integrated PET-CT, additional certainty regarding the presence or absence of FDG uptake in the pulmonary nodule can be achieved because morphologic CT criteria and functional CT criteria are available simultaneously.

**T STAGING**

CT is an important imaging modality for the evaluation of the primary tumor. However, the low accuracy of chest CT in the evaluation of invasion of the chest wall or involvement of the mediastinum and the correct differentiation between tumor and peritumoral atelectasis often prevents precise T staging with CT (8). PET, on the other hand, has the disadvantage of having limited anatomical resolution, which makes the assessment of tumor extension unreliable, particularly if the tumor infiltrates the chest wall or the mediastinum.

It has been demonstrated that integrated PET-CT is a useful tool for the detection of tumor invasion into the chest wall (9–11). Due to the exact anatomic correlation to FDG uptake, the primary tumor can be delineated precisely (Fig. 38.2). Therefore, the diagnosis of chest wall infiltration and mediastinal invasion by the tumor is improved. Lesions with chest wall infiltration are classified as stage T3 and are potentially resectable. Surgical treatment requires en bloc resection of the primary tumor and the contiguous chest wall. Particularly in patients with poor cardiopulmonary reserve, the preoperative determination of chest wall infiltration is desirable in order to avoid extended en bloc resection.

Integrated PET-CT provides important information on mediastinal infiltration as well. Contrast-enhanced CT to evaluate infiltration of hilar and vessels has a relatively low sensitivity, specificity, and accuracy (68%, 72%, and 70%, respectively) (12). Our experience suggests that unenhanced PET-CT imaging is unable to identify direct invasion of the walls of vital mediastinal structures, and this is the scan protocol we currently use in most patients receiving an integrated PET-CT scan. Further research is necessary to evaluate the potential additional diagnostic impact of intravascular contrast agents when performing integrated PET-CT (Fig. 38.3).

It has been shown that FDG-PET is a useful tool for the differentiation of tumor and peritumoral atelectasis (Fig. 38.3). This is particularly important for the planning of radiotherapy in patients with lung cancer associated with an
atelectasis. The information provided by FDG-PET contributes to a change in the radiation field in approximately 30% to 40% of patients (13).

**N STAGING**

**Morphologic Imaging**

Accurate mediastinal staging is essential for the management of patients with NSCLC. Surgical resection is the treatment of choice for early stages of NSCLC. Patients with ipsilateral mediastinal lymph node metastases (N2 disease) are considered to have potentially resectable disease. If contralateral mediastinal lymph node metastases (N3 disease) are present, surgery is generally not indicated. CT and MRI have substantial limitations in depicting mediastinal lymph node metastases (Fig. 38.4). The only CT and MRI criteria for tumor involvement are morphologic; that is, the criteria rely on the size and shape of the lymph nodes. However, normal-size regional lymph nodes may prove to have metastases upon histologic examination, and nodal enlargement can be due to reactive hyperplasia or other nonmalignant conditions. The sensitivity and specificity of determining lymph node metastases for NSCLC by CT are both 60% to 70% (8, 14). Thus, in 30% to 40% of cases, CT scanning will erroneously
Figure 38.2 A 63-year-old man. Conventional CT demonstrated a lung cancer in the left upper lobe. Invasion of the tumor into the chest wall could not be ruled out. PET-CT was performed for staging. Images include a MIP scan (A), an axial CT scan (B), an axial attenuation-corrected PET scan (C), and an axial coregistered PET-CT scan (D). Diagnosis based on the integrated PET-CT imaging: Lung cancer in the left upper lobe. No invasion into the chest wall. No ipsilateral or contralateral mediastinal lymph node metastases. No extrathoracic metastases. Surgery confirmed that the tumor did not invade the chest wall. (See also Cases 7 and 11.)

Figure 38.3 A 63-year-old man with non-small cell lung cancer (NSCLC) of the left lung. PET-CT was performed for staging. Due to the central location of the cancer, a CT with contrast enhancement was added and coregistered with the PET images. The images include a MIP scan (A), a transaxial CT (B,C), and corresponding transaxial PET-CT scans (D,E). PET-CT showed a central tumor with infiltration of the left pulmonary artery and an occlusion of the left upper lobe bronchus with poststenotic atelectasis. In addition, a small ipsilateral mediastinal lymph node metastasis, bilateral renal gland metastases, and an aortocaval lymph node metastasis were found. The FDG-active lesion in the right parotid gland represents a Warthin tumor. (See Case 6.)
suggest the presence of mediastinal lymph node metastases and will miss lymph node metastases in 30% to 40% of cases.

**FDG-PET Imaging**

Several studies have demonstrated that FDG-PET is significantly more accurate than CT in the determination of nodal status (15–17). Since good PET scanners have a fairly high resolution (less than 6 mm), even small lesions with an increased FDG uptake can be detected (Figs. 38.4 and 38.5). This represents a critical advantage of PET over CT and MRI. In our own study of 47 patients, PET assigned the correct N stage in 96% of cases, while CT was correct only in 79% of cases (15). Dwamena et al. (18) performed a meta-analytic comparison of PET and CT in mediastinal staging of NSCLC. The mean sensitivity and specificity (± 95% CI) were 0.79 ± 0.03 and 0.91 ± 0.02, respectively, for PET and 0.60 ± 0.02 and 0.77 ± 0.02, respectively, for CT. These results were confirmed in another meta-analysis including in total more than 1,000 patients (19).

FDG-PET is not without limitations in nodal staging. The presence and site of lymph node metastases should be recorded according to the revised American Thoracic Society lymph node station-mapping system (Table 38.3 and Fig. 38.6). The anatomic accuracy or ability of PET to detect the presence of tumor in specific nodal stations is poor, particularly in hilar and subaortic stations. Belley et al. (20) found an overall sensitivity for detecting the presence of mediastinal metastases regardless of nodal station ranging from 64% to 86% and a specificity from 73% to 81%. In our experience, integrated PET-CT imaging will become the new standard for mediastinal staging (see Figs. 38.4, and 38.5). The high reliability of integrated PET-CT in the exact localization of extrathoracic versus intrathoracic lymph nodes and mediastinal versus hilar lymph nodes might have very important therapeutic implications. The introduction of several induction therapy protocols allows for the possible inclusion of the patients in neoadjuvant trials with a higher resectability rate and a better outcome in selected patients. Still, microscopic foci of metastases within normal-size lymph nodes cannot be detected with any imaging modality. If there is no increased FDG uptake in PET, integrated PET-CT will not provide further information.

**Mediastinoscopy**

Mediastinoscopy remains the gold standard for mediastinal staging. However, not all mediastinal lymph nodes are routinely reachable by mediastinoscopy (para-aortic region, aortopulmonary window). The limited view through the mediastinoscope and the single direction approach of the biopsy prevent 100% accuracy. The accuracy of mediastinoscopy is approximately 90% and surgeon dependent (21). Recently, it has been demonstrated that PET assists mediastinoscopy. Due to the PET information,
mediastinoscopy revealed additional mediastinal disease in 6% of patients (22). FDG-PET may reduce the necessity for mediastinoscopy if the primary tumor is localized in the periphery of the lung and the mediastinum is PET negative. This approach would reduce the need for mediastinoscopy by 12%.

**M STAGING**

Despite radical surgical treatment of potentially curable NSCLC, the overall 5-year survival rate remains low (20% to 40%). One reason for this is undetected extrathoracic metastases, which cause underestimation of the tumor.

Figure 38.5  A 73-year-old man. Conventional staging (bronchoscopy, enhanced high-dose CT of the chest and upper abdomen) revealed an adenocarcinoma in the right lower lobe with ipsilateral mediastinal metastases. PET-CT was performed for staging. The images included a MIP scan (A), axial CT scans (B,D,F,H), and axial coregistered PET-CT scans (C,E,G,I). Diagnosis based on the integrated PET-CT imaging: Multiple lymph node metastases. (See also Case 15.)
TABLE 38.3
LYMPH NODE MAP DEFINITIONS: NODAL STATIONS

N2 nodes—all N2 nodes lie within the mediastinal pleural envelope
1. Highest mediastinal nodes
2. Upper paratracheal nodes
3. Prevascular and retrotracheal nodes
4. Lower paratracheal nodes
5. Subaortic nodes (aortopulmonary window)
6. Para-aortic nodes (ascending aorta or phrenic)
7. Subcarinal nodes
8. Paraesophageal nodes (below carina)
9. Pulmonary ligament nodes

N1 nodes—all N1 nodes lie distal to the mediastinal pleural reflection and within the visceral pleura
10. Hilar nodes
11. Interlobular nodes
12. Lobar nodes
13. Segmental nodes
14. Subsegmental nodes

See Figure 38.6.
stage. The most common sites of distant metastases are the liver, adrenal glands, bone, and the brain. Although the incidence of metastatic disease in NSCLC is high, routine staging of all patients with bone scintigraphy and CT or MRI of the head and abdomen is not routinely performed. The likelihood of a true positive finding in bone scintigraphy, CT, or MRI in an asymptomatic patient is small. Using bone scintigraphy as a routine diagnostic method, only 14% of the positive focal findings in patients with cancer were caused by a metastasis of the known tumor. Also, the meta-analysis by Silvestri et al. (23) demonstrated that the negative predictive value for detecting metastatic disease in CT scans in patients with NSCLC is not higher than that of the clinical evaluation.

Whole-body FDG-PET is an excellent method of screening for extrathoracic metastases (24) (Fig. 38.7). In a meta-analysis of 581 patients, the sensitivity, specificity, and accuracy of FDG-PET were 94%, 97%, and 96%, respectively (19). Current imaging methods are inadequate for accurate M staging of patients. PET detects unexpected extrathoracic metastases in 10% to 20% of patients and changes therapeutic management in about 20% of patients. FDG-PET is more accurate than CT in the evaluation of adrenal metastases (25,26). Marom et al. (27) compared the accuracy of FDG-PET to that of conventional imaging in 100 patients with newly diagnosed NSCLC. In a comparison of bone scintigraphy and FDG-PET for the detection of bone metastases, the levels of accuracy were 87% and 98%, respectively. All hepatic metastases were correctly identified with PET and CT. With CT, however, benign liver lesions were overstaged as metastases, and thus the accuracy of PET was superior to that of CT in the diagnosis of liver metastases.

The advantage of integrated PET-CT imaging is that it provides the exact localization and classification of a hot spot on PET, especially when no morphological alterations are seen on CT images (9–11).

**FALSE-NEGATIVE AND FALSE-POSITIVE FDG-PET RESULTS**

False-negative FDG-PET results have been reported in pulmonary carcinoid tumors and in bronchioloalveolar cell cancers (6,7) (see Fig. 38.1). Carcinoid tumors have a neuroendocrine origin. They are highly differentiated and are low-grade malignant carcinomas. These factors might result in FDG-PET having a lower sensitivity. Bronchioalveolar cell carcinoma is considered a subtype of adenocarcinoma. It presents as a solitary nodule, a pneumonia-like consolidation, or multiple nodes throughout the lung. In a study by Higashi et al., less proliferative potential and longer mean doubling times than for other NSCLCs were found (6).

The spatial resolution limitations of PET also can be responsible for false-negative results. PET cannot detect lymph node metastases smaller than 4 to 6 mm, and some
of the malignant lesions seen on high-resolution CT are smaller than that (see Fig. 45.6). The detection of micrometastases is not possible with any imaging modality. Recently, it has been reported that FDG-PET after induction therapy is less accurate in mediastinal staging than in staging of untreated NSCLC (28). PET overstaged nodal status in 33% of patients, understaged nodal status in 15%, and was correct in 52%. Future studies are needed to correlate FDG-PET before and after treatment with the degree of pathologic response.

False-positive results can be due to the lack of specificity of FDG with regards to inflammatory lesions (see Part VI, Chapters 55–62). Lung empyema, tuberculosis, eosinophilic lung disease, histoplasmosis, aspergillosis, and other infections may have significant uptake of FDG (29) (Figs. 38.8 and 38.9), as may sarcoidosis (Fig. 38.10). Occult lung infarction may induce false interpretation of FDG accumulation in PET imaging (30). Therefore, lesions with an increased FDG accumulation should be histologically confirmed. However, most chronic inflammatory processes do not take up FDG significantly.

It is well known that active muscles accumulate FDG. In some patients with lung cancer, an intense focal FDG accumulation is seen in the lower anterior neck just lateral to the midline. Coregistered PET-CT images have revealed that this focal FDG uptake is frequently localized in the internal laryngeal muscles (31). This finding is a result of compensatory laryngeal muscle activation caused by contralateral recurrent laryngeal nerve palsy due to direct nerve invasion by lung cancer of the left mediastinum or lung apices. This is also found with surgically induced lesions of the recurrent nerve, such as occurs in thyroid cancer surgery (Chapter 37). Knowledge of this finding is important to avoid false-positive PET results (see Fig. 33.23).

Recently, our own group assessed the incidence and etiology of solitary extrapulmonary lesions with increased FDG accumulation (32). In a study population of 350 patients, PET-CT revealed extrapulmonary lesions in 110 patients. In 72 patients, solitary lesions were present. In approximately 50% of patients with solitary extrapulmonary lesions, histopathological correlation revealed metastases of NSCLC, in 25% it revealed an unknown second primary, and in 25% it revealed benign lesions such as acute fracture, colon adenoma, and Warthin tumor (see Figs. 34.30 and 38.3).

**Figure 38.8**  A 78-year-old man with histologically proven NSCLC of the right lower lobe. PET-CT was performed for staging. The images include a MIP scan (A), transaxial CT scans (B, C), and corresponding transaxial PET-CT scans (D, E). Diagnosis based on the integrated PET-CT imaging: Carcinoma in the right lower lobe. Unclear pleural FDG activity (e.g., inflammatory process, pleuritis carcinomatosa). Most likely inflammatory mediastinal lymph nodes. Histopathological examination confirmed an adenocarcinoma of the right lower lobe in combination with an empyema and inflammatory mediastinal lymph nodes. In addition, the patient had considerable calcifications in the aortic arch region.
CT and MRI provide excellent morphological information but often cannot differentiate recurrent or residual tumors from post-therapeutic changes. Benign, nonspecific pleural thickening is an example of a post-treatment change that may be difficult to differentiate from recurrent disease. Thus, some patients may undergo a biopsy to determine tumor viability, although invasive procedures, including transthoracic needle biopsy and open lung biopsy, carry associated risks. Furthermore, due to sampling errors, these procedures do not always provide a definitive answer.

**Figure 38.9** A 62-year-old man. A chest x-ray demonstrated a pulmonary mass in the right middle lobe. PET-CT was performed for further evaluation. The images include a MIP scan (A), axial CT scans (B,D,F,H), and axial coregistered PET-CT scans (C,E,G,I). Diagnosis based on the integrated PET-CT imaging: The findings were suspicious for NSCLC with ipsilateral mediastinal metastases. Histology revealed eosinophilic lung disease mimicking a lung cancer. (See also Cases 12 and 32.)
is the cost savings achieved by preventing patients with unresectable disease from undergoing unnecessary surgery. The cost savings are the result of improved staging of lung carcinoma before deciding on surgery.

In a subsequent study, five decision strategies for selecting potential surgical candidates were compared (36); one was based on thoracic CT alone, while the other four used chest CT plus PET. The expected costs and projected life expectancies of all the strategies were compared. A strategy that uses PET after a negative CT study was shown to be a cost-effective alternative to the CT-alone strategy ($25,286 per life-year saved). Dietlein et al. (37) demonstrated that the implementation of whole-body FDG-PET using a dedicated PET scanner in the preoperative staging of patients with NSCLC and normal-size lymph nodes is clearly cost-effective. However, patients with nodal-positive PET results should not be excluded from biopsy.

Recently, a randomized controlled trial in patients who were suspected of having NSCLC and were scheduled for surgery after conventional workup was performed to test whether FDG-PET reduces the number of thoracotomies (38). Patients were followed up for 1 year. Thoracotomy was regarded as futile if the patient had benign disease, explorative thoracotomy, pathological stage IIIA–IIIB disease, or postoperative relapse or death within 12 months of randomization. The investigators found that addition of PET to the standard workup in routine clinical practice improved the selection of surgically curable patients and prevented unnecessary surgery in 20% of patients with suspected NSCLC.

**REFERENCES**

Small cell lung cancer (SCLC) is the most aggressive type of lung cancer. SCLC is characterized by rapid growth and early metastases, which are present in 60% to 80% of patients at the time of diagnosis. SCLC is associated with a poor survival prognosis, and it has a very strong association with cigarette smoking. It accounts for approximately 20% of all lung cancers. SCLC most often occurs as a large central mass with massive hilar or bilateral mediastinal adenopathy. In general, SCLC does not respond to surgical treatment. Occasionally, SCLC presents as a solitary nodule, which can be resected. In patients with disease confined to the thorax, radiation treatment will be performed. However, the 2-year survival rate is approximately 20%. Patients with extended disease are managed with chemotherapy. Integrated positron emission tomography (PET) and computed tomography (CT) imaging is an accurate method for the assessment of the total tumor extent and plays an important role in the planning of radiation treatment.

**IMAGING**

The staging procedures for SCLC do not differ from those for NSCLC. The primary role for imaging is to accurately distinguish limited from extensive disease. Based on the widespread dissemination of SCLC, a battery of imaging tests is performed, such as computed tomography (CT) of the chest and abdomen, CT or magnetic resonance imaging (MRI) of the brain, and a bone scan. Recently, it has been shown that whole-body fluorodeoxyglucose (FDG) positron emission tomography (PET) is a useful tool for staging SCLC (4,5). FDG-PET was superior to conventional means of staging in the detection of all involved sites, particularly in the assessment of mediastinal lymph node and bone metastases. Our experience suggests that integrated
Figure 39.1  A 48-year-old woman with small cell lung cancer (SCLC). A PET-CT scan was performed for staging. The images, including a MIP scan (A), transaxial CT scans (B,D), and corresponding PET-CT sections (C,E), demonstrated that the primary carcinoma (D,E) was in the left lower lobe of the lung and that lymph node metastases were in the aortopulmonic window (B,C), representing limited disease. Radiation treatment was started.

Figure 39.2  A 47-year-old woman with known SCLC. A PET-CT scan was performed before radiation treatment to assess the extent of disease. The images, including a MIP scan (A), axial CT scans (B,D,F), and PET-CT sections (C,E,G), demonstrated limited disease. Radiation treatment, including of the primary tumor and the bilateral mediastinal lymph node metastases, was started.
PET-CT imaging in SCLC is a highly valuable tool for planning radiation treatment (6) (see Figs. 39.1 and 39.2). It increases the accuracy of target definition by reducing the probability that involved areas will be overlooked.

REFERENCES

Figure 39.3 A 62-year-old man with known SCLC. A PET-CT scan was performed for staging to assess the extent of disease. The images include a MIP scan (A) and coronal PET sections (B,C,D). The images revealed extended disease. Palliative treatment was instituted. (See also Case 10.)
Malignant pleural mesothelioma (MPM) is the most common neoplasm of the pleura and is directly linked to asbestos exposure. The major differential diagnosis is metastatic adenocarcinoma. Mesotheliomas arise from the visceral or parietal pleura. Invasion into the chest wall, diaphragm, and mediastinum may occur, and pleural effusions are common. MPMs metastasize to the ipsilateral (60%) or contralateral lung and to hilar and mediastinal lymph nodes. Distant metastases are rare.

Imaging is particularly helpful in preoperative staging of MPM. Computed tomography (CT) enables early detection of small pleural tumors and pleural effusions. CT demonstrates extension of the tumor along the pleural surfaces and fissures but underestimates tumor chest wall or diaphragmatic invasion and cannot identify pleural fibrosis. MPM avidly takes up fluorodeoxyglucose (FDG), but not into fibrosis, and our experience suggests that integrated positron emission tomography (PET)-CT imaging is a promising method for MPM, as the extent of the tumor as well as mediastinal lymph node involvement can be defined precisely.

INTRODUCTION

Malignant pleural mesothelioma (MPM) is the most common neoplasm of the pleura, and it is 1,000 times more common in a population exposed to asbestos. MPM usually develops no earlier than 20 to 30 years after asbestos exposure. No correlation to the duration or degree of exposure to asbestos or to smoking history has been found, but the incidence of MPM has been rising and is expected to continue until the year 2020. In western Europe, 250,000 men are expected to die from MPM by 2030 (1). Average survival at diagnosis is similar to that of lung cancer (2).

MPM arises from either the visceral or the parietal pleura. Invasion into the chest wall, diaphragm and mediastinum may occur. Pleural effusions are common and can become large. MPM metastasizes to the ipsilateral (60%) or contralateral lung and to hilar and mediastinal lymph nodes. Distant metastases are rare. Histologically, MPM is divided into an epithelial, a mesenchymal, and a mixed type. The epithelial type is the most common and has the best prognosis (3). The major differential diagnosis is metastatic adenocarcinoma. Immunohistochemical analyses may be required for differentiation.

STAGING

The goals of staging are to assess operability and, in patients deemed inoperable, to offer prognostic information. Staging is also important for evaluating patients entering clinical trials and for comparing different studies. The TNM
classification stratifies patients into prognostic categories based on surgical and pathological criteria (e.g., resectability and invasiveness) (4). MPM shows a locoregional growth pattern with direct extension and recurrence within the ipsilateral hemithorax, with increased risk in patients with infiltrated surgical edges or after invasive diagnostic or therapeutic procedures (5). The most frequently affected nodal sites are the mediastinal lymph nodes. Since MPM is primarily a parietal pleural disease, the lymphatic spread pattern is different from that of lung cancer, because N2 rather than N1 nodes may be the first drainage stations (see Table 38.3).

Diagnostic imaging in MPM is required on presentation of suspicious clinical features (6,7). Imaging is particularly helpful in preoperative staging of MPM. Computed tomography (CT) enables early detection of small pleural tumors and pleural effusions and definition of the extension of the tumor along the pleural surfaces and fissures. Sheets of tumor can be followed inferiorly along the diaphragmatic crura. However, tumor invasion into the chest wall or diaphragm can be underestimated by CT. With CT, differentiation between tumor and pleural fibrosis is impossible. CT is often not suitable for establishing the diagnosis of MPM, since diffuse pleural thickening may be due to a benign or malignant process.

PET IMAGING

As with lung cancer, excellent fluorodeoxyglucose (FDG) uptake in malignant pleura MPM has been described (8). Bénard et al. (9) assessed 28 patients with suspected MPM. FDG uptake was significantly higher in malignant than into benign lesions. For a standard uptake value (SUV) cutoff of 2.0, the sensitivity was 91% and the specificity 100%. Epithelial MPM had lower FDG uptake (SUV = 3.7 ± 1.9) than mixed or sarcomatoid MPM (SUV = 6.1 ± 3.4). PET imaging was useful in localizing the areas involved with MPM. Like in non-small cell lung cancer (NSCLC), mediastinal lymph node staging seems to be improved due to the detection of small nodal metastases (less than 8 mm). The role of positron emission tomography (PET) is to differentiate fibrosis from tumor, identify the optimal biopsy site, diagnose recurrence, and monitor therapy response by quantifying disease activity. Schneider et al. (10) demonstrated that PET is particularly valuable for distinguishing between benign and malignant pleural processes. Carretta et al. (11) analyzed 14 patients with pleural thickening or fluid on CT to evaluate the accuracy of FDG-PET in diagnosing pleural involvement by MPM. In the differential diagnosis of pleural disease, the accuracy of PET was 92%, but PET

![Figure 40.1](image_url) A 57-year-old man with malignant pleural mesothelioma (MPM) in the right lung. PET-CT was performed for staging. The images include a MIP scan (A), transaxial CT sections (B,C), corresponding transaxial PET sections (D,E), and corresponding transaxial PET-CT sections (F,G). The images show diffuse pleural thickening in the right lung. The tumor involves the major fissure. Some pleural lesions do not accumulate FDG, suggesting inactive pleural fibrosis.
could not distinguish pleural MPM from metastatic involvement caused by other tumors, such as adenocarcinoma.

PET may also have a role in defining the prognosis for MPM. In order to evaluate prognosis, Bénard et al. (5) studied 28 patients with suspected MPM, assessing the SUV of lesions on PET scans as a predictor of survival. Increased tumor metabolic activity reflected by a high SUV was associated with a poor prognosis in cases of MPM. Thus, the prognostic information provided by FDG-PET could be of value in the management of patients, such as when considering a more aggressive therapy, but the clinical value of PET in MPM has not yet been clearly defined, and histological thoracoscopic diagnosis remains mandatory before planning treatment.

Our experience with integrated PET-CT imaging suggests that it may be an excellent method for staging not only NSCLC but also MPM. Since FDG is not taken up in pleural fibrosis, differential diagnosis of the pleural lesions is possible (Fig. 40.1). With the coregistration of anatomy and metabolic information, the extent and the location of the tumor manifestations can be precisely defined, and even small metastases can be detected and localized (Figs. 40.2 and 40.3). Since pleural fluid cytology and histology have a low diagnostic yield, the diagnosis of MPM cannot be excluded, and if negative, further investigations are mandated. Precise localization of tumor sites with PET-CT is likely to better define where biopsy should be performed, thereby increasing diagnostic accuracy. This is important in order to reduce the number of invasive procedures, because there is a substantial risk of malignant seeding of around 20% in MPM (12). There are some limitations in assessing diaphragmatic invasion with PET-CT due to partial-volume effects on curved surfaces requiring thin slice imaging. Furthermore, since FDG-PET data are obtained during free breathing, imaging of the diaphragmatic regions is least well accomplished.
Quantification of the total tumor burden is desirable to evaluate the response of treatment. The use of SUV_{max} for the assessment of treatment response is limited because it is based only on a single voxel. With dedicated software, the SUV_{max} in a range of 30% to 100% of the entire extent of disease can be calculated. This parameter represents the entire tumor activity. Our first results demonstrate that integrated PET-CT with entire tumor activity measurements identifies which patients with MPM are responding or not responding to chemotherapy more accurately than CT alone and PET alone, respectively (13).

In summary, PET and PET-CT are emerging modalities for the evaluation of MPM. They may have a preoperative role in documenting the extent of pleural disease, defining best biopsy sites, establishing mediastinal lymph node involvement, and evaluating chest wall invasion and trans-diaphragmatic invasion.

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4. Rusch VW. A proposed new international TNM staging system for malignant pleural MPM from the International MPM Interest Group. 
7. Marom EM, Erasmus JJ, Pass HI, et al. The role of imaging in malignant pleural MPM. 
Semin Oncol. 2002;29:26–35.

Figure 40.3 A 64-year-old man with known MPM 2 years after pneumonectomy. Local recurrence in the right chest wall was clinically evident. PET-CT scanning was performed for restaging. The images include a MIP scan (A), transaxial CT sections (B,D,F), and corresponding transaxial PET-CT (C,E,G) sections. The images demonstrated extensive MPM, with infiltration of the thoracic wall, peritoneal metastases, and bone metastasis in the left femur (A,G). The spread of tumor to the peritoneum and bone was unknown prior to the PET-CT imaging. The patient received palliative therapy.
PET and PET-CT of Esophageal and Gastric Cancers

Jamshed B. Bomanji  Farrokh Pakzad  Darren L. Francis  Peter J. Ell

The incidence of gastroesophageal cancers, particularly the incidence of cancer of the esophagus, has been increasing in the Western world. Despite many advances in management, the prognosis from these tumors has remained poor. Currently, anatomical imaging modalities such as computed tomography (CT) and endoscopic ultrasound (EUS) are routinely used in diagnosing and staging esophageal and gastric cancers. However, they have several shortcomings with regard to demonstrating the full extent of disease and in predicting response to therapy. Biological imaging with fluorine 18 fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) and more recently dual modality PET-CT offers significant advantages. The aim of this chapter is to review the available evidence for the continually expanding role of imaging with PET and PET-CT in these conditions (see Fig. 41.1).

BACKGROUND

Esophageal Cancer

The incidence of carcinoma of the esophagus has been increasing in the Western world at a rate exceeding that of all other types of cancer (1). Geographically, the high risk areas are known as the "Asian esophageal cancer belt," which runs through Turkey, the northern provinces of Iran, central Asia, and China and where the incidence of esophageal cancer reaches as high as 150 per 100,000 population (2). It is a cancer that is more common between the ages of 50 and 70 years, with a male to female ratio of 3:1.

Esophageal cancer can be divided into two major histological types, squamous cell carcinoma and adenocarcinoma. The incidence of adenocarcinoma has risen dramatically and is now the most prevalent histological type in western Europe and the United States (3). Accompanying this increase, there has been a shift in the presentation of tumors at the distal esophagus and gastroesophageal junction (4). Squamous cell carcinomas are largely attributed to alcohol, tobacco, and nitrogen compounds, whereas adenocarcinomas are strongly associated with gastroesophageal reflux disease and Barrett esophagus. This has led to recommendations that patients with chronic symptoms that might lead to Barrett esophagus undergo endoscopic screening (5).

Over the last 3 decades, there has been little improvement in the long-term survival from esophageal carcinoma (6,7). Early surgical resection provides the only potential for long-term survival or even cure, an approach that despite its significant morbidity is increasingly advocated in older patients (8). However, up to 50% of patients have metastatic disease either at initial presentation or following apparent curative local therapy. In those who are treated surgically, the primary cause of death is disease recurrence. Clinical stage of the disease is a strong determinant of long-term survival, with 5-year survival decreasing dramatically when the disease is upstaged from stage I–III. In patients with stage IV disease, the 5-year survival is virtually zero (4).
Regional lymph node involvement is a major prognostic factor in esophageal cancer. The presence of lymph node metastases has been shown to be associated with poorer survival (5-year survival of 10% to 12%, compared with 42% to 72% in node-negative disease) (9). Lymph node staging of esophageal cancer is, however, complicated by the rich network of lymphatics that drain the esophagus. For instance, cervical and supraclavicular lymph node chains tend to drain the cervical esophagus, and in tumors of the distal esophagus and gastroesophageal junction, perigastric, celiac, or even para-aortic lymph nodes may be involved.

The distribution of metastases can also be widespread. This has been demonstrated by a 1995 study by Quint et al., who looked at the distribution of metastases in 838 newly diagnosed cases of esophageal cancer (10). Overall, metastases were found in 18% of the cases, of which 75% were preoperatively detected by imaging and/or clinical findings. Table 41.1 summarizes their findings. It was interesting to note that in those with a negative CT of the abdomen and chest, no additional metastases were detected on CT brain or bone scintigraphy. Therefore, the distribution of metastases, being mainly thoracoabdominal, led them to conclude that imaging of the abdomen and chest would be an effective screening method for M1 disease prior to an operation.

### Gastric Cancer

Gastric cancer remains the second most common cause of cancer-related death in the world. Most patients are elderly, and the median age at diagnosis is 65 years (range, 40 to 70). As with esophageal cancer, the incidence of gastric cancer is high in many Asian countries. Histologically, 90% to 95% of gastric cancers are adenocarcinomas. Early-stage gastric cancers tend to be asymptomatic, which is the predominant reason why only 10% to 20% are diagnosed early. The remainder present with stage III or IV disease, and gastric cancers at these stages have an overall 5-year survival rate of no greater than 15% to 20%. Tumors arising in the distal stomach have a slightly better prognosis (5-year survival of approximately 55%). However, the involvement of regional nodes reduces this to 20%. Following a curative gastrectomy, staging and lymph node involvement have also been implicated as strong independent predictors of early recurrence (11).

Tables 41.2 and 41.3 summarize the universally accepted staging system for esophageal and gastric cancers (12). The prognostic significance of this system has been supported by the German Gastric Cancer Group (13). It is at this level of patient assessment where historically most difficulty has arisen. Thus the direction of treatment toward either surgery or chemoradiotherapy depends on accurate staging of the disease.

### TABLE 41.1

<table>
<thead>
<tr>
<th>Site</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal lymph nodes</td>
<td>45%</td>
</tr>
<tr>
<td>Liver</td>
<td>35%</td>
</tr>
<tr>
<td>Lung</td>
<td>20%</td>
</tr>
<tr>
<td>Cervical/supraclavicular lymph nodes</td>
<td>18%</td>
</tr>
<tr>
<td>Bone</td>
<td>9%</td>
</tr>
<tr>
<td>Adrenal</td>
<td>5%</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>2%</td>
</tr>
<tr>
<td>Brain</td>
<td>2%</td>
</tr>
<tr>
<td>Stomach</td>
<td>1%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1%</td>
</tr>
<tr>
<td>Pleura</td>
<td>1%</td>
</tr>
<tr>
<td>Skin</td>
<td>1%</td>
</tr>
<tr>
<td>Body wall</td>
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</tr>
<tr>
<td>Pericardium</td>
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</tr>
<tr>
<td>Spleen</td>
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</tr>
</tbody>
</table>


### TABLE 41.2

<table>
<thead>
<tr>
<th>STAGING OF ESOPHAGEAL CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td>T Descriptor</td>
</tr>
<tr>
<td>Tis Carcinoma in situ</td>
</tr>
<tr>
<td>T1 Tumor invades lamina propria</td>
</tr>
<tr>
<td>T2 Tumor invades muscularis propria</td>
</tr>
<tr>
<td>T3 Tumor invades adventia</td>
</tr>
<tr>
<td>T4 Tumor invades adjacent structures</td>
</tr>
<tr>
<td>N Descriptor</td>
</tr>
<tr>
<td>N0 No regional node metastases</td>
</tr>
<tr>
<td>N1 Regional node metastases</td>
</tr>
<tr>
<td>M Descriptor</td>
</tr>
<tr>
<td>M0 No distant metastases</td>
</tr>
<tr>
<td>M1 Distant metastases</td>
</tr>
<tr>
<td>M1a Metastasis in coeliac lymph node</td>
</tr>
<tr>
<td>M1b Other distant metastases</td>
</tr>
<tr>
<td>M1a Metastasis in cervical nodes</td>
</tr>
<tr>
<td>M1b Other distant metastasis</td>
</tr>
</tbody>
</table>

| Tumors of Lower Esophagus     |
| M1a Not applicable            |
| M1b Nonregional lymph nodes and/or other distant metastases |

| Tumors of the Upper Thoracic Esophagus |
| M1a Metastasis in cervical nodes      |
| M1b Other distant metastasis          |

<table>
<thead>
<tr>
<th>Staging Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
</tr>
<tr>
<td>T1 N0 M0</td>
</tr>
<tr>
<td>III III III III III</td>
</tr>
<tr>
<td>T1 N1 M0</td>
</tr>
<tr>
<td>T3 N0 M0</td>
</tr>
<tr>
<td>IV IV IV IV IV IV</td>
</tr>
<tr>
<td>T2 N1 M0</td>
</tr>
<tr>
<td>T4, Any N, M0</td>
</tr>
<tr>
<td>Any T, Any N, M1</td>
</tr>
<tr>
<td>T1 N1 M0</td>
</tr>
<tr>
<td>IV A IV A IV A IV A</td>
</tr>
<tr>
<td>Any T, Any N, M1a</td>
</tr>
<tr>
<td>T2 N1 M0</td>
</tr>
<tr>
<td>IV B IV B IV B IV B</td>
</tr>
<tr>
<td>Any T, Any N, M1b</td>
</tr>
</tbody>
</table>
The key aims of staging both esophageal and gastric cancer are:

- To determine recurrence risk by assessing the locoregional (T and N) stage,
- To rule out distant metastases.

The gold standard method for the diagnosis of carcinoma of the esophagus and stomach is endoscopy. It offers both direct visualization of the tumor and the ability to acquire a histological diagnosis. There is limited data on the safety and efficacy of intensive endoscopic surveillance for patients with high-grade dysplasia, and no study has established that endoscopic screening and surveillance programs for Barrett esophagus decrease the rate of death from cancer (5). Fluorodeoxyglucose (FDG) positron emission tomography (PET) currently plays no established role in diagnosis but may have a use in the detection of the severe dysplasia that may be found in areas of Barrett esophagus.

Although endoscopy alone provides superb visualization of the mucosa, it does not provide information regarding the depth of tumor invasion or the extent of metastatic disease. This is where endoscopic ultrasound (EUS) is emerging as a powerful tool for accurate assessment of the luminal wall and local lymph node involvement (14–16).

Computed tomography (CT) is currently the most frequently used initial staging tool (17–21). Anatomical imaging with CT, however, has its limitations, as size criteria, such as that used for characterizing lymph nodes, cannot reliably differentiate benign from malignant disease. This is also a particular problem where small nodules in the liver and lung are encountered on CT (22,23). Staging laparoscopy is another tool that has gained favor as an adjunct to CT, and several studies have confirmed its accuracy compared to conventional imaging (24,25). Two prospective randomized trials have in fact shown a higher sensitivity in detecting small distant metastases than achievable with CT (23,26). In addition to staging, laparoscopy can aid palliation of patients with inoperable tumors by avoiding an unnecessary laparotomy (27).

### STAGING OF GASTRIC CANCER

<table>
<thead>
<tr>
<th>T Descriptor</th>
<th>Carcinoma in situ</th>
<th>Tumor invades lamina propria or submucosa</th>
<th>Tumor invades muscularis propria</th>
<th>Tumor invades serosa</th>
<th>Tumor invades adjacent structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>T1</td>
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<td>T2</td>
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<td>T4</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>N Descriptor</th>
<th>None</th>
<th>Metastases in perigastric lymph node (or nodes) within 3cm of the edge of the primary tumor</th>
<th>Metastases in perigastric lymph node (or nodes) more than 3cm from the edge of the primary tumor, along the left gastric, common hepatic, splenic, or coeliac arteries</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td></td>
<td></td>
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</tr>
<tr>
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<td></td>
<td></td>
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<tr>
<td>N2</td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M Descriptor</th>
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<th>Distant metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td></td>
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</tbody>
</table>

### Staging of Recurrent Disease

Development of recurrent gastric or esophageal cancer is nearly always fatal. It has been argued that early detection combined with aggressive treatment may offer improved survival in esophageal cancer (28). However, there seems to be no such evidence for gastric cancer, as current treatment options for recurrent disease do not offer any significant survival benefit (29–31). That said, in the majority of cases, detection and restaging of recurrent disease is performed using CT and, more recently, EUS. However, both these approaches are limited by their reliance on structural change. This, together with technical difficulties in performing endoscopy, invariably leads to loss of accuracy.

### PET

The fact that detection is also dependant on the signal intensity of metabolically active tissue (as opposed to lesion size only) gives PET the unique ability to detect functional or metabolic changes prior to the structural changes observed. This in turn has important clinical advantages with regard to diagnosing, staging, and prognosticating the disease. In this section, the role of PET with FDG will be reviewed. Currently, the breadth of evidence in this field is narrow, and data from series using PET-CT scanners are not yet available. Where possible, however, references will be made to the potential advantages of dual-modality imaging.

### Esophageal Cancer

#### Detection and Staging of Primary Disease

In esophageal cancer, FDG-PET has been consistently demonstrated to be highly sensitive for detecting both adenocarcinomas and squamous cell carcinomas (32–35). In Block’s study of 58 patients with histologically confirmed tumors, PET...
failed to detect the disease in only 2 patients, who subsequently were found to have small and early T-stage tumors (32). In 2000, Flamen et al. reported a sensitivity of 95% for primary tumor visualization in a cohort of 74 patients (36). Once gain, false negatives were associated with small T1 lesions. In 2001, in a tabulated summary of published data on 277 patients and 168 patient studies, Gambhir et al. showed FDG-PET to be 96% sensitive, compared with 81% for CT. On a lesion-by-lesion basis (545 lesions), the sensitivity, specificity, and accuracy of $^{18}$F-FDG-PET was 80%, 95%, and 86%, compared with 68%, 81%, and 73% for CT (37).

So far there is no concrete evidence to suggest that tumor tracer uptake (quantified using standardized uptake values [SUVs]) correlates with depth of tumor invasion (34,36). Furthermore, SUVs also do not seem to distinguish between different histological types (adenocarcinoma vs. squamous cell carcinoma) for CT (34).

The main limitations of imaging with FDG-PET are related to its false-negative and false-positive results. False negatives commonly occur in small and early-stage disease, as previously described. False positives are related to the uptake of tracer in areas of inflammation. This is commonly seen in reflux- or radiation-induced esophagitis (see Fig. 33.17). In most instances, the pattern of tracer accumulation is diffuse and can be correctly interpreted. However, focal accumulation of FDG in areas of suspected malignancy should be histologically confirmed.

To date, there has been only one published series of FDG-PET-CT imaging in esophageal cancer. In 2005, Cerfolio et al. compared CT, EUS with fine needle aspiration, and FDG-PET-CT in the restaging of patients receiving neoadjuvant chemotherapy (38). Their respective accuracy in distinguishing pathologic T4 from T1–T3 disease was 76%, 80%, and 80%, and their respective accuracy in detecting nodal disease was 78%, 78%, and 93%. These results need to be interpreted with caution, as only three patients in their study had T4 disease, none of which were correctly staged by the three imaging modalities. However, a combination of anatomic and biological imaging with dual-modality PET-CT, both in terms of local T staging of the disease and locoregional lymph node staging, shows promise and merits formal investigation.

**Nodal (N) Staging**

As previously outlined, lymph node involvement is the single most important prognostic factor in esophageal cancer. Several studies have compared FDG-PET with CT and EUS in local lymph node staging. Overall sensitivities for FDG-PET have been shown to be superior than those of conventional techniques, with quoted figures ranging from 22% to 76% for PET and from 0% to 87% for CT (32,33,36,39–41) (Fig. 41.1).

In a 2001 study of 53 patients, Kim et al. looked at the detection rates for FDG-PET and CT compared with the histopathological results of resected tumors that underwent an extensive lymphadenectomy (42). Here the sensitivity, specificity, and accuracy of $^{18}$F-FDG-PET in the detection of lymph node groups was 52%, 94%, and 84%, compared with 15%, 97%, and 77% for CT. Similar results have also been reported in a more a recent prospective study by Kato et al. (43). Once again, FDG-PET and CT showed similar specificities. The sensitivity of FDG-PET was superior to that of CT both for detection of lymph node groups and for overall N staging. This gave FDG-PET an incremental value over CT of 14% for lymph node staging.

In recent years, EUS has increasingly proven to be an accurate tool for locoregional staging of esophageal cancer (15,44–49). In 2000, in a comparison of $^{18}$F-FDG-PET and EUS, Flamen et al. demonstrated EUS to be more sensitive than $^{18}$F-FDG-PET (81% vs. 33%) but less specific (67% vs. 89%) (36). Furthermore, combining the results of CT and EUS failed to improve their cumulative specificity over that of $^{18}$F-FDG-PET alone. This clearly underlines the fact that, despite its superior sensitivity, EUS cannot differentiate between benign and malignantly enlarged lymph nodes, where metabolic imaging confers an advantage.

When evaluating locoregional disease, Block et al. described nodal stations as either adjacent or nonadjacent based on their proximity to the primary tumor (32). They felt this was necessary because the lack of spatial resolution with PET might make it difficult to distinguish between the uptake of FDG in the primary tumor and the adjacent nodal basin. Despite this finding, FDG-PET was almost twice as accurate as CT in predicting lymph node involvement (11 of 21 lymph nodes for FDG-PET vs. 6 or 21 for CT). It is believed that the advent of PET-CT cameras will overcome some of these limitations. By accurately localizing FDG-avid disease to either the primary lesion or the adjacent lymph node group, PET-CT is set to significantly improve the accuracy of locoregional staging. In addition, the problem of false negatives that have been attributed to the presence of small-volume disease, the poor spatial resolution of PET, and problematic attenuation in the chest may be overcome with CT attenuation correction.

Despite the reported superior accuracy of FDG-PET, the presence of locoregional lymph nodes, which may be resected with the primary disease, does not at present alter the surgical management of patients with esophageal cancer. Therefore, the impact of FDG-PET on management would occur following detection of distant nodal and systemic metastases that would render a patient inoperable. However, an area that requires further investigation is the potential role of FDG-PET in selecting patients for neoadjuvant treatments. In this respect, accurate locoregional staging with FDG-PET or PET-CT may have a more specific impact on the management of operable tumors.

There have been advocates of the combined use of carbon 11 $[^{11}$C]choline with FDG for the staging of small lymph nodes in the mediastinum (50), but the evidence is weak, and the jury is still out as to its potential benefits (51).

**Distant Metastases**

The identification of distant metastases is one of the most important determinants of operability in esophageal cancer. The impact of FDG-PET in management of these
patients has been predominantly seen where occult local or distant metastases are detected. This has been shown by several studies to occur in as many as 37% of the cases (32,33,40,52,53) (Figs. 41.2 and 41.3).

A more recent prospective study by Heeren et al., performed in 2004, evaluated staging with FDG-PET in 74 patients with a resectable carcinoma of the thoracic esophagus and the gastroesophageal junction (54). Imaging with PET was compared with EUS and CT imaging. Overall, EUS was shown to be superior to the other modalities in staging locoregional lymph node disease. Where 18F-FDG-PET performed better was in detecting distant node spread (stage M1a) and systemic spread (stage M1b). The sensitivity of FDG-PET for detecting distant node metastases was 71%, compared with 14% for EUS, 21% for CT, and 29% for CT and EUS combined. The specificities were not significantly different. Overall FDG-PET improved the sensitivity for detecting distant metastases from 37% for CT and EUS combined to 78%. Ultimately, staging changes occurred in 25% of cases; FDG-PET upstaged 20% (15 of 74) of cases missed by CT and EUS combined, and it downstaged 5% (4 of 74). However, false-positive and -negative results were encountered, and these resulted in incorrect staging in 11% (8 of 74) of cases. The authors therefore suggest the routine but selective use of FDG-PET in patients with operable tumors initially found to have TxN1 to T3Nx disease.

The ability of FDG-PET to detect unsuspected distant metastases has not yet been conclusively demonstrated. At the time of writing, the results of the multicenter prospective trial run by the American College of Surgeon’s Oncology Group (Trial Z0060), which aims to answering this exact question, were not yet available.

In addition to imaging the abdomen and chest with CT, diagnostic laparoscopy is also a widely used staging technique (55). Laparoscopy offers a sensitive method for identifying intra-abdominal metastases, with the added benefit of obtaining histological confirmation and accurately determining the resectability of the primary tumor. It is, however, an invasive method with recognized morbidity and even mortality (55–57). Further, laparoscopic port-site metastases, although rare, have been reported to be a risk.

Figure 41.1 A 65-year-old man with a 6-month history of dysphagia was diagnosed at endoscopy to have a tumor of the middle and the lower third of the esophagus. Biopsy confirmed this to be a squamous cell carcinoma. Preoperative 18F-FDG-PET-CT clearly demonstrated the primary tumor (MIP and sagittal slices shown). In addition, there was focal 18F-FDG uptake in two small (<1 cm) paratracheal lymph nodes 40 mm above the tumor (magnified transaxial slice of one lymph node shown). The information from the PET-CT scan directed an EUS-guided biopsy of these lesions, which were confirmed to contain metastatic spread. The patient was therefore offered chemoradiation and not surgery. (See also Cases 18 and 19.)
Figure 41.2  A 56-year-old man underwent an Ivor-Lewis esophagectomy for an adenocarcinoma of the lower esophagus. Ten months later he presented with epigastric pain, weight loss, and worsening pain in his left hip. The initial contrast-enhanced CT scan of the thorax and the abdomen was suggestive of thickening at the anastomotic site. However, a definite diagnosis of a recurrence could not be made based on morphological parameters alone. FDG-PET-CT was performed. Presented here are MIP (A), PET (B), CT (C), and PET-CT (D) images. As demonstrated by the transaxial FDG-PET-CT image, a focal area of tracer accumulation was detected proximal to the anastomotic site, consistent with a local recurrence. Furthermore, as demonstrated by the MIP image, there was clear evidence of widespread metastatic disease affecting the liver and the bones. In particular, there was involvement of the left femoral head, which accounted for the patient’s hip pain.

Figure 41.3  A 69-year-old man was diagnosed with an inoperable adenocarcinoma of the gastroesophageal junction. A staging FDG-PET-CT carried out prior to the start of medical treatment clearly showed the FDG-avid primary lesion (A: axial fused PET-CT slice). A further focus of FDG uptake was also detected within the abdomen (B–D), which was consistent with a malignant celiac node not previously seen on a staging CT. This example demonstrates how the fusion of biological and anatomical data with integrated PET-CT can be used to modify the radiotherapy field (E, red shaded boxes). In this case, the treatment field was extended to include both the primary lesion and the celiac lymph node metastasis.
activity and patient survival was also demonstrated. More metabolic activity within 2 weeks after therapy was associated with a subsequent decrease of tumor size, an increased rate of curative resections, and histopathologic tumor regression.

40 patients receiving preoperative chemotherapy for adenocarcinoma of the esophagus (69). A reduction of metabolic activity of 30% or more was seen within three cycles of treatment. The concomitant CT detected change in only 27% (11 of 40) of cases. A major impact of this occurrence in 5 patients with equivocal or negative conventional workup, where FDG-PET yielded a true-positive result. Another important advantage of biological imaging with FDG-PET is that it aids in differentiating post-therapy scar from a local recurrence. This has been frequently reported in a number of other cancers but not as yet in esophageal cancer.

**Gastric Cancer**

**Initial Staging**

The evidence supporting the use of FDG-PET in gastric cancer is unclear, as it is limited to a few small studies. An example of staging gastric cancer with PET-CT is shown in Fig. 41.4 (see also Fig. 36.1). Preliminary results by Yeung et al., in a 1998 study, for example, gave FDG-PET an overall sensitivity of 93% (12 of 13 cases) for detecting the primary disease (71). The one false-negative result arose in a diabetic patient with high serum glucose levels. More recently, in 2003, Stahl et al. showed that in a series of 40 patients with locally advanced gastric cancer, only 24 (60%) of the cancers were correctly detected with FDG-PET (73). Interestingly, the rate of detection of intestinal type
tumors was better than that of nonintestinal types (83% vs. 41%). The underlying reason for this difference was postulated to be the relatively higher proportion of mucinous tumors in the nonintestinal type group. The relatively lower FDG uptake in mucinous tumors has been previously reported by other groups (74).

In another small study of 38 patients, quantitative analysis of FDG-PET showed it to have a sensitivity, specificity, and accuracy of 83.3%, 87.5%, and 84.2%, respectively, compared with combined figures for CT, MRI, and ultrasound of 56.7%, 75% and 60.5% (75). FDG-PET imaging after 14 days of therapy correctly predicted histopathologic response in 77% of responders and 86% nonresponders. Once again, this study demonstrated that by detecting response to treatment earlier, the cost and morbidity associated with ineffective treatment can be avoided and alternative and more suitable treatment regimens pursued without delay.

Therapy Response
In terms of response to therapy, in 2003 Ott et al. prospectively evaluated the predictive value of a reduction in $^{18}$F-FDG activity in patients treated by preoperative chemotherapy (76). Eighty percent of the tumors were visualized with sufficient contrast for quantitative analysis (2 of 19 intestinal tumors and 7 of 25 nonintestinal tumors showed only low FDG uptake). FDG-PET imaging after 14 days of therapy correctly predicted histopathologic response in 77% of responders and 86% nonresponders. Once again, this study demonstrated that by detecting response to treatment earlier, the cost and morbidity associated with ineffective treatment can be avoided and alternative and more suitable treatment regimens pursued without delay.

Recurrent Gastric Cancer
Very little has been published regarding the use of FDG-PET in the management of recurrent gastric cancer. Potter et al. retrospectively studied 33 patients who had undergone surgical treatment for gastric cancer with a curative intent (77). In diagnosing recurrent disease, they found a sensitivity and specificity of 70% and 69%, respectively. Such poor results were partly explained by the histological type of the tumor. Their study did, however, demonstrate a significant relationship between $^{18}$F-FDG uptake and survival in this patient group.

Given the lack of available evidence to date, there is little justification for the routine clinical use of FDG-PET or PET-CT in the management of gastric cancer. The recommendations are therefore that they be used as problem-solving tools until further concrete data emerge.

CONCLUSION

Today’s stage-adjusted treatment of advanced esophageal cancers requires a meticulous diagnostic workup. Information from the use of endoscopy, EUS, CT, and MRI is increasingly being supplemented with information provided by FDG-PET. Accurate lesion localization with FDG-PET-CT is set to improve the detection of systemic metastases and may improve the detection of locoregional lymph node metastases, but data from large prospective series are awaited.

The increasing use of neoadjuvant strategies will also have an impact on the survival of advanced esophageal and possibly gastric cancer. It has been shown that patients who respond to neoadjuvant treatments appear to benefit most from subsequent surgical resection. This makes response evaluation and prediction important parameters in therapy planning. Imaging with FDG-PET provides relevant information both quantitatively and qualitatively, helping to assess response as early as 14 days after initiation of treatment.

Earlier detection of response, together with the ever increasing combination therapies being developed, may lead to management regimens that are more patient tailored, helping to avoid unnecessary side effects and minimize...
costs from ineffective treatment. Although the literature is yet to provide concrete evidence of the impact of FDG-PET on the survival of these patients, collective data to date are very promising.

Much of the focus of PET and PET-CT has remained on their use as diagnostic and staging tools. However, current and future developments in tracer technology, coupled with the quantitative nature of imaging with PET, have the potential to offer a vast array of clinical and research applications that may aid in improving the management of gastroesophageal cancers. Such advances may also require that the conventional criteria (e.g., RECIST and the WHO criteria) used for monitoring response to treatment are redefined.

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356  Molecular Anatomic Imaging

INTRODUCTION

Efforts have been made to differentiate benign from malignant liver lesions by morphological and functional imaging modalities. Since most of the tumors found are solid and therefore not easily characterized, additional morphological characteristics have been defined to differentiate benign from malignant lesions using form of the lesion, tissue densities, flow patterns, contrast enhancement over time, and signal intensities. Nevertheless, in many cases histological workup is still needed for definite diagnosis, especially in patients with known cancer.

In the recent years, use of fluorodeoxyglucose (FDG) positron emission tomography (PET) as an adjunct to morphological imaging modalities has increased. The ability to measure the glucose consumption of any kind of tissue by PET and therefore possibly characterize these lesions has attracted the attention of many clinicians. In general, malignant lesions show a higher FDG accumulation due to FDG trapping in tumor cells, which can be explained by decreased intracellular glucose-6-phosphatase (G-6-P) and increased hexokinase (HK) concentrations compared with normal hepatocytes (1). Additionally, this misbalance could also be directly correlated to the grade of tumor aggressiveness (1). Unfortunately, well-differentiated tumor cells may show normal or only slightly increased FDG uptake in relation to surrounding hepatocytes. Additionally, inflammation shows also increased FDG uptake, which is of major concern in the evaluation of pancreatic masses, when malignant disease has to be excluded (2). To overcome this problem, new data-acquisition strategies like dynamic kinetics and delayed FDG imaging, and dedicated contrast-enhanced CT in the same imaging session, could possibly evolve into the modality of choice.
Liver and pancreatic tumors, and possible implications for coregistered PET–computed tomography (CT) imaging are discussed in this chapter.

**LIVER**

**Infectious Diseases of the Liver**

Liver abscess and other infectious diseases, such as echinococcus disease, can be detected by FDG-PET (4–6). Unfortunately, those lesions may be indistinguishable from metastatic disease or primary liver tumors. Further, increased FDG uptake in the intrahepatic bile ducts after interventional therapy interferes with diagnosis. FDG-PET is not suited to be a first-line imaging modality in the detection of infectious disease of the liver but may be useful for follow-up examinations in selected diseases, such as in the measurement of disease activity in echinococcus disease (5).

**Benign Primary Liver Tumors**

Hemangiomas are benign liver lesions that occur in 4% and 7% of the population and may enlarge, especially during increased estrogen levels (pregnancy, iatrogenic). The typical hemangioma is small, asymptomatic, and discovered incidentally. Giant hemangiomas (diameter greater than 5 cm) may become symptomatic due to hemorrhage and thrombosis. Typical radiomorphologic features include hyperechoic lesions in ultrasound; hypodense, well-circumscribed lesions in non-contrast-enhanced CT; and nodular peripheral enhancement in contrast-enhanced CT scans. The imaging modality of choice is magnetic resonance imaging (MRI) by using heavily T2-weighted data acquisition, which demonstrate a typical hyperintense lesion (light bulb sign). Technetium 99m (99mTc)–labeled red blood cells have been used and show a typical increased accumulation during the blood pool phase in delayed imaging, but this technique has been superseded by MRI. FDG-PET imaging shows normal or decreased FDG uptake after 40 to 90 minutes. However, differentiation between tumor necrosis or inflammation by PET imaging is difficult, and therefore PET is not the imaging modality of choice.

Focal nodular hyperplasia (FNH) is rare benign hepatic neoplasm that is mostly seen in young female patients and has no risk of malignant transformation. Tumor tissue includes hepatocytes, bile duct elements, Kupffer cells, and collagenous tissue, which imposes as hypervascular structure. A central fibrous scar is common. 99mTc–sulfur colloid uptake is increased in 70% of the cases. FDG-PET imaging of such lesions shows no increased FDG uptake (7). Therefore, PET imaging is nonspecific and may be only useful for differentiating FNH from liver metastases in cancer patients if radiological imaging procedures fail.

Liver adenomas are less common than FNH, composed only of hepatocytes, and associated with oral contraceptives and glycogen storage disease. Radiological features include hypodense lesions in CT and variable echo-structure in ultrasound. Adenomas show no more uptake of 99mTc–sulfur colloids than does FNH. FDG-PET imaging has been described as showing no significant difference in uptake between adenomas and normal hepatic tissue (8).

In benign cystic lesions, FDG-PET shows decreased FDG uptake. However, only larger lesions (greater than 1 to 2 cm) may be seen as signal void in PET imaging. Therefore, FDG-PET imaging in benign solid hepatic lesions may only be useful for differentiating unclear radiological findings from liver metastases in cancer patients.

**Malignant Primary Liver Tumors**

Malignant primary liver tumors include hepatocellular carcinoma, fibrolamellar carcinoma, cholangiocarcinoma of the intrahepatic bile ducts, and mixed hepatocellular carcinoma and cholangiocarcinoma. Hepatic carcinomas are frequently multifocal and have been shown to involve multiple sites in both liver lobes at the time of exploration. Preoperative assessment should also include a search for extrahepatic metastases, since this condition will preclude a curative approach.

Hepatocellular carcinoma (HCC) is the most common primary visceral malignancy worldwide. The natural history varies widely among global regions, with the highest incidences found in southern Africa and Asia (especially Japan) (5% to 20%). Etiological factors and cofactors include chemical carcinogens (aflatoxin) and cirrhosis, which is irrespective of the etiology. However, cirrhosis induced by hepatitis B and C is a common cause. Carcinogen-related HCC grows fast in normal liver tissue and slower in cirrhotic livers. Solitary, multiple, and diffuse forms are described. Measurement of α-fetoprotein (AFP) may be helpful in diagnosis and as a prognostic factor. Several histological variants are described, and fibrolamellar carcinomas have the best prognosis if diagnosed early. However, the median survival of untreated patients is poor and ranges from 1 to 4 months after diagnosis. Interestingly, extrahepatic metastasis of HCC occurs relatively late in the clinical course and therefore does not significantly shorten the survival time. Whenever the stage of disease allows, surgical treatment should be pursued (9,10).

The diagnostic workup of hepatic lesions includes ultrasound, dynamic contrast-enhanced CT, and MRI. Ultrasound has a rather low sensitivity but a high specificity in detecting HCC. It is used beneficially in screening programs for HCC (11). In CT imaging, lesions appear as an imposing hypodense mass with early arterial enhancement. An advantage of this imaging modality is that it allows the simultaneous evaluation of vascular structures, such as the hepatic and portal veins, and their relationship to the tumor. Further diagnostic workup may include CT arterial portography (CIAP), which is an invasive procedure, since an intra-arterial catheter needs to be placed into the visceral arteries. However, the recently introduced
multi-row helical CT seems to produce equivalent results without invasive procedures such as needed for CTAP (sensitivity, 94%; positive predictive value, 96%) (12).

Torizuka et al. evaluated patients with known HCC by using dynamic and static FDG-PET data acquisition (1). High degrees of correlation were found between the histological grade and the kinetic rate constants as well as the hexokinase activity (Fig. 42.1). A second study by the same authors evaluating the usefulness of FDG-PET in the follow-up of HCC after intervention emphasized that measured activity could be well correlated with tumor activity (13). Moreover, Delbeke et al. reported rather good agreement in the differentiation of malignant and benign solid liver lesions by FDG-PET in a study of 110 consecutive referred patients (8). Interestingly, false-negative results in the detection of HCC occurred in 7 out of 23 patients. In two other studies using static FDG-PET imaging, only low sensitivity ratios in the detection of HCC were calculated, since well-differentiated HCC was not diagnosed due to undetectable changes in FDG uptake (14,15). This could be explained by the rather large number of well-differentiated HCCs in the study population and the low metabolic activity of low-grade HCC, described by Torizuka et al. (Fig. 42.2). On the other hand, FDG-PET was useful in the detection of extrahepatic disease not seen by ultrasound or CT. The conclusion from these findings is that FDG-PET seems not to be suited to the evaluation of patients with unclear solid liver tumors. Only in select cases with known HCC that is moderately to poorly differentiated might FDG-PET be useful for pretherapy detection of additional intra- or extrahepatic lesions and for post-therapy evaluation of recurrent disease. However, larger studies probably using combined dynamic and static FDG-PET data acquisition have to be performed to prove the efficacy of this method.

Only few studies have been performed on the use of FDG-PET for the evaluation of intrahepatic cholangiocarcinoma. This type of hepatic cancer is associated with primary sclerosing cholangitis (16). In a study by Kluge et al., sensitivity and specificity ratios for the detection of primary lesions of over 90% were reported (17). On the other hand, FDG-PET showed poor performance in the detection of locoregional metastases. Its performance in detecting distant metastases was somewhat better. In a study by Fritscher-Ravens et al., several false negatives occurred, especially in patients with mucinous adenocarcinoma; otherwise the same results regarding locoregional and distant metastases were achieved (18). Regarding the use of
PET-CT in the evaluation of cholangiocarcinoma, only limited data are available (19). In a study by Reinhardt et al., FDG-PET-CT was used for the differentiation of extrahepatic bile duct stenoses. With a threshold of 3.5 for the standard uptake value (SUV), all malignant causes for stenoses could be detected. However, the role of unenhanced CT or contrast-enhanced CT was not determined. In summary, detection of distant extrahepatic disease might be a possible application of FDG-PET-CT in this entity, but further prospective evaluations have to be performed.

To date, no conclusive data regarding the detection of gallbladder cancer are available (Fig. 42.3). Rare conditions like primary lymphoma of the liver have been described using FDG-PET (20).

**Figure 42.2** Coronal view of a PET-CT in a patient with well-differentiated to moderately differentiated hepatocellular carcinoma (HCC). A: Non-contrast-enhanced CT shows a large, slightly hyperdense tumor in the right liver lobe with a centrally hypodense area (white arrow). B: PET image shows slightly increased FDG accumulation with centrally missing activity (black arrow). C: Fused PET-CT image clearly assigns the low-activity region in the tumor to the hypodense area in CT, interpreted to be central necrosis in the tumor. (See also Case 26.)

**Figure 42.3** A 64-year-old patient with abdominal pain and weight lost. A: MIP image shows two hot spots, one in the liver (long arrow) and one in the porta hepatis (short arrows). On intravenous contrast-enhanced axial CT (B), PET (C), and fused PET-CT (D) images, increased uptake in tumor originating in the gallbladder wall (arrowheads) is visible. Multiple FDG-active locoregional lymph nodes are detectable (arrows). The diagnosis of an adenocarcinoma of the gallbladder was confirmed intraoperatively (stage T3 N1). (See also Case 21.)
Pancreatic Cancer or Pancreatitis?

Pancreatic cancer is a rather rare disease but accounts for over 4% of all cancer deaths in the United States each year. The poor prognosis is related to the fact that symptoms appear at advanced stages. Even now, there are no tumor-specific markers. Pancreatic cancer can arise from the exocrine pancreas (duct cell carcinoma accounts for 90% of all adenocarcinomas) and from the endocrine pancreas (islet cell tumor), which has a notably better outcome. Imaging modalities concentrate on the local extent of the disease, since curative surgical treatment only can be achieved in local stage disease without evidence of local lymph node involvement or infiltration beyond pancreatic tissue, especially into the splanchnic vasculature.

Spiral CT is the most commonly used imaging modality in adenocarcinoma of the pancreas. In a study by Choi et al., evaluation of dual-phase, contrast-enhanced CT in 22 patients with histologically proven adenocarcinoma of the pancreas demonstrated an accuracy rate of above 94% for the detection of the carcinoma and virtually 100% in the staging of unresectable disease (21). MRI has shown equivalent results. However, clinically much more relevant is the discrimination of pancreatitis from adenocarcinomas in unclear pancreatic masses. Several studies using CT or MRI showed only moderately good performance in this task.

In the last decade, several nonkinetic, semiquantitative FDG-PET studies have been performed in the evaluation of pancreatic masses. Friess et al. showed high sensitivity and specificity ratios (94% and 88%, respectively) in the detection of pancreatic cancer in 80 patients undergoing elective pancreatic surgery (22). Delbeke et al. reported similar results for FDG-PET in a patient population with suspected pancreatic carcinoma (N = 65), and these were also significantly better than those achieved with helical CT (23). However, Sendler et al. evaluated 42 patients with a pancreatic mass using both FDG-PET and CT but obtained moderate results in the detection of adenocarcinomas (FDG-PET: sensitivity, 71%; specificity, 64%) (24). A possible explanation is that different patient populations were examined in those studies or that the SUVs in activated chronic inflammation and well-differentiated adenocarcinomas overlap (Fig. 42.4) (2). To overcome these limitations, delayed imaging and dynamic kinetics have been evaluated. In a study by Nitsche et al., high accordance in the differentiation of pancreatitis and carcinoma was demonstrated when using this combined approach (3). Regarding detection of metastatic disease in the liver, FDG-PET was also highly sensitive. Therefore, a combination of dynamic kinetics and static FDG-PET imaging could be used as an imaging tool to determine whether a pancreatic mass harbors an underlying pancreatic cancer and, if so, whether distant metastases or a secondary tumor are present (Fig. 42.5).

Regarding the use of PET-CT for determining whether a pancreatic mass is chronic pancreatitis or pancreatic
Figure 42.5  A: Coronal FDG-PET image in a patient with suspected pancreatic cancer shows high FDG uptake in the region of the pancreas (arrowhead). B/C: Coronal CT and fused PET-CT image at same location. Circumferential, intermediate FDG uptake is seen located in the gallbladder wall, suggesting cholecystitis (arrow). Histological workup revealed an adenocarcinoma of the pancreas head and chronic inflammatory changes in the gallbladder. (See also Cases 22, 24, and 27.)

Figure 42.6  A 51-year-old patient with painless jaundice. A–C: Initial PET fused with contrast-enhanced CT images showing focal FDG uptake in the head of the pancreas corresponding to a cancer in the distal common bile duct (arrow). D–F: Following preoperative neoadjuvant chemotherapy, PET-CT was repeated for therapy assessment. The tumor is decreasing in size but still FDG active (partial response). A Whipple operation was performed, and tumor was staged as T3N0M0. (See also Case 28.)
carcinoma, Heinrich et al. evaluated 59 patients with suspected pancreatic cancer. These patients were staged using abdominal CT, chest x-ray and CA 19-9 measurement, and FDG-PET-CT, and the findings were confirmed by histology. Cost-benefit analysis was performed based on charged cost of PET-CT and pancreatic resection. The positive and negative predictive values for pancreatic cancer were 91% and 64%, respectively. False-positive results were due to inflammatory pseudotumor, pancreatic tuberculosis, chronic pancreatitis, and focal high-grade dysplasia, which was suspicious for malignancy by brush cytology. PET-CT detected additional distant metastases in five patients and a synchronous rectal cancer in two patients. PET-CT findings changed the management in 16% of patients with pancreatic cancer deemed resectable after routine staging \(p = 0.031\). In total, PET-CT reduced costs by $74,925 ($1,270 per patient) (25). Despite its impact on the staging of pancreatic cancer, neither PET nor PET-CT can replace contrast-enhanced CT and endoscopic ultrasound.

Local extent and especially vascular invasion can only be detected by contrast-enhanced helical CT or MRI. Therefore, PET can only be used as an adjunct to CT or MRI.

In the future, PET-CT, with the inclusion of dynamic kinetics, delayed FDG imaging, and dedicated contrast-enhanced CT in the same imaging session, could possibly evolve into the modality of choice. Furthermore, PET-CT may be useful for therapy assessment in pancreatic cancer (Fig. 42.6).

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PET-CT and SPECT-CT of Other Gastrointestinal Tumors: Somatostatin Receptor–Positive and Gastrointestinal Stromal Tumors

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Somatostatin receptor (SSTR)-positive tumors and gastrointestinal stromal tumors (GISTs) are relatively rare malignant tumors of the abdomen. SSTR-positive tumors typically are somewhat well differentiated and therefore are only amenable to fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging in cases where dedifferentiation has occurred. However, with the introduction of somatostatin receptor analogs for single-photon emission computed tomography (SPECT) imaging, such as indium 111 [111In]pentetreotide, and PET imaging with gallium 68 (68Ga)-DOTATOC, functional imaging methods have become important in tumor staging (see Fig. 43.6) and follow-up. In the imaging of these tumors, it is rare that a head-on comparison of SPECT and PET imaging is possible. Mainly due to the better resolution of PET-CT compared with SPECT-CT, but also due to the favorable uptake kinetics of the PET tracers, PET-CT is the preferred method, as it can identify smaller lesions and is therefore more sensitive. However, the availability of 68Ga-DOTATOC is not yet widespread. It is unclear whether PET with fluorine 18 (18F)-labeled agents such as 18F-Dopa is more or less sensitive than 68Ga-DOTATOC imaging.

GISTs have been virtually unamenable to therapy other than surgery. With the introduction of tyrosine kinase inhibitors, a substantial fraction of these tumors have become treatable, and long-range remissions have occurred. PET plays an important role in therapy assessment, as a reduction of FDG uptake seems to correlate well with the therapy response of the tumor and its metastases. However, CT has a complementary role to play, as it has been reported to detect more GIST lesions than PET alone and will aid lesion localization with PET. Thus, FDG-PET-CT may be considered the modality of choice for GIST staging and for evaluating the therapy response of these tumors.
SOMATOSTATIN RECEPTOR POSITIVE TUMORS

Somatostatin and the Somatostatin Receptors

The neuropeptide somatostatin was first identified in 1973 in ovine hypothalami (1) and has since been recognized as a major neurotransmitter and neuromodulator, with a mostly inhibitory capacity in that it regulates exocrine secretions, glandular secretions, neurotransmission (2), smooth muscle contractility, and absorption of nutrients.

Of particular interest is the ability of somatostatin and somatostatin analogs to act as cytostatic agents in their effect on tumor cells (3), as evidenced in many animal tumor models and cultured tumor cell lines.

Human somatostatin, a 14-amino-acid peptide (somatostatin-14; Fig. 43.1A), appears in several organ systems, such as the central nervous system, the hypothalamic-pituitary system, the gastrointestinal tract, the exocrine and endocrine pancreas, and the immune system. The diverse actions of somatostatin are mediated through interaction with a family of different specific, high-affinity somatostatin receptors (SSTRs) located on the plasma membrane of the target cells. To date, five human SSTR subtypes (SSTR1 to SSTR5) have been cloned and partially characterized (4). All five SSTR subtypes bind the endogenous somatostatin-14 with high affinity (in the nanomolar range). However, the short biologic half-life of somatostatin in vivo (about 2 minutes) prevents its application in the clinic. To overcome this drawback, analogs of somatostatin-14 consisting of 8 amino acids were developed (5).

These octapeptides (Fig. 43.1) exhibit a biological half-life on the order of several hours, and among them octreotide (Fig. 43.1B) is one of the clinically most relevant.

Although all five human SSTR subtypes bind somatostatin-14 with high affinity, there are differences in the binding affinities of the analogs; octreotide, for example, is bound with high affinity by the SSTR2 and SSTR5 receptor subtypes and with a modest affinity by SSTR3 but is not bound by subtypes SSTR1 and SSTR4.

Receptor-binding studies have identified SSTRs in the human brain as well as in numerous peripheral tissues, including the pituitary, pancreas, gut, and thyroid and the adrenal and immune systems, to name a few. The subtype most frequently expressed is usually SSTR2.

SSTRs, however, are not only expressed in the above tissues under physiological conditions. In the past decade, there has been increasing evidence for SSTR expression in various human cancers (6,7), in particular in gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

Neuroendocrine Tumors of the Gastroenteropancreatic System

Phenotypically, the cells of GEP-NETs belong to the system of disseminated neuroendocrine cells. This system is composed of cells that are scattered throughout the mucosa of the gastrointestinal tract or form the islets in the pancreas. These cells have many histologic similarities to neural cells such as secretory granules and the markers chromogranin A, synaptophysin, and neuron-specific enolase. These features
led to the designation "neuroendocrine cells." They constitute the so-called diffuse endocrine system (8).

Misunderstanding was perpetuated for the clinician by the application of different classifications and terminologies to the many varied types of neuroendocrine tumors of the gastrointestinal tract. In the past, pathologists called these tumors carcinoids because their histology is quite similar without special staining. This practice still is continued sometimes. In 1963, these carcinoids were subclassified (9) according to their embryologic site of origin as foregut carcinoids (lung, stomach, duodenum, biliary system, and pancreas), midgut carcinoids (small intestine, appendix, cecum, and proximal colon), and hindgut carcinoids (distal colon and rectum).

This classification was the first to emphasize clinicopathological differences between the tumor groups composing the gastroenteropancreatic neuroendocrine tumors but was not generally accepted by clinicians, because it proved too imprecise in distinguishing between the (biologically) different GEP-NET entities. Therefore, instead of "carcinoid," the neutral terms "neuroendocrine tumor" and "neuroendocrine carcinoma" were chosen for use in the new World Health Organization (WHO) classification of 2000 (10). It relates histopathology to biological behavior (i.e. prognosis). Three major categories of GEP-NETs have been defined: (a) well-differentiated neuroendocrine tumors (benign or low-grade malignancy), (b) well-differentiated neuroendocrine carcinomas, and (c) poorly differentiated neuroendocrine carcinomas. The criteria on which categorization of the tumors is based are, for example, size, presence of metastases, and proliferation index. The proliferation index is determined by the percentage of cells staining positively with a monoclonal antibody directed against a nuclear antigen in proliferating cells (Ki-67/MIB-1) (greater than 2% indicates increased degree of malignancy).

The term “carcinoid” is not completely abandoned. For gastroenteric NETs, it is still used synonymously with the term “well-differentiated neuroendocrine tumor.” The term “malignant carcinoid” is still used synonymously with the term “well-differentiated neuroendocrine carcinoma” (11).

Somatostatin Receptor–Positive GI Tumors

GEP-NETs are among the tumors that most frequently express SSTRs with high density and homogeneous distribution (others include medullary thyroid cancer, small cell lung cancer, meningioma, medulloblastoma, glioma, breast cancer, lymphoma, and renal cell cancer). Pancreatic NETs (e.g., gastrinomas, glucagonomas, and VIPomas) and gut NETs (foregut, midgut, and hindgut NETs) usually express SSTRs in 80% to 100% of the cases. Insulinomas, however, have a lower incidence of SSTR expression (about 50%).

Among the five SSTR subtypes, the SSTR2 subtype is the most frequently expressed in GEP-NETs, while SSTR4 is rarely detected. It is well known that undifferentiated GEP-NETs express SSTRs less often (and, if expressed, in lower densities) than well-differentiated GEP-NETs.

Therapy of GEP-NETs

Management of GEP-NETs is primarily based on surgical removal of the primary lesion and the metastases (12), as these slow-growing tumors are only minimally responsive to systemic chemotherapy.

Neuroendocrine tumors of the gastrointestinal tract and pancreas may present with hormone-related symptoms or without hormonal symptoms (so-called nonfunctioning tumors). Therefore, the treatment might have different aims, such as to control excessive hormonal secretion or retard tumor growth. Surgery is generally considered as the first-line treatment for patients with localized disease, because it can be curative. In patients with metastatic disease, surgery is palliative, directed toward a reduction of the tumor burden and a consequent decrease in hormone secretion.

Cytotoxic treatment has been applied to a number of GEP-NETs, particularly those with high proliferation capacity, with minor beneficial effect.

Interferon alfa has been used for the treatment of classic midgut carcinoids for almost 2 decades and has generated biochemical and symptomatic improvement in about 50% of patients but significant tumor reduction in only 10% to 15%. Stabilization of the disease has been obtained in 60% to 80% of patients up to 3 to 4 years (13,14).

Nonradiolabeled somatostatin analogs have been used for the management of clinical symptoms in patients with GEP-NETs, and significant biochemical and symptomatic improvement has been obtained in 50% to 60% of patients, but tumor reduction has been seen in only 3% to 5%. (14). Beta particle–labeled somatostatin analogs are well-established radionuclide therapy modalities for GEP-NETs (15). Yttrium 90 (90Y)– and lutetium 177 (177Lu)–radiolabeled somatostatin analogs have been used for the treatment of GEP-NETs. The physical characteristics of 90Y and 177Lu suggest that 90Y-labeled analogs are more suitable for radiotherapy of larger tumors, 177Lu-labeled analogs more suitable for smaller tumors (16,17).

Imaging

In practice, imaging of GEP-NETs is routinely performed with standard imaging techniques such as ultrasonography, CT, and MRI. There is little difference in sensitivity between CT and MRI, although the former is probably superior for localizing the primary tumor and thoracic lesions, whereas the latter may be superior in characterizing liver lesions. However, it is occasionally difficult to visualize GEP-NETs with CT or MRI because such tumors are frequently small and can be disseminated over several organ systems. Visualization of SSTRs in GEP-NETs is therefore considered an alternative approach, provided that the density of SSTRs is high enough for this type of imaging.
Somatostatin-Receptor Imaging

As stated above, human somatostatin and SSTRs are found in the cells of neuroendocrine organs and in some non-neuroendocrine cells (6). In addition, tumors that arise from these tissues also contain SSTRs. GEP-NETs possess an especially high density of SSTRs (7,18).

In comparison to nontumoral tissue, tumor cells, especially GEP-NET cells, express a significant higher amount of SSTRs for somatostatin and their analogs. This observation provided the basis for the development of various radiolabeled somatostatin analogs as imaging agents. Since native somatostatin has only limited clinical usefulness due to its short biologic half-life (less than 3 minutes), synthetic somatostatin analogs were developed. Octreotide was the first such analog (5). Native somatostatin-14 binds with high affinity to all SSTR subtypes 1 to 5 (IC$_{50}$ mean value $0.93, 0.15, 0.56, 1.5$, and $0.29$ nmol, respectively), whereas octreotide binds with high affinity only to SSTR2 ($IC_{50} = 0.38$ nmol) and with a somewhat lower affinity to SSTR3 and SSTR5 ($IC_{50} = 7.1$ and $6.3$ nmol, respectively).

Novel chelators, DTPA and DOTA, were designed for labeling with radiometals. The major step forward was achieved by the development of DOTA (19), a universal ligand for labeling with trivalent metal ions (indium, gallium, yttrium, lutetium), and the availability of new radiolabeled somatostatin analogs for scintigraphy (Fig. 43.1C), PET imaging (Fig. 43.1D), and radiopeptide therapy (Fig. 43.1E,F).

Somatostatin Receptor Scintigraphy with Indium 111 Pentetreotide (OctreoScan) SPECT/CT

In the late 1980s, Krenning et al. developed indium 111 [$^{111}$In]pentetreotide ($^{111}$In-diethlenetriamine penta-acetic [DTPA]-d-Phe1)-octreotide. It became the first commercially available radiopeptide (OctreoScan) containing a chelator-bound radiometal (20,21). Since this radiolabeled peptide exhibits a high affinity for the SSTR2 subtype, and because most GEP-NETs predominantly express the SSTR2 subtype, [$^{111}$In]pentetreotide appeared to be a suitable tracer for the visualization of GEP-NETs, especially when combined with SPECT (Figs. 43.2 and 43.3).

Figure 43.2  A female patient with a 2-year history of diarrhea and elevated chromogranin A for no apparent reason. SRS with OctreoScan was performed to exclude or confirm a neuroendocrine gastrointestinal tumor. A,B: Planar whole-body anteroposterior and posteroanterior gamma camera scans 6 hours postinjection without any pathological lesion. C-F: Planar spot scans of the abdomen 6 and 24 hours postinjection were unsuspicuous as well. G: Selected lateral SPECT view depicts a very small lesion (arrow) in the upper abdomen. Exact anatomic localization was not possible. H: SPECT-CT with a hybrid SPECT-CT system (GE Millennium VG, Hawkeye). The suspected lesion was localized in the gastric wall (arrow). Endoscopic surgery revealed a gastric carcinoid; the patient was cured of diarrhea, and the chromogranin A level returned to normal.
The diagnostic use of \([\text{\textsuperscript{111}}\text{In}]\text{pentetreotide}\) (i.e., somatostatin-receptor scintigraphy [SRS]) has been extensively reviewed (22). It is commonsense that SRS is the “gold standard” for a cost-effective diagnosis of GEP-NETs, and its sensitivity ranges from 60% to 90%; it can be beneficial not only for diagnosis but also for staging and follow-up of patients with GEP-NETs. The variation observed in the sensitivity of SRS may be due to the loss of SSTRs in some tumors (SSTR2 expression in insulinomas is about 50%). SRS is usually performed following the guidelines of the European Society of Nuclear Medicine (23) and consists in general of the intravenous administration of 100 to 200 MBq of \([\text{\textsuperscript{111}}\text{In}]\text{pentetreotide}\) and subsequent planar whole-body and spot scans and SPECT scans 4 to 6 hours, 24 hours, and 48 hours postinjection. After intravenous administration, \([\text{\textsuperscript{111}}\text{In}]\text{pentetreotide}\) initially localizes in the thyroid, pituitary gland, liver, spleen, kidney, and bladder. It is rapidly cleared from the plasma and is excreted predominantly into the urine.

There have been a number of direct comparisons between conventional imaging methods and SRS in which SRS demonstrated substantially better performance and also the ability to detect more abnormal lesions (24–26). This was true in patients with an unknown location of primary tumor or metastases, with metastases confined to the liver, and with widespread neoplastic disease. Importantly, SRS had a positive impact in patient management: in the study by Lebtahi et al., SRS changed the surgical strategy in 25% of 160 patients (26). SRS also changed the staging classification of 24% of the patients, reflecting increased detection of metastatic lesions with SRS compared with conventional imaging.

Gibril et al. prospectively evaluated the effect of so-called false-positive findings detected by SRS on patient...
management (25). Most of the false-positive images occurred in the imaging of physiologic conditions or of benign diseases where up-regulation of SSTRs could be anticipated (e.g., in thyroid, pituitary, and granulomatous lung disease).

Recent developments in helical CT have enhanced resolution beyond that of nonhelical CT. In one study with endocrine tumors of the gastrointestinal tract, helical CT correctly staged 92% of patients, compared with 75% staged correctly with SRS (27). This difference is probably due to the higher sensitivity of modern helical CT technology in liver lesion detection. SPECT increases the sensitivity in detecting SSTR-positive tissue, but SRS (planar together with SPECT) continues to be limited in its ability to determine the precise anatomic location of detected foci and often requires correlation with high-resolution imaging modalities for better topographic definition.

SPECT-CT (28,29) provides hardware-coregistered functional and anatomical images. When coupled with a low-dose CT, the images obtained are occasionally not diagnostic. Nevertheless, this system provides adequate information for the precise assessment of SPECT findings in most studies (Fig. 43.4), especially in patients with GEP-NETs. Pfannenberg et al. showed that SPECT could improve the specificity of SRS (30). Thirty-one lesions originally interpreted as benign or equivocal by SRS were reclassified as malignant, and 27 lesions originally interpreted as malignant by SPECT-CT or equivocal by SRS were reclassified as benign. Thus, the two imaging techniques proved to be synergistic and to complement each other.

Krausz et al., in a series of 72 patients with neuroendocrine tumors, reported that hybrid SPECT-CT imaging improved localization of SPECT-detected lesions in 23 out of 44 positive studies (31). These findings affected the diagnostic interpretation of SRS in 32% of the patients and induced changes in management in 14% of cases.

**68Ga-DOTATOC PET-CT**

There is only a limited number of clinical studies with 68Ga-DOTATOC PET in GEP-NETs. In a small series of four patients with GEP-NETs, Kowalski et al. evaluated 68Ga-DOTATOC PET in comparison with [111In]pentetreotide...
SPECT. These authors stated that, like $^{111}$In-pentetreotide, $^{68}$Ga-DOTATOC showed the highest uptake in the spleen, followed by the kidney and the liver (32) (Fig. 43.5A). The highest uptake values in tumor tissue are found about 60 minutes postinjection, but for clinical interpretation, even 40 minutes postinjection are sufficient to depict all tumor manifestations due to the high tumor-to-background ratio.

Hofmann et al. evaluated biokinetics and imaging with $^{68}$Ga-DOTATOC PET in 8 patients with metastatic carcinoid and compared these findings with those for $^{111}$In-pentetreotide (33). They found that $^{68}$Ga-DOTATOC is eliminated from blood more rapidly than has been reported for $^{111}$In-pentetreotide. Adrenal glands and the hypophysis (Fig. 43.5A, E–G) are delineated in almost all cases, and kidney uptake is substantially lower than occurs with $^{111}$In-pentetreotide. Tumor accumulation of $^{68}$Ga-DOTATOC is achieved very quickly (80% within 30 minutes), and renal clearance is rapid. Thus, high early tumor contrast is obtained. The authors stated that imaging should be done as early as 30 to 40 minutes postinjection to obtain maximum tumor-to-background contrast. $^{68}$Ga-DOTATOC PET identified additional lesions not identified on a diagnostic reference CT. $^{68}$Ga-DOTATOC allows for the detection of very small lesions.

It is well known that nuclear medicine images in general and PET images in particular demonstrate function rather than anatomy. However, anatomic landmarks are frequently needed to precisely identify the foci of abnormal uptake. With PET-CT, fusion of the morphological images of the CT can be a valuable adjunct in the interpretation of functional images as well as offer the possibility of overcoming intrinsic limitations in some PET images, like poor spatial resolution, limited signal-to-noise ratio, and poor tracer uptake in the diseased tissue. To date, no major clinical studies have been performed evaluating the benefits of PET-CT imaging with $^{68}$Ga-DOTATOC over PET imaging alone or over SRS SPECT-CT in GEP-NETs.

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**Figure 43.5** Physiological distribution of $^{68}$Ga-DOTATOC in a 48-year-old female patient as demonstrated in a PET-CT scan 40 minutes postinjection of the radiopharmaceutical depicted in MIP-PET (A). Note the strong physiological uptake in the spleen and kidneys (excretion route) and uptake into the liver and the hypophysis (arrow). Coronal CT (B), PET (C), and PET-CT (D) sections show liver and spleen uptake, and axial CT (E), PET (F), and PET-CT (G) of the brain localize the uptake to the hypophysis (arrow).
We have performed a yet unpublished first pilot study of 47 patients with metastatic GEP-NETs performed using a GE Discovery LS PET-CT device. Comparison of \( ^{68}\text{Ga-DOTATOC PET-CT} \) with Octreoscan gives a precise demonstration of the liver lesions and also shows some distinct abdominal foci. \(^{68}\text{Ga-DOTATOC MIP-PET} \) shows multiple lesions in the liver and abdomen; the number of lesions in both areas is considerably greater than in the SPECT-CT scan. \(^{68}\text{Ga-DOTATOC PET-CT fusion images} \) show one of the multiple very small (in the millimeter range) abdominal lymph node metastases not detectable in the gamma camera SPECT-CT. In \(^{18}\text{F-FDG PET-CT images}, \) including MIP-PET, CT, PET, and PET-CT, only a few of the known liver lesions show FDG uptake (giving a mixed intraindividual picture of receptor-positive and hyperbolic tumor manifestations).

Localization of these lesions was significantly more precise with \(^{68}\text{Ga-DOTATOC PET-CT}, \) than on SPECT-CT due to the better spatial resolution of the imaging systems used in PET-CT. The favourable biokinetics of \(^{68}\text{Ga-DOTATOC} \) in combination with the fusion capabilities of PET-CT made an even earlier diagnostic scan possible, because small lesions with poor uptake can readily be characterized.

Further clinical studies will certainly confirm that \(^{68}\text{Ga-DOTATOC PET-CT imaging} \) constitutes a relevant improvement over SRS SPECT-CT and \(^{68}\text{Ga-DOTATOC PET} \) in terms of imaging accuracy and time needed for a whole-body examination.
There are some indications, that fluorine 18 \(^{18}\)F-Dopa is also a suitable molecular tracer for detecting carcinoid tumors. The published results suggest that \(^{18}\)F-Dopa PET is superior to \[^{111}\text{In}^\text{pentetreotide}\] imaging and FDG-PET, but no direct comparison with \(^{68}\)Ga-DOTATOC data is available (34).

\(^{18}\)F-FDG PET-CT

The use of PET imaging in clinical oncology has significantly increased over the last decade. This is mainly the result of the use of the tracer \(^{18}\)F-FDG as a general tool for the study of glucose transport and metabolism in neoplastic tissue. Because neoplastic cells are characterized by a higher FDG uptake than normal cells, \(^{18}\)F-FDG can be used in (biochemical) imaging for the diagnosis and staging of various cancer. Unfortunately, NETs in general and GEP-NETs in particular cannot be visualized efficiently with this tracer, because NETs are mostly well differentiated and slow growing and have a low metabolic rate (35,36).

Although well-differentiated NETs, in general, fail to show significant FDG uptake, increased FDG uptake is seen in less-differentiated NETs. In contrast, SRS is positive in well-differentiated NETs, whereas its sensitivity for the imaging of less-differentiated NETs is clearly low or zero. It is well known that the prognosis of a patient with a GEP-NET is poor if the tumor shows characteristics of dedifferentiation (37). The combination of SRS and FDG-PET (e.g., in SPECT-CT and PET-CT techniques) appears appropriate for the noninvasive evaluation of the degree of dedifferentiation of these tumors and thus constitutes a prognostic tool. Little is known about the clinical significance of the coexistence of dedifferentiated cells within differentiated tumors (Figs. 43.6 and 43.9).

**Figure 43.7** A 68-year-old woman with a history of midgut carcinoid. The patient was referred for restaging 2 years after surgery. \(^{68}\)Ga-DOTATOC PET-CT 40 minutes postinjection, including MIP (A) and coronal section (B), demonstrate an abdominal lesion in addition to two liver lesions. Furthermore, the coronal section shows a cerebral lesion above the normal hypophysis. The abdominal lesion is hardly seen on the planar gamma camera OctreoScan 24-hour images (C, faint abdominal focus —>). PET-CT images (D–F) clearly demonstrate the abdominal lesion to be a mesenteric lymph node metastasis. The brain images show a cerebral meningioma (G,I) and the normal hypophysis (H,J).
GASTROINTESTINAL STROMAL TUMORS

Clinical Aspects

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Most GISTs originate in the stomach or the small intestine, but they may be found in any part of the gastrointestinal tract (Tables 43.1 and 53.1). GIST cells are similar to the interstitial cells of Cajal, which act as neuromotor cells in normal gut motility (38). Gastrointestinal stromal tumors are composed of spindle cells (70%) or epithelioid cells (30%). Sometimes a mixture of the two cell types are found. They are characterized by the expression of KIT. The diagnosis of GIST is performed by immunohistochemistry for CD117 (positive in 95% of GISTs), CD34 (positive in 70%), and other immunohistochemical markers (39). Apart from the presence of metastases and tumor invasion into adjacent organs, histology is used to define the risk of aggressive behavior: mitotic count rate and tumor size serve to rate GISTs from very low risk to high risk (Table 43.2) (40). In

<table>
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<tr>
<th>Location of Primary GISTS</th>
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<tr>
<td>Stomach</td>
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<td>Small bowel</td>
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<tr>
<td>Colon/rectum</td>
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<td>Esophagus</td>
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<td>Mesentery/peritoneum</td>
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Figure 43.8 Examples of patients with GEP-NET tumors and bone metastases. A–C: A 60-year-old man with a GEP-NET of unknown origin and carcinoid syndrome. The patient was referred for detection of the primary and for staging. Images include a MIP-PET with ⁶⁸Ga-DOTATOC (A) and corresponding axial CT (B) and PET-CT (C) images showing a bone metastases in the right pelvis, with some suggested sclerosis on CT. CT (D) and corresponding PET-CT (E) in another patient with a sclerosing bone metastasis in the thoracic spine. CT (F) and corresponding PET-CT (G) in a third patient with a metastasis in the left femur, showing slight sclerosis in the medulla.
addition, the location of the tumor is a key prognostic factor: approximately 70% of gastric GISTs are benign, and approximately 50% of duodenal GIST metastasize (41,42).

GISTs are known to be chemoresistant and insensitive to irradiation. The lack of therapeutic options in inoperable and metastatic disease meant that GIST patients in the past had a generally poor prognosis. Today, most metastatic GISTs may be treated successfully with imatinib (STI 571, Glivec, Gleevec, Novartis, East Hanover, NJ), a tyrosine kinase inhibitor. Thus, in patients with metastases, imatinib therapy will complement complete resection of the primary tumor (39). Although many patients profit from imatinib treatment and exhibit a long-time tumor response, either a partial response or a complete response, some patients do not respond to the treatment or show tumor progression while undergoing imatinib therapy. Therefore, accurate treatment monitoring must be considered crucial for patient management. Due to the lack of tumor markers, the assessment of tumor response is currently based on radiological imaging procedures. CT and FDG-PET are used most frequently for response monitoring. Some centers conduct MRI when assessing the liver for metastases. The imaging findings on CT and MRI are similar when assessing the primary tumor and metastatic disease. For the assessment of treatment response, functional data provided by FDG-PET and FDG-PET-CT are a reliable tool.

**Figure 43.9** A 63-year-old man with a history of metastatic pancreatic NET. The patient was referred for evaluation of recurrent disease and for restaging. Whole-body gamma camera OctreoScan image (A) shows multiple lesions in the liver but no other suspicious foci. SPECT-CT image (B) depicts the multiple liver lesions clearly. 18F-FDG MIP-PET (C) shows high FDG uptake by the multiple liver lesions; the number of lesions is comparable to the number in image A. The high FDG uptake is compatible with the partially undifferentiated histology of the tumor. D: Axial CT. E: FDG-PET. F: PET-CT. Hepatic lesions are clearly depicted in the native CT image and in the fusion image. Note the better spatial resolution of PET-CT (D–E) compared with SPECT-CT (B).
Radiological Appearance of GIST

Primary Tumor

The diagnosis of GIST is primarily based on the histopathology of endoscopically acquired tissue specimens of the tumor. In patients with GIST, imaging procedures are performed for better assessment of extraintestinal tumor invasion as well as for detection of peritoneal and distant metastases. However, in patients with tumors located in the small intestine or in tumors with submucosal tumor cell growth, endoscopic tumor detection may be compromised. In these patients, radiological imaging techniques may hint at the primary lesion. Thus, CT, MRI, and FDG-PET can be used to detect the primary tumor site in patients with histologically proven metastases from GIST.

When using FDG-PET-CT for the assessment of GIST, morphological and functional data are available for characterization of the primary tumor. Both types of data correlate well with macroscopic tumor assessment by the pathologist: in most cases, cross-sectional imaging of a GIST does not demonstrate a relevant intraluminal component based on the tumor’s intramural or submucosal growth. Although most GISTS of the small intestine grow exophytically, about 50% of gastric GISTS grow along the gastric wall rather than as a round mass (43). Exophytic tumor extension may compromise correct determination of the organ of origin on cross-sectional imaging alone, as the tumor may be found in close proximity to adjacent organs or may even infiltrate its surroundings. Even the use of contrast-enhanced CT data as part of the PET-CT examination may not compensate for this limitation. However, in patients with known GIST, the CT component of the PET-CT may be optimized for better assessment of the primary tumor. In cases with gastric or duodenal GIST, CT with water filling of the bowel lumen (hydro-CT) will improve delineation of the tumor and its potential invasion into adjacent structures (Fig. 43.10). Whereas hydro-CT is usually performed with water on stand-alone CT imaging, plain water seems suboptimal for PET-CT because of water absorption from the intestine between the acquisitions of the CT and the PET data. Different substances may be added to prevent intestinal water absorption while offering the same extent of intestinal distension during the CT and PET acquisitions. Our institution currently uses 1 liter of water with 2.5% of mannitol and 0.2% of locust bean gum as additives (44). The contrast agent is administered over 20 minutes before the start of the imaging procedure. When this protocol is used, the stomach, duodenum, and proximal jejunum are sufficiently distended. If the tumor is suspected of being located in the distal jejunum or ileum, 1.5 liters of negative contrast agent should be administered over 40 minutes.

The appearance of the primary tumor on FDG-PET-CT depends mainly on its size. In a study by Burkill et al. (45), 31 of 38 large tumors (>6 cm) were heterogeneous and small tumors (6.4 ± 2.7 cm) were homogeneous in appearance on CT (Fig. 43.11). In a series of 35 patients, Ghanem et al. (46) found similar results, with regular shape and homogeneous density in small GISTs (less than 5 cm). Intermediate-size and large GIST (greater than 5 cm) demonstrated irregular borders and heterogeneous density, with mainly central areas of hypoattenuation. These imaging characteristics apply to gastric tumors and GISTS of other parts of the intestine. According to these results, FDG uptake may be homogeneous in smaller tumors, whereas heterogeneous FDG uptake will be detected in larger lesions. GISTS are FDG-PET positive in the majority of cases. Heterogeneous imaging findings are mainly based on peripheral, rim-like FDG uptake or contrast enhancement, representing viable tumor tissue and a central area of decreased FDG uptake on PET and hypotenuation on CT. Histopathologically, this central area

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<tr>
<th>Tumor Size</th>
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<td>Very low risk</td>
<td>&lt;2 cm</td>
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<tr>
<td>Low risk</td>
<td>2–5 cm</td>
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<tr>
<td>Intermediate risk</td>
<td>&lt;5 cm</td>
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<tr>
<td>High risk</td>
<td>&gt;5 cm</td>
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<tr>
<td>Any size</td>
<td>&gt;10/50 HPF</td>
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HPF, high-power field.

Tumor size measured at single largest dimension.


Figure 43.10 Intestinal distension of the small bowel by a negative oral contrast agent improves delineation of a primary GIST within the jejunum. Without oral contrast, differentiation of the primary tumor from potential peritoneal seeds may have been difficult.
corresponds to either central hemorrhage or central necrosis. Air fluid levels may be detected in large lesions on the CT image. Although initially these air collections were interpreted as caused by superinfection in larger tumors, they rather seem to be caused by communication of the tumor with the intestinal cavity (Fig. 43.12). Of course, these imaging features on FDG-PET-CT are not specific for GIST. Differential diagnoses include leiomyoma, leiomyosarcoma, lymphoma, adenocarcinoma, and metastatic neoplasms.

Calcifications of GIST are rarely found and seem to be more frequent in the benign variant as compared with the malignant GIST. However, differentiation of benign from malignant GIST may not be based on the presence of calcifications, as this imaging feature may be detected in both variants. Both benign and malignant GISTs are FDG-PET positive in the majority of cases. There is a great overlap in the standardized uptake value (SUV) between benign and malignant primaries. For both, FDG-PET and CT, no correlation between malignant potential and the imaging findings has been described, apart from detection of a large tumor size, obvious local invasion, and metastatic lesions (38,47). Even though large GISTs have a higher malignant potential (see Table 43.2) and are commonly associated with central areas of hypoattenuation on CT, Kim et al. (48) did not find a correlation between the presence of hypoattenuated areas and a high mitotic rate in smaller GISTS (less than 5 cm). Thus, central areas of hypoattenuation on CT and central cold spots on FDG-PET may not serve as indicators of malignant tumor growth in smaller primary tumors. Given these limitations when determining a patient’s prognosis with imaging procedures alone, the prognosis should rather be based on a combination of histopathology (Table 43.2) and imaging findings (presence of local tumor invasion and distant metastases).

**Metastases**

The sites most frequently affected by metastases from GIST are the liver and the peritoneum. Peritoneal spread shows
as areas of focally increased FDG uptake in correlation with peritoneal seeds on CT (Fig. 43.13). An omental cake is an uncommon finding. Metastases to the lung, bone, or lymph nodes are rather rare. As with the primary tumor, the imaging findings for metastases are associated with their size. Before the start of pharmacological therapy, small metastases show homogeneously increased FDG uptake on PET and contrast enhancement on CT. Most metastases are hypervascular, which leads to early arterial contrast enhancement on CT and MRI (Fig. 43.14A) (49). However, hepatic lesions may be masked in the portal venous and venous phases on contrast-enhanced MRI and CT because of the assimilation of contrast enhancement by the lesion and the surrounding liver parenchyma (Fig. 43.14B). On unenhanced CT, these liver metastases show as hypoattenuated areas within the liver parenchyma (Fig. 43.14C). Thus, for detection of liver metastases, unenhanced CT may be preferable to a contrast-enhanced examination. An additional contrast-enhanced CT may be performed in cases of FDG-PET–negative findings to more accurately assess the primary tumor and potential peritoneal metastases which may not be well differentiated from bowel loops on the unenhanced scan.

Like the primary tumor, larger metastases show nonhomogeneous FDG uptake, with central cold spots. These cold areas correlate with areas of hypoattenuation on CT. As with the histopathology of the primary tumor, dissection of the metastasis after operative therapy reveals either central hemorrhage or central necrosis in these cases. And as with the primary lesion, calcifications are found rather rarely in metastases.

**Therapy Monitoring**

The response of a GIST to pharmacological therapy with a tyrosine kinase inhibitor can be monitored with morphological imaging procedures or with FDG-PET. FDG-PET and FDG-PET-CT have been shown to more accurately
differentiate responders and nonresponders than CT or MRI (50–52). However, the amount of baseline FDG uptake seems to be nondiscriminating in predicting the subsequent effect of imatinib mesylate (53). Even patients with a high SUV before medication may experience a complete metabolic response after initiation of the therapy. Thus, the assessment of tumor response with FDG-PET should be based on further follow-up rather than on the baseline values of tracer uptake. However, a pretreatment scan is desirable to discriminate FDG-PET–positive tumors from FDG-PET–negative ones and to have a baseline scan for comparing FDG uptake before and after initiation of the therapy. The optimal time for assessment of GIST therapy response with FDG-PET and FDG-PET-CT has not been defined. FDG-PET may show a therapy response of the tumor as soon as 24 hours after the first dose of imatinib. Most cancer centers currently scan their patients between 1 week and 4 weeks after initiation of imatinib therapy. However, if only FDG-PET data are available, false-positive results may occur in selected cases. In our own patient population (50), three patients demonstrated a decrease in the SUV 1 month after initiation of imatinib therapy, but these patients later proved to be nonresponders according to the standard of reference. The reason for the initial decrease in FDG uptake of these nonresponders is yet unknown. Evaluation of PET-CT data correctly characterized two of these patients as nonresponders by detection of new lesions on CT. Thus, addition of CT to PET can improve the assessment of GIST patients. Whether CT and FDG-PET images are read side by side or are acquired as one PET-CT examination seems to be of minor importance. In the study under discussion, FDG-PET-CT was more accurate in assessing tumor response than separately acquired FDG-PET and CT read jointly in only one patient ($N = 20$) (50).

However, detection of new lesions on the CT portion of the PET-CT examination must be analyzed critically to avoid false characterization of a patient as a nonresponder. GIST and its metastases are well known to liquefy when undergoing imatinib therapy, which leads to a decrease in lesion density on CT (Fig. 43.15). Solid lesions previously masked by contrast enhancement similar to that of the harboring organ (usually the liver) will be unmasked when turning cystic and may impress as newly developing

**Figure 43.14** A 42-year-old female patient with hepatic metastasis from a GIST. A: The arterial phase on MRI shows a contrast-enhancing lesion in the right lobe of the liver. B: The CT from the PET-CT examination was acquired in the portal venous contrast-enhancing phase. No hepatic lesion can be detected due to masking of the lesion. C: An unenhanced CT may be preferable to a portal venous phase in GIST patients, as liver metastases will not be masked by similar contrast enhancement of the lesion and its surrounding liver parenchyma.
metastases. Thus, if a new lesion is detected, the previous scan needs to be reassessed for potentially masked lesions. As stated before, masking of lesions is primarily due to similar contrast-enhancing characteristics of the metastasis and its harboring organs. On unenhanced CT scans, GIST metastases usually show as hypodense lesions surrounded by normal parenchyma (e.g., in the liver). Therefore, an unenhanced CT component of the PET-CT examination without intravenous contrast agents may be of benefit in these patients. Using unenhanced CT data, different authors have shown that more lesions may be detected with CT than with FDG-PET. Therefore, both imaging modalities complement one another when staging GIST patients. Reasons for the detection of fewer lesions with PET than with CT may include a limitation in the spatial resolution of PET (54) and breathing-associated smearing of FDG uptake. However, the additional lesions detected with the CT component of the PET-CT are of unknown relevance, as the treatment will be the same. Furthermore, so far no study has been able to histologically prove these additional lesions to be GIST metastases.

Although the use of intravenous contrast may obscure GIST metastases from detection, oral contrast agents will improve lesion detection and localization within the abdomen and should be part of the PET-CT examination. In patients undergoing imatinib therapy, cystic changes of the peritoneal metastases may make these lesions difficult to differentiate from bowel loops if a negative contrast agent is used. In these cases, a positive contrast agent may serve for bowel marking, but potential artifacts should be considered when evaluating the PET-CT images.

As stated before, the assessment of a potential tumor response to treatment is primarily based on the PET component of the combined imaging procedure. The main reason for the limited value of the CT is that CT response criteria, including those of the World Health Organization (WHO) (56) and those of the Response Criteria in Solid Tumors (RECIST) (57), are based on alterations in the lesion’s size. It is well known that even in patients responding to the therapy lesion size may not change until long after the start of the therapy. Thus, only a low agreement has been detected between tumor response and the CT images (50). A delay of
weeks to months may be observed when comparing morphological and functional changes in patients responding to imatinib treatment (55). Patients may even be falsely classified as nonresponders on CT alone because of initial lesion enlargement. Initiation of imatinib treatment may be associated with bleeding within selected metastases, resulting in lesion enlargement. The tumoral blood loss may be severe and require blood substitution. The PET component of the combined PET-CT will reveal these patients to be responders as FDG uptake decreases simultaneously. In this context, it may appear awkward that CT is still considered the modality of choice for the assessment of GIST response to treatment. Of course, financial aspects must be considered to be one reason.

However, there are two criteria not included in the WHO or RECIST criteria that offer accurate assessment of tumor response with CT. As stated above, GISTs liquefy when responding to imatinib. Cystic changes in the primary tumor and its metastases will be detectable in the majority of cases in which there is a response to the therapy (50,58,59). Threshold values have been proposed for more accurate assessment of tumor response on CT. A decrease in Hounsfield units of 25% may indicate a responding GIST, but further research in this field is necessary (50,58–60). Patients with tumor recurrence undergoing therapy will show an increase in FDG uptake on FDG-PET. The corresponding CT image often shows a “nodule within a mass” (61). This nodule-within-a-mass pattern serves as an important indicator of tumor progression on CT. Although lesion size can initially be unchanged in these patients, a newly developed, small, contrast-enhancing lesion can be detected within the liquefied metastasis (Fig. 43.16).

The reason for tumor recurrence is the development of an imatinib-resistant cell clone. Thus, often only one lesion or a limited number of lesions will show tumor recurrence. Treatment options are to increase the dose of imatinib or to pursue a surgical approach. Also, in long-term imatinib responders, additional surgical therapy may be an option. Bauer et al. (62) found residual tumor cells in histopathological specimens of patients with complete functional response and residual cystic lesions on CT. These residual metastases, mainly liver metastases, were resected, and viable tumor cells were found in the periphery of these lesions. Thus, imatinib seems to be able to inactivate but not completely eradicate GIST cells. Even though no increased FDG uptake may be detectable, additional surgical therapy should be discussed if residual lesions are present on CT to lower the risk of tumor recurrence.

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PET and PET-CT
of Colorectal and
Anal Carcinoma

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Colorectal cancer represents the commonest malignancy of the gastrointestinal tract. The application of positron emission tomography (PET) using fluorodeoxyglucose (FDG) has been frequently reported in the management of advanced and metastatic disease, and emerging data are continually redefining its clinical indications. The emergence of dual-modality imaging with integrated PET–computed tomography (CT) has further enhanced the power of imaging with PET, and the development of newer radiopharmaceuticals is bridging the gap between our understanding of cancer biology, from the bench to the patient.

The aims of this chapter are to review the most relevant current applications of FDG-PET, particularly PET-CT, in colorectal cancer. The use of some of the newer PET radiopharmaceuticals will also be outlined. Currently, there is little evidence supporting the use of FDG-PET in anal cancer. Yet, because of the recent overhaul in the management of this relatively uncommon malignancy, the potential use of FDG-PET will also be briefly discussed.

Colorectal Cancer

Background

Worldwide, an estimated 1 million cases of colorectal cancer were diagnosed in 2002. This accounts for more than 9% of all newly diagnosed cancers. Around 372,000 cases occur each year in Europe and 166,000 in the United States. In eastern Europe, the incidence of colorectal cancer (CRC) has been on the increase, while remaining stable in western Europe. The disease is commoner in patients over the age of 65 years, and although overall there is a slight male preponderance, over the age of 65 years this difference becomes negligible.

In the United Kingdom, approximately 55% of patients with CRC present at initial diagnosis with advanced disease (Dukes stages C and D). Of those with earlier disease who receive a curative resection, some 30% to 40% still go on to develop a local recurrence or metastatic disease. Therefore, early diagnosis and accurate staging represents the principal determinant of successful management of CRC.

Currently, the gold standard in diagnosing primary disease is endoscopy. This is followed by computed tomography (CT), which is routinely used for primary staging, surveillance for metastases, and detection of recurrent disease. Other conventional imaging tools such as ultrasound, magnetic resonance imaging (MRI), and, more recently, CT pneumocolonography are routinely applied according to institutional preferences and availability. Overall, however, the indications are that conventional imaging modalities seem to play a suboptimal role in the management of colorectal cancer, and hence much attention has been focused on molecular imaging techniques such as positron emission tomography (PET).

PET offers the clinician both an alternative and complementary means of assessing the gastrointestinal tract. Although fluorodeoxyglucose (FDG) has been the most successful and widely used PET radiopharmaceutical in
oncology, molecular profiling with alternative tracers and the advent of dual-modality PET-CT are reshaping the way we manage colorectal cancer.

Detection of Premalignant Colonic Lesions

Adenomatous polyps are benign neoplasms of colonic mucosa. In asymptomatic patients of average risk, its prevalence is approximately 10% from sigmoidoscopy and 25% from colonoscopy series (1). Worldwide, however, this figure varies among different countries. Colonic adenomas are well established as precursors of CRC (2), where the prevalence in these patients is approximately 1%. Barium enema and colonoscopy represent the gold standard for detecting these lesions, the later offering therapeutic as well as diagnostic benefits. More recently, CT pneumocolonography has also emerged as an alternative and accurate way of detecting polyps in patients unsuitable for colonoscopy.

Adenomatous polyps exhibit an enhanced glycolytic activity, and therefore the incidental detection of polypsis has been reported with FDG-PET (3). In a retrospective study completed by Yassuda et al. in 2001, FDG-PET was shown to have a true positive rate of only 24% (3). This figure did rise to 90%, particularly in polyps greater that 13 mm in size, suggesting that smaller polyps (less than 1 cm) may not be accumulating enough FDG to be detected at the resolution limit of PET. Although PET-CT may help in the localization of intraluminal lesions, the size and FDG avidity of the polyps would remain a limiting factor (Fig. 44.1).

Overall, while FDG-PET and PET-CT are not indicated for the routine detection of colonic polyps, focal FDG accumulation in the colon should not be ignored.

Screening

To date, the use of FDG-PET in screening for CRC has been reported by one study of 3,600 patients (4). Here, the prevalence of CRC was 2.1%, and FDG-PET had a true-positive rate and false-negative rate of 54% and 46%, respectively. These figures, coupled with the cost, availability, and radiation exposure risk of 18F-FDG, do not justify the routine use of FDG-PET and FDG PET-CT for screening purposes.

Role of FDG-PET in the Diagnosis of Primary Colorectal Cancer

The role of FDG-PET in routine preoperative diagnosis of primary CRC has only been reported in small patient...
numbers. Abdel Nabi et al., in 1998, reported FDG-PET to have a sensitivity and specificity of 100% and 48% (N = 48) (5). Similarly, in a 2000 study, Mukai et al. reported a true-positive rate of 98.5% (N = 24) (6). False positives often arise due to focal areas of FDG accumulation in, for example, diverticulitis or adenomatous polyps. Where physiological tracer uptake in the bowel is encountered, lack of anatomical localization with PET can also lead to diagnostic uncertainty. This has been addressed with PET-CT, and although its clinical impact in primary CRC has not yet been conclusively evaluated, early results have shown that PET-CT can improve the certainty of lesion characterization by 30% and the accuracy of staging by 11% (7).

Conventional anatomical imaging modalities remain the cornerstone for staging CRC. Local (T staging) of the tumor cannot be reliably carried out with PET due to its limited resolution and the effect of partial-volume averaging of the FDG signal. Although at present PET-CT imaging protocols limit the diagnostic capability of its CT component, future developments may allow PET-CT to confer advantages over CT alone or MRI alone.

In terms of lymph node staging (N staging), the sensitivity of FDG-PET has been shown to be similar to that of CT and generally poor (22% to 29%) (5,6). As the presence of lymph node metastases on CT are detected according to size criteria, image fusion with PET-CT may help further confirm the presence of disease, even in nonenlarged lymph nodes. A pitfall of this, however, is that false positives could result from the possible accumulation of 18F-FDG in reactive lymph nodes. In preoperative staging, FDG-PET has performed best in detecting hepatic and extra-abdominal metastases. Sensitivities of 88% to 91% and specificities of 91% to 100% have been reported, as compared with 38% and 97% for CT, respectively (5,8). This can lead to a change in treatment modality and the extent of surgery (8).

Overall, the indications are that FDG-PET or PET-CT play a limited role in the routine diagnosis and staging of primary CRC. However, in high-risk patients, its accuracy in detecting extracolonic disease may result in the avoidance of futile surgery.

**FDG-PET and PET-CT in the Detection of Recurrent and Metastatic Disease**

**Locoregional Recurrence**

After apparent curative resection of the primary tumor, the recurrence rate for colorectal cancer is between 30% and 40%, with the majority of recurrences occurring within the first 3 years after surgery (9,10). Of these, approximately 25% are isolated locoregional recurrences, which may be amenable to resection. In order to minimize unnecessary morbidity and mortality from surgical treatment, accurately identifying the extent of recurrent disease is vital for appropriate patient selection.

The role of FDG-PET in detecting recurrent and metastatic colorectal cancer has been demonstrated by several authors (11–31) (Table 44.1 and Fig. 44.2). A particular challenge of anatomical imaging modalities has been to differentiate scar from local recurrence. The reported accuracy of FDG-PET in detecting pelvic recurrences is 95%, as compared with 65% for CT (25). In particular, Valk et al. demonstrated the sensitivity and specificity of FDG-PET to be 93% and 98%, whereas for CT they were 69% and 96%, respectively. This led to significant cost savings from the avoidance of futile surgical intervention (28). Image fusion with PET-CT further adds to the diagnostic accuracy of 18F-FDG-PET. It is particularly effective in characterizing a presacral mass, with a quoted sensitivity of 100% and a quoted specificity of 96% (32).

Intensive follow-up after treatment with regular imaging (ultrasound or CT) and tumor marker levels has consistently been shown to correlate with improved survival figures. Measurement of serum carcinoembryonic antigen (CEA) levels is a simple method that can give a first indication of tumor recurrence in approximately 60% of cases, with a mean sensitivity of 80% (range, 17% to 89%). However, up to 30% of patients have been reported not to express the antigen.

One of the areas where FDG-PET plays a significant role is in the assessment of patients with rising CEA levels and negative conventional imaging (Fig. 44.3). Flanagan et al. showed FDG-PET to have positive and negative predictive values of 89% and 100%, respectively (16). Flanagan et al. also reported similar findings, but their false-positive rate of 21% was significant (15). The question remains whether all patients with a rising CEA should receive an FDG-PET scan. A pitfall of this approach is the false-positive rate of CEA (5% to 16%). On the other hand, routine 18F-FDG PET-CT as a first-line imaging modality, followed by further investigation guided by PET-CT, is also a valid strategy (33,34). This paradigm requires in-depth examination.

**Metastatic Disease**

The principal advantages of FDG-PET are that it is a whole-body modality and that biological signals of disease can be detected before morphological changes become apparent. Detection of these signals often results in the detection of unsuspected metastases, which can occur in 13% to 36% of cases and have a clinical impact in 14% to 65% (12,15,16,19,22–26,35,36). In whole-body imaging, Valk et al. showed the sensitivity of FDG-PET to be higher than that of CT at all sites except for the lungs, where the two were equivalent (28). The differences in detection rate were greatest in the abdomen, pelvis, and retroperitoneum, where almost 30% of lesions missed on CT were detected with 18F-FDG-PET. Lai et al. also reported similar findings, but their study suggested FDG-PET to be superior in the lungs (22). The significant advantage of dual-modality PET-CT imaging is that it aids in differentiating areas of pathology and normal uptake, which is especially relevant to the issues mentioned in this paragraph.
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Figure 44.2 A 63-year-old man previously treated with a right hemicolectomy for a perforated cecal carcinoma presented on follow-up with rising CEA levels. A CT scan of the abdomen and pelvis was negative. FDG-PET-CT demonstrated an area of tracer accumulation corresponding to the anastomotic area and thus representing a local recurrence. (A) MIP image, (B) Axial CT; (C) Axial FDG-PET; (D) axial PET/CT fused image. (See also Case 47.)

Figure 44.3 A 63-year-old man with a complicated history of ulcerative colitis underwent a subtotal colectomy and ileoanal pouch formation 10 years ago. Six years later, he developed an adenocarcinoma within the pouch, which was excised. On follow-up, he was found to have rising CEA levels, but conventional imaging results were negative. FDG-PET-CT correctly identified a small focus of FDG activity consistent with a pelvic recurrence. This was not amenable to further surgery due to its dense adhesion to small bowel, as shown on the PET-CT images. The patient was therefore treated by palliative chemotherapy. (A) Coronal section of FDG PET scan; (B) Axial CT; (C) axial FDG-PET; (D) axial PET/CT fused image.
The liver is the commonest site for CRC metastases, which can occur in up to 40% of patients after a curative resection (Fig. 44.4). Of these, less than 5% are amenable to surgical resection, which can achieve a median 5-year survival rate of approximately 30% (range, 12% to 41%) (37–49). Although solitary liver metastases confer a better prognosis, with more aggressive regimens that include a combination of multiple or sequential hepatic resections, intraoperative radiofrequency ablation (50), and selective hepatic embolization, improvements in survival figures are being continually achieved. Ultimately, the accuracy of the preoperative assessment of hepatic and extrahepatic tumor burden becomes the main determinant of outcome.

Ultrasonography and contrast-enhanced CT currently represent the first-line imaging modalities of choice in the assessment of liver metastases. MRI may represent an alternative to the above but requires validation.

FDG-PET, as compared to conventional imaging with CT, has consistently been shown to have superior sensitivity and specificity in detecting liver metastases. Table 44.1 summarizes these findings (5,15,22,25,26,28,29,51–59). A meta-analysis by Heubner et al. gave FDG-PET a weighted average sensitivity of 90.86% (range, 86.2% to 95.62%) and specificity of 96.97% (range, 92.5% to 100%) (54). A point of note, however, is that the majority of these studies prospectively analyzed the FDG-PET data and compared them to retrospectively reviewed CT results. The CT scans were also carried out using different imaging protocols, resulting in significant data heterogeneity. Therefore, although FDG-PET over all demonstrated an exquisitely high detection rate, its comparison with CT requires a more careful consideration.

Recently it has been suggested that the preoperative assessment of patients with liver metastases correlates with improved long-term survival. By improving patient selection for surgery, FDG-PET has been reported to result in 5-year survival rates as high as 58%, compared with a median of 30% for conventional imaging (60). The question remains whether FDG-PET and PET-CT should be routinely used in the preoperative assessment of liver metastases. One factor that may be of significance is the “clinical risk score” of the patient (40). A recent study by Schüllser-Fiorenza et al. suggested that patients with a clinical risk score of 0 and an isolated hepatic metastasis should only “undergo conventional imaging before surgical exploration” (61). This is backed up by other recent papers that
have shown FDG-PET and PET-CT to provide information regarding liver metastases similar to that achievable with contrast-enhanced multi-detector CT. However, detection of unrecognized extrahepatic disease and intrahepatic recurrences following liver surgery remains the strength of FDG-PET and PET-CT imaging (62,63).

Clearly, the emerging multi-detector CT technology is continually narrowing the gap between the capabilities of CT and FDG-PET in detecting colorectal liver metastases. Despite this, in characterizing lesions less than 1 cm, there is no consensus on the best imaging modality to use.

The Impact of Dual-Modality Imaging with PET-CT in Colorectal Cancer
The incremental value of 18F-FDG PET-CT over FDG-PET alone has been demonstrated in a retrospective study by Cohade et al. (7). In 45 patients, 18F-FDG PET-CT achieved a 50% reduction in the proportion of equivocal and probable lesions, a 25% improvement in lesion localization, and a 11% increase in accuracy of staging (from 78% to 89%). Interpretation of the CT component of PET-CT alone was also shown by the same group to provide valuable additional information. Similar results were reported in a larger series of 204 patients with suspicious malignant lesions, of which 34 patients had a gastrointestinal malignancy.

More recently, a comparison between whole-body 18F-FDG PET-CT and MRI (in a range of solid malignancies, including CRC) revealed that, overall, PET-CT was superior in all staging categories (64). However, interestingly, MRI was superior to 18F-FDG PET-CT in detecting liver and bone metastases. Currently, the limitation of PET lies in detecting small (less than 5 mm) liver lesions, where high-resolution MRI may perform better.

The impact of accurately diagnosing and staging CRC is clear. As larger prospective series emerge, the true clinical value of dual-modality imaging will become more apparent. The area where PET-CT shows real promise is in directing the subsequent investigation and treatment of patients. The superior sensitivity of PET, coupled with anatomical information provided by the CT scan, can, for example, help increase the yield of image-guided biopsies (65). With the biological boundaries of the tumor volume in mind, surgeons can also perform more precise resections, and radiotherapy planning can also be altered, ultimately providing treatment that is more patient specific (66).

Therapy Response Monitoring with PET
Measuring tumor response to treatment based on morphological parameters has been a widely debated subject (e.g., Response Criteria in Solid Tumors [RECIST] and World Health Organization criteria). For this reason, quantitative imaging of tumor metabolism with FDG-PET confers important advantages. However, the evidence to date for the use of FDG-PET in treatment response is small.

Response to Radiotherapy
It has been shown that a reduction in FDG uptake correlates better with palliative benefit of radiotherapy than CEA levels (67). Early after radiation treatment, an increase in FDG uptake is seen that is attributed to the induced local inflammatory response. Although a clear timepoint has not been demonstrated, the presence of activity at 6 to 8 weeks following radiotherapy is often taken as evidence of residual disease. In locally advanced rectal cancer treated with chemoradiation, Guillem et al. demonstrated that a reduction in mean FDG SUVs at 4 to 5 weeks following chemoirradiation was a predictor of long-term outcome (68). Furthermore, the presence of hypermetabolic foci up to 6 months after radiation therapy of rectal tumors can be a strong indicator of disease recurrence (69).

As previously mentioned, one of the specific advantages of PET-CT is that it aids in radiotherapy planning. The addition of metabolic boundaries to anatomical data can lead to significant alteration of gross tumor volume (GTV) estimations, thus improving the effectiveness of treatment and reducing unwanted side effects (65).

Response to Chemotherapy
5-Fluorouracil (5-FU) has been the most successful and widely used chemotherapeutic agent in colorectal cancer for over 40 years. However, overall response rates to it in advanced disease have been poor. Newer agents such as oxaliplatin and irinotecan have had response rates of up to 70%, but they are also associated with some debilitating side effects. The need for appropriate patient selection is therefore clear, and hence the ability of PET to potentially detect early biological response could be important.

The evidence to date has been encouraging. Findlay et al. examined 18F-FDG uptake parameters in 27 liver metastases (tumor-to-normal-liver ratio (T:L) and SUV) at 1, 2, and 4–5 weeks post-treatment with 5-FU (70). Reduction in the T:L ratio of 67% and 99% were observed in responders and nonresponders, respectively (p < 0.01) (70). Use of 18F-labeled fluorouracil (18F-FU) has also yielded interesting results. Early evidence in human studies demonstrated that responsive tumors were associated with a higher 18F-FU uptake than in nonresponsive tumors (71).

FDG-PET has also been recently used to determine biological response to novel antibody-based agents. An example is bevacizumab, an anti-VEGF monoclonal antibody recently licensed for use in the treatment of advanced colorectal cancer (Fig. 44.5). A reduction in tumor 18F-FDG uptake has been shown to correspond with a reduction in blood supply as measured using dynamic CT and histopathological findings (72).

Monitoring Local Ablative Therapy
Local ablative therapy of colorectal liver metastases is an increasingly accepted means of treating liver and lung metastases not amenable to resection. Where liver metastases have been treated by radiofrequency ablation, FDG-PET is more
accurate than CT for early recognition of incomplete tumor destruction (73–75).

Limitations of 18F-FDG-PET
One of the key limitations of imaging with FDG-PET is lesion size, as lesions less than 1 cm are frequently missed due to partial-volume effects. This is particularly important in the liver, as there is currently no single imaging modality of choice for detecting such small metastases. False-negative findings also commonly occur in mucinous tumors. This has been attributed to the relatively low cellularity of this tumor type and is possibly a result of the abundant mucin (which is rich in polymucosaccharides) competing with 18F-FDG for uptake sites (76).

Activated macrophages and inflammatory tissue also have a high uptake of 18F-FDG, possibly leading to false-positive findings. This is of significance in inflammatory bowel disease and in a mass resulting from diverticulitis. Granulomatous diseases such as sarcoidosis and tuberculosis may also produce false-positive results that may lead to unnecessary invasive investigations in order confirm them.

Finally, as normal bowel also demonstrates background 18F-FDG uptake, this uptake can occasionally lead to diagnostic uncertainty. Careful clinical assessment, appreciation of the pattern of uptake, and correlation between CT and PET-CT findings can all help avoid wrong interpretations (52).

New Developments in Radiotracer Technology
Emerging advances in PET-CT and radioligand development are paving the way toward a better understanding of cancer function and biology. Probing the cellular and molecular events of tumorigenesis in vivo has the potential to accelerate cancer research by shortening the gap between preclinical and clinical research.

A number of tracers other than FDG have been assessed in CRC but with varying success. For example, measuring cellular proliferation with labeled thymidine and its analogs has received considerable interest. In addition, carbon 11 [11C]thymidine has been used in several cancers, including gastrointestinal tumors. The rapid metabolism of [11C]thymidine into its labeled metabolites and the short half life of 11C (20 minutes) have limited its routine use, however. The subsequent introduction of the thymidine analog [18F]-3′-deoxy-3′-fluorothymidine (18F-FLT) has been a welcome development (77).

In locally advanced and metastatic colorectal cancer, Francis et al. showed that FDG-PET is still superior to 18F-FLT-PET
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for whole-body staging (78). Although 18F-FLT-PET detected tumors at all primary and peritoneal sites, its sensitivity for detecting liver metastases was very poor (37% for 18F-FLT-PET vs. 97% for FDG-PET). Approximately 30% of injected 18F-FLT is catabolized in the liver by glucuronidation, a factor that results in high background levels of tracer and therefore a reduced detection rate for liver lesions. Furthermore, background 18F-FLT uptake in highly proliferating organs such as the bone marrow makes the interpretation of bony spread difficult (79).

18F-FLT is unlikely to be of diagnostic or staging value, but it may have prognostic implications. 18F-FLT SUVs have been shown to strongly correlate with histological proliferation marker Ki-67 antigen expression (80). Conversely, no correlation was found between FDG SUVs and Ki-67. This therefore suggests that glycolysis and proliferation may have independent prognostic functions in tumorigenesis. Furthermore, as 18F-FLT uptake mirrors relative activity of the salvage pathway of pyrimidine synthesis, there is at least a theoretical basis supporting its use for investigating biological response to agents that inhibit the de novo pathway (e.g., 5-FU). This, however, requires further evaluation in the future.

Another recent 18F-labeled tracer is the pyrimidine analog 18F-FAMU, which has the potential to image the DNA synthetic pathways (81). As with 18F-FLT, imaging of the upper abdomen with 18F-FAMU is restricted by high levels of physiological uptake by the liver, and therefore this tracer is unlikely to be of clinical value.

ANAL CANCER

Anal cancer is a rare disease that accounts for no more that 4% of cancers of the lower gastrointestinal tract. Its incidence is higher among homosexual men and higher still in those who are HIV positive. Squamous carcinoma is the most common histological subtype. It predominantly spreads via the lymphatic system, and around 10% of patients present with synchronous nodal disease. Hematogenous spread is less common, but up to 10% to 17% of patients can present with liver and lung metastases. The majority of patients have symptoms at presentation, which often prompts early diagnosis.

Diagnosing anal cancer is mainly done through cytopathological or histological means. Locoregional staging includes imaging with ultrasound, CT, or MRI of the pelvis, the latter allowing a more accurate visualization of the pelvic organs. Over the past few years, there has been a significant revision in how anal cancer is diagnosed and managed. Currently, surgery is used as a diagnostic and supportive measure, although complete excision of an early tumor is associated with 5-year survival of more than 80%. Primary therapy of advanced disease is with synchronous chemoradiation. Overall, the prognosis of anal cancer is dependant on a number of factors, such as age, sex, stage, nodal status, and response to chemoradiation. Well-differentiated tumors tend to have favorable outcomes (5-year survival greater than 75%), while prognosis in those with a high-grade tumor and lymph node spread remains abysmal (5-year survival less than 20%). The role of imaging in accurately staging the disease therefore is of vital importance.

To date there has been no formal evaluation of FDG-PET or PET-CT in the management of anal cancer. Anecdotal evidence does, however, support its use in advanced disease, where equivocal metastatic lesions can be investigated. Detecting spread to lymph nodes is a vital part of staging, as lymph node metastases confer particularly poor prognosis (5-year survival less than 20%) (Fig. 44.6). Currently,
ultrasound-guided fine needle aspiration cytology (FNAC) and sentinel lymph node biopsy are being evaluated. FDG-PET-CT, which has the advantage of being noninvasive, may be of value in detecting occult lymph node disease. However, extrapolating from the low sensitivity of FDG-PET in detecting lymph nodes in CRC, this at present seems unlikely.

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**SUMMARY**

There is currently little evidence supporting the use of 18F-FDG-PET for screening asymptomatic individuals, and current modalities appear better suited for detection of primary CRC in symptomatic patients. There is also little evidence supporting the routine use of 18F-FDG-PET in staging primary disease, but large series using PET-CT are avidly anticipated.

With respect to imaging suspected recurrent disease, both FDG-PET and PET-CT are more sensitive and specific than conventional techniques. Using them can result in altered clinical management and cost savings. Recently, the clinical impact of FDG-PET and PET-CT in detecting hepatic lesions has been questioned. The detection of small lesions remains a challenge, and the indications are that the clinical yield from using PET to assess hepatic metastases is higher in patients with a higher clinical risk score.

Despite much advancement in the field of tracer technology, FDG seems to have remained the gold standard for diagnostic use. Other tracers may indeed aid in answering specific questions, particularly when molecular profiling of colorectal cancer in vivo is of interest. PET also appears to have a specific role in the evaluation of patients undergoing radiotherapy and chemotherapy, a role that requires further expansion with the addition of new specific and nonspecific tracers.

There is a complete void of evidence regarding the application of FDG-PET in the management of anal cancer. Currently, the only reason for using FDG-PET and PET-CT in anal cancer would be to determine metastatic spread in locally advanced disease, but their role in staging local lymph node disease requires formal examination.

Finally, true image fusion with PET-CT confers many important advantages. The challenge now is to precisely define its routine application in the management of lower gastrointestinal malignancy.
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INTRODUCTION

As discussed elsewhere in this book, cancers differ functionally and to some extent anatomically from normal tissues, allowing detection by functional and anatomic as well as hybrid imaging methods. Like many epithelial cancers, breast cancers have a variety of phenotypic deviations from normal breast tissue. These include, but are by no means limited to, the following:

- Increased tumor blood flow and increased vascular permeability compared with normal breast tissue (the physiology by which gadolinium contrast magnetic resonance imaging (MRI) of breast cancer appears to produce its signal);
- Increased levels of glucose metabolism;
- Increased amino acid transport and protein synthesis;
- Increased receptor expression (such as overexpression of the estrogen receptor);
- Increased DNA proliferation rates; and
- Hypoxia in many of tumors.

All of these processes can be imaged with positron emission tomography (PET). Although PET tracers targeting these processes have been evaluated to some extent in breast cancer, most clinical work using PET in breast cancer
imaging has been performed with the tracer fluorodeoxyglucose (FDG) (1,2).

We and others have shown that the vast majority of breast cancers overexpress the glucose transporter molecule GLUT-1 and that there is a general relationship between the viable cancer cell number and the FDG accumulation in primary breast cancers. There is a correlation between the GLUT-1 levels, the number of viable cancer cells, and the FDG accumulation in these tumors (3–5). In addition, there is a positive relationship between the intensity of FDG uptake and the degree of aggressiveness of breast cancers (6). By contrast, measured total hexokinase levels are not well correlated with the extent of FDG uptake into breast cancers (7).

Initial human study of breast cancer imaging with PET evaluated tumor blood flow, oxygen extraction, and oxygen utilization in nine patients using carbon 11 (¹¹C)- and oxygen 15 (¹⁵O)-labeled tracers. In these studies, regional blood flow was higher in the tumors than in surrounding normal breast. Although oxygen utilization was slightly higher in the tumors than in normal breast, the oxygen extraction ratio was significantly lower (8). A subsequent study in 20 patients showed mean tumor blood flow to be about five to six times higher than flow in normal breast tissue (9). While PET can image tumor blood flow, this sort of tracer application has only limited clinical application. The short half-life of ¹⁵O (2 minutes) is only practical at sites located near a medical cyclotron, and it remains a research tool for imaging breast cancer at the present time.

Several other studies of the use of PET for imaging tumor blood flow were reported recently. Mankoff et al. reported that changes in tumor blood flow using [¹⁵O]water were predictive of an early response to therapy (10,11). Zasadny et al. showed that FDG uptake and [¹⁵O]water are somewhat correlated (12).

Wahl and colleagues have preliminarily reported on the use of the generator-produced agent 62C-PTSM for breast cancer imaging. They demonstrated the feasibility of using this radiotracer, which can be substituted for ¹⁵O to measure blood flow, for imaging some primary and systemically metastatic breast cancers (13).

PET imaging of estrogen receptors in breast cancer has been performed for some time, mainly in the research setting. Thirteen women with primary breast masses were imaged with 16 alpha-[¹⁸F]-fluor-o-17 beta-estradiol (FES) (14). PET demonstrated uptake of the radiotracer in the primary breast mass and the diseased axillary nodes in several cases. An excellent correlation (r = 0.96) was reported in this study between the estrogen-receptor concentration measured in the tumors and the extent of FES uptake into the tumors. A larger follow-up study by the same investigators evaluated in 16 patients with 57 known foci of metastatic disease and demonstrated 93% sensitivity for lesion detection (15). Patients who received antiestrogen therapy showed a decline in the fraction of FES reaching the tumors post-treatment (15). Imaging tumors that were estrogen receptor–negative was not successful with this approach. Despite the early and promising work with this agent, it has not achieved widespread clinical utilization, in part because it obviously does not target estrogen receptor–negative tumors and because treatment trials with aromatase inhibitors have a relatively low risk. Fluorodeoxyglucose-based tracers have been used most extensively in the research setting. Recent data on aromatase inhibitors suggest that such treatments might be quite useful in breast cancer therapy.

Tracers of proliferation, such as (¹⁸F)-3’-deoxy-3’-fluoro-l-thymidine (¹⁸F-FLT), have recently been applied to a limited extent in breast cancer imaging. In a recent pilot study of eight primary tumors imaged before treatment, all eight tumors were detected by ¹⁸F-FLT-PET, with a mean standardized uptake value (SUVmean) of only 1.7 and a mean tumor-nontumor ratio (TNT) of 5.0 (16). FLT only detected two or seven patients with axillary metastases, and these two patients’ axillary metastases were quite large lesions and clearly palpable. FLT does appear to image the proliferation rate of breast cancers quite accurately. However, as in a study of tumor, K(i) and fractional retention of radiotracer determined by spectral analysis correlated with the Ki-67 labeling (proliferation) index (r = 0.92, p < 0.0001 and r = 0.92, p < 0.0001, respectively). In this study, primary, axillary, and systemic metastases could be detected in many cases (17). While FLT is an interesting tracer, it has relatively low uptake into breast cancers, which may limit its clinical utility as a detection agent for smaller tumors, although more study is needed.

FDG is currently by far the most commonly used PET tracer to image breast cancer. As discussed elsewhere in this book in detail, this radiopharmaceutical is transported into breast cancer cells, most likely substantially by the facilitative glucose transporter protein GLUT-1, which is typically overexpressed in many breast cancers. It is then phosphorylated by hexokinases, especially HKII, in cancer cells to FDG-6-phosphate, a polar material that is retained within the cell (1). PET imaging detects the intracellular FDG-6-phosphate in tumors. FDG has a half-life of 109 minutes, so it is more practical for use in a clinical setting than the very short lived positron-emitting isotopes. Much of the FDG used in the United States and to some extent in the rest of the world is at medical centers that are remote from a medical cyclotron, and it sometimes comes from a manufacturing site hundreds of miles away from the PET camera.

FDG was first introduced for breast cancer imaging by a planar imaging (non-PET) technique by Minn et al. in 1989 (18). Using a specially collimated gamma camera (non-PET, nontomographic), the investigators studied 17 patients with breast cancer and were able to detect the tumor in 14 (82%), including 6 of 8 known lymph node metastases. FDG was also able to detect bone metastases and was more sensitive for detecting lytic or mixed lesions than purely sclerotic lesions. In assessing treatment response in ten patients, increased FDG uptake was consistently associated with disease progression, while declines...
in FDG uptake were often, but not invariably, associated with resolving or stable disease (18). However, planar imaging is a very insensitive technique, and images are limited by low resolution and sensitivity.

In preliminary reports in 1989, Wahl and Kubota separately reported on the feasibility of imaging breast cancer using PET with FDG in several patients (19,20). Subsequently, in a larger series, Wahl et al. showed the feasibility of imaging the primary tumor and the regional and systemic metastases of breast cancer using FDG-PET (21). The FDG-PET method detected 25 of 25 known foci of breast cancer, including primary lesions (10), soft-tissue lesions (5), and bone metastases (10). Four additional nodal lesions that had not been previously identified were also detected. Several of the primary cancers were detected in women with radiographically dense breasts. It must be noted, however, that the primary lesions evaluated were all greater than 2 cm in size and therefore larger than most cancers detected by screening mammography.

In preclinical studies, FDG uptake in vitro and in vivo in breast cancer declined with rising glucose levels, suggesting strongly that PET imaging should be performed in the fasted state (22). These results have been confirmed clinically in various human cancers, and all PET centers perform breast cancer imaging in fasting patients (23). Uptake of the tracer is lower in diabetics than in euglycemic patients.

In general terms, the use of FDG-PET in breast cancer imaging can be discussed in terms of evaluation of the primary lesion, evaluation for regional and distant metastatic disease, and evaluation of treatment response and overall in the context of patient management approaches. Unless otherwise stated, the following results were obtained with whole-body dedicated PET scanners and not with the more recent technologies of dedicated PET breast-imaging devices or PET-CT, which are discussed at the end of this chapter.

**EVALUATION OF PRIMARY LESIONS**

Early changes in the molecular characteristics of breast tissues result in physiological changes, which then induce the anatomic alterations we recognize as “cancer”; imaging with mammography has long been the standard method of detecting primary breast cancers. Mammography, however, detects the mass or the calcifications produced by the genetic changes that caused the tumor to develop. In many instances, the appearance of benign and the appearance of malignant masses and calcifications on anatomic imaging overlap with one another. This overlap in anatomic appearance often requires that biopsies be performed to determine the nature of the lesion. In the United States, about 70% to 80% of breast biopsies result in benign histological samples and thus represent false-positive anatomic imaging tests. Compared with the simple anatomic imaging approaches, functional imaging of tumor biology holds the promise of substantially reducing the number of false-positive biopsies and increasing the overall accuracy of imaging. Mammography is sometimes falsely negative as well, especially in women with radiodense breast tissues (2).

While the study of Wahl et al. succeeded in detecting untreated primary lesions of breast cancer by FDG-PET (as well as locoregional and systemic metastases), this small study demonstrating proof of the concept was restricted to large primary lesions and did not address the more critical and clinically relevant issue of detection of smaller lesions in the breast (21). Since imaging devices for PET have been gradually improving, past results may not always be indicative of the current state of the art in PET. Higher resolution systems are now available, and thus smaller lesions should be detectable.

Using whole-body PET imaging without attenuation correction, Hoh et al. were able to detect 15 of 17 foci of primary breast carcinoma as well as regional and systemic metastases (24). In a study of transverse PET with attenuation correction in 11 patients with primary breast cancer, 10 of 11 primary lesions were identified by FDG-PET (25). Only modest uptake was seen in patients with fibrocystic disease. The tumor-to-normal-tissue uptake ratio was 4.9:1. In a larger prospective study, Adler et al. reported FDG-PET results using attenuation correction and PET in 28 patients with 35 suspicious breast masses. Twenty-six out of 27 malignant lesions were identified (sensitivity, 96%) and separated (in retrospect) from the 8 benign breast lesions (26). The separation was based on the FDG uptake levels in the primary lesions. In this study, there was a modest but significant correlation between the pathological nuclear grade of the tumors and the quantity of FDG uptake.

Dehdashiti et al. evaluated 32 breast masses, of which 24 were malignant, using FDG-PET. They found FDG uptake to be much greater, on average, in the breast cancers than in the benign lesions (SUV = 4.5 ± 2.8 versus 1.05 ± .41), and using a 2.0 SUV cutoff value for diagnosis of malignancy, they achieved an 88% sensitivity and a 100% specificity for detection of primary breast lesions (27).

For FDG-PET, Bassa et al. reported a sensitivity of 100% for the detection of locally advanced primary breast cancers and a sensitivity of 77% for the detection of nodal metastases prior to treatment (28). These results were better than those obtained by anatomic imaging methods. The detection of some primary breast cancers that are locally advanced may be challenging anatomically, but this high sensitivity value must not be considered representative of the performance of PET across a full range of primary lesion sizes. Small lesions will clearly be more difficult to detect than larger lesions due to the size-based resolution and sensitivity limitations of dedicated PET scanners, which typically have approximately 10 mm FWHM (full width at half maximum) reconstructed resolution. Evaluation of the method in patients with suspected but undiagnosed primary lesions of all sizes is more clinically relevant.
Avril et al. initially reported findings in 51 patients with 72 suspicious breast masses, 57% of which proved to be malignant. In this study, malignant lesions had a mean SUV 2.5 times that of benign lesions (29). By correcting for partial-volume effects, sensitivity was increased from 75% to 92%, while specificity was decreased from 100% to 97%. The detection of lesions less than 1 cm in diameter was not optimal, however, due to resolution limitations of the whole-body camera used in the study.

This same group subsequently reported findings in 185 patients with breast cancer using FDG. These included 132 cancers and 53 benign lesions. The overall sensitivity was much lower, only 64%, and the specificity was 94%, using standard visual analysis. When a lower visual threshold of malignancy was used in interpreting these same studies, the sensitivity increased to 80% and the specificity declined to 76% (30). Nearly two thirds of invasive lobular cancers were FDG-PET negative, compared with about 24% of invasive ductal cancers. In this study, there was a clear relationship between tumor size and lesion detectability. Using the most sensitive visual detection approach, only 68% sensitivity was obtained in primary tumors less than 2 cm in diameter. Sensitivity was higher for larger lesions, reaching 92% for 2- to 5-cm lesions. All three lesions over 5 cm in diameter were detected (30). Lobular carcinomas have low GLUT-1 expression, likely tumors less than 2 cm in diameter. Sensitivity was higher for larger lesions, reaching 92% for 2- to 5-cm lesions. All three lesions over 5 cm in diameter were detected (30). Lobular carcinomas have low GLUT-1 expression, likely accounting for the lower sensitivity of PET in these types of tumors (30).

Results similar to those obtained in this large series were reported by Yutani et al., who found a 79% sensitivity for detecting primary breast cancer (31). They also showed that FDG clearly achieved higher target-to-background ratios than technetium 99m [Tc]sestamibi (MIBI) (6:1 vs. 3.5:1), again indicating that not all tracers are equivalent for breast imaging (31). Both lesion histology and size affect the rate of primary cancer detection using FDG-PET. Certainly, a technique with low sensitivity is not suitable for screening, so negative PET findings in lesions less than 2 cm in diameter have limited negative predictive value.

Positive PET results must always be considered of serious concern, with very high and focal FDG uptake having a strong positive predictive value for cancer. Ishimori reported the discovery of two incidental breast cancers out of 1,912 patients studied with FDG-PET-CT for recurrent tumor in the breast following a known diagnosis of breast cancer (38). FDG-PET using whole-body imaging devices appears to be more specific but less sensitive than MRI.

The relationship between the MRI signal and the FDG-PET signal was studied in 20 patients with large or locally advanced primary breast cancer. A significant association (\( p < 0.05 \)) was observed between the calculated exchange rate constants of both pharmacokinetic models and SUV determined by FDG-PET. This was a modest relationship, accounting for less than half of the findings. Thus, the SUV and the MRI enhancement rate are related but not equivalent (39). As with most tracers, delivery does have a role in the total signal detected.

FDG is currently the dominant tracer in breast cancer imaging, as it is in most cancers, but the use of alternative tracers has been explored to some extent in breast cancer, as discussed briefly earlier in this chapter. The studies have generally included a small number of patients. \[^{11}C\]-L-methyl-methionine PET has been used in the imaging of primary breast cancers and in the assessment of their response to chemotherapy. In a pilot study of primary and metastatic breast cancers, \[^{11}C\]-l-methionine uptake in primary breast cancer was less than in the liver but more than in most normal tissues. All tumors over 3 cm in size were detected, but three smaller tumors were not detected. Increased uptake of \[^{11}C\]-l-methionine was associated with a large S-phase fraction (SPI) measured with flow cytometry (\( r = 0.77, p = 0.01 \)). These data indicate that \[^{11}C\]-l-methionine can be used to image breast cancers but weigh against its being useful in small lesions or in the liver due to high background uptake (40). The need for an onsite cyclotron for use of \[^{11}C\]-l-methionine makes its widespread clinical application even less likely. However, other tracers with higher uptake into breast tumors and lower background activity could be developed, making the PET more potent for assessing primary lesions even有更好的 resolution scanners
increasingly become available (both dedicated to the breast and for whole-body applications). It should be noted that in the United States the use of noninvasive diagnostic tests to help characterize a lesion as malignant or benign is especially challenging because a missed diagnosis of cancer often leads to litigation. For this reason, biopsy and excision remain widely used as the primary approach to the diagnosis of breast cancer in the United States following lesion detection by anatomic methods.

**DETECTION OF PRIMARY LESIONS WITH POSITRON CAMERAS DEDICATED TO BREAST IMAGING**

Although FDG is the most common tracer used in breast cancer imaging with PET, it should be noted that nearly all PET scanners used in breast imaging to date have been designed as whole-body scanning devices, not optimized to image the breast alone but rather constructed to function as all-purpose devices. In performance, they represent a compromise as compared with dedicated breast-imaging instruments, analogous to using a chest x-ray device to perform mammography and thus obtaining less than optimal breast images. Dedicated breast-imaging devices have more potential for successful imaging of small lesions in the breast than whole-body PET scanners.

This area is in rapid development, and to date only studies with a small number of patients have been performed. In principle, a smaller PET imaging device devoted to imaging the breast would avoid much of the soft-tissue attenuation faced by whole-body PET scanners. The devices could be less expensive yet more sensitive than whole-body PET scanners and could lead to development of radionuclide-guided biopsies (41). They are, however, limited by partial-volume effects and the degree of the localization of FDG or other PET tracers in the tumor compared with normal breast (42).

Raylman reviewed issues of detectability with FDG positron emission mammography (PEM) in phantom studies. In brief, in the absence of breast background, simulated breast lesions as small as 5 mm could be detected. However, as background activity was increased to the levels expected in women with more metabolically active breasts, and as breast thickness also was increased, only lesions 12 mm in diameter and larger were detected. This indicates that dedicated breast devices will likely do better than whole-body tomographs and that the role of FDG and PET in evaluating primary breast lesions will require continued re-evaluation as improved instruments are developed (42). The reliable detection of lesions smaller than 12 mm is essential for any method to achieve clinical utilization.

Several groups have been carrying out studies with dedicated high-resolution PET breast-imaging devices. Gagnon et al. have shown the feasibility of PEM devices in patient studies (43), and more sensitive devices are being made using different detector materials (44). One of the other potential benefits of dedicated devices is that their images could be coregistered with those of a mammographic imaging device to display both anatomic and PET data simultaneously (45). Recently, using dedicated breast-imaging devices, sensitivities of about 86% and specificities of 91% were reported for a dedicated positron breast-imaging device that has a resolution of less than 2 mm (46). Using this dedicated breast-imaging PET device, “PEM,” in a prospective multicenter study, 44 women with confirmed breast cancers were imaged with a high-resolution PEM scanner (Naviscan PET Systems, Rockville, MD) with FDG. The sensitivity of PEM was 89% for the primary cancer, and an additional 4 incidental primary breast cancers were identified with PEM. Of the 19 patients undergoing breast-conserving surgery, PEM correctly predicted 6 of 8 patients (75%) with positive margins and 11 of 11 (100%) with negative margins (47).

Using a newer large-field-of-view, high-sensitivity detector system, positron emission mammography demonstrated 20 focal abnormalities, of which 18 were proven to be malignant and two benign by histology. Three of 20 histologically malignant lesions detected by conventional mammography were not demonstrated by PET mammography. The overall sensitivity of PET mammography for malignancy was 86%, with a positive predictive value of 90% in this small series (48).

PET and positron emission mammography must also be considered in the context of other imaging modalities used for the diagnosis of breast cancer. In addition to the relative insensitivity whole-body PET for small lesions, PET is not a realistic candidate for use in cancer screening of low-risk populations due to its high current cost per study. As FDG prices decline and dedicated instruments are developed that are less expensive, this could change, but it is unlikely that FDG-PET costs could drop to those of mammograms in the near future. This is in contrast to screening mammography, which has been shown to save lives and is the key method for breast cancer detection. Mammography is, however, of somewhat less value for detecting cancers in women with dense breasts (especially younger women), assessing the breast after biopsy, characterizing lesions as malignant or benign, determining whether disease is unifocal or multifocal, and predicting or assessing response to treatment. Mammography cannot determine whether the tumor is localized or metastatic. It is in these groups of patients that PET may have its greatest potential role in the assessment of primary lesions.

**DETECTION OF REGIONAL AND SYSTEMIC METASTATIC DISEASE**

Clinical studies have supported preclinical findings in rodents of high ratios of tumor tracer uptake to normal lymph node uptake, which suggested that FDG might permit detection of lymph node metastases. It was noted that when FDG was injected subcutaneously, there was intense
tracer uptake in the lymph nodes proximal to the injection site (49). In a preliminary study, Wahl et al. were able to correctly characterize 8 of 9 axillae with FDG-PET in the preoperative setting using tracer injection in the arm opposite to the side of the tumor (50). No false-positive findings occurred, but there was one false-negative result.

Several other reports of imaging axillary nodal metastases from breast cancer with PET have now appeared. In a report by Tse, using the whole-body PET technique, 11 of 14 axillae were accurately characterized as to the presence or absence of metastases (51). In 5 cases, there was uptake of FDG in the axillary nodal region, and in each instance there was tumor involvement of the axilla. In a prospective study of 20 patients with newly diagnosed breast cancer who underwent axillary lymph node dissections following PET scans, 9 of 10 patients with nodal metastases were correctly diagnosed, while 10 of 10 disease-free axillae did not show increased uptake (52).

Figure 45.1 shows a whole-body FDG-PET scan in a patient with a primary left breast cancer and palpable axillary lymph nodes. The PET scan confirms FDG uptake in the primary tumor and axillary metastases and also demonstrates high axillary and supraclavicular lymph node metastases, which were not clinically apparent. Figure 45.2 demonstrates the potential usefulness of fused PET-CT images for anatomic localization of focal uptake in the axillary or chest wall region.

Subsequent reports have suggested that the sensitivity of PET for detecting nodal metastases is substantially lower than initially reported. Avril et al. reported a sensitivity of 82% for the detection of nodal metastases in breast cancer, along with a specificity of 96% (53). In this series, sensitivity was higher in patients with large primary lesions and lower in those with small primary lesions. Clearly, PET performed using moderate resolution whole-body PET devices finds fewer positive foci of FDG uptake than are found at pathologic examination. Utech et al. reported that 100% of the 44 tumor-positive axillae in 124 patients with primary breast cancer were detected by PET, while PET was negative in 75% of the 80 tumor-negative axillae (54). Yutani et al. obtained only 50% sensitivity for detecting axillary metastases, which was still better than the 38% sensitivity of MIBI (55). Accuracy values are typically somewhat higher than sensitivity values, since pathologically negative axillae are more common than positive axillae in most series.

Crippa, in a study of melanoma, which typically shows much higher FDG uptake than breast cancer, found that the detectability of nodal metastasis was highly dependent on the size of the lesions. In melanoma, PET succeeded in detecting all nodal metastases more than 1 cm in diameter, 83% of metastases 6 to 10 mm in diameter, and only 23% of those 5 mm or less (56). Because of these encouraging but mixed results, a large prospective study was needed to establish the false-negative rate for staging the axilla with FDG-PET. PET can be expected to have a higher false-negative rate than sentinel lymph node imaging and histological examination of tissue.

A large NCI-sponsored multicenter trial evaluating the accuracy of PET for staging the axilla was completed and reported on recently (57). In that study, 360 female patients aged over 18 with newly diagnosed, untreated invasive breast carcinoma were evaluated. Surgery had to be planned, including axillary dissection, within 30 days of
the PET scan. These patients had no prior therapy or intercurrent illnesses. There were three blinded readers who examined both the attenuation-corrected and the non-attenuation-corrected images. In the overall population, the prevalence of axillary metastases was 35%. For the detection of axillary nodal metastases, the mean estimated area under the receiver operator curve for the three readers was 0.74 (range, 0.70 to 0.76).

When the finding of at least one probably or definitely abnormal axillary focus was the criterion for a positive axilla, the mean (and range) sensitivity, specificity, and positive- and negative-predictive values for PET were 61% (54% to 67%), 80% (79% to 81%), 62% (60% to 64%), and 79% (76% to 81%), respectively. From this study, it was concluded that FDG-PET has moderate accuracy in detecting axillary metastases and that PET commonly fails to detect axillae involved with small and few nodal metastases. It was also concluded that while FDG-PET is highly predictive for tumor involvement when multiple intense foci of tracer uptake are identified in the axillae, FDG-PET could not be recommended for routine staging of the axilla in most patients with newly diagnosed breast cancer. The prognostic value of PET is not yet determined but may still be substantial, and it warrants further study.

The large multicenter study described above compared PET staging of the axilla to axillary dissection and pathological assessment of the axilla. Increasingly, sentinel lymph node sampling is replacing axillary dissection due to its lower morbidity and good performance. In many studies, sentinel node sampling has had a sensitivity relative to axillary dissections of well over 90%. Thus, the performance of PET versus sentinel node imaging in staging the axilla is relevant to current practice patterns. A Canadian study of 98 patients demonstrated a sensitivity of 40% and a specificity of 97% versus axillary dissection, with a similar performance in comparison with sentinel node sampling. PET accuracy was better in patients with high-grade and larger tumors. Increased size and number of positive nodes were also associated with a positive PET scan. These findings suggest PET could be useful as a means of circumventing the need for lymph node dissection only if the test was positive (58).

While the overall sensitivity of PET is too low, especially in small nodal lesions, which typically result from small primary tumors, PET is able to detect larger metastases,
including metastases to the internal mammary lymph nodes. Such nodal metastases are equivalent to axillary lymph node metastases in their prognostic significance and are of particular relevance for medially situated primary breast tumors. No careful study in which all internal mammary lymph nodes were biopsied to establish the sensitivity of PET for detecting such metastases has been performed, but there are cases in which only the internal mammary nodes were positive and PET added very useful information for staging and treatment planning. Similarly, a clearly positive PET scan of the axilla may be expected to carry a very high positive predictive value for detecting metastases. It is possible to speculate that PET could be performed at diagnosis in larger primary breast cancers to establish the presence of axillary nodal metastases, which could then be treated by neoadjuvant chemotherapy.

In a retrospective study, internal mammary nodal tracer uptake seen with FDG-PET was compared with standard radiographic imaging and was correlated with putative risk factors for internal mammary involvement and with clinical patterns of failure. Abnormal FDG uptake in these nodes was seen in 7 of 28 women with locally advanced breast carcinoma at presentation (25%). Prospective conventional chest imaging failed to identify internal mammary metastases in any of these patients. Internal mammary uptake on PET was associated with a large size of the primary tumor ($p = 0.03$) and with inflammatory disease ($p = 0.04$) (59).

PET may also be useful in the assessment of axillary adenopathy when patients present with axillary nodal tumor and no known cancer in the breast or other systemic metastases. In such situations, PET with FDG has been able to locate primary lesions in the breast and elsewhere that were not clearly detected by other methods (60–63). MRI may be superior in this setting, however. PET-CT should improve on the performance of PET alone in the diagnosis of axillary nodal metastases, but it has not been extensively studied. Examples of a positive PET-CT in the axilla are shown in Figures 45.2 and 45.3 (see Case 2).

Given the limitations resulting from partial-volume effects with current scanners, PET is unlikely to replace sentinel node dissection in patients with small primary tumors, in whom small nodal metastases would be most likely. Rather, the greatest potential role for PET is in evaluating the axillae of patients with large primary tumors in whom neoadjuvant chemotherapy is planned and in whom axillary sampling would generally not be performed before surgery. Patients viewed as having a high risk for

![Figure 45.3](image-url)
internal mammary lymph node metastases may also benefit from PET imaging.

It is of interest that there appears to be substantial prognostic information available from a baseline PET imaging study. Inoue et al. showed that the prognosis was worse for patients with a high SUV primary lesion than a lower SUV lesion and that if the primary tumor SUV was high and there were axillary lymph nodes visualized, then the prognosis was much worse than if the primary tumor had low FDG uptake and no axillary nodes were identified (44.4% 5-year survival if FDG uptake was high and nodes were positive on PET vs. 96.8% 5-year survival if FDG uptake was low in the primary and lymph nodes were negative) (64). Primary lesion uptake is related to lesion size, however, so that this prognostic value is, in part, related to lesion size.

**SYSTEMIC METASTATIC DISEASE ASSESSMENT**

Whole-body PET is superior to conventional diagnostic imaging for many but not all systemic metastases of breast cancer (21,27). Dehdashti et al. reported 89% sensitivity and 100% specificity for the detection of 21 proven metastases using an SUV cutoff value of 2.0 (27). While there is high FDG uptake into untreated primary breast cancers, this uptake is typically lower than in other tumors such as lung cancer (65). Detection of primary and metastatic lesions using FDG-PET may be more challenging in breast cancer than in some other malignant tumors.

In bone metastases, there have been varying results. Two studies showed FDG-PET scanning to be more sensitive overall than 

$$^{99m}\text{Tc}-\text{methylene diphosphonate (MDP)}$$ imaging due to its greater sensitivity in the detection of predominantly lytic metastases (66,67). Cook showed that FDG-PET detected a mean of 14.1 metastatic lesions in the skeleton versus 7.8 by 

$$^{99m}\text{Tc}$$ bone scan (67). He and his colleagues also showed that patients with osteolytic lesions that had higher FDG uptake levels had a poorer prognosis. Blastic lesions may be better detected by 

$$^{99m}\text{Tc}$$ bone scan than by FDG-PET.

Figure 45.2 shows a metastasis in a thoracic vertebra in a patient with primary breast cancer. Gallowitsch reported in a retrospective series that FDG-PET detected just 61% of bone metastases in breast cancer while conventional bone scan detected 97% ($p < 0.05$) (68). Other reports have shown a comparable sensitivity for PET and 

$$^{99m}\text{Tc}-\text{MDP}$$ bone scanning in detecting metastases (95%), but there was lower specificity for the 

$$^{99m}\text{Tc}-\text{MDP}$$ bone scanning than for FDG-PET (94.5% vs. 78.7%) (69). An advantage of FDG is that it can potentially monitor tumor response in bone (70).

Because it can be difficult to secure "gold standard" proof for skeletal lesions, direct comparative studies between PET with FDG and bone imaging with 

$$^{99m}\text{Tc}-\text{MDP}$$ are limited. A small recent comparison study in 15 patients with breast cancer who had both FDG-PET and 

$$^{99m}\text{Tc}$$ bone scintigraphy showed in the lesion-by-lesion analysis that the sensitivity for diagnosing bone metastases was 85% for 

$$^{99m}\text{Tc}-\text{MDP}$$ SPECT and 17% for FDG-PET. Bone SPECT was significantly more sensitive ($p < 0.0001$) and accurate ($p < 0.0001$) than FDG-PET in this small study. No statistically significant difference was seen with regard to specificity (71).

A recent, larger study from Japan showed much more comparable accuracy between FDG-PET and bone scan. In that study, among the 89 patients with breast cancer who had undergone both FDG-PET and bone scintigraphy within 1 month between September 2003 and December 2004, 55 with bone metastases were studied. The bone metastases were visually classified by multi-slice CT into four types according to their appearance on CT: (a) osteolytic-osteoblastic, (b) osteolytic, (c) mixed, and (d) invisible. They were compared in terms of tracer uptake on FDG-PET or bone scintigraphy and SUV$_{\text{mean}}$ on FDG-PET. The sensitivity, specificity, and accuracy of bone scintigraphy were 78.2%, 82.4%, and 79.8%, respectively, and those of FDG-PET were 80.0%, 88.2%, and 83.1%, respectively, revealing no significant differences (72).

Based on the CT image type, the visualization rates for bone scintigraphy and FDG-PET were respectively 100% and 55.6% for the blastic type, 70.0% and 100.0% for the lytic type, 84.2% and 94.7% for the mixed type, and 25.0% and 87.5% for the invisible type. The bone scintigraphy visualization rate for the blastic type was significantly higher than the FDG-PET rate, and the opposite was the case for the invisible type. The SUV$_{\text{mean}}$ values for the blastic, lytic, mixed, and invisible types were 1.72 ± 0.28, 4.14 ± 2.20, 2.97 ± 1.98, and 2.25 ± 0.80, respectively, showing that the SUV$_{\text{mean}}$ tended to be higher for the lytic type than for the blastic type (72). FDG-PET demonstrated a low visualization rate for osteoblastic bone metastases. Although FDG-PET is useful for the detection of bone metastases from breast cancer, it is apparent that it suffers from some limitations in depicting metastases of the osteoblastic type (72). Recently it was reported that about 30% of PET-positive lesions believed to represent bone metastases are in fact not abnormal on CT imaging (73).

It seems clear that there are breast cancer metastases to bone that are not seen well with FDG and that can only be seen with bone-avid tracers (Fig. 45.4) (74). Less clear is the significance of 

$$^{99m}\text{Tc}$$-MDP-visualized but FDG-negative lesions. For example, some sclerotic lesions could potentially be healed metastases, which are seen on bone scan but not on FDG-PET. FDG is not the only PET agent potentially be healed metastases, which are seen on bone scan but not on FDG-PET. FDG-PET imaging of bone itself, and scans with this agent have a very high sensitivity for lesion detection compared with 

$$^{99m}\text{Tc}$$ bone scans (e.g., 64 bone metastases detected by 

$$^{18}\text{F}$$-fluoride ion PET imaging of bone itself, and scans with this agent have a very high sensitivity for lesion detection compared with 

$$^{99m}\text{Tc}$$ bone scans (e.g., 64 bone metastases detected by 

$$^{18}\text{F}$$-PET vs. 29 metastases by 

$$^{99m}\text{Tc}$$-MDP scanning) (75). 

$$^{18}\text{F}$$-fluoride ion PET imaging is also reasonably sensitive for lytic lesions. This method is not in wide clinical use at present. Na$$^{18}\text{F}$$-PET has been reported to be more sensitive
than planar $^{99m}$Tc bone scanning in the detection of cancer bone metastases (76).

PET with FDG is an accurate tool for imaging soft-tissue metastases. A study of 109 patients showed FDG-PET to be 89% accurate for characterizing the primary lesion, 91% accurate for characterizing nodal status (with only 10% false negatives), and equal to other conventional diagnostic methods for detecting visceral metastases (19 of 19 detected) (77). This study must be interpreted with some caution, as the detectability of lesions depends on lesion size. Metastatic disease in these patients was not necessarily detected at an early stage, possibly reducing the apparent difference between PET and conventional imaging.

Several groups have reported that FDG-PET is a very sensitive method for the detection of brachial plexus metastases of breast cancer, even at a stage when MRI is equivocal (78,79). A potential challenge in evaluating the upper mediastinum and thorax with FDG-PET is the presence of metabolically active fat, “USA fat” or “brown fat” (80,81). Such fat can cause a high-level signal and potentially may obscure the detection of nodal metastases or soft-tissue lesions. This can be confusing, and care must be taken to confirm that there is soft tissue underlying the lesion rather than fatty tissue on CT (compare Fig. 45.3 with Fig. 33.24; also see Cases 2 and 71).

Skeletal and visceral metastases are most commonly encountered in the context of tumor recurrence when a patient who has been treated for primary breast cancer presents at a later time with laboratory or clinical evidence of recurrence. FDG-PET is a reasonable alternative to CT for the detection of systemic metastases. Figure 45.5 shows whole-body FDG-PET-CT images obtained in a breast cancer patient who was found to have an elevated serum marker level. PET-CT shows a prominent liver metastasis, which on the unenhanced CT is hardly noted.

The whole-body FDG-PET scan in Figure 45.6 was obtained in a patient who had a history of breast cancer surgery 22 months earlier and known liver metastases and who was found to have an indefinite opacity in the upper zone of the right lung by CT imaging. PET images showed uptake into an intrapulmonary metastasis in the left lower lobe and the hilar region, but additional metastases too small to accumulate FDG were noted on the lung window CT.

Extensive bone metastases are well appreciated on sagittal midline scans, and the CT scan can show sclerotic non-FDG-avid lesions to good advantage (83). It should be noted that colony-stimulating factors can markedly increase FDG uptake in bone and can potentially obscure the visualization of bone metastases by FDG. We have shown that the
granulocyte colony-stimulating factor (G-CSF) effects can be minimized by delaying the time from G-CSF dosing until PET scanning by at least 2 to 3 weeks (83).

Although PET can assess the entire body for metastases, it has limitations that should be recognized. In addition to failing to detect a moderate number of bone metastases of a predominantly blastic nature (some of which may be inactive), FDG-PET is not optimal for the detection of brain metastases due to the high normal background FDG activity of cerebral gray matter. Griffeth et al. showed this in a variety of metastatic cancers (84). Similarly, small pulmonary lesions may escape detection due to the effects on resolution of partial-volume averaging and respiratory motion. For lesions less than 5 mm, PET with FDG will often be negative. Thus, PET is a valuable tool for detecting visceral metastases but has limitations related to lesion size, lesion tracer uptake, and normal tissue background activity, as well as physiologic patient motion.

In general, whole-body PET can serve as a single scan to assess the entire body for the presence or absence of cancer with high accuracy. In a meta-analysis of 16 studies of 808 subjects with breast cancer, the median sensitivity was 92.7% and the median specificity 81.6% for metastatic disease (85). PET with FDG is clearly a useful tool for staging and restaging breast cancer systemically, and this is the predominant reason for using PET and PET-CT in our patients. This use parallels the use reported in a study of 42 women with breast cancer who had unfavorable prognostic factors studied in the Netherlands. In these women, management was altered in 5 of 42, and additional lesions were found in 5 women (86).

**ASSESSMENT OF TREATMENT RESPONSE**

A diagnostic PET scan ideally would predict whether a tumor was likely to respond to a given type of therapy before the therapy was started. Short of this, a PET scan before and again soon after treatment began might be able to provide an early indication of efficacy. Both approaches have been evaluated in breast cancer. PET imaging with estrogen receptor–binding ligands can measure breast cancer estrogen receptor levels before treatment. Similarly, the early efficacy of cancer treatment can be evaluated by assessing early treatment-induced changes in FDG uptake from baseline levels.

Tumors expressing estrogen receptors have been shown to be more likely to respond to anti-estrogen therapy than tumors with lower-level receptor expression. In 43 women with breast cancer, PET scans with FDG and FES were done prior to treatment. In this study, all estrogen receptor–negative tumors were negative on FES scans, but only 70% of the estrogen receptor–positive tumors were positive, possibly because of partial-volume effects in smaller tumors or the levels of estrogen receptor expression.
About 76% of the patients responded to the anti-estrogen therapy, as was predicted by the FES scans. Using FDG, all tumors were detected, and in four instances additional lesions were seen that had not been detected by anatomic imaging. A rise in FDG uptake in lesions after treatment, which has been referred to as “metabolic flare,” was associated with effective hormonal therapy in a group of 11 patients. Thus, FDG-PET can in some instances depict the metabolic changes induced downstream following the binding of ligands to receptors (87,88). Since FDG-PET mainly images viable cancer cells, it is logical to follow the efficacy of cancer therapy using FDG-PET.

A prospective evaluation by Wahl et al. of PET during breast cancer chemohormonotherapy demonstrated that women treated with a multi-agent regimen experienced rapid and significant declines in tumor FDG uptake, k3 kinetic rate constants, and Ki (or influx constants) for FDG as soon as 8 days after treatment was initiated (89). Further declines in FDG uptake were apparent after 21, 42, and 63 days of treatment in the patients who went on to have a complete or partial response, while no significant decline in FDG uptake was seen in the nonresponding patients (n = 3) when examined at 63 days after initiation of treatment. This study also showed that the metabolic changes antedated anatomic changes and that the substantial declines in tumor glucose metabolism were apparent in the responding patient population despite an absence of change in tumor size.

Figure 45.6 A 42-year-old female patient with a history of breast cancer with known liver metastases. PET-CT shows unsuspected FDG-avid intrapulmonary metastasis in the left lower lobe (A) and the left hilar region (B). Analysis of the CT images using a lung window setting reveals additional multiple intrapulmonary nodules without FDG uptake (arrow) corresponding to small multiple intrapulmonary metastases.
Similar results were reported by Jansson et al. in primary and metastatic breast cancer using both FDG and [18F]FMAU labeled with 18F have shown early promise in this setting (97). Simi-
larly, Mankoff has compared FDG and 18O[water] PET studies and has found that 18O[water] PET analysis of 18F-FDG-PET images correctly predicted the response in all patients as early as after the first cycle of chemotherapy. As assessed by 18F-FDG-PET, the overall survival in nonresponders (n = 5) was 8.8 months, compared with 19.2 months in responders (n = 6). These limited data in metastatic breast cancer strongly suggest PET is a useful tool for quickly assessing and predicting response to therapy.

There are confounding situations, like after hormonal therapy, where there can be a rise in tracer uptake (flare response) that appears to predict a good outcome (87). A challenge with FDG response studies assessing therapy is to determine exactly what cutoff value for the decline in FDG uptake is most predictive. This will likely vary by treatment type. Receiver Operating Characteristic (ROC) analysis has been used in some studies, and it seems clear that the larger and more rapid the decline in FDG uptake, the more likely an effective response will be seen, although there is clearly overlap among response groups in these analyses.

OTHER PET RADIOTRACERS

Other PET tracers can be used to assess treatment response, but they are less practical and not as easy to use as FDG. For example, 18O-labeled water uptake (reflective of tumor blood flow) declines with effective therapy, as shown in a 19-patient study of doxorubicin and docetaxel (97). Similarly, Mankoff has compared FDG and 18O[water] PET studies and has found that 18O[water] flow may be more predictive of response than the change in FDG uptake in the tumor (10,11). Combining PET with FDG and MRI in assessing treatment response may also be more useful than either method alone (95).

Another area of potential utility in planning the treatment of breast cancer is the use of labeled chemotherapeutic agents to predict treatment response. While this area has not yet been proven to be effective, a variety of labeled compounds have been made that may have potential for treatment monitoring. For example, labeled taxanes and labeled Xeloda (capecitabine) have been developed (98). Eventually, such labeled agents might have a role in predicting tumor response to treatment.

Labeling substrates for DNA synthesis may also prove to be useful as an alternative to assessing glycolysis or protein synthesis. Both fluorothymidine (FLT) and FMAU labeled with 18F have shown early promise in this setting (99,100). Similarly, assessing the oxygenation status of breast cancers using hypoxia-specific tracers such
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as [18F]-fluoromisonidazole (FMISO) has shown potential. While FDG uptake and FMISO uptake are correlated in a variety of cancer types, including breast cancer, they are only moderately correlated, and FMISO may provide unique information regarding tumor biology not available from FDG, as hypoxic tumors often are resistant to radiation therapy and chemotherapy (101).

PET-CT IN BREAST CANCER IMAGING

Most of the published literature using FDG-PET in breast cancer has been done with conventional PET-only cameras. However, in the last several years, there has been a rapid trend toward performing all PET as PET-CT. The initial data with PET-CT have been encouraging in patients with breast cancer. In one report, 58 female patients underwent PET-CT restaging of breast cancer. PET staged 46 of these patients correctly (79.3%), overstaged 7 (12.1%), and understaged 5 (8.6%). Integrated PET-CT staged 52 of the patients correctly (89.7%), overstaged 4 (6.9%), and understaged 2 patients (3.4%). The staging accuracy of PET-CT was not significantly better than that of PET alone (p = 0.059). Lesions exhibiting mild hypermetabolic activity, benign inflammatory lesions, and physiological variants largely explained the incorrect PET findings (102). Although integrated PET-CT only marginally improved the restaging accuracy over PET alone (p = 0.059) in breast cancer patients, the statistical power of the study was relatively modest, and a 10% improvement in accuracy is in line with other reports on the use of PET-CT versus PET in other cancers. Most would argue that a legitimate increase in diagnostic accuracy of 10% is highly relevant clinically.

In a study that included 75 patients with known breast cancer undergoing PET-CT, the initial PET-CT study for each patient was retrospectively reviewed to determine whether improved diagnostic confidence regarding lesion localization and characterization was observed with PET-CT as compared with PET alone. PET-CT and CT findings were compared regarding lesion characterization and staging in 69 of the 75 patients, and in the case of discordant findings, comparison with histological or informative follow-up results was also performed. Fifty of the 75 patients exhibited increased FDG uptake in a total of 95 regions. In the comparison of PET-CT and PET, PET-CT resulted in improved diagnostic confidence in 30 (60%) of these 50 patients and in 52 (55%) of the 95 regions. In the comparison between PET-CT and CT in 69 patients, PET-CT demonstrated significantly better accuracy than CT (p <0.05). PET-CT showed definitely positive findings in 60 regions with malignancies, and CT exhibited positive findings in 43 (72%) of these. PET-CT and CT accurately staged 59 (86%) and 53 (77%) of the 69 patients, respectively. This initial evaluation also strongly suggests that PET-CT is preferable to PET or CT in the diagnosis of breast cancer (103).

OTHER PET-RELATED APPROACHES TO BREAST CANCER

The ability of PET to detect breast cancer in radiodense breasts when other methods fail to detect the tumor presents a new set of problems in diagnosis. Specifically, when such lesions are identified with PET, they may be very difficult to locate for biopsy. Raylman et al. have explored stereotactic biopsy techniques for breast cancer based on sinogram projections of PET or SPECT images (104). Based on the location of “hot spots” in multiple angular projections, biopsy needles can be precisely placed into tumor foci. Although this approach has not been explored extensively in clinical trials, it offers an attractive means of obtaining biopsy confirmation of lesions that are seen by radionuclide imaging but not by other methods.

An alternative approach that can be useful involves combining the anatomic information of CT or MRI with the metabolic information of PET into a single “anatomometabolic” image able to precisely localize an FDG-avid focus on an anatomical template for biopsy (105). A variety of methods are under evaluation for such fusions. At present, PET-CT methods are clearly the most attractive and the most commonly performed.

Another area where PET-related methods may prove useful is in the intraoperative localization of tumors. Methods for detecting the emitted positron but not the photon are capable of precise localization of tumor foci in experimental model systems. We have used such a positron-sensitive probe to locate the precise margin of breast cancer following FDG injection at the time of experimental surgery in rodent models of breast carcinoma. This approach offers the potential to reduce deformation caused by surgical procedures in patients with breast cancer by allowing the removal all of the tumor but less normal tissue (106). It is in the earliest stages of clinical evaluation, so it remains an area for future study and opportunity in the application of PET methodologies to improve the management of patients with breast cancer.

COST-EFFECTIVENESS OF PET IN BREAST CANCER AND CHANGES IN MANAGEMENT

The cost of PET imaging is much higher than that of a mammogram, so it is unlikely that PET will have a major role in breast cancer screening in the general patient population unless there are major changes in the technology and its pricing. It is possible that PET could be used in selected very high risk populations and might have the potential to be cost-effective in such settings. PET is currently more commonly used to stage breast cancers for systemic extent as well as to follow the response of these cancers to therapy.

To be cost-effective, the information from PET must alter management appropriately. Recently, management
alterations were shown to occur in about 30% of patients based on PET scan results (107). Although these data were based on a survey instrument supplied to referring physicians, and only a minority of the surveys were returned, they were based on actual patient data and clearly indicate that major management decisions are made by the referring physicians using PET data. It should be noted that these management changes were often substantial in nature (e.g., a switch from chemotherapy to radiation therapy or from surgery to chemotherapy). The economic impact of such changes is expected to be substantial.

Another study of the role of PET was performed in 165 women referred for FDG-PET imaging. This was a diverse group of patients, but distant metastases were diagnosed in about 5% of them and caused a major change in patient management (108). As in clinical areas, if a major diagnostic decision is to be made, accurate imaging information is an important part of the data set used to make such decisions. Thus, PET can have great clinical impact in the management of patients with breast cancer.

As the performance characteristics of PET are better understood, it is possible to perform cost-benefit analyses of the technology. Sloka et al. used quantitative decision tree modeling to assess the cost-effectiveness of a positron emission tomography (PET)-based management scenario for breast cancer in Canada (109). Two patient management scenarios were compared (with and without PET). A cost savings of $695 per person is expected for the PET strategy, along with an increase in life expectancy (7.4 days), in comparison with the non-PET strategy. This cost savings remained even when the data were subjected to sensitivity analysis. While it is quite difficult to predict whether lifespan will be changed by PET, these data certainly suggest PET-based management will be cost competitive with non-PET based approaches.

**SUMMARY**

The roles of PET and PET-CT in the imaging management of patients with known or suspected breast cancer continue to evolve. In the assessment of primary lesions, PET sometimes detects cancers not detected by standard methods, and incidental cancers of the breast can be detected when whole-body PET studies are performed in large numbers of patients. Size limitations with current whole-body scanners limit the accuracy of the method for detecting small primary tumors. While intense tracer uptake of FDG-PET is usually indicative of cancer and low uptake generally suggests lack of cancer, in most cases this differentiation whether the lesion is cancerous or not, is best addressed by biopsy. In our experience, primary breast cancers are not uncommonly discovered with whole-body PET imaging.

In women with breast implants, PET may have a growing and important role in the assessment of the entire breast. PET also appears to hold promise in the detection of occult lesions in the breast when positive axillary nodes are found without a known primary tumor. Similarly, PET may offer advantages in breasts that show postoperative changes. However, there can also be FDG uptake in inflammatory tissue, and PET is not likely to be able to separate infection from tumor. It is likely that PET will come to have a greater role in detecting primary breast lesions as dedicated devices for breast imaging are developed that have better resolution and performance than current instruments.

The results for FDG-PET imaging in axillary and internal mammary nodal staging have been variable. PET will miss small nodal metastases, while larger ones will generally be detected. PET can detect internal mammary nodes, but the accuracy of the method in this setting is not known, although it is likely to be similar to that for detecting axillary metastases. PET may have a major role in staging the axilla in patients with larger primary breast cancers, who then may be treated with neoadjuvant chemotherapy without the need for axillary dissection or preoperative sentinel node biopsy if PET is clearly positive. Similarly, an unequivocally positive FDG-PET study of the axilla may obviate the need for sentinel node surgery and may move the treatment plan to axillary dissection. A negative PET scan cannot be accepted as evidence of absence of axillary metastases, and PET is not as sensitive as axillary dissection or sentinel lymph node surgery.

Clearly, PET can provide accurate staging for distant metastatic disease. Bone scans with $[^{18}F]$-fluoride ion are highly sensitive for metastases, and FDG imaging is also effective. However, FDG-PET can miss some blastic skeletal metastases. PET is effective for detecting recurrences in soft tissues and the brachial plexus region in particular. The use of PET results in planning the treatment of individual patients is very promising. While the results must be confirmed in larger studies, it appears safe to conclude that the failure of a chemotherapy regimen to decrease FDG uptake promptly in breast cancer is a bad prognostic sign. This does not hold true for hormonal therapy. At present, radio-labeled estrogens are not widely available. Alternative tracers may prove useful in the assessment of treatment response.

The clinical use of PET has expanded remarkably in the past several years. While initially used only for problem solving, PET-CT is increasingly applied as the initial staging tool for breast cancer disease activity. There is also growing use of PET in the monitoring of patients with breast cancer during therapy. Good candidates for baseline PET studies at diagnosis include patients who have large or high-risk lesions and may have a greater chance of systemic metastases at presentation, patients with medial lesions, and patients in whom sentinel node sampling or axillary dissection is not planned. Similarly, patients who will be treated primarily with chemotherapy are well suited for early monitoring by PET and should have a baseline study. PET is clearly a useful tool for following disease progression and response to treatment for systemic disease. In many practices, assessing the breast cancer patient for efficacy of
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treatment of disseminated metastatic disease using PET is a common and important approach to patient management.

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SPECT-CT Imaging of Sentinel Lymph Nodes in Breast Cancer

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One of the promising clinical uses of integrated single-photon emission computed tomography (SPECT) and computed tomography (CT) in breast cancer is in the detection of the sentinel lymph node(s) (SLN). Tomography rather than planar imaging is better able to distinguish a SLN close to the injection site, and integrated imaging defines the anatomical location of the SLN to better advantage for the surgeon. Although the literature on this technique is still sparse, we at our institution exclusively use SPECT-CT for SLN detection, since this technique has become available and early results indicate that the procedure is superior to planar and SPECT-only imaging (see Fig. 46.1).

RATIONALE

The most common site of regional metastasis of breast cancer is the axillary lymph nodes. Additional drainage sites are supraclavicular, internal mammary, intramammary, and interpectoral nodes. The status of lymph nodes is the most important prognostic variable in the staging of breast cancer. Patients with histologically negative axillary lymph nodes have significantly better survival rates than patients with positive nodes. Clinical evaluation for predicting nodal disease is inadequate.

Lymphatic mapping of the sentinel lymph node (SLN) with radiolabeled colloid is a promising technique to investigate the drainage nodal basins of breast cancer as well as other cancers. The lymphatic mapping is followed by SLN biopsy for the histologic examination and detection of microscopic metastases. In many cases, particularly in the United States, SLN localization and sampling have eliminated many full axillary lymph node dissections. In breast cancer, SLN biopsy has the great advantage of being a minimally invasive procedure. Therefore, the risk of lymphedema, which often occurs after axillary lymph node dissection, is minimized. With the SLN information, full axillary lymph node dissections can be restricted only to patients who show microscopic lymph node involvement.

To facilitate a minimally invasive biopsy, an accurate localization of SLN is necessary. For localization of SLN, the current classification system of the American Joint Committee (AJCC) is used. The lymph nodes are divided into low axillary (level I); mid-axillary (level II); high axillary, apical (level III); supraclavicular; and internal mammary nodal stations.

Until now, planar images have been used for SLN imaging. However, limitations of planar images for the detection of SLN in breast cancer are well known. SLN close to the injection site can be overlooked and may result in false-negative cases. The exact anatomical localization of the SLN is difficult using planar as well as single-photon emission computed tomography (SPECT) images. These weak points of planar imaging can be overcome by integrated
SPECT and computed tomography (CT) scanning, combining the benefits of SPECT and the anatomical information of CT.

**TECHNIQUE**

At our institution, the protocol for SPECT-CT imaging of the SLN in breast cancer consists of a standard dose of 80 MBq Tc99m-labeled Nanocoll in a volume of 3 mL. The radiopharmaceutical is injected into the peritumoral tissue at three sites and intradermally over the site of the tumor. After the injection, the patients are asked to perform a light massage to the breast. Approximately 40 minutes post-injection, integrated SPECT-CT is initiated. For this, the patients are positioned supine with the arms above the head. First, a non-contrast-enhanced CT of one field of view covering the chest and neck is performed. Afterwards the SPECT is performed over one field of view (128*128 matrix, axial length: 45 cm) covering the same area as the CT. Images are obtained in steps of 3 degrees with an acquisition time of 20 seconds per step. The resulting total acquisition time of the SPECT-CT is 27 minutes. SPECT images are reconstructed with the IRAC OSEM algorithm (subsets of ordered subset expectation maximization). The CT data are used for attenuation correction and image fusion.

**RESULTS**

This technique improves the accuracy of SLN localization in breast cancer, especially minimizing the false-negative rate (1). In our experience with 41 consecutive patients, we achieved comparable results (2). On SPECT-CT, we were able to localize the SLN in all patients. In one patient, SLN could not be detected on planar images. In 82% of patients, the localization by SPECT-CT was more precise, due to the anatomical information (Fig. 46.1). The pectoralis minor muscle marks the border between Level I/II and Level II/III. With this anatomical information by SPECT-CT, lymph node stations could be more accurately defined. Additionally, in 10% of the cases, lymph nodes close to the injection site, missed on the planar images were detected (Fig. 46.2). In case of a contamination, SPECT-CT might be helpful in assigning the exact localization of the accumulation of the radiotracer.

The early experience suggests that the exact localization by SPECT-CT of all nodal groups, including the internal mammary and supraclavicular nodes, has a high impact.

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**Figure 46.1**

A: SPECT-CT. B: SPECT. C: CT. On the CT, the pectoralis minor muscle is clearly seen (in orange) and marks the border of LI/II and LI/III. On fused SPECT-CT images, one LI and one LIII sentinel lymph node can be seen.

**Figure 46.2**

Left to right: Planar scintigraphy (left anterior oblique), sagittal SPECT, and sagittal SPECT-CT. On planar images, a singular LI axillary sentinel lymph node was diagnosed. On sagittal SPECT and SPECT-CT images, an additional intramammary sentinel lymph node (arrow) can be detected close to the injection site.
on the further management of breast cancer patients at initial diagnosis. In one third of the patients, extra-axillary SLNs were found. Microscopic disease in internal mammary and supraclavicular nodal groups has an important impact on the survival of the patients. A significant decrease in survival in patients has been reported when internal mammary and axillary lymph nodes were involved. According to the revised TNM staging system, microscopic disease in internal mammary nodes in the presence of positive axillary nodes represents pN3b. Because detection and precise localization of internal mammary SLN was difficult, surgical resection was not routinely performed until now. With the use of SPECT-CT, the exact anatomical localization can be given to the surgeon and a minimally invasive biopsy can be performed. In our institution, an adjuvant radiation treatment of the internal mammary nodal stations is discussed in patients with a positive internal mammary SLN. The involvement of supraclavicular lymph nodes (SCLN) represents advanced regional lymph node metastases. Because of the bad prognosis, ipsilateral SCLN metastasis represents the highest nodal stage pN3c.

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PET and PET-CT in Kidney Tumors and Bladder Cancer

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The role of positron emission tomography (PET) and integrated PET and computed tomography (CT) in the diagnosis and follow-up of renal cell carcinoma (RCC) is not clear, and the literature is controversial. The reason for this is twofold. RCC is not always a fast-growing tumor and thus may not result in high fluoro deoxyglucose (FDG) avidity, and FDG is excreted through the kidneys; thus contrast of potential tumor to background is lacking. Procedures to “rinse” the kidneys (e.g., by giving furosemide) should be used, but it has not been clearly demonstrated that this is advantageous. As with many tumors, FDG-PET is probably best for the detection of distant disease. Use of FDG-PET(-CT) should probably be restricted to staging of suspected metastatic disease and to monitor therapy effects when toxic drug regimes are applied (see Fig. 47.1). The situation with bladder cancer is similar in that local tumor manifestations are also obscured by the high FDG activity in the bladder. The use of FDG-PET and PET-CT in bladder cancer should be as restrictive at this time point as for RCC.

Current imaging tests, including computed tomography (CT), magnetic resonance imaging (MRI), and skeletal scintigraphy are not sufficiently accurate to detect recurrent and metastatic disease. Preliminary studies of positron emission tomography (PET) imaging of RCC with fluoro deoxyglucose (FDG) have revealed a promising role in the evaluation of indeterminate renal masses, in preoperative staging and assessment of tumor burden, in detection of osseous and nonosseous metastases, in restaging after therapy, and in the determination of the effect of imaging findings on clinical management (2–12) (Fig. 47.1). However, other FDG-PET studies have demonstrated less distinctive results and no advantage over standard imaging methods (13,14). Moreover, there is currently little experience with PET-CT in the evaluation of kidney masses, but as with the imaging evaluation of other cancers, PET-CT will likely provide valuable information on exact tumor localization, on definition of disease extent, and in avoiding potential pitfalls (e.g., urine in renal pelvis).
A relatively high false-negative rate has been reported with FDG-PET in the imaging evaluation of RCC when compared with histologic analysis of surgical specimens (14,15). Other studies have reported high accuracy in characterizing indeterminate renal masses with a mean tumor-to-kidney uptake ratio of 3.0 and average and maximum standardized uptake values (SUVs) of 7.9 ± 4.9 and 6.0 ± 3.6, respectively (4,16). The superiority of FDG-PET in detecting metastases as compared with CT and bone scintigraphy has also been shown (15,17,18). In a recent retrospective investigation of 66 patients with known or suspected RCC who had undergone both conventional and FDG-PET imaging evaluations, PET exhibited the following diagnostic performance: for primary tumor, sensitivity of
and in RCC (average SUV of 1.28). PET investigation with 15O water and 15O CO in evaluating valuable information on the in vivo biology of angiogenesis (4).

such intervention in improving lesion detection remains the renal collecting system, although the exact benefit of (lasix) has been proposed to improve urine clearance from renal bed. Intravenous administration of furosemide significant correlation with tumor grade or extent (26).

carcinomas. Positive staining for GLUT-1 did not show any positive staining was recognized only in the areas of clear cell with the spindle cell type. In the mixed cell subtype, positive staining for GLUT-1, whereas no positive staining for GLUT-1 was seen in the mixed subtype, positive staining was recognized only in the areas of clear cell RCC did not. Animal models of implanted RCC have also demonstrated the potential utility of PET immuno-PET with the long half-life positron emitters (e.g., 89Zr and 124I) in conjunction with monoclonal antibodies (31).

FDG-PET can also alter clinical management in up to 40% of patients with suspicious locally recurrent and metastatic renal cancer (14,19). In a recent study of the utility of FDG-PET in restaging RCC, a sensitivity of 87% was reported at a specificity of 100% (20). In another report of the diagnostic performance of FDG-PET in restaging RCC, a sensitivity of 71%, specificity of 75%, accuracy of 72%, negative predictive value of 33%, and positive predictive value of 94% were noted (21). A recent study reported positive and negative predictive values of 100% and 67%, respectively, for detection of distant RCC metastases (22). Therefore, FDG-PET appears to offer modest diagnostic accuracy in restaging and in detecting metastatic disease in RCC. A negative study may not exclude disease, whereas a positive study is highly suspicious for malignancy (21,23).

The diagnostic accuracy of FDG-PET appears not to be improved by semi-quantitative analysis, which is probably owing to the fundamental variability of glucometabolism in RCC (24). The mixed observations of FDG accumulation in RCC are probably related to the heterogeneous expression of GLUT-1 (glucose transporter 1) in RCC (25). The expression of GLUT-1 may be dependent on cell subtype. In an immunohistochemical study of glucose transporters in RCC, 85% of clear cell subtype was positive for GLUT-1, whereas no positive staining for GLUT-1 was seen with the spindle cell type. In the mixed cell subtype, positive staining was recognized only in the areas of clear cell carcinomas. Positive staining for GLUT-1 did not show any significant correlation with tumor grade or extent (26).

Since FDG is excreted in the urine, the intense urine activity may confound lesion detection in and near the renal bed. Intravenous administration of furosemide (lasix) has been proposed to improve urine clearance from the renal collecting system, although the exact benefit of such intervention in improving lesion detection remains undefined (4).

Other PET tracers (e.g., 11C acetate) may also be useful in the imaging evaluation of patients with suspected RCC (27). In a recent report, there was a statistically significant difference between the levels of 11C acetate uptake in angiomyolipoma lesions (average SUV of 1.84 ± 0.48) and in RCC (average SUV of 1.28 ± 0.31) (28). Another PET investigation with 15O water and 15O CO in evaluating vascular physiology has demonstrated that PET can provide valuable information on the in vivo biology of angiogenesis and can assess the effects of antiangiogenic therapy (29). Amino acid metabolism and protein synthesis in renal masses have been investigated with PET and the synthetic radiotracers, 1-amino-3-[18F]fluorocyclobutane-1-carboxylic acid ([18F-FACBC] (30). Although papillary RCC demonstrated elevated amino acid metabolism, clear cell RCC did not. Animal models of implanted RCC have also demonstrated the potential utility of PET immuno-PET with the long half-life positron emitters (e.g., 89Zr and 124I) in conjunction with monoclonal antibodies (31).

**BLADDER CANCER**

Bladder cancer is the most frequent malignant tumor of the urinary tract and more common in the age group between 50 and 70 years. Typical presentation is hematuria. Depth of tumor penetration into the bladder wall forms the basis for disease staging and is the most important prognostic factor. Transitional cell carcinoma is the most common histopathology, but squamous cell and adenocarcinoma may also occur. Diagnostic procedures may include cystoscopy with biopsy, excretory urography or retrograde pyelogram, pelvic ultrasound, and CT of the chest, abdomen, and pelvis. Superficial lesions may be treated with endoscopic resection, fulguration, or photodynamic therapy. Cystectomy with urinary diversion is indicated when the tumor is invasive. Radiotherapy may be used as adjuvant therapy, in combination with other therapies, or as a palliative measure. There is no established systemic chemotherapeutic regimen for the treatment of metastatic bladder carcinoma. The 5-year survival is about 90% for superficial disease and about 60% for invasive disease. Systemic disease has a dismal prognosis (1,32).

FDG-PET has been found to be modestly accurate in the diagnosis of bladder cancer and in the detection of pelvic lymph node and distant metastases (7,10,11,33–35). The intense excreted FDG activity in the urinary bladder is the main hindrance in the evaluation of the organ and the adjacent pelvic structures including the lymph nodes. Use of furosemide (lasix) and/or bladder lavage may help in reducing the urine activity, but the exact utility of such intervention is not established. The primary bladder carcinoma and lymph node metastases demonstrate relatively high FDG accumulation (33). In a preliminary study of 12 patients with histologically proven bladder cancer, FDG-PET detected 80% of tumor mass lesions (36). For lymph node staging, a sensitivity of 67% and a specificity of 86% have been reported (37). A recent study found a positive predictive value of 88% and a negative predictive value of 67% for the detection of distant metastases (22) (Fig. 47.2).

Other PET radiotracers including 11C methionine and 11C choline may also be potentially useful in the imaging evaluation of bladder carcinoma (38–41). In particular, the lack of urinary accumulation of 11C choline in the bladder...
may facilitate tumor detection, although premalignant and small noninvasive lesions may be missed (38). The exact role of these and other potential PET radionuclides and the use of PET-CT in this clinical setting will need to be defined.

REFERENCES

INTRODUCTION

In testicular neoplasms, two groups have to be differentiated: seminomatous and nonseminomatous testicular cancers. Essentially, tumors with a histologic mixture of seminoma and nonseminoma cell types should be managed as nonseminomas. Nonseminomas include embryonal carcinoma, teratoma, yolk sac carcinoma, and choriocarcinoma as well as various combinations of these cell subtypes. A tumor that appears to have seminoma histology but that has elevated serum levels of alpha fetoprotein (AFP) should be treated as nonseminoma. Elevation of the beta human chorionic gonadotropin (beta-hCG) alone is found in approximately 15% of the patients with seminoma.

In testicular cancer, the initial staging procedures are usually performed after surgical excision and histologic workup of the primary tumor (Fig. 48.1). Surgical staging procedures as well as morphologic imaging studies have been used extensively for staging and restaging of disease. Fluorodeoxyglucose (FDG) positron emission tomography (PET) holds substantial promise in the staging as well as restaging of these tumors. In PET-alone imaging, the lack of anatomic landmarks may hamper the diagnostic efficacy, since physiologic uptake of $^{18}$FDG is seen in the kidneys and ureters.

TESTICULAR CANCER SUBTYPES

Testicular cancer is a well-treatable, often curable cancer that develops in young and middle-aged men. Germ cell tumors (GCT) are the most frequent solid tumors in men between the ages of 20 and 35 years. GCT are categorized histologically into two major subgroups: seminomatous and nonseminomatous testicular cancers.

Seminomas represent 50% of all GCT and are the most common tumors in individuals with undescended testes. Elevated human chorionic gonadotropin (hCG) is present in 15% to 20% of tumors. Seminomas are sensitive to radiation and chemotherapy. For all stages of seminoma combined, the cure rate exceeds 90% (1,2).

Nonseminomatous GCT are mostly mixed cancers, consisting of two or more cell types. The presence of any nonseminomatous cell type is responsible for the prognosis and management decisions. Embryonal cell carcinoma is the most important component of mixed testicular tumors and
the most aggressive GCT. Choriocarcinoma is usually associated with widespread hematogenous metastases and high levels of hCG. Teratomas consist of cell types from more than one germ cell layer (mature, immature, with malignant transformation). Although a mature teratoma may be histologically benign, it is derived from a totipotential, malignant precursor cell. Therefore, a teratoma in a postpubertal male must be considered to be a malignant GCT. PET/CT can also be used for staging of extragonadal GCT (Fig. 48.2).

**Diagnostic Procedures and Treatment in Testicular Cancer**

Diagnostic evaluation of retroperitoneal lymph nodes at the level of the kidneys is an important aspect of treatment planning as well as restaging in adults with testicular cancer. Lymphatic spread of testicular cancer is typically along the spermatic veins. These veins are discharging into the left renal vein and inferior vena cava on each side, respectively. Therefore, the typical localizations of the initial distant metastases by lymphatic spread are at the level of the kidneys in the retroperitoneum. Further organs of distant metastases of hematogenous spread are the lungs and liver (Fig. 48.3).

Staging as well as treatment control is usually made by computed tomography (CT), ultrasonography (US), or elevated tumor markers. False-negative findings are common in CT-based staging. Tumor markers are highly specific although not sensitive, since only a part of the tumors is positive for tumor markers. Owing to the lack of sensitivity and specificity of the conventional diagnostic methods, surgical staging is necessary for the correct classification of residual masses. Histologic examinations reveal necrosis/fibrosis in 40% to 50% and persistent viable malignancy in 20% to 40% of the cases. Although teratomas should be resected because malignant transformation may occur, approximately 40% of patients with residual masses after chemotherapy would not need laparotomy if viable residual tumors could be excluded noninvasively.

Treatment of GCT is based on surgery with additional radiotherapy and/or chemotherapy depending on the type and stage of disease. Overall prognosis is good (survival rate 85%) for patients with seminoma or nonseminomatous GCT with low tumor markers (hCG, AFP, and lactate dehydrogenase [LDH]) and absence of visceral metastases, although it is poor if high tumor markers and/or visceral metastases are present.
**Figure 48.2** A patient with extragonadal germ cell tumor (A) with a large bulk in the mediastinum (B) and involvement of the humerus (C) and the spine (D).

**Figure 48.3** A 38-year-old patient with mixed germ cell tumor. There is retroperitoneal metastasis, as can be seen on the coronal PET-CTs (A,B). This localizes into the inferior vena cava as can be clearly seen by comparing CT and PET-CT axial sections at the corresponding level (C,D). Note that the tumor is crossing from the left to the right along the course of the spermatic vein and left renal vein (E,F).
FDG-PET IN THE STAGING OF GERM CELL TUMORS

A major therapeutic problem in GCT is the indication for surgical resection of residual masses after chemotherapy. Response to therapy can be assessed by a decrease of tumor mass on CT or normalization of tumor marker levels. Residual masses are common after chemotherapy in seminoma and malignant teratoma. In teratomas, 20% of such masses are malignant teratomas. Two thirds of patients with bulky seminomas have a residual mass after chemotherapy, and 15% contain residual malignant disease. For either histologic subtype of GCT, it is not possible with conventional imaging techniques to distinguish residual and recurrent malignant tissue from fibrosis, necrosis, or differentiated teratoma. Cremerius et al. (3) reported the results of 54 PET-studies in 33 patients with GCT. True-positive PET scans revealed significantly higher FDG uptake in seminomas than in nonseminomatous testicular carcinomas. The lowest FDG uptake was found in mixed tumors. The diagnostic accuracy of FDG-PET and CT in seminomas was 90% and 79%, respectively. The diagnostic accuracy of FDG-PET and CT in nonseminomatous testicular cancers was 81% and 52%, respectively. The advantage of PET over CT in these tumors was based mostly on its higher specificity (92% and 50%). The authors discuss a transient suppression of metabolic activity in GCT shortly after chemotherapy regardless of their final therapy response. They conclude that PET scanning should not be performed earlier than 2 weeks after completion of therapy. In another retrospective study by Hain et al. (4), FDG-PET was evaluated in the detection of metastatic testicular carcinoma at diagnosis. Thirty-one patients (13 with seminoma, 18 with nonseminomatous GCT: 13 teratomas, 5 mixed) were staged by FDG-PET. FDG-PET identified metastatic disease in 10 and was negative in 16. Interestingly, there were no false-positives but five false-negative findings. Accordingly, the positive predictive value was 100%. They concluded that FDG-PET, at diagnosis, is capable of detecting metastases that are not identified by other imaging techniques (4). Stephens et al. (5) found poor sensitivities of FDG-PET for teratoma. In their study, 30 patients with postchemotherapy residual masses were evaluated. FDG-PET did not differentiate necrotic/fibrous tissue from teratoma. However, FDG-PET was able to differentiate viable GCT from residual necrotic/fibrous tissue or teratoma.

In a study by De Santis et al. (6), pure seminomatous tumors were evaluated after chemotherapy in 51 patients and compared with histology, CT, tumor markers, and/or physical examination during follow-up. All bulky lesions (greater than 3 cm) were correctly assessed, and 95% of lesions smaller than 3 cm were correctly predicted by PET imaging. They concluded that FDG PET was the best predictor of viable residual tumor in postchemotherapy seminoma residuals and should be used as a standard tool for clinical decision making in this patient group (6).

Kollmannsberger et al. (7) evaluated the ability of FDG-PET to predict the viability of residual masses after chemotherapy in metastatic nonseminomatous germ cell tumors. PET results and corresponding CT scan and tumor marker results in 85 residual lesions from 45 patients were
compared. FDG-PET showed increased tracer uptake in 32 of 85 residual lesions, with 29 true-positive (TP) lesions and three false-positive (FP) lesions. Essentially, sensitivities and specificities for the prediction of residual mass viability were as follows: for PET, 59% sensitivity and 92% specificity; for radiologic monitoring, 55% sensitivity and 86% specificity; and for tumor markers, 42% sensitivity and 100% specificity. The positive and negative predictive values for PET were 91% and 62%, respectively. Overall, FDG-PET imaging used in conjunction with conventional staging methods offered additional information for the prediction of residual mass histology in patients with nonseminomatous GCT. Therefore, a positive PET is highly predictive for the presence of viable carcinoma. Other useful indications for a PET examination include patients with multiple residual masses and patients with marker-negative disease (7).

CONCLUSION

FDG-PET is recommended in staging as well as for evaluation of recurrent testicular cancer, including seminoma as well as nonseminomatous tumors. The use of PET/CT could be of additional help, since classification of FDG-avid lesions in the retroperitoneum owing to exact localization can be expected; however, conclusive data are not yet available. Well-differentiated teratomas are regarded as one of the few histologies in which FDG-PET is not useful since it does not show any FDG avidity (Fig. 48.4).

REFERENCES

INTRODUCTION

Prostate cancer is the leading cancer diagnosed and the second leading cause of cancer death in men. Sixty percent of all newly diagnosed prostate cancers and approximately 80% of all deaths from this cause occur in men aged 70 years and older. However, mortality rates are much lower than the incidence rates because survival is generally quite high. The causes of prostate cancer are not known.

Only insufficient evidence is present to establish whether screening by digital rectal examination or serum prostate-specific antigen (PSA) results in a decrease in mortality from prostate cancer. Diagnostic imaging includes ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) for local staging and bone scanning for detection of osseous metastases. As with most cancer types, adequate therapy is stage dependent. Whenever the prostate cancer is confined to the organ without evidence of local or distant metastases, radical prostatectomy, external-beam irradiation, and interstitial implantation of radioisotopes are used with similar therapeutic effects (1,2).

Nuclear imaging includes, in addition to bone scanning, some more specific agents, which have been evaluated, but the major impact may be coming from positron emission tomography (PET). Fluorodeoxyglucose (FDG)-PET has shown promising initial results for prostate cancer staging and restaging. The role of choline-PET seems to be limited to N and M staging, because differentiation of benign prostatic hypertrophy from cancerous prostate lesions at initial staging is not possible with any choline PET-radiotracer analog. In patients with recurrent prostate cancer, PET with choline analogs is a promising imaging modality to detect local recurrence and lymph node metastases. Because of intestinal choline uptake and the close anatomic association with bowel, differentiation of tumor from normal choline uptake can be difficult. We therefore feel that the use of integrated PET/computed tomography (CT) in choline-PET examinations is a must (see Fig. 49.1).

Fluorodeoxyglucose (FDG)-PET has very limited value in prostate cancer; as with the well-differentiated and relatively slowly growing cancers, no FDG uptake is observed. Only when the cancer becomes androgen independent do the tumor manifestations become FDG avid.

Non-PET Radiopharmaceuticals in Prostate Imaging

Bone scanning with Tc-labeled phosphonates is still an important staging method in the staging and follow-up...
of patients with suspected or proven bone metastases of prostate cancer. The use of integrated single-photon emission computed tomography (SPECT)/CT in the detection of bone metastases in general is discussed in Chapter 52.

ProstaScint ($^{111}$indium-labeled capromab pendetide) is a type II membrane glycoprotein strongly associated with prostate cancer and labeled with $^{111}$indium used for planar and SPECT imaging in prostate cancer patients. Initial results reported encouraging results in the detection of local recurrence after therapy (8). However, during further investigations these results have been questioned, especially regarding extra-prostatic disease (9). ProstaScint is also being applied for evaluating patients with biochemical failure and in trying to discern metastasis before definitive therapy.

**PET RADIOPHARMACEUTICALS IN PROSTATE IMAGING**

Initially, FDG was used for staging and restaging of prostate cancer; however, initial results were discouraging because only a few aggressive androgen-receptor-negative prostate cancers accumulate FDG. Therefore, different $^{11}$C- and $^{18}$F-labeled radiotracers have been developed in the last 5 years, and these show better detection rates of prostate cancer at initial staging as well as restaging compared with $^{18}$F-FDG. Choline derivatives like $^{18}$F-choline (FCH) and $^{11}$C-choline can be used for staging and restaging of prostate cancer (5,10,11). Studies using $^{11}$C-acetate have also shown promising results (12). For clinical purposes, the F-labeled compound is obviously more desirable than the very short lived $^{11}$C compounds. We at our institution have therefore elected to work with FCH. Interestingly, the uptake mechanism of choline is still unclear; it is suggested that a process other than proliferation is responsible for the uptake of choline in prostate cancer.

**F-Choline Image Acquisition Protocol**

Our acquisition protocol consists of a low-dose nonenhanced CT for attenuation and anatomic referencing purposes and is followed by the injection of approximately...
200 MBq of FCH. Two minutes after the intravenous injection of FCH, the PET emission scan is initiated at the pelvis, with the first field of view covering the bladder (10,13). This is essential, because FCH is excreted by the kidney and can be found in the bladder as early as 5 minutes postinjection. With an acquisition time of 3 minutes per bed position, the first field of view, containing the prostate and the bladder, is imaged within this 5-minute time window, and so the scans are free of activity in the bladder. Acquisition is then continued cranially very much as in a standard FDG-PET protocol (see Chapter 19). After completion of the scan, the images are reconstructed and viewed as PET-CT images for accurate interpretation of FCH accumulation. Without the anatomic information, FCH-PET alone is of less value, as some lymph nodes lie close to the gastrointestinal tract, which has a physiologic FCH uptake. Thus, tumorous (i.e., FCH-accumulating) lymph nodes can be missed, if no anatomic information is provided. There is also physiologic FCH accumulation in the rectum, which might be misinterpreted as activity in the prostate. Other sites of physiologic FCH accumulation are the salivary glands, the liver, and the spleen as well as the kidneys (10) (see Fig. 33.27).

**F-Choline PET-CT Imaging Results**

Promising results are reported in staging of high-risk patients (Gleason ≥6 and/or PSA >10 ng/mL). T staging is not possible because of accumulation of FCH in benign prostatic hyperplasia and the limited spatial resolution of PET. In N staging, the limitation is a standard one: the inability to detect micrometastases. In M staging, FCH-PET seems to be superior to bone scanning (14) (Fig. 49.1). Other studies show that 18fluorine-PET is superior to FCH-PET in detection of osseous metastases. Our own data demonstrate that FCH-PET-CT at initial staging showed no metastases in 31 patients who later underwent radical prostatectomy. Six months after surgery,
Chapter 49: PET-CT and SPECT-CT in Prostate Cancer

Figure 49.4 A 74-year-old patient with history of prostate cancer treated with radiotherapy 3 years ago. Biochemical recurrence with a PSA of 2.2 ng/mL. CT (A); choline PET (B); PET-CT (C) fused images. A 18F-choline-positive local recurrence is noted in the region of the right seminal vesicle (proven by biopsy).

PSA remained less than 0.05 ng/mL in 27 of 31 patients, proving no remaining prostatic tissue or metastases. In 4 of 31 patients, PSA levels were greater than 0.1 ng/mL (0.1–0.36; three fourths of patients after R1 resection). In 22 patients, lymphadenectomy was performed (93 lymph nodes [LN]). Of the resected lymph nodes, 1 in 93 was true–FCH-positive (HP: metastasis >1 cm) (Fig. 49.3) and 4 of 93 LN (of two patients) were false–FCH-negative HP-histopathology (HP: metastases <3 mm). Three of 37 patients showed FCH-positive bone metastases proven by bone scan.

In restaging, the detection of recurrence is fairly reliable in patients without antihormonal treatment and a PSA of greater than 2 ng/mL or with antihormonal treatment and rising PSA owing to hormone-independent tumor tissue. It has been shown that, contrary to previous results, FCH-PET/CT can be positive in patients with PSA levels of less than 5 ng/mL. FCH-PET/CT at restaging showed local recurrence in 16 patients (Fig. 49.4), all verified by MRI, biopsy, or dropping PSA levels during radiotherapy (RT). Seven patients with proven local recurrence did not show any pathologic FCH uptake (PSA in 5/7 patients <2 ng/mL, in 2/7 >2 ng/mL). In 13 patients, PET-CT revealed FCH-positive LN. A total of 16 LN were surgically removed in four patients. HP verified metastases in all LN. Seven patients showed FCH-positive bone metastases proven by bone scan or MRI. In patients with antihormonal treatment and no detectable PSA, the site of tumor cannot be depicted with FCH-PET/CT.

Other tracers with comparable results are 11C-choline and 11C-acetate (5,6,12). As stated, the main advantage of 18F-marked radiotracers is the longer half-life, allowing transportation to sites without a cyclotron.

Routine prostate cancer imaging for staging or restaging using a PET radiopharmaceutical is not yet a reality, and clear-cut clinically useful indications of choline-based tracer PET will have to be established and the clinical effectiveness proven. The indications for FDG-PET are limited to cases of aggressive prostate cancer in which imaging restaging information is relevant (Fig. 49.2).
REFERENCES

INTRODUCTION

The gynecologic malignancies include cancers of the vulva, vagina, cervix, uterus, fallopian tubes, and ovaries. Initial diagnosis and staging of most gynecologic malignancies are commonly achieved by history and physical examination and by use of selected imaging studies. Accurate staging of gynecologic cancers is important for both selecting appropriate therapy and predicting prognosis. Most gynecologic cancers initially spread regionally and then through lymphatic channels rather than through hematogenous dissemination to distant organs. With locally advanced disease, the status of pelvic and para-aortic lymph nodes is an important determinant of prognosis and guides treatment planning in patients undergoing radiation therapy. Computed tomography (CT) is the most widely used imaging method for assessment of nodal involvement and detection of distant metastatic disease. Despite its high resolution and excellent depiction of anatomy, CT is limited by its inability to detect small-volume metastatic involvement in normal-size lymph nodes and to determine whether enlarged nodes represent metastasis or reactive hyperplasia (which is particularly problematic in patients with large necrotic tumors with significant associated inflammation). Recognition of small peritoneal tumor deposits is also difficult on CT.

Over the last decade, fluorodeoxyglucose (FDG) positron emission tomography (PET) has become an
established oncologic imaging tool for many forms of cancers. The functional information about regional glucose metabolism provided by FDG-PET provides for greater sensitivity and specificity in most cancer imaging applications by comparison with CT and other anatomic imaging methods. The role of PET in gynecologic cancers is evolving, but the current literature suggests that PET is superior to conventional imaging modalities for evaluating patients with cervical and ovarian cancers. The role of PET in other gynecologic cancers is less well defined. The recent development and rapid dissemination of integrated PET-CT scanners that allow functional and anatomic information to be obtained in a single examination represents an important advance in PET imaging technology, resulting in a synergistic improvement in the accuracy of interpretation of both PET and CT images. Accordingly, the performance of PET based on published studies performed with conventional PET scanners is now being reevaluated in light of emerging PET-CT results. This chapter will discuss the role of PET and PET-CT in the management of gynecologic cancers.

PATIENT PREPARATION AND IMAGING

Patient preparation for imaging of gynecologic tumors is similar to that for oncologic imaging generally. However, because of the potential for artifacts and interpretation errors related to intense FDG activity in urinary tract structures (e.g., streak artifacts, confusion of ureteral activity with lymph nodes), various interventions to minimize the amount of FDG in the urinary tract have been used in different clinical services. The current general use of iterative reconstruction algorithms instead of filtered back projection has eliminated most of the image artifacts related to intense urinary tract activity. Nevertheless, in some centers, urinary tract preparation is still performed for evaluation of gynecologic cancers. Most often this involves placement of a Foley catheter, intravenous administration of fluids (1,000 to 1,500 mL of 0.9% or 0.45% saline solution to be infused during the course of the study), and intravenous administration of 20 mg of furosemide before or after injection of FDG. The Foley catheter should be placed before injection of FDG to minimize radiation exposure to technical or nursing staff. Some investigators prefer the use of continuous bladder irrigation with a double-lumen catheter for the duration of the study.

The PET imaging methods used in patients with gynecologic tumors are also similar to those used for other cancers (see Chapter 19). For PET-CT, the administration of oral contrast agents is helpful for delineating bowel loops and makes image interpretation easier (1). There is no consensus regarding the need for administration of intravenous contrast agents (2). Several investigators have suggested that delayed PET imaging (>2 hours after injection of FDG) improves the sensitivity for detection of nodal metastasis in cervical cancer and peritoneal deposits in ovarian cancer (3–5).

CERVICAL CANCER

Worldwide, cervical cancer is the second most common cause of cancer-related deaths in women. Although less common in the United States, cervical cancer is still expected to account for approximately 10,370 new cancer diagnoses as well as 3,710 deaths in 2005 (6). Squamous cell carcinomas represent more than 90% of cervical cancers and originate in the surface epithelium of the cervix; adenocarcinomas represent approximately 5% to 9% of cervical cancers and originate in the cervical glandular tissue. Adenosquamous carcinoma is relatively infrequent and represents about 2% to 5% of all cervical carcinomas. Rare cervical sarcomas and small cell carcinomas account for the remainder.

Staging

Cervical cancer typically disseminates in a predictable fashion, with initial spread to local structures and regional lymphatics and later hematogenous spread to distant organs, such as bone and lung. The pattern of nodal metastasis is also predictable: tumor spreads from the primary lesion sequentially to pelvic lymph nodes, para-aortic lymph nodes, and supraclavicular lymph nodes. Cervical cancer is staged clinically based on the Fédération Internationale de Gynécologie et d’Obstétrique (FIGO) staging system. Involvement of a pelvic or para-aortic lymph node does not alter the FIGO clinical stage of disease, but indicates a worse prognosis and may have an important impact on therapy (7–10). Because of limitations of conventional radiologic techniques for evaluating lymph nodes, surgical assessment of para-aortic nodes is considered the gold standard. However, exploratory laparotomy and nodal dissection has not had a demonstrable impact on survival. Moreover, because of the morbidity associated with surgical staging, this procedure is not widely used; thus, the search for an accurate noninvasive staging method is an ongoing process.

FDG-PET appears to be well suited for imaging of cervical carcinoma. Most primary tumors, except for very small lesions, are readily seen on PET images and exhibit intense FDG uptake. In our experience, primary squamous cell carcinomas and adenoscarcinomas have similar FDG avidity. In a review of 230 patients with cervical cancer (squamous cell carcinoma 200, adenocarcinoma 30), we found that the mean maximum standardized uptake value (SUVmax) of squamous cell carcinomas was slightly higher than that of adenoscarcinoma, but the difference was not significant (11.7 versus 9.6) (unpublished data). However, because of its relatively poor spatial resolution and inability to assess parametrial invasion or involvement of adjacent organs reliably, FDG-PET is of limited value for staging of the primary tumor.

A number of studies have shown that FDG-PET is superior to conventional imaging methods for detecting metastatic disease, particularly lymph node metastasis...
(11–17). Havrilesky et al. (17) recently reported a systematic review of the published literature up through 2003. They included only those studies involving 12 or more subjects who had PET performed with a dedicated scanner with specified resolution, and with clinical follow-up of 6 months or longer or histopathology as the reference standard. In patients with newly diagnosed cervical cancer, the pooled sensitivity of PET was 79% (95% confidence interval [CI], 65%–90%), and the pooled specificity was 99% (96%–99%) for detection of pelvic lymph nodes metastasis (17). Two studies were identified that each compared PET with magnetic resonance imaging (MRI) and CT (17). MRI had a pooled sensitivity of 72% (53%–87%) and pooled specificity of 96% (92%–98%), whereas CT had a pooled sensitivity of 47% (21%–73%) (there were insufficient data to calculate a pooled specificity). In four prospective studies in which histology after para-aortic lymphadenectomy was used as the reference standard, the pooled sensitivity of PET for the detection of para-aortic nodal metastasis was 84% (95% CI 68%–94%) and the pooled specificity was 95% (89%–98%) (17). In three of these studies, the inclusion criteria for study entry included a negative CT or MRI of the abdomen (17). Thus, the accuracy of conventional imaging could not be calculated. The fourth study did not require a negative abdominal imaging study prior to surgery (17). The sensitivity and specificity of MRI in the 12 patients who underwent aortic node sampling were 67% and 100%, respectively.

False-negative results for detection of nodal metastasis are chiefly related to the limited resolution of PET and, thus, its inability to detect microscopic disease and small macroscopic tumor deposits. In a recent study that evaluated the sensitivity of FDG-PET by comparison with surgical lymphadenectomy in patients with early-stage cervical cancer, we found that the mean size of tumor deposits was larger in PET-positive pelvic nodes (15.2 mm; range 2 to 35 mm) than in PET-negative nodes (7.3 mm; range 0.3 to 20 mm) (18). False-positive results are most likely related to uptake of FDG in hyperplastic nodes or misinterpretation of physiologic activity in bowel or the urinary tract as nodal metastasis. The use of PET-CT has been shown to improve the accuracy of staging in various cancers, since the combined functional and anatomic information allows for a significant improvement in lesion localization and differentiation of physiologic FDG uptake from pathologic FDG uptake (19). This leads to a decrease in the frequencies of both false-positive and false-negative results.

Our own studies have shown that FDG-PET is superior to CT and lymphangiography in showing unsuspected sites of metastasis in pelvic lymph nodes, extrapelvic lymph nodes, and visceral organs in patients with newly diagnosed advanced cervical cancer (20). FDG-PET showed abnormalities consistent with metastasis more often than did CT in pelvic lymph nodes (67% vs. 20%) and in para-aortic lymph nodes (21% vs. 7%) (Fig. 50.1). PET also showed disease in supraclavicular lymph nodes in 8% (21) (Fig. 50.2). These initial results have been sustained in subsequent evaluations (unpublished) of data from our prospective registry that now includes over 400 patients.

**Figure 50.1** Advanced cervical carcinoma. Coronal (A) CT, (B) PET-CT fusion, and (C) PET images demonstrate intense FDG uptake within the patient’s known primary cervical carcinoma (arrow) and pelvic lymph node metastases (small arrows). Transaxial (D) CT, (E) PET-CT fusion, and (F) PET images demonstrate increased FDG uptake within a subcentimeter para-aortic lymph node (small arrow). The barium in the colon and the iodinated contrast material in the ureters are from a separate diagnostic CT examination performed earlier on the same day.
The role of PET-CT in staging of cervical cancer needs to be determined. The literature currently contains limited data on the use of PET-CT in cervical cancer; however, it is expected that PET-CT image fusion will allow for easier distinction of pathologic and physiologic tracer uptake and, thus, improve the accuracy of image interpretation (22). Based on the results in the literature to date, the United States Centers for Medicare and Medicaid Services in January 2005 approved coverage for use of FDG-PET in initial staging of patients with cervical cancer who have no evidence of extrapelvic metastatic disease on CT or MRI.

An evolving, competing imaging method for detection of metastatic disease in lymph nodes is MR lymphography with ultrasmall superparamagnetic iron oxide (USPIO) particles as the contrast agent. After intravenous injection, USPIO is taken up by macrophages in healthy lymph nodes and produces a loss of T1 signal, whereas the signal of metastatic tissue remains unchanged (23). Rockall et al. (24) recently have shown that USPIO-MRI is superior to standard size criteria for detection of metastatic lymph nodes in patients with endometrial and cervical cancer. In 44 patients, 768 pelvic or para-aortic lymph nodes were sampled histologically, of which 335 were correlated on MRI; 17 malignant lymph nodes were found in 11 of the 44 patients. MRI using USPIO criteria had significantly higher sensitivity than the size criteria for detecting lymph node metastasis on both a node-by-node basis (93% versus 29%) and a patient-by-patient basis (100% versus 27%). However, no significant differences were noted in the specificity or positive- and negative-predictive values between the two methods. The false-negative rate was relatively high with both methods, resulting in low positive-predictive values (61% versus 56%). The false-negative results were mainly due to failure in identifying involved lymph nodes in the parametrium and occurred only in patients with cervical cancer. Further studies in larger populations are needed to establish the use of this technique in clinical practice.

### Directing Therapy

The use of FDG-PET in pretreatment clinical staging has had a significant impact on the therapeutic management of patients with cervix carcinoma. The standard treatment of advanced cervical carcinoma is radiotherapy with concurrent chemotherapy (25–27). Radiotherapy is directed at the pelvis to encompass primary disease as well as pelvic lymph nodes. The radiotherapy port is expanded to include the para-aortic lymph node region only in patients who have evidence of para-aortic nodal disease. Patients who have evidence of disease beyond the para-aortic lymph nodes at the time of initial diagnosis have little chance of a cure and receive palliative therapy. Based on the findings in the study of Grigsby et al. (21), we now routinely administer curative para-aortic irradiation to patients with CT-negative, FDG-positive para-aortic nodal disease, whereas no irradiation to this region would have been administered to such patients in the past before the use of PET to assess for para-aortic disease. Fourteen patients in that analysis had para-aortic disease detected by FDG-PET that was not detected by CT. These patients had
their radiation portals increased to include the para-aortic nodal region. Currently we are investigating the use of PET-CT-guided intensity-modulated radiotherapy (IMRT) to deliver higher doses to para-aortic nodes that have FDG-avid disease by PET-CT (28). Fused PET-CT images can be used to differentiate tumor from adjacent normal structures more reliably and thus allow for delivery of higher doses of radiation to the tumor while decreasing radiation dose to normal structures.

FDG-PET may also be useful in determining whether concurrent chemotherapy should be administered to patients with advanced-stage disease. A recent study from the Gynecologic Oncology Group (GOG 109) randomized patients with pathologically positive pelvic lymph nodes to either radiotherapy alone or to radiotherapy with concurrent and adjuvant cisplatin and 5-fluorouracil chemotherapy. The study demonstrated that there was both a superior disease-free and overall survival advantage when chemotherapy was added to radiation therapy (29). A subsequent report from this study demonstrated that there was no benefit to the use of concurrent chemotherapy in patients with only one positive lymph node (30). A similar finding was demonstrated by Grigsby et al. (31). In this retrospective analysis of 65 patients, there was no apparent clinical benefit to the use of concurrent chemotherapy with primary irradiation in patients who had no evidence of lymph node metastasis by FDG-PET. Thus, FDG-PET may be useful to select a subgroup of patients with locally advanced cervical cancer without evidence of lymph node metastases who may not benefit from the administration of concurrent chemotherapy. Larger prospective studies need to be done to confirm these results.

**Prognosis**

Several prognostic factors have been identified for patients with carcinoma of the cervix. These include patient age, tumor histology, tumor stage, tumor size, lymph node metastasis, and tumor hypoxia (32,33). In a study of 101 patients with newly diagnosed cervical cancer, Grigsby et al. (21) demonstrated that the lymph node status determined by FDG-PET is predictive of progression-free and overall survival in patients with cervical cancer. The 2-year disease-free survival was better predicted by PET evidence of lymph node involvement than by CT findings. Based on the imaging findings in the pelvic lymph nodes, the 2-year disease-free survival was 84% for CT−/PET− patients, 64% for CT−/PET+ patients, and 48% for CT+/PET+ patients ($p = 0.05$). Based on the imaging findings in the para-aortic nodes, the 2-year disease-free survival was 78% in CT−/PET− patients, 31% for CT−/PET+ patients, and 14% for CT+/PET+ patients ($p \leq 0.0001$). None of the patients with PET+ supravaclavicular lymph nodes survived 2 years. The PET-determined status of the para-aortic nodes was the strongest predictor of survival in a multivariate logistic regression analysis. These results suggest an opportunity to salvage some patients with para-aortic nodal metastasis defined by PET, as described above. In a recent review of data from 256 patients in our registry, we also found that the extent of lymph node involvement is inversely correlated with survival (34).

Recently, Miller and Grigsby (35) evaluated the usefulness of tumor volume measurement with FDG-PET in 57 patients with cervical cancer. Tumor volume and lymph node status determined by PET and FIGO stage determined by clinical examination were predictive of progression-free survival; tumor volume and lymph node involvement by PET predicted overall survival. The presence of lymph node involvement did not correlate with tumor volume. Most recently, we have demonstrated that the results of post-treatment surveillance FDG-PET studies in patients with cervical cancer are strongly predictive of patient survival (36). We have also found that FDG-PET demonstrated metastatic involvement in the left supraclavicular lymph nodes in 8% of our patient population; this finding has a positive-predictive value of 100% and indicates a dismal prognosis, despite aggressive therapy (37). Similarly, we found that the cause-specific survival for patients with FIGO stage IIIIB carcinoma is highly dependent on the extent of lymph node metastasis demonstrated by whole-body FDG-PET at initial presentation (38). The 3-year estimates of cause-specific survival were 73% for those with no lymph node metastasis, 58% for those with only pelvic lymph node metastasis, 29% for those with pelvic and para-aortic lymph node metastasis, and 0% for those with pelvic, para-aortic, and supraclavicular lymph node metastasis ($p = 0.0005$). In a recent review of 96 patients with cervical cancer, we found that FDG uptake within the primary cervical tumor, as measured by the $SUV_{max}$, is predictive of disease-free survival in patients undergoing radiotherapy for cervical cancer (39). Thus, high FDG uptake may be useful in identifying patients who need more aggressive initial therapy.

In patients with cervical cancer, tumor hypoxia is an important prognostic factor indicating decreased overall and disease-free survival (33,40–42). Hypoxic tumors are resistant to radiotherapy and chemotherapy (43). Various therapeutic strategies directed toward tumor hypoxia have been unsuccessful, in part because a clinically relevant tool for determining and monitoring tumor oxygenation has not been available. The only established method for assessing the oxygenation status of tumors in vivo uses oxygen electrodes. However, this method is not clinically practical because it is invasive and subject to sampling errors, and can be used only in readily accessible tumors. We recently showed that a new tracer, $^{60}$Cu-labeled diacetyl-bis(N$^4$-methylthiosemicarbazone) ($^{60}$Cu-ATSM), accumulates avidly in hypoxic tissues but washes out rapidly from normoxic tissues (44). We studied 27 patients with advanced cervical cancer and demonstrated an inverse relationship between tumor uptake of $^{60}$Cu-ATSM and response to therapy (45) (and unpublished data). In addition, progression-free and overall survival were significantly worse in patients...
with increased pretreatment primary tumor uptake of $^{60}$Cu-ATSM. In these patients, we found no significant difference in tumor FDG uptake in subjects with hypoxic (ATSM-avid) tumors versus those with normoxic tumors. Thus, $^{60}$Cu-ATSM-PET imaging of hypoxia provides prognostic information that cannot be derived from FDG-PET, and this examination has the potential to be used to monitor hypoxic-directed therapy in patients with hypoxic cervical cancer.

**Posttherapy Monitoring**

Approximately 30% of cervical cancer patients will ultimately fail after definitive treatment (46). Clinical and radiologic techniques have been used for early detection of recurrent disease with much success. FDG-PET has also been shown to have a role in the posttreatment monitoring of patients with cervical cancer (Fig. 50.3). In a large retrospective study by Ryu et al. (47), 249 women with previously treated cervical cancer without overt evidence of recurrence underwent FDG-PET as part of their routine follow-up. Eighty patients (32%) were found to have abnormal FDG uptake; 28 (11%) had clinically or histologically confirmed recurrent disease. The sensitivity and specificity of FDG-PET for detection of recurrent disease were 90% and 76%, respectively. The positive- and negative-predictive values were 35% and 98%, respectively. There was a high false-positive rate associated with FDG uptake in the pulmonary hila, lungs, and neck, as well as in the inguinal and axillary regions. Most of the recurrences were detected within 6 to 18 months after diagnosis. In another series by Unger et al. (48), FDG-PET detected recurrences in 31% of asymptomatic patients and in 67% of symptomatic patients. In symptomatic patients, the sensitivity of FDG-PET was 100%, the specificity was 86%, and the positive- and negative-predictive values were 93% and 100%, respectively. By comparison, in asymptomatic patients, the sensitivity of FDG-PET was 80%, the specificity was 100%, and the positive- and negative-predictive values were 100% and 89%, respectively. In a study by Grigsby et al. (36), 152 patients previously treated with radiotherapy with or without concurrent chemotherapy who were free of FDG-avid sites on PET (obtained an average of 3 months posttherapy) had 5-year cause-specific and overall survival of 80% and 92%, respectively. Persistent abnormal uptake in the cervix or lymph nodes was found in 20 patients, and their cause-specific survival was 32%. New areas of increased FDG uptake in previously unirradiated regions were found in 18 patients, none of whom were alive at 5 years. Posttherapy PET abnormalities were found to be the most significant predictor of death from cervical cancer in this study. Together these results point to a significant impact of FDG-PET findings on treatment strategy after primary therapy.

Other groups have investigated the use of FDG-PET in combination with other biomarkers, such as squamous cell carcinoma (SCC) antigen (49). In a phase II study, 27 patients with previously treated cervical cancer underwent FDG-PET for unexplained elevation of serum SCC antigen levels found during follow-up evaluation. PET showed FDG-avid lesions in 17 of 18 patients with proven recurrent disease; 12 of these patients had distant recurrences only, 2 had local recurrences only, and 3 had both local and distant recurrences. As a result of PET imaging, only 7 of the 18 patients with recurrent disease were treated with curative intent as compared with 16 of 30 patients treated.

**Figure 50.3** Recurrent cervical carcinoma. This patient underwent chemoradiotherapy for cervical cancer 1 year ago. Coronal and transaxial CT (A,D), PET-CT fusion (B,E), and PET images (C,F) demonstrate intense FDG uptake (arrows) within a small (0.8 cm) aortocaval lymph node. Transperitoneal left periaortic lymph node dissection was positive for recurrent disease.
with curative intent in the historical control group. PET imaging allowed better selection of patients for salvage therapy, which resulted in a trend toward increased overall survival of those treated compared with a historical control group. These promising results will need to be confirmed in further investigations to better define the role of FDG-PET in combination with molecular biomarkers. Additionally, Yen et al. (50) in a prospective study examined the role of FDG-PET imaging in patients with biopsy-confirmed relapse of disease or unexplained elevation of serum tumor marker levels with documented relapse after treatment. Fifty-five women were enrolled, 36 (66%) had treatment modifications as a result of the PET findings, and the remaining 19 were treated as originally planned. Of those patients whose plans were modified, 25% received salvage therapy with curative intent, but the modality or field of irradiation was changed, and 75% received only palliative treatment. Together these results demonstrate the usefulness of FDG-PET for determining the intent and optimal scope of salvage therapy in patients with recurrent cervical cancer.

**OVARIAN CANCER**

Ovarian cancer is the leading cause of death from gynecologic cancers; approximately 80% of women with stage III or IV disease die within 5 years (51). In the United States, it was estimated that nearly 20,180 new cases of ovarian cancer would be diagnosed and that 15,310 women would die from this disease in 2006 (6). Ovarian cancer is a potentially curable disease if it is diagnosed at an early stage; however, early-stage disease is often silent clinically, and thus two thirds of patients have advanced disease (stages III or IV) at initial presentation. Nearly 90% of ovarian cancers are epithelial carcinomas, a diverse group consisting of serous, mucinous, clear cell, endometrioid, and undifferentiated types. The remaining 10% are ovarian germ cell tumors and stromal tumors. Ovarian cancer spreads early by the shedding of tumor cells into the peritoneal cavity; these cells proliferate as parietal and visceral peritoneal implants. Ovarian cancer also spreads through lymphatics to inguinal, pelvic, para-aortic, and mediastinal lymph nodes. Approximately 80% of patients with advanced ovarian cancer have elevated levels of the serum tumor marker CA-125. This tumor marker is widely used to assess the effectiveness of response and to detect tumor recurrence; abnormal levels of this marker often precede clinical and radiologic signs of disease recurrence. Because of the limitation of radiologic methods, ovarian cancer is currently staged surgically both at initial diagnosis and at recurrence.

**Diagnosis and Staging of Ovarian Cancer**

Ovarian cancer typically presents as an adnexal mass. Early detection of ovarian cancer is a clinical challenge. To improve the detection of ovarian cancer at an early stage of disease, transvaginal ultrasonography is considered part of the routine gynecologic examination. Sonography has 90% sensitivity for detecting pelvic masses and determining their origin (52). However, there is a considerable overlap in the imaging features of malignant and benign ovarian lesions. In addition, sonography is limited in defining the extent of disease; in particular, sonography is not accurate in evaluating metastatic spread to the peritoneum. Similarly, CT is of little use in early detection of ovarian cancer. MRI has been shown to have a higher diagnostic accuracy than CT in differentiating benign from malignant ovarian tumors (91% vs. 78%) (53). Nonetheless, MRI is limited in its ability to detect small lesions and occasionally in determining whether a large adnexal mass is unilateral or bilateral (54).

Several investigators have evaluated the clinical usefulness of FDG-PET for diagnosis of ovarian cancer. Grab et al. (55) studied 101 patients with asymptomatic adnexal masses to determine the diagnostic accuracy of MRI, FDG-PET, and sonography for characterization of adnexal masses. The sensitivity, specificity, and accuracy were 83%, 84%, and 84%, respectively, for MRI; 58%, 80%, and 77%, respectively, for FDG-PET; and 92%, 60%, and 63%, respectively, for sonography for differentiating benign from malignant adnexal masses. Kawahara et al. (56) performed FDG-PET and MRI in 38 women selected after screening for ovarian masses by ultrasonography; 23 had malignant lesions and 15 had benign lesions. MRI alone, FDG-PET alone, and MRI with FDG-PET in combination had sensitivities of 91%, 78%, and 91%, respectively; specificities of 87%, 87%, and 87%, respectively; and diagnostic accuracy of 92%, 82%, and 92%, respectively, for differentiating benign from malignant ovarian masses. Thus, the addition of FDG-PET to MRI did not yield significant additional information. The relatively low sensitivity of FDG-PET is likely attributable to the cystic nature of many ovarian tumors and the small tumor volume in early stages of disease. Another important limitation is the moderately intense accumulation of FDG in the ovaries of normal premenopausal women (Fig. 50.4). Lerman et al. (57) reported increased ovarian uptake of FDG (SUV 5.7 ± 1.5) in 21 premenopausal patients without known ovarian malignancy; 15 of the women were at the midphase of the ovulatory cycle and 3 had oligomenorrhea. These investigators reported that a threshold ovarian SUV of 7.9 separated benign from malignant lesions with sensitivity, specificity, accuracy, positive-predictive value, and negative-predictive value of 57%, 95%, 85%, 80%, and 86%, respectively. Hubner et al. (58) compared the results of FDG-PET and CT with surgical and pathologic findings in 51 patients with suspected ovarian cancer. A good correlation was noted between FDG-PET results and histologic findings. The sensitivity, specificity, positive-predictive value, and negative-predictive value for PET were 83%, 80%, 86%, and 76%, respectively, and those for CT were 82%, 53%, 77%, and 62%, respectively. The combined information...
from CT and PET had a positive-predictive value of 95% if both CT and PET were positive and a negative-predictive value of 100% if both CT and PET were negative. At the present time, because of limitations of current imaging techniques (including FDG-PET), sonography remains the noninvasive method of choice for evaluation of adnexal masses; however, all masses with sonographic findings suspicious for malignancy require surgical evaluation for histologic confirmation and staging.

**Residual or Recurrent Ovarian Cancer**

Surgical tumor debulking is performed in all patients with ovarian cancer. Patients with early-stage disease, limited to the ovary or pelvis, (stages I and II, respectively) have a 5-year overall survival in the 80% to 95% range following surgery (59). For selected patients with early-stage disease limited to the ovary and those with well-differentiated, completely encapsulated tumors (e.g., stage IA, grade 1), no further treatment is necessary. However, most patients with advanced disease involving the upper abdomen or beyond (stages III and IV, respectively) will require postoperative chemotherapy to eradicate residual disease. Long-term survival in these patients is only 10% to 30% (60). Unfortunately, despite an initial response to chemotherapy in most patients, relapse is a frequent problem. After first-line treatment of ovarian cancer, 36% to 73% of patients have residual disease despite normalization of tumor marker levels and negative results of conventional imaging studies (61). Early detection of recurrence may provide a better chance for salvage therapy, which may result in prolonged remission. Recurrent or residual ovarian cancer is notoriously difficult to diagnose; conventional imaging methods and CA-125 measurements are unreliable for determining the presence of recurrent disease. Conventional imaging modalities are especially limited for detection of peritoneal recurrence of ovarian cancer. CA-125 elevation is not helpful in localizing the disease, but the knowledge of the location of recurrence is necessary to guide tailored salvage treatment. Therefore, second-look surgery is routinely performed when recurrent disease is suspected. However, second-look surgery also can be falsely negative in the absence of gross tumor.

Several investigators have evaluated the clinical usefulness of FDG-PET in detecting recurrent or residual ovarian cancer (Figs. 50.5 and 50.6) (17,62,63–66). FDG-PET has been shown to be superior to conventional imaging and measurement of CA-125 in detecting recurrent ovarian cancer. A recent systematic review of the literature for detection of recurrent ovarian cancer reported six studies that addressed patients with clinical suspicion for recurrent disease. The pooled sensitivity and specificity were 90% (95% CI 82%–95%) and 86% (67%–96%), respectively, for PET, 68% (49%–83%) and 58% (33%–80%), respectively, for conventional imaging), and 81% (62%–92%) and 83% (58%–96%), respectively, for CA-125 measurement (17). Nakamoto et al. (62) reported a possible therapeutic impact of FDG-PET in this clinical setting. They showed that the results of FDG-PET led to a change in management in 5 of 12 patients (42%) who were initially suspected of having recurrent disease.

In patients with no clinical or radiologic evidence of disease, FDG-PET was found to be useful, although limited in the detection of small-volume disease. Havrilisky et al. (17) found three studies that addressed patients with negative conventional imaging and CA-125 measurements in whom surveillance FDG-PET was used to detect recurrent or persistent ovarian cancer. The pooled sensitivity and specificity of PET were 54% (95% CI 39%–69%) and 73% (56%–87%), respectively. Using PET in patients with
Figure 50.5 Recurrent ovarian carcinoma. This patient underwent surgery and chemotherapy for ovarian carcinoma 2 years ago. She now has an increasing serum CA-125 level and ascites. Coronal and transaxial CT (A,D), PET-CT fusion (B,E), and PET images (C,F) demonstrate increased FDG uptake within a small nodule in the pelvis (arrows), consistent with recurrent disease. (See also Case 33.)

Figure 50.6 Recurrent ovarian carcinoma. This patient had surgery and chemotherapy 1 year ago for ovarian carcinoma. She now has an increasing serum CA-125 level. Coronal (top) and transaxial (bottom) CT (A,D), PET-CT (B,E) fusion, and PET (C,F) images demonstrate increased FDG uptake within a left pelvic soft tissue nodule (arrows). Fine-needle aspirate of this nodule was consistent with recurrent ovarian cancer.
suspected recurrence based on elevated tumor markers has been demonstrated to increase the reliability of PET in patients with ovarian carcinoma. Havrilchyk et al. (17) also found three studies that addressed patients with rising CA-125 levels and negative or equivocal conventional imaging studies. The pooled sensitivity and specificity of PET were 96% (88%–99%) and 80% (44%–97%), respectively.

Response to Therapy

The current standard treatment for patients with advanced ovarian cancer is primary cytoreductive surgery followed by chemotherapy. Neoadjuvant chemotherapy followed by interval debulking surgery is under investigation as an alternative approach for the initial management of bulky ovarian cancer, aiming at the improvement of surgical efficiency. Patients who have received neoadjuvant chemotherapy prior to debulking surgery have had lower associated morbidity compared with patients undergoing primary cytoreduction. Moreover, the neoadjuvant chemotherapy approach provides preoperative knowledge of tumor chemosensitivity, allowing for selection of more effective therapy following surgery. Although responsiveness to neoadjuvant chemotherapy followed by standard surgery is associated with progression-free and overall survival comparable with that achieved with conventional treatment, nonresponsiveness to neoadjuvant therapy seems to be associated with a poorer prognosis and reduced overall survival (67). Thus, responsiveness to neoadjuvant therapy is not uniform and it is thus important to identify patients who may not benefit from such therapy. Recently, Artil et al. (68) have investigated the usefulness of FDG-PET in predicting the effectiveness of chemotherapy and subsequent patient outcome early after institution of neoadjuvant therapy. FDG-PET was performed in 33 patients before and after the first and third cycle of chemotherapy. A significant correlation was found between changes in tumor FDG uptake after the first and third cycle of chemotherapy and overall survival. At a threshold of a 20% reduction in tumor FDG uptake after the first cycle, the median overall survival was longer in metabolic responders than in nonresponders (38.3 months versus 23.1 months). In addition, at a threshold of a 55% decrease in tumor FDG uptake after the third cycle, median overall survival was also longer in metabolic responders than in nonresponders (38.9 months versus 19.7 months). No correlation was observed between conventional clinical response criteria or CA-125 response criteria and overall survival.

Second-look laparotomy is not recommended in patients with stage I disease who have undergone appropriate therapy because of its low yield of positive findings; however, it is frequently used in patients with advanced-stage ovarian cancer, as more than 50% of such patients will have a positive result (69). Even among those with a negative result (no disease identified), the risk of recurrence exceeds 50%. Second-look laparotomy is expensive and is associated with the morbidity of major abdominal surgery. Unfortunately, conventional imaging methods have been shown to be of limited value in this clinical setting. Accordingly, investigators continue to search for other accurate, noninvasive diagnostic modalities to substitute for second-look laparotomy in the follow-up of patients with ovarian carcinoma. Several studies have compared FDG-PET with second-look laparotomy. To assess the clinical usefulness of FDG-PET in evaluation of response to therapy, Rose et al. (61) studied 22 patients with FDG-PET after the completion of therapy and before second-look laparotomy. All patients had achieved complete response clinically and radiologically, as well as normalization of CA-125 levels. Thirteen of 22 patients had residual disease pathologically. FDG-PET had a sensitivity of only 10% and a specificity of 42% in this study. FDG-PET detected one site of macroscopic disease (1.5 cm) and was negative at the remaining eight sites of macroscopic disease and at all four sites of microscopic disease. However, FDG-PET may be useful in the follow-up of patients with advanced ovarian cancer who have a high risk for recurrence. Kim et al. (70) also compared the prognostic value of FDG-PET and second-look laparotomy findings in a group of patients with advanced ovarian carcinoma (FIGO stage III or IV) who had completed cytoreductive surgery and adjuvant chemotherapy. Thirty patients underwent second-look laparotomy, and a separate group of 25 patients underwent FDG-PET without second-look laparotomy. With a median follow-up of 36 months, the disease-free and progression-free intervals were not significantly different between the two groups, and the authors concluded that FDG-PET could be used in place of second-look laparotomy for the follow-up of patients with ovarian carcinoma. The results of this small study must be confirmed by a prospective trial before this approach can be adopted.

These studies suggest that FDG-PET may play some role in confirming or detecting residual macroscopic disease that is clinically suspected, especially in patients with advanced disease at high risk for residual disease. However, PET is unlikely to replace laparotomy for restaging of most ovarian cancers during the period immediately after therapy or with early recurrent disease. This is because of the inability of PET to detect microscopic spread of disease or even macroscopic lesions smaller than 1 cm because of its poor spatial resolution.

One way to overcome this limitation of PET, at least in part, may be with the use of PET-CT scanners. PET-CT should improve disease detection by increasing radiologic sensitivity and specificity. Fused PET-CT images are clearly helpful in localizing pathologic activity and differentiating this activity from physiologic radiotracer uptake. In a recent prospective study, Nanni et al. (63) prospectively evaluated the sensitivity, specificity, and accuracy of FDG-PET-CT in 41 patients with a suspicion for recurrent ovarian carcinomas. All patients were initially treated for ovarian cancer with surgery and radiochemotherapy or radiochemotherapy alone. After conventional imaging (CT, MRI, and ultrasonography) and CA-125 measurement,
patients underwent additional FDG-PET-CT. The researchers found that FDG-PET had 88% sensitivity, 71% specificity, and 85% accuracy, all of which were superior to historical results of conventional imaging. The PET-CT findings resulted in a change in therapeutic management of 23 patients (56%); 3 patients underwent surgery for local pelvic recurrence, and 20 patients received second-line chemotherapy. The use of combined PET-CT allowed effective anatomic localization of recurrent disease. Sironi et al. (64) prospectively investigated the accuracy of combined PET-CT for detection of persistent disease in 31 women who underwent first-line cytoreductive surgery followed by platinum-based chemotherapy. Before second-look surgery, all patients underwent FDG-PET-CT. Seventeen (55%) of 31 patients were found to have persistent disease on histologic analysis at second-look surgery. PET-CT correctly identified 32 of 41 lesions found on histologic analysis (13 of 16 lymph nodes, 18 of 21 peritoneal lesions, and 1 of 4 pelvic lesions). All nine lesions missed on PET-CT were less than 0.5 cm in maximum diameter. The overall lesion-based sensitivity, specificity, accuracy, positive-predictive value, and negative-predictive value for detection of recurrent tumor 1 cm or larger were 78%, 75%, 77%, 89%, and 57%, respectively.

Bristow et al. (65) have also evaluated the utility of PET-CT for detection of recurrent ovarian carcinoma in patients with tumor masses 1 cm or larger. In a prospective study, patients with clinically occult disease by conventional CT imaging, but suspected recurrent disease based on rising CA-125 levels, underwent PET-CT. Twenty-two patients meeting these criteria underwent surgical assessment after PET-CT, and 21 (95%) had pathologically confirmed recurrent disease. Tumor nodules 1 cm or larger were detected surgically in 18 patients (82%), and optimal secondary cytoreductive surgery (residual disease <1 cm) was accomplished in 15 of 18, with complete cytoreduction (no gross residual disease) achieved in 13 of 18. PET-CT demonstrated focal increased FDG uptake suspicious for recurrent disease in 16 patients, and recurrent disease 1 cm or larger was found at surgery in 15. There were three cases with surgically documented disease 1 cm or larger despite negative PET-CT. The sensitivity and specificity of PET-CT for detection of recurrent tumor 1 cm or larger were 83% and 75%, respectively. The positive- and negative-predictive values for detection of recurrent tumor 1 cm or larger were 94% and 50%, respectively. These results show that PET-CT findings identify patients with suboptimal-volume recurrent disease.

In a retrospective study, Bristow et al. (66) also investigated the use of PET-CT for detecting recurrent ovarian carcinoma limited to retroperitoneal lymphadenopathy. They identified 14 patients with recurrent disease confined to retroperitoneal nodes on PET-CT in the setting of a rising CA-125 level and negative or equivocal conventional CT at least 6 months after primary therapy. All patients underwent surgical assessment of the abnormal lymph node regions, and 11 of 14 (79%) were found to have recurrent disease in the nodal regions identified by PET-CT. False-negative results were chiefly related to small nodal deposits of tumor. Together these results suggest that PET-CT is a useful imaging technique in properly selected patients with suspected recurrent ovarian carcinoma. Additionally, PET-CT allows for increased anatomic specificity and directed surgical resection.

**OTHER GYNECOLOGIC TUMORS**

**Endometrial Cancer**

Endometrial cancer is the most common gynecologic cancer in the United States; an estimated 41,200 new cases and 7,350 deaths were expected in 2006 (6). About 75% of endometrial cancers are adenocarcinomas that arise from the glands of the uterine lining. Endometrial cancer is a disease of postmenopausal women and is surgically staged and treated. There are no reports of the use of FDG-PET for diagnosis of primary endometrial cancer. However, it might be expected that FDG-PET would have limited accuracy for this purpose because increased uterine FDG uptake may occur with benign conditions including uterine bleeding (e.g., menstruation, postpartum) and leiomyomata (Fig. 50.7) (71,72).

Surgical staging of endometrial cancer includes an exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, and peritoneal cytology. The extent of lymph node sampling remains controversial. Conventional imaging methods, such as CT and MRI, have been unreliable in detecting pelvic and para-aortic lymph node metastases (73,74). Our group conducted a prospective study evaluating the sensitivity and specificity of FDG-PET imaging for detecting pelvic and para-aortic lymph node metastases in patients undergoing surgical staging for newly diagnosed high-risk uterine corpus cancer (75). One of our 19 patients did not undergo lymphadenectomy because FDG-PET was suspicious for nodal and pulmonary metastases; disseminated disease was confirmed by percutaneous nodal biopsy. The primary tumor was seen on PET in 16 of 19 patients (84%). FDG-PET was found to have 60% sensitivity and 98% specificity for detection of pelvic and para-aortic lymph node metastases. Because of its limited sensitivity, FDG-PET should not replace lymphadenectomy in most patients, but it may be useful in guiding adjuvant therapy in patients who are poor surgical candidates.

Other groups have investigated the role of FDG-PET in the postoperative or posttherapy setting (76,77). In a retrospective study by Belhocine et al. (76), 41 FDG-PET studies were performed on 34 patients with previously treated endometrial cancer and compared with the results of clinical examination and conventional imaging procedures. The researchers found the sensitivity, specificity, diagnostic accuracy, and positive- and negative-predictive values of
FDG-PET for residual/recurrent disease to be 96%, 78%, 90%, 89%, and 91%, respectively. In 26 studies, FDG-PET detected recurrent disease that was confirmed by histology (n = 7) or by clinical and radiologic outcomes (n = 19). In 88% of these cases, FDG-PET confirmed recurrence initially suspected based on the results of other studies. FDG-PET was able to detect asymptomatic recurrences in the remaining 12% of patients. In 35% of cases, FDG-PET significantly altered treatment decisions by detecting otherwise unsuspected distant metastases. Saga et al. (77) evaluated 21 postoperative patients with endometrial cancer (FIGO stages IA–IVA) who underwent 30 FDG-PET examinations to evaluate for recurrence or to assess response to treatment. When evaluated in conjunction with anatomic information available from CT or MRI, FDG-PET had a sensitivity of 100%, specificity of 88%, and an accuracy of 93%. Additionally, FDG-PET was able to detect unsuspected metastatic disease in 19% of patients and changed the management of 7 patients (33%). FDG-PET had a high negative-predictive value for excluding recurrence, with no false-negative result after a minimal follow-up of 5 months.

Based on the current literature, FDG-PET is more sensitive in the postoperative or posttherapy setting than in the preoperative setting in patients with endometrial cancer (Figs. 50.8 and 50.9). This is likely because of the larger metastatic tumor burden present in the posttherapy setting versus the microscopic metastatic disease present at initial diagnosis. Larger prospective studies will be needed to confirm these results.

**Vulvar and Vaginal Cancers**

Data in the literature are limited regarding the use of PET in vaginal and vulvar cancers. Carcinoma of the vagina is a rare neoplasm; an estimated 2,420 new cases were expected in the United States in 2006 (6). Epidemiologically and histologically it is similar to the much more common carcinoma of the cervix and, as such, is often treated similarly. As discussed in this review, FDG-PET is the best available imaging method for lymph node staging at the time of diagnosis for cervical cancer (13,78). Similar efficacy of FDG-PET also has been demonstrated recently by Lamoreaux et al. (79) in a prospective registry study of 23 consecutive patients with newly diagnosed vaginal cancer (FIGO stages II–IVA). Of 21 patients with intact tumor at the time of evaluation (2 had previous excision prior to imaging), CT and FDG-PET demonstrated primary disease in 43% and 100% of patients, respectively. CT demonstrated abnormally enlarged groin lymph nodes in three patients and both groin and pelvic lymph nodes in one patient (4 of 23, 17%). FDG-PET demonstrated abnormal uptake in the groin nodes of four patients, pelvic lymph nodes in two patients, and both groin and pelvic lymph

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**Figure 50.7** Menstruation. Sagittal CT (A), PET-CT (B) fusion, and PET (C) images demonstrate mildly increased FDG uptake within the uterine cavity (arrow) in a menstruating patient (see also Chapter 33).
Figure 50.8  Recurrent endometrial carcinoma. This patient had surgery and chemotherapy 2 years ago for endometrial carcinoma. She has developed recurrent disease in the pelvis. Coronal (top) and transaxial (bottom) CT (A,D), PET-CT (B,E) fusion, and PET (C-F) images demonstrate increased FDG uptake within a pelvic soft tissue mass (arrow). In addition, a small soft tissue density with increased FDG uptake is noted adjacent to the liver (small arrow), indicating peritoneal dissemination of the tumor and rendering the patient unsuitable for attempted surgical salvage.

Figure 50.9  Recurrent endometrial carcinoma. This patient underwent surgery and radiotherapy 5 years ago. She developed several recurrences, which successfully responded to chemotherapy and were felt to be clinically free of disease. Coronal and transaxial CT (A,D), PET-CT fusion (B,E), and PET images (C,F) demonstrate unsuspected foci of increased FDG uptake in the retroperitoneum corresponding to left para-aortic lymph nodes (arrow).
nodes in two patients (8 of 23, 35%). FDG-PET identified four additional foci of disease consistent with nodal metastases. The detection of lymph node metastasis can have prognostic as well as therapeutic implications. Pingley et al. (80), in a study of 134 patients with vaginal cancer, demonstrated that the presence of lymph node metastases was an indicator of poor prognosis. It is expected that FDG-PET in vaginal cancer, as in cervical cancer, may be important in altering treatment options or in determining the appropriate volume of radiotherapy, although no modifications to therapy were made in our initial study based on FDG-PET findings.

Vulvar carcinoma accounts for approximately 5% of all gynecologic malignancies; an estimated 3,740 new cases were expected in 2006 (6). About 90% of vulvar cancers are squamous cell carcinomas. Vulvar cancer commonly spreads to groin lymph nodes, and therefore, the treatment of this cancer typically includes a radical vulvectomy and either unilateral or bilateral groin lymphadenectomy. The status of the groin lymph nodes is an important determinant of treatment and prognosis in vulvar cancer. In a pilot study of 15 patients with vulvar cancer, we showed that FDG-PET had a sensitivity of 80%, specificity of 90%, positive-predictive value of 80%, and negative-predictive value of 90% for showing metastases in the inguinal region (Fig. 50.10) (81).

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INTRODUCTION

Similar to the soft tissue sarcomas (see Chapter 53), malignant bone tumors constitute a heterogeneous group and originate from mesenchymal tissues. They arise in bony or cartilage tissue and may have variable calcification and soft tissue extension at presentation. Osteosarcoma and the Ewing sarcoma family of tumors (ESFT), which include peripheral neuroectodermal tumors (PNET), are important childhood cancers and account for approximately one third of them. Adult bone tumors may include the same diagnoses, although adults are more likely to present with osteosarcoma and chondrosarcomas. Generally, younger patients have overall better outcomes than adults with bone and cartilage tumors. Newer limb salvage surgical procedures have enabled the current generation of patients to have excellent functional results after resection and treatment (1,2). Positron emission tomography (PET) imaging experience has contributed to characterization of these tumors and patient follow-up. The use of PET and single-photon emission computed tomography (SPECT) in the diagnosis of benign bone tumors is discussed in Chapter 65.

Positron emission tomography (PET) imaging using fluorodeoxyglucose (FDG) is currently being evaluated in bone sarcoma diagnosis and patient treatment response assessment. Studies are showing that it can be used to distinguish low-grade from high-grade tumors and to assess whether there is tumor recurrence. As a whole-body imaging technique, it can easily identify synchronous tumor as in the case of Ewing sarcoma and metastases from other tumor types can easily be identified. Figure 51.1 shows some examples of bone sarcoma appearance on FDG-PET. The tumor uptake is usually intense, and the extent of tumors is easily distinguished. The use of PET and single-photon emission computed tomography (SPECT) in benign bone tumors is discussed in Chapter 65.
range in cellular differentiation and biologic behavior. Their origin may be from the bone cortex, periosteum, marrow cavity, and joint surfaces (cartilage).

**OSTEOSARCOMA**

**Background**

These tumors have a peak incidence in the second decade of life, with very few patients younger than 10 years of age or older than 50 years of age (3). Most osteosarcomas are present in the extremities, with 15% to 20% of patients presenting with pulmonary metastases (the main site). Occasional metastases are present in the bone, lymph nodes, and brain. Osteosarcomas are metaphyseal tumors. Risk factors for osteosarcoma include prior radiation therapy (3% of tumors), germ line retinoblastoma gene (Rb) mutation, germ line p53 mutations, and Rothmund-Thomson syndrome. Other associations with osteosarcoma have been described for growth abnormalities, trauma, fetal x-ray exposure, fluoride in water, and parental x-ray exposure. Table 51.1 shows the frequency for occurrence at different sites of primary osteosarcomas. Patients with metastatic disease have a significantly worse prognosis (4). There are many subtypes of osteosarcomas. Table 51.2 lists the histologic types of osteosarcoma and their frequencies of occurrence. They are classified according to the French or FNCLCC grading system for sarcomas (5).

The classic osteosarcomas are treated with neoadjuvant chemotherapy. Standard chemotherapy consists of intensive use of doxorubicin, cisplatin, and high-dose methotrexate. Prognostic factors at presentation include the presence of metastases and the presence of chemotherapy resistance. Five-year survival, depending on the level of chemotherapy resistance, is 60% to 80%. Survival for this period without chemotherapy is closer to 50%. Postresection treatment may include radiation therapy to the tumor bed and likely includes additional chemotherapy. This later aspect of treatment is included if there was significant tumor response to neoadjuvant chemotherapy (prior to resection). The low-grade types are treated with wide resection and typically only recur in 5% of cases. Five-year survival is high unless a degeneration to a higher-grade malignant process takes place in a local recurrence.

<table>
<thead>
<tr>
<th><strong>TABLE 51.1</strong></th>
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<td><strong>OSTEOSARCOMA PRIMARY TUMOR SITES</strong></td>
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<td>Femur</td>
<td>44%</td>
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<tr>
<td>Tibia</td>
<td>17%</td>
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<td>Humerus</td>
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<td>Pelvis</td>
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<td>Other (including mandible)</td>
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**Patient Evaluation**

This process consists of a standard, careful patient assessment for the presence of malignancy and ability to tolerate chemotherapy for patients with high-grade tumors. To characterize the primary tumor site, plain film, magnetic resonance imaging (MRI), and computed tomography (CT) are usually performed. A whole body bone scan and chest CT scan are performed to detect lung metastases.
Figure 51.1 FDG-PET bone sarcoma examples. These display the heterogeneity in tumor uptake and skeletal locations of these tumors. Primary osteosarcoma in the left pelvis (A,B) in a coronal PET (A) and on axial CT (B), showing bone destruction. Telangiectatic osteosarcoma in the left distal femur (C–G). Diagnostic FDG-PET (C: axial; D: coronal; and E: sagittal views) and MRI images (F: axial; G: sagittal) show heterogeneity. The areas with less uptake on FDG-PET images are likely necrotic. Fibroblastic osteosarcoma in the wrist (H–K). This is a small tumor with relatively homogenous uptake in PET (H: axial; I: coronal), although MRI (J: coronal; K: axial) shows more complexity. This later aspect is likely owing to tumor edema. Leiomyosarcoma of bone in the left proximal femur (L–N), showing bony destruction on CT (L) and intense FDG activity on two coronal sections (M,N). Parosteal osteosarcoma in the right proximal femur. Diagnostic FDG-PET (O,P) and MRI images (Q,R). The FDG uptake pattern shows it to be a highly heterogenous tumor.
Patients also receive a hearing test to determine baseline function before possible ototoxicity from cisplatin. Renal and liver function at baseline also are assessed to help monitor likely toxic effects of chemotherapy. The addition of fluorodeoxyglucose (FDG) PET-CT to this process is not part of conventional practice yet; however, it will likely take its place in diagnosis in the osteosarcoma patient. Several authors have found that FDG-PET is useful in bone tumor assessment (6–9). They found that the level of tumor metabolic activity assessed with FDG-PET indicated tumor grade and provided prognostic information. Often the distinction between benign and malignant tumors was facilitated. Schulte et al. (6) found that sarcomas had much higher uptake than most benign tumors, but active benign tumors could not always be distinguished from malignant ones. If the mass was assessed using a bone tumor to background ratio of greater than 3.0, the sensitivity of the FDG-PET image for determination of malignancy was 93%. The specificity of this measure was 66.7%, and the accuracy was 81.7%. Feldman et al. (7) found that a tumor standardized uptake value (SUV) greater than 2.0 had an overall sensitivity of 91.7% to distinguish malignant lesions. The data used to separate benign from malignant bone tumors had a significance of p > 0.001. This information was found to be a highly useful adjunct to patient assessment and treatment planning. Figure 51.1 shows several examples of malignant bone tumors with their correlative anatomic imaging. These are often highly heterogenous tumors on FDG and anatomic imaging appearance, which is owing to their multiple populations of bone- and cartilage-forming elements, hemorrhage, cystic degeneration, and areas of variable cellular differentiation.

**EWING SARCOMA FAMILY OF TUMORS (ESFT)**

**Background**

These are high-grade tumors with a peak incidence in patients of approximately 15 years of age. Table 51.2 lists the ESFT. They most commonly present with pain and a mass, with duration of symptoms before diagnosis an average of 48 months. They occur most frequently in the extremities (53%) and pelvis (24%), but also occur in most other skeletal sites to some extent. ESFT are presumed to arise from the postsynaptic neural crest precursors. Consequently they present a range of neuronal differentiation by histologic and antigen markers. The presence of the EWS-FLI1 fusion protein has been found to carry prognostic information (10). Often tumors are assessed for this gene abnormality to assess tumor biologic risk. Risk factors for the development of ESFT are little known as they have no association with known cancer susceptibility genes, are rarely associated with radiation therapy, and are rarely familial. They do have an association with a family history of gastric cancer and occur most commonly in Caucasians and Hispanic ethnic groups.

**ESFT Patient Evaluation**

ESFT patients are assessed for treatment in a similar protocol as patients with other bone tumors listed above. Since they more frequently present with metastatic disease, the whole-body assessment is particularly important for treatment planning. Between 15% and 30% of patients have metastatic disease at diagnosis of the primary tumor. The most likely sites for metastases are lung (53%), bone (43%), and bone marrow (16%). Whole-body PET-CT is particularly useful for patient staging in addition to the chest CT scan with contrast and the bone scan. With FDG-PET, the ESFT/PNET have an intense homogenous appearance. The SUV ranges are not extremely high, with an overall lower median than those for the osteosarcomas (11). Figure 51.2 shows two examples of FDG-PET scans in ESFT patients.

**MALIGNANT CARTILAGE TUMORS**

**Background**

These tumors usually occur in older adults and take many forms. Table 51.2 lists the types of malignant cartilage tumors. The primary chondrosarcomas most commonly arise in the proximal humerus, proximal femur, and pelvis in the obturator ring and medial wall of the acetabulum. They are painful and present as a mass. Their differentiation ranges from low to high grade, which may be difficult to distinguish with standard imaging and histologic appearance of the biopsy specimen. Generally, higher-grade tumors have an increased fluid content. Most of the chondrosarcomas are low- to intermediate-grade variants (75%) which have 5-year survival rates between 70% and 80%. The patients with high-grade tumors (25%) have a decreased survival rate of 50% at 5 years from diagnosis. A particularly high-risk form of chondrosarcoma is the spine tumor, with which 75% of patients expire from progressive disease.

Secondary chondrosarcomas have similar sites of occurrence as the primary tumor types. These tumors are distinguished by arising from enchondromas. Patients with hereditary multiple exostoses have higher rates of malignant transformation of their exostoses. These are usually low- to intermediate-grade tumors with little metastatic potential, and patients have an overall 80% survival 5 years after diagnosis. The clear cell and mesenchymal chondrosarcoma variants are much less common. They have distinctive histologic features as their names imply. The clear cell types occur mostly in the proximal femur (50%) and have low local recurrence rates and good overall survival (50%). The mesenchymal varieties present in adults as painful lytic tumors in the femur, ribs, pelvis, or face. They have only a 10% 5-year survival on average and are treated often with chemotherapy and wide resection.
Chapter 51: PET-CT and SPECT-CT of Malignant Bone Tumors

Chondrosarcoma Patient Evaluation

Complete radiologic and clinical evaluation of the painful cartilage tumor mass is the mainstay for chondrosarcoma patient evaluation. Since most of these tumors are low to intermediate grade, they have low metastatic potential. Tumors with more aggressive radiologic appearance undergo biopsy to establish the tumor grade. The FDG-PET scan can contribute to this aspect of the patient evaluation by assessing tumor metabolism and its relationship to tumor aggressiveness. High-grade tumors can be distinguished from low-grade and benign types easily with use of the tumor SUV. This is perhaps the most important contribution the FDG-PET scan can make to sarcoma patient treatment assessment. The radiologic and histologic appearances of these tumors do not consistently predict the biologic aggressiveness of cartilage tumors. However, it is more difficult to separate benign cartilage tumors from low-grade chondrosarcomas using any of the standard FDG-PET imaging criteria (12,13). Most recently, Lee et al. (12) found that a tumor SUV cut-off of 2.3 for grade II or III masses had a positive-predictive value of 0.82 and a negative-predictive value of 0.96. Brenner et al. (14) found that a combination of the cartilage tumor histologic grade and FDG SUV identified patients at risk for recurrence. Most important, patients in this series who had tumor SUVs lower than 3.0 with intermediate- or low-grade tumor diagnoses rarely had local recurrences. These patients could be identified as low risk and treated conservatively. Figure 51.3 shows an example of a cartilage tumor FDG scan. Overall, these tumors show homogenous FDG uptake with relatively low SUV compared with other tumor groups. Even high-grade tumors may not show very high rates of metabolism, which may explain their relatively poor response and control with chemotherapy.

Figure 51.2  Two examples of Ewing sarcomas: 20-year-old patient with Ewing sarcoma of the right iliac wing. Axial PET/CT images show the high uptake in the soft tissue tumor part (SUVmax 5.1) and osteolytic changes in the bone (A-B). (Courtesy of Dr. Klaus Strobel, Zurich, Switzerland.) Similar case of a Ewing sarcoma of the right hemipelvis with central necrosis, demonstrated by PET (C) and T2w MRI (D). These tumors occur in multiple locations, and metastases are frequent.

Figure 51.3  Example of a malignant cartilage tumor. These tumors usually show homogenous relatively low FDG uptake. Treatment response to chemotherapy in high-grade tumors may be difficult to assess because of these low tumor metabolic rates. Intermediate-grade chondrosarcoma in the left distal femur. The image intensity in this coronal PET image is increased to demonstrate the lobular cartilage pattern of uptake. (See also Case 69.)
FDG PET IN BONE TUMOR RESPONSE ASSESSMENT

Similar to the soft tissue sarcoma patients (see Chapter 53), the bone tumor patients show response to chemotherapy on FDG-PET scans. These tumors are much less studied than the soft tissue types, but results are similar in a few limited patient studies. Franzius et al. (15) found that patients with tumor to background ratios in FDG uptake decrease by 30% or greater in patients who had good histologic response observed in the resected tumor. These results were superior to the change in conventional bone scan appearance. Hawkins et al. (16) recently found that a change in the SUV maximum in FDG tumor uptake compared with baseline was highly predictive of patient outcome. Both these studies demonstrate the beginnings of work to determine the utility of FDG-PET in bone tumor assessment and treatment planning in an individual patient. Figure 51.4 shows one example of tumor response observed with baseline and repeat FDG-PET and one example of a recurrent osteosarcoma in the distal portion of a femoral bone allograft, which can also be detected with FDG-PET. This may become particularly valuable, as patients with resected bone tumors have hardware placed that causes major artifacts on anatomic imaging (see also Chapter 62). The increasing use of PET-CT scans will likely provide important information for response assessment for surgical resection and adjuvant radiotherapy treatment. As investigations with new specific tracers progress, it is likely that patients with malignant bone tumors will be evaluated for their special characteristics in tumor biology and treatment response.

REFERENCES

Chapter 51: PET-CT and SPECT-CT of Malignant Bone Tumors

PET-CT and SPECT-CT of Bone Metastases

Klaus Strobel    Daniela B. Husarik    Thomas F. Hany

The skeletal system is the third most common localization of distant metastases of malignant tumors, following the lungs and liver. Early detection of bone metastases (BM) allows for accurate staging, rapid initiation of therapy, and possible reduction of related morbidity. Diagnostic imaging plays an important role in the detection of distant metastases and especially of bone metastases (BM). There is a wide range of imaging methods to assess bone involvement: conventional x-ray studies, computed tomography (CT), magnetic resonance imaging (MRI), and several nuclear medicine techniques including bone scintigraphy (BS) with single-photon emission computed tomography (SPECT) or SPECT-CT, and positron emission tomography (PET)-CT, using different tracers, including the PET tracer fluorodeoxyglucose (FDG), 18F-fluoride, 18F-choline (FCH), and 18F-DOPA (dihydroxyphenylalanine). BS with technetium-labeled phosphate complexes has been the „work horse“ since the early 1980s in detecting bone metastases with high sensitivity. Introduction of SPECT and SPECT-CT imaging techniques have increased specificity in the differentiation of bone metastases as an adjunct to planar bone scintigraphy. Additionally, lesions detected in BS can be correlated with conventional x-ray views or CT to assess the stability and search for pathologic fractures. FDG-PET has shown a comparable sensitivity for the detection of BM compared with planar BS. But FDG-PET has some limitations, depending on the type of malignancy: it is inferior to BS in detecting osteoblastic metastases (breast or prostate) and BM in patients with osteosarcoma. FDG-PET/CT can overcome some of these limitations if the CT information is not used only for anatomic localization of PET lesions (see Fig. 52.1). 18F-fluoride is superior to FDG-PET in FDG-negative tumors. FDG-PET seems to be superior in early stages of bone metastases. Initial results indicate that FCH is a potential substance for N and M staging of patients with prostate cancer with increased PSA levels.

GENERAL REMARKS ON IMAGING

At an early stage, x-ray–based techniques may fail to detect bone metastases (BM), since frequently no morphologic alterations are present. Morphologic imaging modalities can be successful in the detection of these lesions only if bony structures (and not only soft tissue) have been altered by the malignant process. Bone scanning (BS) with Tc-phosphonate compounds has been established as the gold standard for the detection of bone metastases in the workup of several malignant diseases such as breast or prostate cancer. It represents a molecular rather than an anatomic imaging technique, as it measures the molecular process of bone accretion. This technique is very sensitive in detecting skeletal metastases; however, because of increased tracer uptake in degenerative, inflammatory, and other benign diseases, it has relatively low specificity. BS in combination with SPECT, but particularly SPECT-CT, can decrease the need to perform additional investigations, because the combination of BS and x-ray imaging techniques in combination are sensitive and specific. The value of BS has its limitations in detecting BM as in some tumors such as renal cell carcinoma, and multiple myeloma tracer accumulation occurs in only 20% to 50% of
lesions. In addition, the “flare effect” is a well-known phenomenon, in which successful therapy results in a benign reparative process in the affected bone, thus also showing increased activity on BS. This precludes the use of BS to monitor treatment response of BM (1,2).

MRI is an imaging modality with high diagnostic performance in the detection of bone metastases, permitting the evaluation of bone marrow, spinal cord, and soft tissue structures. In the spine and pelvis, MRI is more sensitive than planar BS, whereas BS is more sensitive in detecting BM in the ribs and skull (3). With further technologic development, whole-body MRI may become widely used for oncologic staging of bone metastases not only in pediatric patients but also in adults. With the use of rapid sequences (diffusion-weighted echo-planar MRI, STIR-sequences) and new scanner designs, whole-body images can be obtained in approximately 15 minutes. The main advantage of MRI is the absence of radiation exposure. However, initial studies comparing whole-body MRI to FDG-PET have demonstrated that PET imaging in the detection of bone metastases is superior to MRI (4).

In the daily routine, most PET and PET/CT studies are performed using FDG as tracer. FDG, like MRI, seems to be highly sensitive in detecting BM at early stages when only the bone marrow itself is affected. Osteolytic BM have a higher glycolytic rate compared with relatively acellular osteoblastic BM; therefore, FDG-PET may be more successful in detecting osteolytic than osteoblastic metastases (5) (Fig. 52.1). Therefore, the architecture and morphology of metastases (sclerotic, mixed, lytic) is of major importance. The anatomic localization is relevant in this respect for detection in PET imaging, because small lesions in the long bones frequently have an osteoblastic response and are well detected with BS or with 18F-fluoride PET. Inversely, vertebral body lesions often show limited osteoblastic response and may be better detected with FDG-PET.

18F-fluoride is an interesting nonspecific bone-seeking PET tracer with an accumulation mechanism similar to the Tc-phosphonate compounds used in conventional bone scanning. Both depend on bone reparation rather than tumor cell viability (Fig. 52.2). The first pass blood extraction rate of 18F-fluoride through the capillary membrane is almost 100% in comparison with only 64% of the larger 99mTc-diphosphonate complexes (6). Higher spatial resolution and shorter acquisition times of 18F-fluoride PET imaging compared with conventional bone scanning results in better overall image quality (7). Initial studies indicate that 18F-fluoride is more sensitive than conventional bone scanning in detecting skeletal metastases in patients with prostate, lung, and thyroid cancer (8). Most additional lesions noted were located in the spine. In a study by Even-Sapir et al. (9), 18F-fluoride–PET was compared with 18F-fluoride–PET/CT in the assessment of malignant skeletal disease in 44 patients. In a patient-based analysis, the sensitivity of 18F-PET and 18F-PET/CT was 88% and 100%, respectively (p < 0.05) and the specificity was 56% and 88%, respectively. Because there are data that suggest that 18F-fluoride–PET may be cost effective, some authors expect that “classic” BS will be replaced by 18F-fluoride–PET completely in the coming years (7,10). Some authors have proposed a two-in-one PET investigation with combined application of FDG and 18F-fluoride for complete staging of skeletal and soft tissue metastases. Whether this approach will play a role in the future has to be evaluated in further studies (11).
BONE METASTASES IN BREAST CANCER

Bone is the most common site of breast cancer metastases (see also Chapter 45). Bone is also the most frequent localization of recurrence after treatment. Up to 90% of patients who have terminal breast cancer develop bone metastases (12). Although prognosis of women with visceral metastases from breast cancer is poor, bone metastases in breast cancer does not necessarily imply a poor outcome. Early detection and treatment of bone metastases prior to the development of functional deficits is important. In most institutions, bone scanning is the method of choice to detect bone metastases in breast cancer patients. Bone scanning is widely available, a whole-body method, and very sensitive. A negative bone scan has a high negative-predictive value to exclude bone metastases and can be used as a baseline investigation. Because increased bone uptake is not specific for tumor, further evaluation of active regions with x-ray views, SPECT, SPECT/CT, or MRI is sometimes necessary for correct diagnosis. There is a controversial discussion in the literature concerning whether BS or FDG-PET is more effective in detecting bone metastases in breast cancer (Fig. 52.3). In a recently published paper by Uematsu et al. (13), SPECT was superior to FDG-PET in detecting bone metastases, and the authors concluded that surveillance of metastatic spread to the skeleton in breast cancer patients based on FDG-PET alone is inadequate. Breast cancer metastases are often osteoblastic, and several publications point out that, because of the lower metabolic activity of osteoblastic compared with osteolytic metastases, the former may elude detection with PET imaging alone (14). Interestingly, in this study the patients with a mixed pattern or sclerotic metastases had a significantly better survival than patients with osteolytic lesions. Osteolytic lesions have a higher glycolytic rate, grow rapidly, and are aggressive. In contrast, osteoblastic metastases are relatively acellular. Cook et al. (5) measured the mean SUV of sclerotic, mixed, and osteolytic metastases to be 0.95, 3.6, and 6.6, respectively, in breast cancer patients. Nakai et al. (15) reported that the visualization rate of osteoblastic bone metastases with bone scintigraphy/FDG-PET was 100%/55.6%, 70.0%/100.0% for the lytic type and 84.2%/94.7% for the mixed type in 89 breast cancer patients. Overall there was no significant difference of FDG-PET compared with bone scintigraphy.

Whole-body FDG-PET is a useful diagnostic test for detecting recurrent or metastatic lesions of breast carcinoma. However, the sensitivity of FDG-PET for bone metastases in breast cancer appears to be lower than that to other organs. All the studies mentioned above were...
done by using PET-alone systems. In our experience, the combined approach using PET/CT in the evaluation of breast cancer patients with bone metastases has several advantages: correct anatomic localization of FDG-active bone lesions; evaluation of osteolytic lesions in weight-bearing bones concerning stability, particularly in the spine, pelvis, and proximal femora; detection of pathologic fractures; detection of sclerotic metastases with a pathognomonic morphologic pattern without FDG uptake; and last but not least, the possibility of guiding biopsy to prove bone metastases. Edmunds et al. (16) compared FDG-PET/CT with PET alone and bone scan in 25 breast cancer patients and found a sensitivity of 91% and a specificity of 95% for FDG-PET/CT, which was superior to the other methods. Lavely et al. (17) reported similar results in a study that compared bone scans and FDG-PET with regard to bone metastases in breast cancer patients.

Data concerning the use of FDG-PET or PET/CT in monitoring therapy response in patients with bone metastases of breast cancer are still limited. As pointed out, the flare effect is a well-known phenomenon that precludes the use of BS to monitor treatment response of bone metastases (12). Early prediction of response to chemotherapy in metastatic breast cancer using sequential 18F-FDG-PET was investigated in 26 patients with 6 metastases of which 4 were in the bone. Interestingly, sequential 18F-FDG-PET allowed prediction of response to treatment after the first cycle of chemotherapy (18).

**BONE METASTASES IN LUNG CANCER**

FDG-PET/CT has proven to be effective in T, N, and M staging of patients with non–small cell lung cancer (NSCLC) (19) (see Chapter 38). Bone metastases are already present in 20% to 30% of lung cancer patients at initial diagnosis and in 35% to 66% at autopsy (20). Several studies compared bone scans and FDG-PET with regard to bone metastases in NSCLC (21–23). Gayed et al. (23) showed similar results indicating that bone scan (BS) may have a higher sensitivity (81%–84%) compared with FDG-PET (73%–67%) but lower specificity (BS: 78%–84%; PET: 88%–96%) (20). In cases with osteolytic metastases, FDG-PET was demonstrated to be superior to BS (24).

Hetzel et al. (10) compared 18F-fluoride-PET imaging with bone scintigraphy in combination with SPECT imaging in 103 patients. As a result of SPECT and 18F-fluoride-PET imaging, clinical management was changed in 8 (7.8%) and 10 (9.7%) patients, respectively. We think that FDG-PET/CT can eliminate the need for a staging BS in NSCLC. In our institution, PET/CT has already replaced bone scintigraphy in staging of NSCLC patients with PET-positive primary lung tumors (25). Only in patients with FDG-inactive primary NSCLC such as bronchioalveolar carcinomas should an additional BS be considered.

**BONE METASTASES IN PROSTATE CANCER**

Prostate cancer is the most common malignant tumor in men. Initial curative treatment includes surgery and
internal or external radiation treatment. Clinical staging alone often understages disease. Preoperative BS is recommended in patients with PSA levels greater than 10 to 20 ng/L. Furthermore, BS is recommended in patients with rising PSA after radical prostatectomy or radiation therapy. Prostate cancer is one of the typical cancers with false-negative results on FDG-PET, especially if osseous metastases are osteoblastic. The sparse studies in which bone scans have been compared with FDG-PET underline the poor performance of FDG-PET in the detection of osseous metastases with a sensitivity of 65% (26,27).

Because of the generally low uptake of FDG in prostate cancer, other PET tracers have been developed. Our experience is based on PET prostate cancer imaging with 18F-Choline (FCH) (28) (see chapter 49). FCH shows high physiologic uptake in the liver, spleen, and pancreas and in the urinary excretion system with irregular activity in the bowel. FCH-PET/CT seems to be a promising tool in the evaluation of patients with elevated PSA and suspicion for bone metastases. Preliminary results indicate that this tracer is accurate in detecting lymph node metastases as well as bone metastases (7,28) (Fig. 49.1). In a study by Langsteger et al. (7) using FCH-PET/CT in 49 patients, PET downstaged 2 (4%) patients because suspicious bone lesions in BS could be excluded with FCH-PET/CT. In 6 (12%) patients, FCH-PET upstaged the patients with a resulting change in management from surgery to radiation therapy or hormone therapy. We believe that in the future, 18F-Choline PET/CT may replace BS in high-risk patients (Gleason score >7 or PSA >10 ng/mL or doubling time <3 months).

BONE METASTASES IN MALIGNANT BONE TUMORS

Primary malignant bone tumors usually show an increased glucose metabolism, and FDG-PET may be used for the grading as well as therapy assessment (see Chapter 51) (29,30). Malignant bone tumors are rare, and consequently, only sparse evidence exists concerning the role of PET and PET/CT in differentiating bone metastases from primary malignant bone tumors. Franzius et al. (31) compared FDG-PET with bone scintigraphy in 70 patients with malignant bone tumors. None of the five osseous metastases from osteosarcoma were detected by FDG-PET, but all of them were true-positive using bone scintigraphy. Inverse results were found in patients with Ewing sarcoma, in which FDG-PET was superior to BS.

OTHER TUMORS

For some other solid tumors, FDG-PET/CT seems to be useful in the detection or exclusion of bone metastases. Encouraging results are reported in primary staging of patients with cholangiocellular (Fig. 42.1) and pancreatic cancer (Fig. 52.4), in which detection of bone metastases was clearly superior to other imaging modalities and had a major impact on treatment strategy (32–34).

In nonsolid malignant tumors like lymphoma, FDG-PET/CT seems to be very accurate in detecting bone involvement and has replaced BS as the routine imaging method.

Figure 52.4. A 42-year-old patient with weight loss, abdominal pain, and biopsy-proven cancer of the pancreatic body. Staging CT showed no extrahepatic metastases. Patient was scheduled for Whipple operation. FDG-PET/CT (A–D) for preoperative staging showed multiple bone metastases. Therapy was changed to palliative chemotherapy.
(see Chapter 55). Whether FDG-PET can replace standard bone iliac crest marrow biopsy in lymphoma patients is under controversial debate (see Chapter 55) (35–37). In patients with multiple myeloma, FDG seems to perform better than bone scan (38). Further studies using FDG-PET/CT have to be performed to give a final recommendation for these types of tumors.

REFERENCES


INTRODUCTION

Soft tissue sarcomas are a heterogeneous group of tumors that originate from mesenchymal tissue elements. They are well characterized by high-resolution magnetic resonance (MR) and computed tomography (CT) imaging, clinically important issues such as tumor grade, stage, and response to treatment. The variety in soft tissue sarcoma characteristics, origin, and biologic behavior make them particularly interesting for molecular imaging techniques using positron emission tomography (PET). The challenges that these tumors pose in their diagnosis and management have contributed to the definition of the role of clinical PET in sarcoma and are a developing area of PET research. With limited effective chemotherapy and radiotherapy treatment schemes available for these patients, the current emphasis in management includes identifying high-risk patients and those who may have greater sensitivity to treatment. PET imaging has made a significant contribution to these patient management issues by providing important biologic information for an individual patient tumor.

SARCOMA CLASSIFICATION

Although considered to be rare tumors, soft tissue sarcomas occur at an incidence of 1 to 2 per 100,000 people in
the United States. They are derived from mesenchymal tissues, which are the body structures that compose the soft, nonorgan, nonepithelial tissues. These tissues are muscles, connective tissue, fat, peripheral nerves, and blood vessels. Sarcomas derived from these elements show differentiation features of these tissues and retain some characteristics of the tissue of origin. Skeletal muscle is derived from myoblasts, which contain muscle fibers composed of actin and myosin. Connective tissue is composed primarily of fibroblasts, fibril structures of collagen and elastin, and ground substance, or matrix. Fat tissues are of two types. White fat, composed of lipocytes, is primarily located in the subcutaneous tissues, mediastinum, retroperitoneum, and abdomen. Brown fat is located in the neck, mediastinum, interscapular area, axillae, and the perirenal region (Fig. 33.24). Brown fat cells have many mitochondria, vacuolated cytoplasm, and a nucleus in the central location. They have a distinct microscopic and functional imaging appearance. Peripheral nerves are composed of axons, fibroblasts, perineural cells, and Schwann cells. Perineural cells originate from fibroblasts, and the Schwann cells are thought to be derived from the neuroectoderm. Blood vessels are composed of endothelial cells, pericytes, smooth muscle cells, and glomus cells. In most of today’s tumor classifications, the histologic type is determined by the type of differentiation that the cell exhibits rather than its presumed origin. On biopsy specimens, histopathologic diagnosis consists of light microscopic examination, the use of special tissue element stains, and immunocytochemistry to help characterize the cell type and level of differentiation. A list of common soft tissue sarcoma histologic types and age group associations is shown in Table 53.1. Increasingly, gene expression profiles are being used to help classify and predict the biologic behavior of soft tissue tumors (1–3). Standard radiologic examination consists of plain x-ray films, CT, and MRI. Benign and malignant tumors are not often easily distinguished by anatomic imaging. However, certain features such as size, structure of apparent origin, heterogeneity in density, and calcification can provide important clues as to the probability of malignancy. Patient factors such as age and tumor location are also significant for other relationships to tumor type.

Sixty percent of soft tissue sarcomas occur in the limbs. Most of these occur in the lower extremities deep to fascial tissues. They are less commonly found in superficial locations in areas such as the hand and foot. Deep soft tissue sarcomas can grow to large dimensions before coming to clinical attention. Presumably, large (>5 cm in any dimension) tumors are considered to be at least intermediate grade until subjected to further assessment, which includes biopsy.

**SARCOMA PATIENT EVALUATION**

The assessment of patients with sarcoma consists of determining the stage and grade of the tumor as accurately as possible for treatment planning. Both provide prognostic information for risk of metastasis and local recurrence. In sarcoma, the tumor stage refers to the site, size, and histologic grade of the tumor. Currently there are several systems in use for sarcoma staging. Most commonly used is the American Joint Conference on Cancer (AJCC) system, which is based on the Tumor-Node-Metastasis (TNM) assessment (4). Tumor grading systems are designed to reflect the prognosis for the sarcoma patient. The most commonly used scheme for providing histologic diagnosis and tumor grade is the French system (FNCLCC) (5). In this system, some tumors have fixed grades, such as low grade, or rarely metastasizing, or variable grade based on histologic features. The FNCLCC diagnosis and grading system for soft tissue sarcomas is shown in Table 53.2. Additional clinical grading is performed by the clinician, which is best described by an assimilation of all the clinical features of the patient. These include patient age and overall health status, symptoms, biopsy quality and tumor histologic type, tumor size, location, grade, radiologic appearance, and more recently, pattern and level of FDG uptake. In many centers, this clinical assessment is used to make the decision...
### TABLE 53.2
SOFT TISSUE SARCOMAS LISTED BY TUMOR GRADE (FNCLCC)

| Low grade (FNCLCC grade I) | b. Giant cell MFH/undifferentiated pleomorphic sarcoma with giant cells  
| 1. Adipocytic tumors | c. Inflammatory MFH/undifferentiated pleomorphic sarcoma with prominent inflammation  
| a. Atypical lipomatous tumor/well-differentiated liposarcoma | 4. Smooth muscle tumors  
| 2. Fibroblastic/myofibroblastic | a. Leiomyosarcoma  
| a. Locally aggressive | 5. Skeletal muscle tumor  
| i. Superficial fibromatoses | a. Pleomorphic rhabdomyosarcoma  
| ii. Desmoid-type fibromatoses | 6. Vascular tumors  
| iii. Lipofibromatosis | a. Angiosarcoma of soft tissue  
| b. Rarely metastasizing | 7. Chondro-osseous tumors  
| i. Solitary fibrous tumor and hemangiopericytoma | a. Extra-skeletal osteosarcoma  
| ii. Inflammatory myofibroblastic tumor | 8. Tumors of uncertain differentiation  
| iii. Low-grade myofibroblastic tumor | a. Atypical/malignant ossifying fibromyxoid tumor  
| iv. Infantile fibrosarcoma | b. Synovial sarcoma  
| 3. Fibrohistiocytic tumors | c. Epithelioid sarcoma  
| a. Rarely metastasizing | d. Alveolar soft part sarcoma  
| i. Plexiform fibrohistiocytic tumor | e. Clear cell sarcoma of soft tissue  
| ii. Giant cell tumor of soft tissues | f. Desmoplastic small round cell tumor  
| 4. Vascular tumors | g. Extra-renal rhabdoid tumor  
| a. Rarely metastasizing | h. Malignant mesenchymoma  
| i. Kaposiform hemangioendothelioma | i. Intimal sarcoma  
| ii. Retiform hemangioendothelioma | 9. Peripheral nerve tumors  
| iii. Papillary intralymphatic angioendothelioma | a. Malignant peripheral nerve sheath tumor  
| iv. Composite hemangioendothelioma | b. Epithelioid malignant peripheral nerve sheath tumor  
| 5. Tumors of uncertain differentiation | Unclassified tumors  
| a. Rarely metastasizing | 1. Fibroblastic/myofibroblastic tumors  
| i. Angiomatoid fibrous histiocytoma | a. Low-grade fibromyxoid sarcoma hyalinizing spindle cell tumor  
| ii. Ossifying fibromyxoid tumor | b. Embryonal rhabdomyosarcoma  
| iii. Mixed tumor/myoepithelioma/parachordoma | 2. Skeletal muscle tumors  
| b. Neoplasms with perivascular epithelioid cell differentiation (PEComa) | a. Alveolar rhabdomyosarcoma  
| i. Clear cell myomelanocytic | 3. Vascular tumors  
| Variable grade (FNCLCC grade I, II, or III) | a. Kaposi sarcoma  
| 1. Adipocyte tumors | b. Epithelioid hemangioendothelioma  
| a. De-differentiated liposarcoma | 4. Tumors of uncertain differentiation  
| b. Myxoid liposarcoma | a. Extra-skeletal myxoid chondrosarcoma  
| c. Round cell liposarcoma | b. Primitive (or peripheral) neuroectodermal tumors (PNET)/extra-skeletal Ewing tumor  
| d. Liposarcoma not otherwise specified (NOS) | i. PNET  
| 2. Fibroblastic/myofibroblastic tumors | ii. Gastrointestinal tumors (GIST)  
| a. Atypical solitary fibrous tumor/ hemangiopericytoma | iii. Dermatofibrosarcoma Protubersans  
| b. Adult fibrosarcoma | FDG-PET in Soft Tissue Sarcoma Diagnosis  
| c. Myxofibrosarcoma | The use of FDG-PET in sarcoma patient assessment has risen steadily with the growth of clinical PET practice in cancer imaging. Several articles have appeared that undertook  
| d. Sclerosing epithelioid fibrosarcoma |  
| 3. Fibrohistiocytic tumors |  
| a. Pleomorphic malignant fibrous histiocytoma (MFH)/ undifferentiated pleomorphic sarcoma |  
| for neoadjuvant chemotherapy or radiotherapy versus proceeding directly to surgical resection. A typical set of treatment guidelines for soft tissue sarcomas is presented in Table 53.3. Local variations on these guidelines are quite common.  


meta-analyses of the available literature on the use of FDG-PET in sarcoma patient management (6–8). Overall, these reviews indicate utility for FDG-PET in sarcoma patient management, but point out that prospective imaging studies with larger patient populations are needed to more definitively address this role. This has been a difficult task, as most authors do not have large series of these tumors with similar histologies to study. They have shown that FDG-PET is useful in detecting extent of disease and for identifying metastases. However, since sarcomas often show marked heterogeneity in cell type and FDG uptake spatial distribution, accurate diagnosis of tumor grade for treatment planning is often difficult. Many clinicians perform diagnostic biopsies in the outpatient clinic for convenience and as a means to reduce operating room use. However, these small-core biopsies incised in a surgically convenient location may not be reflective of the most biologically aggressive area of the tumor. The resulting diagnosis then can suffer from sampling error, and the working diagnosis for treatment planning can have an error in tumor grade. This error can result in a misapplication of neoadjuvant therapy. FDG-PET imaging of sarcoma for diagnosis provides several advantages. The entire body and the entire tumor volume is examined, so sites of disease are detected with a high level of sensitivity and correlation with anatomic imaging.

The presence of necrosis is a tumor feature that automatically indicates a high-grade tumor in sarcomas with variable grades (Table 53.3). This deterioration is easily seen on FDG-PET images and is an important prognostic finding. Figure 53.1 shows several examples of the presence of heterogeneous tumor uptake with tumor necrosis in sarcomas. The exception to this visual finding is the presence

**TABLE 53.3**

<table>
<thead>
<tr>
<th>SOFT TISSUE SARCOMA TREATMENT PRACTICES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Low grade (FNCLCC grade I)</td>
</tr>
<tr>
<td>a. Resection</td>
</tr>
<tr>
<td>i. Wide as standard</td>
</tr>
<tr>
<td>ii. Radiation with marginal resections</td>
</tr>
<tr>
<td>2. High grade (FNCLCC grade II or III)</td>
</tr>
<tr>
<td>a. Neoadjuvant chemotherapy</td>
</tr>
<tr>
<td>b. Wide resection</td>
</tr>
<tr>
<td>c. Adjuvant chemotherapy</td>
</tr>
<tr>
<td>d. Postoperative radiation</td>
</tr>
<tr>
<td>3. Tumors with special therapeutic molecular targets</td>
</tr>
<tr>
<td>a. Special molecular therapy agents</td>
</tr>
</tbody>
</table>

![Figure 53.1](image-url) Examples of FDG-PET images of tumors showing heterogeneous areas of tumor necrosis. The presence of necrosis in a tumor with a potential of variable grade signifies it as a high-grade process. Coronal FDG-PET images (A–C) of a patient with a large pleomorphic rhabdomyosarcoma in the anterior left thigh. There are multiple contiguous areas of tumor necrosis present. MRI (D) and FDG-PET (E) coronal images of the left thigh with a large liposarcoma present. This shows areas of round cell de-differentiation (areas of higher FDG uptake) and more benign fat in areas with little FDG uptake. The MRI appearance is heterogeneous also. FDG-PET image (F) of a myxoid round cell liposarcoma in the left anterior thigh showing areas of myxoid degeneration.
of tumor elements that show little metabolic activity such as cartilage, fibrous serous fluid, blood, or ground substance accumulation.

Assessment of tumor grade from the FDG-PET image is a related goal for diagnosis. It stands to reason that the most biologically aggressive region of the tumor is reflected by a regional increase in FDG uptake. Sarcoma behavior is dictated by the most biologically aggressive component. Consequently, this is the area most critical to biopsy for diagnosis. On histologic examination, these areas have increased cellularity and mitotic rate, and often have increased levels of specific markers of tumor aggressiveness. Folpe et al. (9) found that increased tumor standardized uptake value (SUV) was associated with histopathologic grade, cellularity, mitotic activity, maximum-intensity projection (MIB) labeling index, and P53 overexpression in a series of both soft tissue and bone sarcomas. These data lend support to the concept that FDG-PET images can be used effectively to guide biopsy. Hain et al. (10) imaged 20 patients with soft tissue masses and clinical presentations suggestive of malignancy with FDG. Tumor regions thought to be malignant were found to be representative of the most malignant regions of the rest of the tumor. Tumors that were found to be benign on resection did not show significant FDG uptake.

There are numerous published reports from investigators exploring the use of FDG-PET to grade sarcomas prior to treatment (11–19). These reports showed that there is a significant ability of the technique to distinguish benign or low-grade from high-grade from high-grade tumors. Lucas et al. (17) found in a series of 30 patients that all high-grade tumors were correctly identified using qualitative image assessment, but ability to distinguish between a benign and a low-grade tumor was reduced. Using a quantitative assessment, they found a 95% sensitivity and a 75% specificity for diagnosis. This result is similar to the work published in other studies. Figures 53.2 and 53.3 show several examples of soft tissue sarcomas with different histologic types and tumor grades.

With a number of published studies on sarcoma diagnosis in the literature over the last decade, several authors have performed meta-analyses to review the general pertinent findings from the group of studies. Ioannidis and

**Figure 53.2** Examples of soft tissue sarcomas. Sarcoma NOS (not otherwise specified) (high grade) in the right shoulder showing homogenous FDG uptake (A) and correlating CT (B). Synovial cell sarcoma of the right shoulder with vertebral metastases at presentation (C: FDG-PET of primary; D: FDG-PET; E: MRI of vertebral metastasis). (See also Cases 62 and 64).
Lau (6) performed a meta-analysis of 15 studies with 441 soft tissue lesions analyzed with receiver operator curves. Sensitivity and specificity for distinguishing benign from malignant using qualitative visualization were 92% and 73%, respectively. All intermediate- to high-grade tumors were identified visually. Using quantitative and semiquantitative data for tumors with SUV greater than 2.0, sensitivity was 87% and specificity was 79%. For a higher SUV discrimination point at 3.0, sensitivity was 74% and specificity was 87%. The quantitative MRGlux level of 6.0 showed lower values of 74% sensitivity and 73% specificity. The conclusion from this large analysis was similar to findings of the individual reports: FDG-PET is helpful in assessing soft tissue masses in recurrent and primary tumors, but performs less well at this time in differentiating low-grade tumors from benign lesions. This finding was similar to that of the analysis of Franzius et al. (7), and Aoki et al. (8) who both added that specific prospective studies in larger patient groups and groups with specific tumor histologies should be undertaken.

**Image Fusion in Sarcoma Imaging**

The advent of widespread use of combination PET-CT imaging devices has increased specificity for tumor staging in many cancers. Few data have been published on the improvement of FDG-PET diagnosis with the use of fused images. Ioannidis and Lau (6) did not find an improvement in diagnostic sensitivity or specificity with the use of PET image fusion with CT images in the meta-analysis. Similarly, Hain et al. (10) also coregistered the FDG-PET images with MRI scans. They found that the coregistration did not significantly add to regional tumor assessment for biopsy.

Addition of anatomic images in this combined imaging technique can apply to FDG-PET for sarcoma patient staging. However, in the diagnosis of sarcoma, where the clinical issue primarily is differentiation of low- from high-grade tumor, this combination does not yield an increase in specificity. Certainly, analysis of surgical margins and other anatomic features for surgical planning are facilitated by the use of PET and CT images overlaid. This anatomic precision and detail for combined functional imaging and anatomic assessment is likely more effectively produced by the use of PET/MR fusion images. Somer et al. (20) demonstrated the feasibility of a fused or overlaid MR/PET image. Externally placed fiducials in patients with masses in the lower extremity or back were used to coregister images in these areas where anatomic features cannot be used for rigid body alignment techniques. MR images can register irregular anatomic distortions, which can be alleviated in this study with the use of imaging fiducials. As work of this type progresses, it is likely that fused MR/PET images will become standard for sarcoma resection planning, especially under the common circumstances where only a 1- to 2-mm surgical margin is attainable owing to tumor proximity to critical structures (Fig. 53.4).

**FDG-PET in Sarcoma Local Recurrence**

Most soft tissue sarcomas have relatively high local recurrence rates. This is likely owing to several factors. Low-grade
tumors are not effectively treated with neoadjuvant and adjuvant therapy because of their low growth rate. Also, they are often characterized by infiltrative margins that wrap around vital structures such as neurovascular bundles. High-grade tumors also show treatment resistance owing to up-regulation of stress-induced genes related to hypoxia, neovascularization, and de-differentiation.

Overall, most authors have found FDG-PET to be of benefit in the evaluation of tumor recurrence. Forty percent to 60% of soft tissue tumors recur or metastasize. This behavior occurs across all tumor grades and types and presents a dilemma for patient assessment and treatment planning. Figure 53.5 shows examples of recurrent and metastatic soft tissue sarcomas. Soft tissue sarcoma tumor recurrence is often difficult to detect by anatomic imaging. After typical resection and radiotherapy, scarring and alterations in anatomy result. Many soft tissue sarcomas recur in a manner resembling scar tissue formation, and so on, because of their mesenchymal origins (21–24). Kole et al. (21), using the calculated tumor glucose metabolic rate, found a 93% detection rate for recurrent tumors over a large size range (0.5–20 cm). One patient in this series with a recurrent low-grade liposarcoma did not have a positive image. In this series of 28 patients, the tumor glucose metabolic rate correlated with the histologic grade in the tumor recurrence as well.

Recurrent tumor in the extremity stump after amputation can also be difficult to detect by anatomic imaging. Similar to other resection sites, the stump shows scarring and ongoing inflammation in weight-bearing areas. A FDG-PET imaging series by Hain et al. (25) demonstrated diffuse uptake in the stump end for up to 18 months after resection. Interpretation of FDG-PET images required clinical examination to correlate image appearance with areas of local tissue pressure breakdown. However, FDG-PET areas of increased focal uptake in the stump unassociated with tissue pressure deteriorations represented recurrent tumor. A soft tissue tumor recurrence in an amputation stump is shown in Figure 53.6.

FDG-PET in Imaging Tumor Response

Increasing numbers of sarcoma treatment groups are implementing neoadjuvant chemo and/or radiotherapy for large intermediate- and high-grade tumors. Standard anatomic imaging criteria for treatment response such as response evaluation criteria in solid tumors (RECIST) in CT do not necessarily report sarcoma treatment responses (26,27). This is likely owing to the fact that sarcomas are derived from mesenchymal elements. Many tumors can contain populations of stromal or structural elements such as fibrous tissue, fat, and bone that do not decrease in volume in response to cytotoxic therapy. As in several other cancer histologies, new biologically targeted agents are being investigated for sarcoma patients, because so many have disease resistant to standard therapy. In this new class of therapeutic agents, antitumor activity may be characterized by cytostatic response as opposed to cytotoxic responses. A tumor cytostatic response may stop tumor cell proliferation and metabolism, but may not necessarily result in tumor shrinkage until much later timepoints beyond the treatment and observation interval.

Overall, FDG-PET has been shown to identify treatment response (28). There is not a great deal of literature published on this topic. One review article suggests that more studies are required for the pediatric soft tissue sarcoma population to contribute guidelines (29). This, however, assumes careful criteria for definition of response in sarcomas. In tumor clinical service meetings, review of sarcoma response to treatment data often shows residual FDG uptake in tumor at low levels by both visual and semiquantitative analysis. Once again, the unique properties of soft
tissue sarcomas dictate the picture of response to treatment. Sarcomas can respond to treatment certainly by loss of proliferating tumor cells, but also with fibrosis and granulation tissue formation, coagulative and liquefactive necrosis, hemorrhage, and serous fluid accumulation. Some of these processes, particularly scar and granulation tissue formation, are energetic and will accumulate FDG. Many residual sarcomas with SUV of 1.5 to 2.5 are called 100% nonviable in the resection specimen, and the treatment repair process along with inflammation may be responsible for the dis-

Figure 53.5  FDG and cross-sectional imaging examples of recurrent and metastatic soft tissue sarcoma. Recurrent leiomyosarcoma in the left proximal thigh. This is a medium-sized mass with relatively homogenous FDG uptake (A) and coronal MRI (B). FDG (C) and CT (D, E) images of a patient with metastatic sarcoma NOS (not otherwise specified). There is a large shoulder mass with likely a necrotic central zone (arrow), pulmonary mass, and a large heterogeneous left pelvis mass that is partially out of the field of view (arrow head).

Figure 53.6  Soft tissue recurrence in an amputation. These are the postamputation coronal FDG-PET (A) and MRI (B) images obtained at 1-year follow-up showing recurrence of an epithelioid sarcoma at the base of the amputation and metastatic involvement of brachial plexus lymph nodes.
crepancy. Figure 53.7 shows several examples of soft tissue sarcoma treatment response. In 1999, the EORTC conference on tumor response to treatment guidelines suggested that at least a 25% decrease between pretreatment and posttreatment SUV be used to reliably indicate treatment response (30) (Table 53.4). Use of this system requires careful adherence to imaging timepoints after FDG injection, blood glucose levels, and image analysis. Consistency between imaging studies in a patient and within the patient group will increase confidence in treatment response assessment.

**Figure 53.7** Imaging examples of sarcoma response to treatment. Baseline whole-body scans (A,B: PET; C: CT) of a patient with a gastrointestinal stromal tumor (GIST). (Courtesy of Dr. Annick Van Den Abbeele Boston, Massachusetts Pretherapy FDG uptake is shown in the large mass in the gastric region. Same examinations (D,E: FDG-PET; F: CT) obtained of the patient 1 month following initiation of Gleevec therapy. Images show a nearly complete response to treatment. (See also Case 25).

Limited field of view FDG coronal pelvis images of a patient with a high-grade sarcoma NOS (not otherwise specified) in the left pelvis. The left image (G) was taken before neoadjuvant Adriamycin-based chemotherapy. The right image (H) was taken after the standard four cycles of chemotherapy and in the week prior to resection. This tumor shows a heterogeneous response to treatment, with a still viable and actively metabolizing tumor outer rim.

Limited field of view coronal anterior lower leg images of a patient with a rhabdomyosarcoma in the pretibial region. Left image (I) acquired prior to neoadjuvant Adriamycin-based chemotherapy. The mass is small and relatively homogenous. The right image (J) was obtained after neoadjuvant chemotherapy and shows almost complete response to treatment. The small level of residual FDG uptake posttherapy in the tumor bed was shown to be scar tissue, which is showing low-level metabolism.
TABLE 53.4
EORTC PET RECOMMENDATIONS FOR TUMOR RESPONSE

<table>
<thead>
<tr>
<th>Tumor Response</th>
<th>FDG Uptake in Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>FDG uptake in all lesions comparable to background activity</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>&gt;25% decrease of SUV in all target lesions</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>Changes in SUV of &lt;25%</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>&gt;25% increase of SUV in at least one target lesion or the appearance of new lesions (regardless of the SUV changes in the target lesions)</td>
</tr>
</tbody>
</table>

is particularly critical in patients with partial responses, observations early after therapy, and in nonresponders. In most cases, an increase in tumor SUV during or after therapy with no anatomic size decrease implies a nonresponse or disease progression.

PET Imaging and Patient Outcome

This is a vigorous area in molecular imaging research. An important goal for noninvasive molecular imaging is to generate prognostic information for a disease process. This prognostic capability has initial tumor biologic characterization and response assessment as major components. Both these aspects of prognosis by noninvasive imaging require at least semiquantitative assessment of imaging data. In histologic cancer response assessment, tumor regression scores are associated with more favorable patient outcome.

Similar results have been found in other cancers and in sarcoma using FDG-PET (31). Eary et al. (32) studied a mixed group of bone and soft tissue sarcomas from a clinical practice population. They found that the tumor initial SUV\textsubscript{max} was independently predictive of outcome compared with other clinical variables. Scheutze et al. (33) later evaluated treatment response in a group of patients with high-grade soft tissue sarcomas treated with neoadjuvant chemotherapy using FDG-PET. They determined the relationship of FDG-PET imaging findings to patient outcome. Patients whose tumor SUV\textsubscript{max} was greater than 6.0 prior to treatment, and who had a less than 40% decrease in tumor SUV\textsubscript{max} after treatment, had a disease recurrence estimate of 90% by 4 years after therapy. Patients with a greater than 40% decrease in tumor SUV\textsubscript{max} had a significantly improved outcome with lower risk for tumor recurrence and death. They concluded that the clinical FDG-PET scan may hold promise as a means to assess sarcoma patients for neoadjuvant chemotherapy benefit, similar to the results for patients with other cancer histologies.

A recent tumor/therapy combination that further demonstrates the concept that a decrease in tumor FDG uptake is predictive of improved patient outcome is treatment of gastrointestinal stromal tumor (GIST) with imatinib mesylate (see Chapter 43). GISTs are tumors that probably arise from the mesenchymal cells of the gastrointestinal tract. Similarly to selected other tumors, these neoplasms have a mutation in the KIT gene that allows increased activation of tyrosine kinases (34,35). This abnormality increases tumor growth and slows apoptosis. The specific inhibition of the mutated tumor cellular KIT pathway has been shown to be effective in patients with advanced GIST. This is particularly remarkable since these tumors are highly resistant to conventional treatment. Tumor responses observed as changes in size by anatomic imaging are often delayed. However, tumor metabolic responses determined by FDG PET decreases in tumor metabolism were highly predictive of patient outcome. Stroobants et al. (36) found that a FDG-PET response assessed according to the EORTC PET recommendations was associated with a 92% progression-free survival compared with FDG-PET nonresponders, who had 12% survival over the same period. Patients with clinical responses also showed significant FDG-PET responses. In those patients with complete responses, most of these changes were observed within 1 week after therapy. Other groups have shown similar significant results (37,38). Goerres et al. (39) found that GIST patients with FDG-negative tumors at the start of treatment had better outcomes than those with residual metabolic activity. They also found that the use of PET-CT enabled improved tumor characterization.

Soft Tissue Sarcoma Imaging with Other PET-Imaging Agents

Several PET investigators have evaluated new biologically specific imaging agents to assess sarcoma patient risk for poor outcomes in response to treatment. These new agents, which can be used to more specifically probe the cancer process than FDG, may provide significant complementary information to both anatomic and metabolism imaging. Perhaps the most studied is [18F] fluoromisonidazole (FMISO), an agent to quantitate tissue hypoxia. This PET imaging agent derived from misonidazole binds to tissue with low oxygen concentration (less than 10 mm Hg) (40). This aspect of tumor biology is important for understanding the treatment resistance of sarcomas (41). Hypoxia is an aspect of abnormal tumor metabolism mostly caused by unregulated cell growth and a greater tissue demand for oxygen for energy metabolism. Hypoxia is also the stimulus for tumor expression of new stress response proteins in survival attempts. Several hypoxia related genes are upregulated and mediated by downstream tissue transcription factors. There is also an intimate association of tissue
hypoxia with tumor angiogenesis (42). Tissue hypoxia results in a multifactorial response, with processes such as reduced apoptotic cell death, G1 cell cycle arrest, and increased glucose transporter activity becoming more apparent. Consequently, a PET imaging agent that reports the level of tumor hypoxia is useful to understand tumor biology, treatment resistance, and design of treatment strategies for overcoming hypoxia-induced tumor treatment failure. Soft tissue sarcomas are known to show high and variable levels of tissue hypoxia, which may be one of the factors responsible for their relative treatment resistance and poor patient outcome. Rajendran et al. (43) published results from a series of soft tissue sarcoma patients who were imaged with FMISO to assess their levels of tumor hypoxia. They found that there were significant levels of hypoxia in 76% of patients studied (Fig. 53.8). These levels were not correlated with tumor grade, tumor size, or FDG uptake levels. Regional tumor hypoxia and metabolism also did not correlate in most patients, demonstrating that this tumor biologic parameter provides complementary information in sarcoma patient assessment.

Cell synthesis is another parameter being investigated in PET cancer imaging to gain understanding of tumor biology. This aspect of tumor biology has been approached in general with the use of agents that reflect DNA synthesis or cellular proliferation, cell membrane synthesis, or protein synthesis. However, few studies have been done in sarcomas with these agents. In the latter category, sarcomas were studied with L-[-1-11C]tyrosine by Plaat et al. (44). They found that there was a correlation between the tumor protein synthesis rate measured with this agent using PET and immunohistochemical staining with the MIB-1 antibody that reflects cell undergoing mitosis. This aspect of tumor assessment will likely have a place in tumor pretherapy grading as well as posttreatment assessment with specific new targeted therapies.

The experience with PET and other nuclear tomographic imaging methods in soft tissue sarcoma is relatively new compared with that experience in other cancer histologies. Studies often have smaller patient numbers than would be desired because of the relative infrequency of each tumor subtype and the heterogeneity in tumor biologic presentation and behavior. However, new targeted therapies aimed at specific molecular targets will likely offer sarcoma patients increased benefits and more positive outcomes. Since so many sarcomas are large and based in the extremities, they are excellent tumors for investigational imaging protocols that can be used to evaluate these new therapy agents. PET imaging techniques can be readily used to make important observations with these new therapies. The quantitative tissue uptake information and array of new imaging agents available will make direct contributions to patient care in small homogenous patient groups. This is an exciting future for imaging and one that carries hope for increased survival for patients with soft tissue sarcoma.

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INTRODUCTION

In 2004, malignant melanoma was the fifth and seventh most common cancer in men and women, respectively, in the United States. The incidence of cutaneous malignant melanoma among whites living in the United States, Australia, and in Western Europe is still increasing, but this increase is partly owing to improved screening programs. According to the American Cancer Society, malignant melanoma accounts for 1% to 2% deaths per year.

In 2002, the American Joint Committee on Cancer introduced a revised staging system. Malignant melanoma prognostic factors now include primary tumor thickness, microscopic or macroscopic lymph node metastasis, number and location of lymph node metastases, and the sites of distant metastases. Stages I and II refer to localized melanoma. Early malignant melanoma is curable by means of surgical excision. Stage III melanoma refers to cases with lymph node metastases, either in regional nodes or as satellite or in-transit metastases. Patients with distant metastases are classified as stage IV. Despite the enormous progress of modern oncology, the prognosis of metastasizing melanoma has remained particularly poor. Patients with regional lymphatic metastasis have a cure rate of approximately 20%, whereas no curative treatment is currently available for generalized metastatic melanoma.

Accurate staging of malignant melanoma is essential for the early detection of metastases and for choosing the appropriate treatment. The high mortality rate of malignant melanoma is owing to its early hematogenous spread, and the location of metastases is unpredictable. The skin, subcutaneous tissue, and distant lymph nodes are the most
common sites of distant metastases, but melanoma can metastasize to all organs. The early detection and surgical excision of single distant metastases are important for improving survival (Fig. 54.1).

Whole-body fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging has been shown to be superior to conventional imaging methods in staging patients with high-risk melanoma. In many institutions worldwide, FDG-PET imaging has nearly replaced the standard battery of imaging tests for staging high-risk malignant melanoma, such as chest X-ray films, ultrasound of lymph node stations and abdomen, computed tomography (CT) of the chest and abdomen, and bone scan. With these conventional techniques, false-negative and false-positive findings are quite common. Whole-body FDG-PET has a major impact in the management of patients with melanoma. Surgical resection is the treatment of choice for regional lymph node metastases or single distant metastases. Whole-body FDG-PET should be used to exclude occult metastases in patients in whom surgery is planned. If multiple metastases are present, chemotherapy is the therapy of choice. In extended disease, only palliative therapy is indicated. Whole-body FDG-PET plays an important role in the evaluation of patients, when immunotherapy is considered. Adjuvant treatment with recombinant interferon alpha is indicated only in disease-free patients after resection of high-risk melanoma. FDG-PET is also useful in evaluating the treatment response.

However, limitations of FDG-PET imaging have been recognized. The sensitivity of FDG-PET in the detection of microscopic tumor spread to the sentinel lymph node is poor. Although malignant melanoma is one of the most avidly FDG-accumulating tumors, the spatial resolution of 5 mm of dedicated PET scanners is limited. The early spread of disease to regional lymph nodes often involves only some tumor cells. It has been shown that FDG accumulation in nodal metastasis is dependent on the size of the metastasis and on nodal tumor involvement of more than 50% or capsular infiltration. Sentinel lymph node (SLN) scintigraphy and biopsy have been established as accurate baseline techniques for the determination of tumor spread to regional lymph nodes. Because of physiologic FDG uptake in the brain, FDG-PET is of limited value to screen for brain metastases. In our institution, however, we always include the brain in the whole-body PET examination. In some cases, unknown and unexpected brain metastasis can be detected. In the assessment of pulmonary metastases of melanoma, FDG-PET shows a higher specificity but lower sensitivity than CT. In our experience, this limitation can be overcome by the use of PET-CT imaging. Growing pulmonary nodules even without FDG accumulation are highly suspicious for metastases.

In our institution, whole-body integrated PET-CT scanning with FDG has become the standard diagnostic tool for staging patients with high-risk malignant melanoma,
that is, Breslow thickness greater than 4 mm or known metastases. For baseline staging, SLN scintigraphy and biopsy are routinely performed in all patients with a malignant melanoma.

**CLINICAL CHARACTERISTICS**

Cutaneous malignant melanoma is the most aggressive cancer of the skin. No other tumor is increasing faster in number of new cases diagnosed (1). As with most cancers, the causes of malignant melanoma are multifactorial. Numerous studies have demonstrated that the development and progression of melanoma are based on increasing levels of cutaneous solar exposure, especially ultraviolet B radiation, in combination with the genotype, phenotype, and immunocompetence of the patient.

Melanomas can be located anywhere in the body, but most commonly occur on the lower extremities in women and on the back in men. Any pigmented lesion with a change in size, configuration, or color should be considered a potential melanoma, and an excisional biopsy should be performed. Fortunately, nowadays most patients are diagnosed early, so that malignant melanoma can be cured with surgical excision of the primary lesion. Nevertheless, late diagnosis in locations that are not visible to the patient, such as the scalp, neck, and back, or in a plantar location are fairly common. The widely varying mortality reports in the literature depend more on the stage of diagnosis than on variations in surgical and treatment technique.

**CLASSIFICATION AND STAGING**

Histologic verification and accurate microstaging of tumor thickness are essential for treatment decisions and to predict the risk of metastases. Two methods have been used. The Breslow microstaging method measures the thickness of the lesion using an ocular micrometer to define the total vertical height of the melanoma from its surface to the deepest part of the lesion. The Clark microstaging method categorizes different levels of invasion that reflect depth of penetration into the dermal layers and the subcutaneous fat (i.e., levels II, III, IV, or V). It has been demonstrated that the Breslow tumor thickness is the most important prognostic factor in clinically localized melanoma and is a more reproducible parameter than interpreting the level of invasion (2).

In 2002, the American Joint Committee on Cancer introduced a revised staging system for malignant melanoma (3). Stages I and II include localized melanomas up to 2.0 mm thickness and negative lymph nodes. Stage III includes regional lymph-node metastases. Stage IV describes cases with distant metastases. Important prognostic factors such as microscopic or macroscopic nodal involvement, the number of positive nodes, the anatomic location of nodal and distant metastases have been included in this staging system.

Lesions with a Breslow thickness less than 1.0 mm have an excellent prognosis not differing significantly from that of the general population, whereas those greater than 4 mm in thickness have a 10-year survival of less than 40%. Once patients develop metastases, other prognostic factors have to be considered. The number of metastatic nodes has a significant prognostic value. The high mortality of patients with melanoma is caused by its early hematogenous spread. The skin, subcutaneous tissue, and distant lymph nodes are the most common sites of distant metastases, but melanoma can metastasize to all organs. Early detection and surgical excision of single distant metastases are important in improving the prognosis. Significant factors predicting survival in patients with distant metastases are the number of metastatic sites and the remission duration (less than 12 months versus more than 12 months). The results of vaccine therapies for melanoma suggest that immune and clinical responses are promising in patients with metastatic disease (4–6).

Our group has demonstrated that whole-body staging at baseline remains limited (7). One hundred consecutive patients with malignant melanoma and a tumor thickness greater than 1.0 mm were enrolled in the study. All patients underwent extensive baseline staging including physical examination, ultrasound (US) of the abdomen and regional lymph nodes, SLN scintigraphy and biopsy, chest x-ray film, and whole-body FDG-PET. Twenty-six percent of patients had a positive sentinel lymph node among 90% with microscopic disease. The macroscopic nodal metastases could be detected by physical examination, US, or PET.

Patients with a melanoma thickness of 1.0 to 4.0 mm have an increased risk of occult regional nodal metastases, but have a relatively low risk (less than 20%) of distant metastases. Patients with melanomas thicker than 4.0 mm have a high risk (greater than 70%) of distant metastases. In our institution, an integrated PET-CT with FDG will be performed for whole-body staging only in patients with a primary malignant melanoma greater than 4.0 mm or known metastasis. Because of the erratic pattern of distant metastases, whole-body staging is recommended (Fig. 54.2). The clinical course of melanoma can be characterized by the risk of relapse and death well beyond 10 years after the initial diagnosis. Therefore, lifetime annual clinical follow-up has been recommended. According to the Guidelines of the Swiss Society of Dermatology, PET or PET-CT scanning is annually recommended in the first 5 years after the diagnosis of high-risk melanoma.

**STAGING METHODS**

In the past, a combination of conventional imaging modalities was used for staging of malignant melanoma, that is, chest x-ray film; ultrasound of the abdomen and lymph nodes of the axilla, cervical region, and groin; and CT. However, these methods are intrinsically spot imaging methods and better used to evaluate a given region rather than the entire body. Furthermore, identification of tumor tissue
(e.g., in normal-sized lymph nodes) is difficult with these methods. If a lesion is detected, further procedures such as biopsies or follow-up examinations are necessary to confirm or exclude malignancy. CT is known to have a high rate of false-positive findings if applied as a screening method in patients with malignant melanoma (8). Because of the limitations of morphologic imaging modalities, several radiopharmaceuticals have been used in nuclear medicine to visualize metastases of melanoma. These include $^{67}$gallium-citrate (9), immunoscintigraphy with monoclonal antibodies (10), $^{111}$indium-pentetreotide (11), $^{99m}$technetium-MIBI (12), $^{125}$iodine-methyltyrosin (13), $^{18}$fluorine-fluoroethyltyrosine (14), $^{123}$iodine-iodobenzufuran (15), $^{18}$fluorine-fluorodopa (16,17), $^{76}$bromine-bromodeoxyuridine (18), and $^{18}$fluorine-fluorodesoxyuridine (19). Because of limited sensitivity, these radiotracers were found to be suitable for screening of melanoma only in exceptional cases. Several $^{11}$carbon-labeled radiopharmaceuticals have been used for experimental studies in malignant melanoma. Because of the short half-life of $^{11}$carbon, the clinical use of these tracers for whole-body staging remains limited.

Whole-body PET and PET-CT Imaging with FDG

Malignant melanoma shows one of the highest FDG uptakes of all tumors (20). Whole-body PET using FDG has been proven to be a highly effective and cost-saving modality to screen for metastases of malignant melanoma throughout the body. With the exception of the brain and the lung, whole-body FDG-PET can largely replace the standard battery of imaging tests currently performed on high-risk patients (Figs. 54.2 and 54.3).

Our group reported in a study of 33 patients a sensitivity of 92% with a specificity of 77% for reading the PET images without clinical information (21). Specificity improved to 100% when clinical information such as location of biopsy sites or location of subcutaneous injections of interferon were obtained. PET was also highly accurate in differentiating benign from malignant lesions. In six patients (18%), whole-body PET depicted previously unknown metastases. In four of these six patients, the metastases were surgically removed. The excellent results in staging high-risk melanoma patients with whole-body FDG-PET were confirmed in larger patient studies in other PET centers worldwide (22–28).

This author performed a meta-analysis of the literature for staging of high-risk melanoma with FDG-PET (29). PET studies for the microscopic tumor involvement of SLN were excluded. Only PET studies with the definitive confirmation of lesions were included. A total of 323 lesions could be included for the meta-analysis. An overall sensitivity of 90% (95% confidence level, 86%–94%) and an overall specificity of 87% (95% confidence level, 79%–95%) were determined. Other reviews of the FDG-PET literature...
have been published (30,31). Since studies for the detection of microscopic tumor involvement of lymph nodes were included in these analyses, the accuracy of FDG-PET was lower than in our results.

**Imaging Protocol**

Details of PET imaging protocols are discussed in Chapter 19. Because of the erratic pattern of metastases of malignant melanoma, whole-body FDG-PET and PET-CT scanning were frequently required. In our institution, only combined PET-CT systems are available. A whole-body PET-CT scan is routinely performed from the head to the knees. If the primary tumor is located in a lower limb, additional PET-CT scanning is performed from the knee to the feet for the detection of satellite lesions or in-transit metastases. These lesions are classified as stage N3. An additional 3-D brain PET scan is performed in patients with a high risk for brain metastases (for example, when the primary tumor was located in the head).

**T Staging**

There is no role for FDG-PET or PET-CT imaging in the initial diagnosis of malignant melanoma. Since most malignant melanomas develop in the cutis, these lesions are simply visible by clinical examination and amenable to diagnostic biopsy. In addition, the size of most primary melanomas is far below the spatial resolution of PET and PET-CT imaging.

Lymph node metastases of malignant melanoma with an unknown primary occur quite often. Because of the metastases, patients are classified as stage III. To our knowledge there are no reports that a primary malignant melanoma of unknown origin was initially detected by PET or PET-CT imaging. It is assumed that in most cases the primary melanoma lesions have been detected and eliminated by the immune system of the patients. This fact stimulates researchers to develop new immune therapies and vaccine therapies (4–6).

**N Staging**

Regional nodal metastases are the most common site of metastatic melanoma (Fig. 54.4). In the past, full lymph node dissection of the likely nodal basin was performed to identify nodal involvement. This procedure has been replaced by SLN scintigraphy and biopsy. With the use of dynamic lymphoscintigraphy, the first and possibly second draining node can be directly visualized. The localization of the nodes can be marked on the skin after scintigraphy and preoperatively by the probe. Since the nodes are superficial, they can be easily localized and surgically extirpated. We perceive no benefit in performing melanoma SLN scintigraphy with SPECT in contradistinction to other situations (see Chapters 35 and 46). With this technique followed by extensive immunohistopathologic examination, microscopic tumor involvement in the regional lymph nodes can be accurately diagnosed. The use of SLN scintigraphy has shown that many primary melanomas of the head, neck, and trunk drain to unexpected nodal basins. Surgical excision of metastatic nodes is the only effective treatment for cure and local/regional disease control. In patients with a positive sentinel lymph node, regional lymphadenectomy and adjuvant therapy are considered. However, up to now there is no evidence that early detection of positive lymph nodes improves survival.

Dedicated PET scanners have a spatial resolution of 5 to 6 mm. No imaging modality is able to detect micrometastases. Therefore, PET and PET-CT imaging are not useful to determine subclinical microscopic tumor spread to lymph nodes (7,32–37). The diagnostic accuracy of FDG-PET for lymph metastases has been analyzed in detail (38). FDG-PET

**Figure 54.3** Patient with known left cervical metastasis of malignant melanoma. PET/CT imaging detected an unexpected distant metastasis in the liver. Coronal PET sections show an increased FDG uptake in the right neck (A) with corresponding CT and PET/CT sections (C,D). In addition, coronal PET sections show a focal lesion with increased FDG uptake in the right lobe of the liver (B). The corresponding unenhanced CT section shows no focal pathology in the same section (E). The PET-CT image demonstrates that the increased FDG accumulation is located in liver segment VI or VII (F).
detected 100% of metastases 10 mm or larger, 83% of metastases 6 to 10 mm, and 23% of metastases up to 5 mm. Moreover, FDG-PET had a high sensitivity (>93%) only for metastases with more than 50% nodal involvement or with capsular infiltration.

**M Staging**

FDG-PET and PET-CT have a high clinical value in the detection of metastatic melanoma. In a single examination, the whole body can be screened for metastases. The early detection of metastases is crucial for the optimal management of patients. Several studies have demonstrated that whole-body FDG-PET imaging is an accurate method for staging, in the follow-up of high-risk patients, and in the restaging of patients with known distant metastases to evaluate for tumor response (Fig. 54.5). Our group demonstrated that FDG-PET is superior to conventional staging (21). Other studies confirmed the superiority of PET over...
CT in the evaluation of high-risk melanoma patients (22–28).

However, some limitations of FDG-PET imaging have been recognized. Because of the physiologic FDG uptake in the cortex, CT and MR are generally superior to FDG-PET in the detection of brain metastases (21). However, in our institution the brain is always included in the whole-body PET-CT examination, and images have to be carefully analyzed in search of metastases. In some cases, clinically occult brain metastasis have been detected (Fig. 54.6). In patients with neurologic symptoms, MR of the brain is the reference method to diagnose or exclude brain metastases. Because of the small tumor volume, cutaneous and subcutaneous lesions can be missed by PET imaging (21). Therefore, thorough clinical examination of the patients is mandatory. In the assessment of pulmonary metastases of melanoma, FDG-PET shows a higher specificity but lower sensitivity than CT (23,39). In a more recent study, the sensitivity of CT and PET were 93% and 57%, respectively, in the evaluation of lung nodules (40). To our experience, this limitation of PET imaging can be overcome by the use of integrated PET-CT imaging (41). FDG-inactive but solid pulmonary nodules without calcification are highly suspicious for lung metastases. Since we implemented integrated PET-CT scanning in staging of melanoma patients, we have encountered cases with FDG-inactive lung metastases (Fig. 54.7). An explanation might be the slow proliferating rate of these lesions. Therefore, dedicated CT analysis is strongly recommend to improve the sensitivity and the accuracy of the integrated PET-CT imaging in the staging of the patients with high-risk melanoma.

Surgical excision of metastases is recommended if only one or a few sites of disease is apparent (42). Therefore, the number and the location of metastases should be exactly defined. Today, whole-body integrated PET-CT imaging is the best single examination to identify and to localize the metastases (Fig. 54.8).

**RECURRENT MELANOMA**

FDG-PET and PET-CT have a strong role in the evaluation of patients with clinical recurrence. The superiority of PET over conventional staging has been reported (40). In a recent study, 156 patients with recurrent melanoma were...
Figure 54.7  A 30-year-old woman 8 years after resection of a malignant melanoma with a subcutaneous metastasis of the right lower arm. A right-sided axillary lymph node metastasis was known. PET-CT was performed for whole-body staging. Maximum-intensity projection (MIP) image (A), transaxial CT section (B), corresponding PET section (C), and corresponding PET-CT image (D), respectively, demonstrate the known FDG-active right axillary lymph node metastasis. In addition, transaxial CT sections demonstrate two solid nodules in the left lower lung (E,H). Corresponding PET sections (F,I) and corresponding PET-CT images (G,J), respectively, demonstrated only a slightly increased FDG accumulation in these lesions. The pulmonary lesions were interpreted as lung metastases of melanoma.

Three months after the resection of the axillary metastasis, a follow-up PET-CT examination was performed. No residual tumor or recurrence was found in the right axilla. MIP image (K), corresponding PET section (M,P,S), and corresponding PET-CT images (N,O,T), respectively, show a strongly increased FDG-accumulation in the lung lesions. Transaxial CT sections demonstrate an increase in volume of the lung metastases in the left lung and a new metastasis in the right lung (L,O,R).
examined by both PET and CT (43). The overall accuracy of PET was 81% compared with 52% for other methods.

**PITFALLS OF PET AND PET-CT USING FDG**

It is well known that FDG is not a tumor-specific substance. False-positive results may be caused by an increased FDG uptake in inflammatory lesions or postoperative changes (44–45) (see also Chapter 33). Therefore, the clinical correlation of lesions with increased FDG uptake is obligatory to exclude tracer uptake in recent sites of surgery or infected or inflamed lesions. Other common benign lesions with a focal FDG uptake are colonic adenomas (Chapter 44), inflammatory changes such as villonodular synovitis and tendinitis (46) (Fig. 54.9, Chapter 62), Warthin tumors (Figs. 34.30 and 38.4), acute fractures (Fig. 33.12). In one patient, PET-CT imaging demonstrated multiple FDG-active lesions throughout the whole body.

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**Figure 54.8** Patient with palpable infraclavicular metastases of malignant melanoma. PET was performed preoperatively to exclude further metastases. Coronal FDG-PET section demonstrates multiple circular FDG lesions infraclavicularly on the right side (A). This finding is typical for metastases with central necrosis. The CT section shows enlarged lymph nodes in the same region (B). PET/CT locates the FDG uptake into the enlarged lymph nodes (C). In addition, coronal PET section demonstrates a focal lesion with high FDG accumulation distinct from the infraclavicular lesions in the right paratracheal region (D). The CT section shows multiple lymph nodes (E). PET-CT image demonstrates clearly the lymph node with increased FDG uptake (F).

**Figure 54.9** A 73-year-old man 3 months after resection of a malignant melanoma of the right foot. SLN biopsy revealed tumor spread to an inguinal lymph node. Maximum-intensity projection (MIP) image (A) and transaxial PET image (B) demonstrate an increased FDG accumulation in the right pelvic region. The corresponding CT image (C) and PET-CT image (D) ruled out a lymph node metastasis. The lesion represents tendinitis mimicking metastasis.
This patient was treated with immunotherapy before PET-CT scanning. The histopathologic examination revealed sarcoma-like lesions, which were mimicking generalized metastatic melanoma in PET-CT imaging. Therefore, histologic confirmation of lesions is recommended, particularly when PET or PET-CT findings might result in a change of treatment.

COST EFFECTIVENESS OF WHOLE-BODY FDG-PET

Several studies have examined the cost effectiveness of whole-body FDG-PET in melanoma patients. Our group (47) reviewed treatment records of 100 patients with newly diagnosed high-risk malignant melanoma. In patients with known metastatic disease, all metastases had been removed. Two staging procedures were defined: Conventional staging consisted of physical examination, chest x-ray film, and ultrasound of lymph nodes and abdomen. Any suspicious lesion after conventional staging resulted in additional CT scans and histopathologic correlation. Staging with whole-body PET included inspection of the skin. Suspicious lesions were confirmed by biopsy or another imaging modality. The review found 172 staging protocols that could be analyzed for cost comparison. The total cost of conventional staging was approximately $170,000, compared with approximately $173,000 for PET, which was thus only about 2% more. Among the 72 patients with metastatic disease, conventional staging costs were $145,000 whereas PET staging costs were $130,000. In this subset, the PET protocol cost approximately 11% less than conventional staging. Gambhir et al. (48) compared the cost effectiveness of the imaging strategies using conventional staging alone, including body CT and brain MRI, versus conventional staging with whole-body FDG-PET. Sixty patients with suspected recurrence from malignant melanoma were included in this study. The study looked also at survival, using measures of life expectancy based on the literature, and savings owing to changes in patient management resulting from the use of PET. The incremental cost-effectiveness ratio of the PET-DG-PET strategy, compared with the conventional staging strategy, was $3,000 to $8,000 per year of life saved, a figure far below the standard of $50,000 per year of life saved used by U.S. health economists to characterize a cost-effective intervention.

In another study, the impact of FDG-PET on patient stage and management was evaluated from the referring physician’s perspective (49). Referring physicians indicated that whole-body FDG-PET changed the clinical stage in 29% of patients. Twenty percent of patients were up-staged and 10% of patients were down-staged. The PET findings resulted in inter-modality management changes in 29% of patients. Intra-modality management change occurred in 18% of patients. This survey-based study of referring physicians demonstrated that FDG-PET has a major impact on the management of melanoma patients. In this author’s experience, PET changes the treatment in 20% of patients with high-risk melanoma (21). Other groups reported an even higher influence of FDG-PET on the diagnostic and therapeutic management of patients. In one study, PET resulted in a change in surgical management in 16 of 45 patients (36%). The addition of FDG-PET to the diagnostic algorithm resulted in a savings-to-cost ratio of 2:1 because of the avoidance of unnecessary procedures (50). In a recent study in patients with recurrent melanoma, PET results changed the clinical management of 36% of patients in comparison to conventional staging (43). The third German Interdisciplinary Consensus Conference on clinical use of PET in oncology stated that FDG-PET is established for diagnosis of recurrence or follow-up in patients with pT3 and pT4 tumors or following metastases (51).

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PET and SPECT-CT in Lymphoma

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Positron emission tomography (PET) using fluorodeoxyglucose (FDG) is now widely used for staging and monitoring treatment results in patients with Hodgkin disease (HD) and non-Hodgkin lymphoma (NHL). PET provides information complementary to conventional staging procedures for the staging of patients with HD and aggressive NHL. It is unlikely, however, that PET will fully replace conventional staging procedures in the staging of lymphoma patients. Moreover, the increasing use of integrated PET/computed tomography (CT) systems will probably result in a significant improvement in the diagnostic accuracy of both systems and will change the discussion to another level. The use of FDG-PET in low-grade lymphoma remains controversial. The most important current indication for PET is evaluation at the end of treatment. All patients with residual masses on conventional staging procedures should undergo FDG-PET to differentiate residual tissue from necrotic tissue. If PET is positive, before starting salvage therapy, a close correlation with clinical data, other imaging modalities, and/or biopsy is mandatory to exclude false-positive uptake. Patients with a negative PET have a good prognosis, but unfortunately, PET cannot exclude minimal residual disease, possibly leading to a later relapse. Promising data indicate that PET may be useful to identify early treatment failure after a few cycles of chemotherapy and before stem cell transplantation.

INTRODUCTION

Positron emission tomography (PET) using fluorodeoxyglucose (FDG) is now widely used for staging and monitoring treatment results in patients with Hodgkin disease (HD) and non-Hodgkin lymphoma (NHL). Together, HD and NHL constitute only 8% of all malignancies, but most patients are young and potentially curable. In contrast to many solid tumors, lymphomas are highly sensitive to chemotherapy or radiotherapy, and substantial long-term cure rates of 90% for HD and 50% for aggressive NHL are expected with the current treatment options. However, the magnitude of late treatment-related morbidity and mortality, especially in young HD patients treated with combination chemo-radiotherapy, and the fact that many NHL patients still cannot be cured with standard induction therapy, has tempered the initial enthusiasm. Accordingly, tailoring the intensity of the treatment to individual patients has become very important. FDG-PET has potential advantages to optimize the management of lymphoma patients in three principal domains: improving the accuracy of initial staging, assessing the response to treatment earlier and more accurately, and optimizing the follow-up after therapy. In this chapter, the value of PET in these different areas is discussed.

INITIAL STAGING

Until recently, staging of lymphoma was done by ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI). Although these imaging tools allow exquisite anatomic detail, in essence they all require alterations of anatomic structures to suggest tumor. Minimally
affected lymph nodes of normal size or parenchymal involvement with insufficient contrast to surrounding tissue may therefore be missed, whereas inflammatory enlarged lymph nodes may be erroneously interpreted as representing tumor deposits. With regard to bone marrow involvement, iliac crest biopsy is performed routinely, but because of the frequently patchy involvement, lesions can be missed with this focal approach. Therefore, there has always been a strong need for a sensitive noninvasive imaging technique that uses other than anatomic characteristics of tissue to detect tumor activity.

The first imaging tool largely independent of morphologic criteria was 67-gallium single-photon emission computed tomography (67Ga-SPECT). This technique was routinely used for the evaluation of residual masses after chemotherapy in lymphoma patients and has been shown to be very useful in the monitoring of disease response (1–3). Soon, 67Ga-SPECT became a standard method for therapy assessment. In 1997, Paul (4) reported on the use of FDG-PET for the detection of lymphomas compared with 67Ga and stated that FDG was superior to 67Ga for the detection of lymphoma. This prompted more extensive research into the role of FDG-PET for the staging of lymphoma patients. In comparison with 67Ga-SPECT, FDG-PET seems to be the favorable technique because of the superior resolution and sensitivity of PET imaging methods together with better interpretability of abdominal findings, the lower radiation burden (7 mSv for FDG-PET versus 37 mSv for 67Ga-SPECT), and the shorter examination time (2 hours for FDG-PET versus 3 days for 67Ga-SPECT).

Over the last decade, numerous articles have appeared concerning the role of FDG-PET in initial staging of lymphoma patients (5). Because FDG-PET has been introduced into the clinical environment without randomized trials or rigorous testing that required the investigator and patients to be blinded to the results of a new imaging modality, its precise role in disease staging has not been well defined. Moreover, all published data suffer from methodologic problems inherent to lymphoma imaging studies because a biopsy was obtained for only a few lymph nodes. For ethical reasons, previously unknown lesions detected by PET were sampled only when the results potentially influenced staging and treatment. The calculation of sensitivity and specificity is not possible in the absence of histologic proof. The methodology used in nearly all studies is mostly in favor of imaging techniques with high sensitivity and low specificity (6). Nevertheless, despite these limitations, in a recent meta-analysis (7) on the use of FDG-PET for initial staging of lymphoma that included 20 eligible studies between 1995 and 2004, the pooled sensitivity was 90.9% and the pooled false-positive rate was 10.3% for FDG-PET in initial staging. The pooled sensitivity and false-positive rate appeared to be higher in patients with HD compared with those with NHL. These latter findings should be interpreted with caution because they are based on a small number of patients. Conversely, NHL is a highly heterogeneous disease that includes a large series of different entities; therefore, the diagnostic accuracy of FDG-PET may differ within the group of patients with NHL. Although most studies investigated both HD and NHL together, separate analyses are mandatory since staging results may lead to different patient management and outcome in both groups.

**Hodgkin Disease**

Several studies have investigated the role of FDG-PET in lymph node staging. Clinical findings, ultrasound (US), CT, MRI, and iliac crest biopsy have been compared. Moog et al. (8) studied discordant findings between FDG-PET and CT and demonstrated that disease was present in areas of increased FDG uptake and that there was no evidence of disease in enlarged nodes on CT when FDG was negative. Bangerter et al. (9) studied 44 patients with newly diagnosed HD. FDG-PET was positive in 38 of 44 patients (86%) at sites of documented active disease. Unfortunately, in six other cases PET either failed to visualize sites of HD (n = 4) or indicated a false-positive result (n = 2). A limitation of this study is that not all positive FDG-PET results were confirmed by biopsy and that some PET results may have been incorrectly interpreted as malignant. Jerusalem et al. (10) evaluated the role of FDG-PET compared to routine procedures for staging in 33 patients with HD. PET results were confirmed by biopsy only if they had an impact on patient management. The sensitivity of FDG-PET to detect all known pathologic lymph nodes was 83% for peripheral lymph nodes, 91% for thoracic lymph nodes, and 75% for abdominal and pelvic lymph nodes. PET detected focal liver infiltration in only one patient. Weihrauch et al. (11) studied 22 HD patients in whom 77 lesions were detected by FDG-PET, CT, or both. In 48 lesions (62%), the results were concordant; in 20 (26%), lesions only PET was positive; and in 9 lesions, only CT was positive.

Overall, there is little doubt that FDG-PET detects more lesions than CT and also more active disease in lesions that are not positive on CT based on size criteria. But, it is not certain that FDG-PET detects all disease, and it is difficult to calculate the false-positive rate with FDG-PET from literature. Moreover, the potential impact of false-positive or false-negative PET findings on treatment strategy has not been reported. Organ involvement in newly diagnosed HD, specifically the spleen, was studied by Rini et al. (12). In 32 patients, they found that FDG-PET was more accurate than 67Ga scintigraphy: it was twice as sensitive with similar specificity. Some studies also assessed the accuracy in detection of bone marrow involvement in comparison with iliac crest biopsies. Carr et al. (13) reported that FDG-PET can correctly assess bone marrow disease status in a high proportion of patients and has the potential to reduce the need for bone marrow biopsy. Twelve HD patients underwent FDG-PET and unilateral iliac crest marrow aspirates and biopsies. Two cases were concordantly positive, six were discordantly negative, and in four patients the FDG-PET scan was positive and biopsy negative. Subsequent biopsy
in one confirmed BM involvement, two cases were confirmed to be false-negative, and one remained equivocal. In the two false-positive patients, reactive myeloid hyperplasia characteristic of some HD patients may explain increased FDG uptake. From this and other studies (14), it can be concluded that FDG-PET scanning may improve the sensitivity of bone marrow disease detection in HD over blind bone marrow biopsy, in the sense that it can guide the localization where the biopsy should be preferentially taken (Fig. 55.1).

A more relevant question is how FDG-PET affects the staging of primary lymphoma and hence patient management. Bangerter et al. (9) detected unknown lesions in five patients; one patient was up-staged from stage I to II, three patients from stage II to IV, and one patient from stage III to IV. In another patient, PET indicated a down-staging from stage II to I. As a result of changing stage, treatment strategy had to be changed in each case (6/44 = 14%). Similarly, Partridge et al. (15) retrospectively compared CT (chest, abdomen, and pelvis) and FDG-PET in the staging of 44 patients with HD. Up-staging by PET was reported in 18 of 44 patients (40.9%) and down-staging in 3 of 44 patients (6.8%). In a study by Weihrauch et al. (11), staging was altered in 4 of 22 patients based on PET. In contrast to these studies, in which in most cases there was an up-staging based on PET, Jerusalem et al. (10) reported down-staging in 4 of 33 patients, including a biopsy-proven case. However, one of these cases was down-staged in error. PET suggested an up-staging in three patients. Also, the study from Hueltenschmidt et al. (16) showed down-staging in 7 of 25 patients based on FDG-PET and up-staging in only 3 patients compared with conventional staging procedures: 1 from stage I to IV and 2 from stage II to III.

The main issue is whether a change in disease stage alters the therapy management of the patient. This was the case in all patients of Bangerter, in half of the patients in the study of Partridge, but in only two patients in the study of Hueltenschmidt and in one case in the two other studies (Jerusalem and Weihrauch). Apparently, differences in study design, whether the study was conducted in a primary or tertiary care center, whether it was a single or multicenter study, and the timepoint enormously affected the final decision making. In general, good-risk localized patients (stage IA and IIA) are treated with a limited course of chemotherapy and field radiotherapy whereas advanced-stage HD patients receive several courses of combination chemotherapy. So a stage change from IA to IIA may lead to a change in radiotherapy field and a change from IIA to IIIA may influence the course of chemotherapy. Other changes will not affect the patient management. This issue was addressed in by Naumann et al. (17). They analyzed the therapeutic relevance according to the initial stage of patients and found the highest impact in early-stage HD with treatment intensification in 20% of the patients. Whether or not a change in therapy translates into an improved survival has not yet been fully addressed. In a recent study of Munker et al. (18), the contribution of PET to the prognosis of patients with HD was investigated. Of the 73 patients, 21 patients (28.8%) were up-staged by FDG-PET. If only early-stage patients and major stage

Figure 55.1 PET scan of four patients with Hodgkin’s disease. Diffuse increased FDG uptake in the bone marrow (BM) is seen in patients A and B. Bone marrow biopsy revealed reactive BM in patient A and diffuse involvement in patient B. Note that in patient B diffuse increased FDG uptake in liver and spleen is also seen, which makes lymphoma involvement of the BM much more likely. More focal BM uptake was seen in patients C and D. BM biopsy at the iliac crest was positive in patient C but negative in patient D, which is not surprising since only one focus distant from the biopsy site is present. Additional MRI of the spine confirmed lymphoma involvement of one vertebral body. (See also Case 55)
changes are considered (stage IA–IIB to III–IV), among 49 patients, 10 were up-staged to III or IV, whereas in 39 patients, staging was unchanged following PET. Interestingly, in the former group, three relapsed or were refractory compared to none in the latter group ($p < 0.006$). In advanced-stage patients, a trend toward treatment failure was apparent in patients who were up-staged by PET. It must be noted, however, that a change of treatment may ultimately not result in improved survival; as for HD, many patients can be cured with salvage therapy. From all the available literature, it appears that FDG-PET in HD improves the accuracy of staging, but in the absence of evidence that this leads to survival benefits, the high cost of FDG-PET remains an important issue and cost-benefit studies are warranted.

**Non-Hodgkin Lymphoma**

Most studies using FDG-PET have been conducted in NHL patients. From the beginning, authors have suggested that the accuracy of FDG-PET depends on histologic subtype. For aggressive NHL, FDG-PET is accepted as a useful tool for staging, but for indolent NHL, the results are very confounding, and fewer studies have appeared on this matter.

**Indolent NHL**

The FDG uptake in lymphoma patients is correlated to histologic grade and proliferative activity. In a recent large study, Schöder et al. (19) concluded that the standardized uptake value (SUV) is lower for indolent lymphoma than for aggressive lymphoma, that patients with a SUV greater than 10 have a high likelihood of aggressive lymphoma compared with those with a SUV less than 6, which is likely associated with indolent lymphoma. These results are similar to other previously reported smaller studies (20–22).

Only limited and conflicting data have been published about the sensitivity of FDG-PET in low-grade NHL. Najjar et al. (23) reported sensitivity and specificity for FDG-PET of 87% and 100%, respectively, in 36 indolent lymphoma patients, and Wirth et al. (24) reported PET-positive findings of 90%. In contrast to these studies, Jerusalem et al. (25) studied 36 patients with low-grade NHL. PET detected 40% more abnormal lymph node areas than conventional staging in follicular lymphoma, but was inappropriate for the staging of small lymphocytic lymphoma for which it detected less than 58% of abnormal lymph node areas. The number of patients with mucosa-associated lymphoid tissue (MALT) or mantle cell lymphoma was too low to permit any conclusion. The location of nodal lesions was important: PET showed more lesions than conventional staging for peripheral (34% more lymph node areas detected) and thoracic lymph nodes (39% more lymph node areas detected) but not for abdominal or pelvic lymph nodes (26% fewer areas detected). The sensitivity to detect bone marrow infiltration was unacceptably low regardless of the histologic subtype. In contrast, PET was as effective as standard procedures for the detection of other extranodal localizations, although a few localizations were detected only by PET and a few others only by conventional procedures. Overall, because of the frequent false-negativity of FDG-PET and the general lack of impact of stage alone on the therapy given, the evidence for including FDG-PET in the routine diagnostic staging of indolent lymphoma is not strong. Further studies are warranted to see whether FDG-PET can be used in the staging of some subtypes of indolent lymphoma that probably express sufficient FDG avidity.

**Aggressive NHL**

Elstrom et al. (26) studied 70 patients with aggressive NHL and correlated the results with the pathologic diagnosis. Disease was detected in 100% of patients with diffuse large B-cell lymphoma and mantle cell lymphoma. In contrast, only 40% of peripheral T-cell NHL were detected, suggesting that FDG-PET is more useful for B-cell than T-cell lymphoma. In the same study, anaplastic large cell and Burkitt’s lymphoma also could be detected. Most authors (27–32) studied patients with both HD and NHL of various histologic subtypes and compared the FDG-PET results with those of CT or $^{67}$gallium scanning in a lesion-based analysis. The results are similar to those reported for HD-only patients in that FDG-PET visualizes more lesions than CT and surely is superior to $^{67}$Ga scintigraphy, but lack of histologic proof is a known methodologic problem. Also, as for HD, the role of FDG-PET in the assessment of bone marrow involvement in NHL is not yet fully established. The group from Liège (33) reported a study comprising only patients with histologically proven aggressive NHL. Forty patients were studied at initial diagnosis, and 13 patients underwent PET for restaging after disease recurrence. The results of PET were compared with the results of conventional staging including clinical examination; CT of the thorax, abdomen, and pelvis; and bone marrow biopsy. PET identified 39 clinically undetected lymph node areas, whereas clinical examination showed only 9 additional lesions not seen by PET. Fifty-nine lymph node areas were detected by PET and clinical examination. PET identified 21 thoracic and abdominopelvic lymph node regions not seen by CT, whereas CT showed only 5 areas not demonstrated by PET. Both imaging techniques showed the same 56 areas of lymph node infiltration in the thorax, abdomen, or pelvis. The results suggested that FDG-PET is more sensitive than clinical examination and CT for the detection of lymph node regions infiltrated by NHL. PET is as effective as CT for the detection of extranodal disease excluding bone marrow. PET and CT identified the same 47 lesions, whereas 6 lesions were identified only by PET and 7 lesions were shown only by CT. PET missed known bone marrow infiltration in five patients. On the other hand, bone marrow infiltration suspected by PET was confirmed by biopsy in six of ten patients. The authors concluded that FDG-PET is an efficient, noninvasive method for staging and restaging aggressive NHL, but bone marrow biopsy still needs to be performed in addition to PET.
FDG-PET can replace bone scintigraphy in primary staging of malignant lymphoma (34). Osteolytic lesions, which are commonly observed in NHL, can escape scintigraphic detection. FDG-PET can identify osseous involvement with a high positive-predictive value and is more sensitive and specific than bone scintigraphy. Fifty-six patients (34 HD, 22 NHL) were studied by both imaging techniques. Bone scintigraphy showed skeletal involvement in 20 regions of 12 patients compared with PET, which showed 30 regions in the same patients. FDG-PET detected 12 additional regions in 5 other patients; these results were verified in 3 and unresolved in 2 patients. Conversely, bone scintigraphy identified five abnormalities in five other patients; these results were found to be erroneous in 3 and unresolved in 2 patients. FDG-PET may also be useful to differentiate primary CNS lymphoma from nonneoplastic lesions such as toxoplasmosis in patients with AIDS (35–38) (also see Chapter 24).

The key issue remains whether the increased detection of disease sites using FDG-PET alters staging and consequently the therapy given. In the study of Buchmann et al. (39), FDG-PET led to up-staging and change in therapy in only 4 of 52 patients. It should also be noted that in most centers NHL patients, in contrast to HD patients, receive the same therapy regardless of the stage at initial diagnosis. In these settings, the rationale for FDG-PET scanning is mainly to improve the evaluation of response assessment scans.

Use of Integrated PET-CT Systems

Isolated PET scanners are progressively being replaced by PET-CT systems, which combine a PET and a CT scanner in a single instrument, coregistering the anatomic information of CT with the functional images of PET. This approach can result in a significant improvement of the diagnostic accuracy of the PET findings, because the more accurate anatomic localization leads to fewer false-positive results owing to inter-patient variability in physiologic FDG uptake (Figs. 55.2 and 33.24). A study by Allen-Auerbach et al. (40) showed that PET-CT was superior to PET alone with reported accuracies of 93% and 84%, respectively. Freudenberg et al. (41) showed a sensitivity of 78% for CT alone, 86% for PET alone, and 93% for PET-CT. The clinical impact of combined PET-CT data was assessed by Raanani et al. (42) in 103 patients. The addition of PET-CT to CT changes the management decisions in approximately a quarter of NHL patients and a third of HD patients, mostly in early stages. It is likely that PET-CT will emerge as the pre-eminent tool in lymphoma imaging. Further studies are warranted to investigate whether intravenous contrast and whether high or low multi ampire seconds is mandatory.

EVALUATION OF TREATMENT RESPONSE

One of the most challenging aspects in lymphoma imaging is the assessment of response to treatment. The limitations of conventional imaging procedures are well known. Tumor volume reduction based on morphologic criteria is a late sign of effective therapy. Residual masses may be present at the end of treatment, even in patients responding very well, with normalization of all clinical and biologic abnormalities. Unfortunately, there are no reliable characteristics for CT that permit one to differentiate between malignant and fibrotic or necrotic tissue. MRI did not prove to be more
useful than CT for predicting the nature of such residual masses (43). Functional imaging modalities such as $^{67}$Ga scintigraphy and more recently FDG-PET provides information complementary to conventional imaging techniques.

**Evaluation of Residual Disease at the End of Treatment**

Obtaining a complete remission (CR) after first-line chemotherapy is the main objective in lymphoma patients as it is usually associated with a longer progression-free survival (PFS). This is in contrast with a partial remission (PR), which is associated with a poorer clinical outcome (44). Approximately two thirds of patients with HD present with a residual mass, but less than 20% will ultimately relapse (45). Similarly, in NHL, residual tumor masses will be present in about 50% of patients with aggressive NHL, whereas only 25% of these patients will relapse (45). Therefore, many residual masses after completion of therapy essentially consist of fibrotic tissue. Since structural imaging cannot reliably discriminate fibrotic from viable tumor masses, international experts have tried to refine the criteria defining a complete response. Because of the uncertainty in the definition of a CR, a new category of response, “complete remission unconfirmed,” was created to reflect the unknown significance of persisting radiologic abnormalities in patients who seem to be otherwise in CR (46).

Despite the introduction of high-resolution CT and despite the introduction of this new term used to describe the response to treatment, CT and MRI cannot reliably predict the clinical outcome after therapy. Early identification of patients who have not been cured by their primary treatment is important, however, because a better outcome can be expected after further treatment when such patients are treated at an earlier stage with lower tumor burden.

Functional imaging with $^{67}$Ga was for many years the imaging technique of choice to characterize residual masses after treatment (47). However, its sensitivity varies with the localization and size of the lesion (48). $^{67}$Ga scintigraphy is more accurate for evaluating masses in the mediastinum than in the abdomen, and sensitivity decreases for lesions smaller than 1.5 cm. Also, nonspecific uptake in the hilar regions and in the thymus of young patients with thymic rebound after chemotherapy can lead to false-positive findings. Since not all lymphomas take up $^{67}$Ga, a baseline study is necessary to prove gallium avidity.

Over the last years, $^{67}$Ga scintigraphy has been gradually replaced by FDG-PET, given its higher sensitivity and resolution and more favorable dosimetry. Several studies have shown the effectiveness of FDG-PET in the detection of residual disease at the end of treatment. Many of the early studies were performed on mixed lymphoma populations, including both NHL and HD. In a recent review (49), the results of 8 studies with mixed populations (174 HD and 183 NHL patients) were pooled, and a sensitivity of 79%, specificity of 94%, positive-predictive value (PPV) of 82%, and negative-predictive value (NPV) of 93% for PET at the end of treatment were calculated. The authors concluded that FDG-PET is the imaging technique of choice for the end-of-treatment evaluation in patients with lymphoma, but close correlation with clinical data, other imaging modalities, and/or biopsy are mandatory to exclude results that are either false-positive (inflammatory changes, FDG uptake in brown fat or muscle) or false-negative (minimal residual disease, HD and NHL are, however, two disease entities with clearly different histopathology, treatment, and prognosis, so results of PET should ideally be analyzed separately as was done in more recent publications.

**Hodgkin Disease**

HD is one of the few adult malignancies that in most instances can be successfully treated. Compared with patients with NHL, patients with HD are younger and present more often with stage I or II disease and are often treated with combination chemo-radiotherapy. However, late morbidity with cardiovascular toxicity and secondary malignancies are being increasingly recognized and this in turn has lead to question the standard use of radiotherapy for residual masses. Treatment in these patients should be limited to a minimum, without compromising the clinical outcome. The high negative-predictive value of FDG-PET can be of special interest to select patients with nonviable residual masses after chemotherapy in whom radiotherapy can be omitted. Table 55.1 presents an overview of different studies that report specifically on the value of PET at the end of treatment in HD (50–59). A high negative-predictive value of FDG-PET has been consistently reported by most studies and clearly identifies patients with an excellent prognosis. Relapses are infrequent and occur rarely within the first year after the end of treatment, probably reflecting minimal tumor burden below the detection limit of the PET system at the time of restaging. Since a substantial number of patients still receive additional radiotherapy (RT) after a negative PET scan, the reported NPV can, however, be overestimated. Furthermore, almost all patients with early-stage HD have a negative posttreatment PET and survive without relapse, probably reflecting the excellent prognosis of these patients more than the NPV of PET. The question of whether radiotherapy can be omitted in early-stage HD with a negative PET scan after first-line chemotherapy is therefore still unanswered. It is hoped that this will be resolved once we know the results of the ongoing randomized National Cancer Research Institute Phase III trial in the United Kingdom in which patients with clinical stage I A/I IA HD who are PET-negative after three cycles of ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) are randomized between either involved field radiotherapy or no further treatment.

In contrast to the NPV, the positive-predictive value (PPV) is much more variable (25%–100%) in HD compared with NHL, especially in studies focusing on patients with residual masses (53–55). False-positive FDG uptake in a residual mass, although rare, is more frequent after radiation therapy or chemoradiation than after chemotherapy alone and is caused by transient inflammatory changes, which can last for up to 2 to 3 months. Therefore,
it is better to perform PET before the start of RT or to wait at least 3 months after completion of RT. This posttherapy inflammatory FDG uptake is typically mild (equal to or less than mediastinal blood pool activity) and diffuse throughout the residual mass, but it is to date unclear if the use of SUV thresholds will improve accuracies (53,54). HD patients are often young and develop thymus hyperplasia at the end of treatment. This results in a typical pattern on FDG-PET (butterfly-shaped configuration with moderate and homogeneous FDG uptake), which often can be differentiated from residual lymphoma (more intense and focal) (60) (Fig. 55.3). Intense FDG uptake in muscle and brown fat tissue is also more frequently seen in lean and young patients and can hamper the detection of residual disease.

### Table 55.1

<table>
<thead>
<tr>
<th>Author</th>
<th>Reference</th>
<th>Year</th>
<th>Patients (n)</th>
<th>NPV (%)</th>
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<th>Mean FU (months)</th>
<th>PFS at 1 year</th>
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<td>24</td>
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<td>88</td>
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<td>48</td>
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<td>40</td>
<td>ns</td>
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<td>32</td>
<td>94*</td>
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NS, not specified; NPV, negative-predictive value; PPV, positive-predictive value; FU, follow-up; PFS, progression-free survival; PET, positron emission tomography. *PFS at 3 years.

**Figure 55.3** Residual increased FDG uptake after ABVD therapy in two patients with HD. The typical butterfly-shaped configuration is suggestive for thymic hyperplasia (A), and this patient remained in complete remission after a follow-up of 36 months. The more focal uptake seen in patient B is more suspected for residual tumor; progression in the residual mass was seen 6 months later on CT.
nodes after treatment (61). The use of combined PET-CT images is often necessary to come to a firm conclusion (Fig. 55.4). Finally, inflammatory lesions are known to cause false-positive PET findings and occur more frequently after chemotherapy. Correlation of PET findings with the pretreatment scan (a new lesion in a previously no involved region is rarely lymphoma), clinical history, or other imaging modalities can help to identify these lesions. If these pitfalls are recognized, the PPV in HD probably equals that of NHL (80%) and is highly suggestive for residual lymphoma for which more aggressive treatment should be considered. In equivocal cases, a close follow-up or additional diagnostic procedures are warranted.

Non-Hodgkin Lymphoma

Although response to therapy and clinical outcome have been considerably improved with the use of doxorubicin-containing chemotherapy regimens, less than half of patients with newly diagnosed aggressive NHL can be cured with standard induction therapy (62). The main question in the posttherapy evaluation of NHL patients is: “Can FDG-PET identify those patients with insufficient response to treatment, and thus, poorer clinical outcome?” In this setting, a high positive-predictive value is fundamental.

Figure 55.4  Persistent FDG uptake in the cervical and mediastinal region, 3 months after completion of chemo-radiotherapy. Based on PET alone, no discrimination is possible between residual lymphoma and physiologic uptake in muscle and/or brown fat tissue (A–E). Comparison with CT (F) and fusion image (G) locate all hot spots to be in brown fat tissue. Increased FDG uptake in the left upper lobe is related to radiation pneumonitis (arrow). Based on PET-CT, it was concluded that the patient achieved a complete remission. No further treatment was administered and after a 2-year follow-up, there is still no evidence of disease.

Only a few studies have specifically focused on NHL. Spaepen et al. (63) performed FDG-PET at the end of first-line chemotherapy in 93 patients with aggressive NHL. The PET scan was normal in 67 patients, and only 11 (16%) relapsed after a median follow-up of 2 years. Conventional imaging offered no additional value in predicting relapse. Twenty-six patients showed persistent abnormal FDG uptake, and all relapsed. Because standard restaging also suggested residual disease, 12 patients received immediate secondary treatment. In the other 14 patients, only PET predicted persistent disease. The 2-year PFS rate for patients with a negative scan was 85% compared with only 4% for patients with a positive PET. Mikhaeel et al. (64) compared FDG-PET with CT in 45 patients with aggressive NHL. FDG-PET was more accurate than CT in assessing remission status following treatment. All 9 patients with persistent FDG uptake relapsed compared with only 6 of the 36 patients (17%) with a negative PET scan. The 1-year PFS was 0% for the PET-positive group compared with 83% for the PET-negative group. Both studies show that persistent abnormal FDG uptake in initially involved sites is highly predictive for residual disease whereas a normal PET scan does not exclude disease. This is in contrast with HD, for which a negative scan, especially, is more predictive because false-positive rates are higher.
Two recent studies reported on interpretation of combined PET and CT. Reinhardt et al. (59) performed PET and CT at the end of treatment in a mixed population of HD and NHL \( (n = 101) \). There was no additional value of PET in the patients with progressive disease (PD) on CT (all five were also PET-positive) or those with a CR on CT \( (n = 20, \) all PET-negative, 3-year PFS = 100%). However, in the subgroup of patients with either PR \( (n = 19) \) or stable disease (SD) \( (n = 57) \), PET could differentiate them into low risk \( (\leq 20\%) \) or high risk of relapse \( (\geq 80\%) \) depending on the metabolic response. Juweid et al. (63) compared responses in 54 patients with aggressive NHL according to the standard International Working Group (IWC) criteria (46) and new combined PET-CT response criteria. In these new criteria, patients with no evidence of residual disease on PET were classified as complete response (CR) regardless of the CT response, whereas those with persistent FDG uptake were classified as SD or PD based on the CT response. A substantially higher proportion of patients were assigned to the CR category by PET-CT response criteria compared with IWC alone (35/54 vs. 17/54). The new classification also appears to better discriminate between CR/Ru (unconfirmed CR) and partial response (PR), with a larger difference in outcome between the response groups: the 2-year PFS was 91% for CR and 42% for PR patients according to the new criteria compared with 88% and 68%, respectively, according to IWC criteria. An international harmonization working group was established to update the current criteria of response in lymphoma patients and also to include new technologies like PET. These criteria were proposed by Cheson et al. (66) at the 2005 American Society of Hematology meeting. A summary of the proposed combined PET-CT response criteria is given in Table 55.2.

It is important to mention that most of the studies on NHL included mainly patients with aggressive NHL. Separate analyses are necessary for low-grade lymphomas since FDG-PET appears to be of less value, sometimes failing to demonstrate disease seen on conventional imaging in the pretreatment evaluation, which surely could hamper the interpretation of the posttreatment scans. Moreover, strictly extrapolating the conclusions of aggressive to low-grade lymphomas is difficult, since they have lower cure rates and different treatment options.

### Integrated PET-CT

Although FDG-PET has a high sensitivity and specificity for lymphoma, the localization of lesions detected by PET is sometimes difficult because of the limited anatomic resolution. This drawback is mostly resolved by the use of integrated PET-CT system. Schaefer et al. (40) evaluated the diagnostic value of low-dose nonenhanced CT (PET-CT) compared with state-of-the-art contrast-enhanced CT for staging and restaging in 60 patients \( (42 \) HD; 18 NHL). PET-CT was more sensitive and specific than contrast-enhanced CT for evaluation of lymph node and organ involvement. PET-CT proved to be especially valuable in exclusion of disease in CT abnormalities. For the restaging examinations \( (n = 41) \), PET-CT revealed additional findings that led to a change of treatment in six (15%) patients compared with only one (2.4%) patient with contrast-enhanced CT. Freudenberg et al. (41) compared CT, PET, side-by-side reading of PET and CT, and integrated PET-CT in 27 patients \( (9 \) HD; 18 NHL) at the end of therapy. Region-based evaluation showed a sensitivity for regional lymph node involvement of 61%, 78%, 91%, and 96%, respectively \( (p = 0.02) \). Compared with side-by-side reading, integrated PET-CT changed the management in two patients. In this study, oral and IV contrast was used in all patients. Further studies are necessary to evaluate if integrated PET-CT without contrast performs equally well.

### Early Response Assessment for Risk Stratification

Since more aggressive but also more toxic treatment modalities are available, there is a growing interest in the use of risk-directed approaches determined by prognostic factors.
that predict for relapse. The International Prognostic Index (IPI) (68,69) summarizes different prognostic clinical factors at presentation and has become an established parameter for risk stratification. The clinical features incorporated in the IPI reflect the biologic heterogeneity of the disease. However, the duration of CR and thus long-term clinical outcome might be significantly more affected by the sensitivity of the tumor to the chemotherapy than the clinical prognostic factors at presentation, and further prognostication of outcome early during treatment leading to a rapid change of therapy might improve outcome and survival.

Morphologic imaging modalities as criteria for early response monitoring are inefficient for early differentiation between responders and nonresponders since several courses of chemotherapy are necessary before treatment effectiveness can be reliably determined. Using CT findings as a criterion for early response may label an unacceptable number of patients as poor responders and expose them to more aggressive or experimental therapy, even if these patients can achieve a durable complete response with chemotherapy.

Over the last years, promising results with FDG-PET have been obtained in the evaluation of response early during treatment. Because glucose provides the primary source of carbons for the de novo synthesis of nucleic acids, lipids, and amino acids, FDG uptake is closely related to the number of viable cells (70) and the proliferation capacity of these cells (71). Treatment-induced changes resulting in tumor cell death or growth arrest therefore result in a subsequent reduction in FDG uptake, making this technique a sensitive and early marker of response. The first report in lymphoma by Römer et al. (72) in 11 patients with NHL documented a rapid decrease of FDG uptake as early as 7 days after treatment. However, FDG uptake at 42 days correlated better with long-term outcome than the 7 days’ parameters. Since then, several studies have correlated PET response during treatment with final outcome, focusing on the value of PET during first-line induction treatment or prior to stem cell transplantation (Table 55.3).

### Early Response Assessment of First-line Chemotherapy

To date most experience has been gained in non-Hodgkin lymphoma (Fig. 55.5, Table 55.3). In a study of 28 NHL patients, Jerusalem et al. (73) found a significantly longer PFS in patients who were PET-negative after two to five cycles of polychemotherapy. However, this study was hampered by the considerable heterogeneity of the study population, which included patients with not only newly diagnosed aggressive NHL but also those with low-grade or relapsing NHL, who have clearly different outcomes and treatment protocols. Mikhaeel et al. (64) evaluated PET after two to four cycles of chemotherapy in 23 patients with aggressive NHL. The interim scan provided valuable

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**TABLE 55.3**

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<tr>
<th>Author</th>
<th>Reference</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Histology</th>
<th>Timing of PET</th>
<th>PPV for Relapse (%)</th>
<th>% PFS at 1 Year</th>
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<td>77</td>
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<td>Becherer et al.</td>
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<td>Filmont et al.</td>
<td>84</td>
<td>2003</td>
<td>21 HD/NHL</td>
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<td>Schot et al.</td>
<td>85</td>
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<td>Spaepen et al.</td>
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PPV, positive-predictive value; PFS, progression-free survival; PFS at 2 years; NHL, non-Hodgkin lymphoma; HD, Hodgkin disease.
information regarding early assessment of response and long-term prognosis, with no relapses in patients with no or minimal residual disease compared with 87.5% relapse rate in patients with persistent PET activity. Kostakoglu et al. (74) performed a PET scan after one cycle and at the end of chemotherapy in a series of 23 patients including both NHL and HD. Early PET correlated better with PFS than PET performed at the end of treatment ($r^2 = 0.45$ vs. 0.17) with a more favorable sensitivity and positive-predictive value of 82% versus 45.5% and 90% versus 83%, respectively. Compared with other studies, the low sensitivity at the end of treatment is especially striking (only 45%) but is probably related to the use of a gamma-based PET system, which is known to underperform in lesions less than 1.5 cm or with minimal tumor burden. Zijlstra et al. (75) also found that residual disease on PET after two cycles of CHOP therapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) was associated with a higher change of relapse, although the PPV was relatively low compared with the other studies. However, false-positive FDG uptake in two patients was related to a second primary. A similar example is shown in Figure 55.6.

The first larger prospective series was published by Spaepen et al. (76). They performed a PET scan after three to four cycles of anthracycline-based first-line treatment in 70 patients with aggressive NHL. Persistent abnormal FDG uptake was seen in 33 patients, and none of them achieved a durable CR. Of the 37 patients with a negative PET scan, 31 achieved a durable CR, with a median follow-up of 3 years. Comparisons between groups indicated a statistically significant association between FDG-PET findings and PFS and OS. In a multivariate analysis, FDG-PET at midtreatment was an
even stronger prognostic factor for PFS ($p < 0.0000001$) and overall survival (OS) ($p < 0.000009$) than the IPI ($p < 0.11$ and $p < 0.03$, respectively). Also, Mikhael et al. (77), retrospectively evaluated the performance of PET after two to three cycles of chemotherapy in 121 patients with high-grade NHL and found it to be a good predictor of outcome, independent of the other prognostic factors, with an estimated 5-year PFS of 89% for the PET-negative group compared with only 16% for the PET-positive group. They were the first to score PET not only as either positive or negative, but also to include a third category of minimal residual uptake (MRU), defined as low-grade uptake in an area of previously noted disease. In this subgroup, the 5-year PFS was 59%, but when data were analyzed according to the initial disease stage, MRU patients behaved similarly to PET-negative patients in the early stages and as PET-positive in the advanced stages. One possible explanation could be that MRU represented small-volume residual disease but was eradicated with radiotherapy that was routinely used in early stages and rarely in advanced stages. Finally, Haioun et al. (78) prospectively evaluated PET after two cycles of anthracycline-based first-line chemotherapy in 90 patients with aggressive NHL of whom 85 were diffuse large B-cell lymphomas. Outcomes differed significantly between PET-negative ($n = 54$) and PET-positive ($n = 36$) groups with an estimated 2-year event-free survival of 82% and 43%, respectively. Compared with other studies, the PPV of PET was low. A possible explanation could be the timing of the early PET scan, which was done often within 10 days of the last chemotherapy owing to the use of intensified schedules given every 2 weeks. An animal study (79) showed that high FDG uptake in macrophages present in the stromal reaction, which is maximal after 10 days following chemotherapy, can mimic viable tumor in lymphoma sites. Another explanation could be that residual disease was eradicated by consolidative high-dose therapy with autologous stem cell transplantation, which was performed immediately following first-line therapy as part of a protocol in 36 of 90 patients.

Only two studies evaluated the use of early PET in Hodgkin disease. Hutchings et al. (80) looked retrospectively at PET response after two to three cycles in 85 patients with HD. PETs were scored as either positive (13/85), negative (63/85), or MRU (9/85). Relapses were seen in 12 patients (8 PET-positive, 1 PET-MRU, 3 PET-negative). The projected 5-year PFS for PET-negative patients (including MRU) was 92% compared with 39% for PET-positive patients, with relapses occurring much later in the PET-negative group (mean time to relapse of 24 months vs. 9 months). Compared with NHL, PET in HD seems to have a similar NPV but a lower PPV. Again, the possible explanation is the frequent addition of radiotherapy, especially in the early stages. In this study, all patients with advanced-stage disease and a positive PET scan relapsed. Recently, the results of a prospective multicenter study by the Danish lymphoma group was published (81): 77 consecutive, newly diagnosed patients underwent FDG-PET at staging, after two and four cycles of chemotherapy, and after completion of chemotherapy. Median follow-up was 23 months. PET scans were interpreted as positive (61/77) or negative (16/77). Low uptake in small-volume disease was regarded as negative. The 2-year PFS for PET-negative patients after two cycles was 96.0% compared with 0% for the PET-positive patients. There was no obvious difference between the prognostic value of FDG-PET after two and four cycles. In addition to visual image interpretation, SUV values were calculated. For each patient, the SUV\textsubscript{max} within a residual mass was correlated with outcome: all patients with SUV\textsubscript{max} greater than 5 relapsed compared with none of the patients with SUV\textsubscript{max} less than 3. Patients with SUV\textsubscript{max} between 3 and 5 had a 2-year PFS of 86%.

We can conclude that FDG-PET after a few cycles of chemotherapy is an important prognostic factor. Persistent abnormal FDG uptake at interim PET, probably reflecting deposits of chemoresistant cell clones, is associated with a short PFS. However, no published reports have yet demonstrated that PET-response–adapted therapy also improves outcome. Large prospective two-arm studies are now warranted to compare clinical outcomes in patients with a positive midtreatment FDG-PET who either continue to receive the established therapy or change to a more aggressive or more experimental one. Other studies have to investigate the best timing for the interim scan (after one, two or three cycles; and with what interval between the last chemotherapy course and the PET scan?), the importance of a pretreatment scan, and how best to evaluate response (visual or semiquantitative?).

**Prognostic Value of FDG-PET in the Pretransplant Setting**

Improvements in therapy may mean that patients with nonresponding or relapsing disease represent a cohort that has an even more unfavorable prognosis. Currently, many centers consider high-dose therapy with autologous stem cell transplantation as the treatment of choice for these poor-prognosis lymphoma patients. The most important prognostic factors to predict favorable outcome after stem cell transplantation are the duration of remission prior to progressive disease and the chemosensitivity of the tumor to salvage therapy administered prior to stem cell transplantation. Since FDG-PET has become a potential tool to differentiate between responders and nonresponders early during chemotherapy, several groups have investigated the value of FDG-PET to identify patients who would benefit from this aggressive treatment (82–86) (Table 55.3). Again, high PPVs with short PFS are recorded in patients with persistent disease on PET. Coexisting inflammatory disease is more frequently seen in this population and can cause false-positive PET results. Correlations of PET, clinical data, and morphologic imaging data are therefore essential. Superior PPVs are obtained if PET is performed just prior to transplantation (>87%) compared with those performed early during the administration of salvage therapy (PPV = 65%) (Schot et al. [85]). This is not surprising since resistant clones can become apparent only when the sensitive ones are killed.
This also explains why only a major decrease in the amount of FDG uptake, and not the reduction in metabolic volume, is predictive for favorable outcome (85). Further studies are necessary to define the optimal timing of PET and response criteria before this technique can be used as a standard practice to determine patient eligibility for high-dose therapy with stem cell transplantation.

**USE OF PET FOR SURVEILLANCE DURING FOLLOW-UP**

Following restaging after completion of therapy, patients should be seen at regular intervals. General history, physical examination, and blood chemistry are recommended at each visit. The appropriate use and frequency of imaging such as CT scanning in the routine follow-up is not clear, since retrospective studies have shown that most relapses are detected as a result of investigation of symptoms rather than by routine screening of asymptomatic patients. To date only one study, by Jerusalem et al. (87), looked at the value of PET for the detection of preclinical relapse in the follow-up of patients with HD. PET was performed in 36 patients every 4 to 6 months for 2 to 3 years after the end of polychemotherapy and/or radiotherapy. A confirmatory scan was performed 4 to 6 weeks later in any patient with abnormal FDG uptake. Eleven patients had a positive scan, of whom only five patients were confirmed to have relapsed. All five events were first identified by FDG-PET and never initially diagnosed by clinical examination, laboratory findings, or CT. No relapses were encountered when PET was negative. In 6 of the 11 patients (55%), PET scans were falsely positive, but in each case the confirmatory PET scan was negative. These false-positive results were related to inflammatory or nonspecific uptake such as atypical uptake in the thymus or digestive tract, which may mimic tumor relapse (Fig. 55.7). It is still unclear whether early detection of recurrence on PET also results in improved overall survival. Further studies are clearly required to fully evaluate the potential of PET in the early detection of asymptomatic relapses because of the potential for a disproportional fraction of false-positive findings resulting in an increase of cost without proven benefit.

**FUTURE PERSPECTIVES**

Although FDG is the most frequently used PET tracer, it does have limitations. Nonspecific uptake can result in false-positive results, and high background activity in some areas, such as the brain, can prevent detection of small amounts of tumor tissue. Besides demonstrating hyperglycolysis, malignant cells also exhibit an accelerated protein metabolism and proliferation capacity, which can be visualized in vivo by the use of radiolabeled amino acids and nucleic acids, respectively.

Accumulation of radiolabeled amino acids mainly reflects the increased transport across the membrane. They are rarely incorporated into proteins. Several amino acids have been radiolabeled, but most clinical experience has
been gained with $^{11}$C-labelled methionine (MET) and $^{11}$C- or $^{18}$F-labeled tyrosine (TYR) owing to their ease of synthesis, good biodistribution, and lack of formation of radiolabeled metabolites in vivo. Results were disappointing, however. Sutinen et al. (88) evaluated FDG and MET-PET in the initial staging of 19 lymphoma patients and found comparable results in detecting of nodal disease, but detection of extranodal involvement was often hampered on MET-PET owing to physiologic accumulation of MET in liver and bone marrow. Hustinx et al. (89) compared F-TYR-PET with FDG-PET in the staging of ten lymphoma patients and found a significantly lower sensitivity for F-TYR-PET compared with FDG-PET.

The most exciting new tracer for the future is probably $^{18}$F-fluoro-thymidine (FLT), a marker of cell proliferation (90). Accumulation of FLT in cancer cells is dependent on cellular thymidine kinase-1 (TK-1) activity, the key enzyme of the pyrimidine salvage pathway of DNA synthesis. Although FLT itself is not incorporated in DNA, FLT uptake is correlated with DNA synthesis and cell growth, since TK-1 is functional only in the S phase of the cell cycle. FLT has been suggested as a new marker for monitoring tumor proliferation and response to therapy. In a pilot study in seven NHL patients by Buchmann et al. (91), FLT-PET was found suitable for imaging of NHL manifestations. The authors observed a low $^{18}$F-FLT uptake in indolent NHL and a higher uptake in NHL in transformation and aggressive NHL. $^{18}$F-FLT mainly accumulated physiologically in bones with hematopoietic marrow and in the liver. In comparison with $^{18}$F-FDG-PET, the physiologic uptake of $^{18}$F-FLT was lower in the myocardium and in the brain. These preliminary results will be the basis for further studies evaluating the role of $^{18}$F-FLT PET for the noninvasive assessment of proliferation in vivo by measuring the correlation of intratumoral $^{18}$F-FLT uptake and the tissue proliferation indices evaluated by Ki-67 immunostaining.

The integration of PET in radiation treatment planning is currently an active field of research (see Chapter 57). This interest is driven by the introduction of new radiotherapy techniques that make it possible to accurately conform the dose distribution to a certain target volume and reduce the dose and thus toxicity to the normal surrounding tissue. This high-precision radiotherapy requires very accurate assessment of the tumor extent to minimize geographic misses. Because PET is more accurate than CT for differentiating benign from malignant tissue, the additional use of PET in radiation planning has been found beneficial in several tumor types. Although PET could have a role in determining which lymphoma patients should receive consolidation radiotherapy, no data are available yet on the role of PET in tumor delineation in lymphoma patients. The high incidence of late morbidity and toxicity, especially when used in combination with chemotherapy, has changed the use of radiotherapy in this setting from extended radiation fields in the past (e.g., mantle, inverted Y, or subtotal nodal) to involved fields with lower doses (20 Gy), and in the near future, even smaller volumes than involved fields, such as lymph node fields, are advocated by pediatric groups and are under consideration for future adult treatment programs. These smaller fields require better targeting, and future studies will show if the use of PET can be helpful.

**CONCLUSIONS**

PET can provide complementary information in addition to that of conventional procedures for the staging of patients with HD and NHL. In some patients, the disease stage and subsequent management are modified, but the impact on outcome remains unknown. The data today do not support the use of PET as the only imaging modality for staging lymphoma because of the potential for PET-negative tumor lesions that are detectable by conventional imaging, such as contrast-enhanced CT. Furthermore, PET findings not seen by CT should be confirmed by histopathology or additional imaging before any change in management is contemplated.

Another argument for performing a baseline PET is the fact that it facilitates the evaluation of residual disease after therapy, currently the most established indication for PET in lymphoma. All patients with HD or aggressive NHL with residual masses observed by conventional staging procedures should undergo FDG-PET to detect residual tumor. If PET is positive, before starting salvage therapy, a close correlation with clinical data, other imaging modalities, and/or biopsy is mandatory to exclude false-positive uptake. Patients with a negative PET have a good prognosis, but unfortunately, PET cannot exclude minimal residual disease, possibly leading to a later relapse. The increased use of combined PET-CT scanners resulted in the formulation of new response criteria including both PET and CT results. Promising data indicate that PET may also be useful for identifying treatment failure in some patients early, after a few cycles of chemotherapy. These patients may be candidates for alternative treatment such as myeloablative chemotherapy followed by stem cell transplantation. Finally, PET may also be useful in the routine follow-up of asymptomatic patients after the end of treatment. However, further studies are clearly required before using PET routinely for these two latter indications.

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PET and PET-CT in Multiple Myeloma

Sven N. Reske       Anja Dankerl

Multiple myeloma (MM) represents a malignant clonal proliferation of plasma cells and commonly results in an overproduction of monoclonal immunoglobulins. Clinical presentation is usually associated with lytic bone lesions; extramedullary involvement mainly occurs in relapsing disease and may be attributed to aggressive illness. Diagnosis includes various blood and urine tests as well as radiographic bone survey, computed tomography (CT), and magnetic resonance imaging (MRI). Functional imaging with fluoro-deoxyglucose (FDG) positron emission tomography (PET), best performed with CT-coregistration, is able to detect active myeloma and can be helpful in differentiating between posttherapeutic changes and residual or recurrent MM manifestations. Persistent findings after induction therapy predict early relapse. FDG-PET results were especially helpful in identifying focal recurrent disease in patients with nonsecretory or hyposecretory disease. Because of the increased synthesis of immunoglobulin in MM, amino acid use provides a new approach for functional imaging. Bone marrow uptake in patients with Durie/Salmon stages II to III was increased compared with homogenous and low uptake in controls. All patients with MM had $^{13}$C-methionine-positive osteolyses respective to extramedullary manifestations. Active MM displayed high $^{13}$C-methionine uptake. Based on these results, active MM could reliably be imaged with $^{13}$C-methionine PET-CT. Lesions with increased $^{13}$C-methionine uptake and normal bone structure suggest new metabolic active lesions developing earlier than structural osteolytic bone changes.

INTRODUCTION

Plasma cell neoplasms represent a spectrum of diseases characterized by clonal proliferation and accumulation of immunoglobulin (Ig)-producing terminally differentiated B cells. The spectrum includes clinically benign common conditions such as monoclonal gammopathy of unknown significance (MGUS) as well as rare disorders such as Castleman disease and γ heavy-chain disease; indolent conditions such as Waldenström macroglobulinemia (WM); the more common malignant entity plasma cell myeloma, a disseminated B-cell malignancy; and a more aggressive form, plasma cell leukemia, with circulating malignant plasma cells in the blood. All of these disorders share common features of plasma cell morphology, production of Ig molecules, and immune dysfunction. A plasma cell neoplasm is considered to originate from a single B cell, with resultant monoclonal protein secretion that characterizes its type (1,2).

EPIDEMIOLOGY

- The incidence rate is 4 per 100,000 per year.
- Approximately 15,000 new cases are diagnosed each year in the United States.
- The current prevalence of myeloma in the United States is about 50,000, and 10,800 deaths from the disease were reported in 2001. Worldwide, it is estimated that there are at least 32,000 new cases reported and 24,000 deaths each year.
- Myeloma is twice as common among African Americans as compared with whites and affects men more than women (2).
Patients with multiple myeloma (MM) may be entirely asymptomatic and diagnosed on routine blood testing or may present with a myriad of symptoms: hematologic manifestations, bone-related problems, infections, various organ dysfunctions, neurologic complaints, or bleeding tendencies. These signs and symptoms result from direct tumor involvement in bone marrow or extramedullary plasmacytomas, the effect of the protein produced by the tumor cells deposited in various organs, production of cytokines by the tumor cells or by the bone marrow microenvironment, and effects on the immune system.

**Hypercalcemia and Bone Disease**

The mechanism of bone abnormalities in myeloma, especially destruction, is an unbalanced process of increased osteoclast activity and suppressed osteoblast activity. These changes are due to an increase in osteoclast-activating factors produced predominantly by the bone marrow microenvironment but also by myeloma cells. As a result, osteoporosis and lytic bone lesions develop. These bone changes frequently involve the vertebral column and result in compression fractures, lytic bone lesions, and related pain. A new onset of back pain or other bone pain is a frequent presenting symptom in myeloma patients. Changes in the cytokine milieu and bone destruction may also lead to development of hypercalcemia, which is observed in approximately 25% of patients at some stage of the disease. Symptoms of high calcium levels include mental status changes, lethargy, constipation, and vomiting.

**Extramedullary Disease**

Extramedullary disease manifestations are uncommon in patients with myeloma at presentation. However, such manifestations have been observed in the setting of advanced-stage disease or relapse after allogeneic transplantation. Solitary or multiple extramedullary plasmacytomas have been described in the liver, spleen, lymph nodes, kidneys, subcutaneous tissues, and brain parenchyma. Extramedullary involvement may be suspected in patients who have more aggressive features of myeloma.

**DIAGNOSIS AND STAGING**

Because myeloma patients present with various symptoms not specific to the disease, the diagnosis of myeloma is quite often delayed. An older patient with a new onset of unexplained back pain or bone pain, recurrent infection, anemia, or renal insufficiency should be screened for myeloma. Additional findings such as hyperproteinemia or proteinuria, anemia, hypoalbuminemia, low Ig levels, or marked elevation of erythrocyte sedimentation rate should prompt a further complete evaluation for diagnosis of plasma cell myeloma.

The initial evaluation includes a hemogram, complete skeletal radiographic survey, serum and urine protein electrophoresis and immunofixation, quantitative Ig levels, urinary protein excretion in 24 hours, and bone marrow aspiration and biopsy. The diagnostic criteria for MGUS, smoldering and indolent myeloma, and MM are shown in Table 56.1 (3).

**Staging and Risk Assessment**

**Radiographic Evaluation**

The radiographic survey of bone is a standard diagnostic evaluation. It shows osteopenia in an early phase of the disease and, with increasing tumor burden, lytic punched-out lesions. Osteosclerotic lesions are observed in POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes). Because of the predominant osteolytic activity with osteoblastic inactivity, bone scans seldom give positive results—unless a recent fracture has occurred—and are therefore not useful in the diagnosis of MM.
Functional imaging with either magnetic resonance imaging (MRI) of bone marrow or fluoro-deoxyglucose (FDG) positron emission tomography (PET), best performed in conjunction with computed tomography (CT), provides a better assessment of tumor burden and is essential in the workup of patients with solitary plasmacytomas of bone (3,4). There are typical imaging patterns on MRI: one third have diffuse involvement of the bone marrow, one third have focal lesions, and the remaining third have heterogeneous focal and diffused marrow involvement (4). Because myeloma is a macrofocal disease, random bone marrow sampling may not be diagnostic or predictive of disease status.

A focal marrow plasmacytoma can be further analyzed through CT-guided fine-needle aspiration, which allows cytologic diagnosis and further risk assessment based on evaluation of the results of cytogenetic and FISH (fluorescence in situ hybridization) analysis, as well as labeling index (1).

**FDG-PET and PET-CT**

PET has also been evaluated in a few studies and may provide a better functional definition of lesions observed on MRI or CT, as well as allowing selection of lesions for biopsy. Durie et al. (5) examined 66 patients with MGUS (14 patients), active untreated MM (16 patients), 10 patients with disease in remission, and 26 patients with relapsing MM. Negative whole body FDG-PET scans reliably predicted stable MGUS. All patients with untreated MM had focal or diffuse increased FDG bone marrow uptake, indicative of active MM. In particular, 25% of the patients with newly diagnosed MM had positive FDG-PET findings, despite fully negative skeletal surveys. Another 23% to 25% of newly diagnosed or relapsed MM patients had extramedullary MM, which was confirmed by biopsy or other imaging techniques. This extramedullary FDG uptake was a very poor prognostic factor, as indicated by the median survival of only 7 months of these patients with extramedullary, FDG-positive MM. Persistent positive findings after induction therapy predicted early relapse. The FDG-PET results were especially helpful in identifying focal recurrent disease in patients with nonsecretory or hyposecretory disease amenable to local irradiation therapy (5).

Bredella et al. (6) reported in a series of 23 patients a sensitivity and specificity of 80% and 92%, respectively, for detecting active myeloma. Two subcentimeter lytic lesions detected at skeletal surveys had no or only very mild FDG uptake. There was also one false-positive finding observed 3 weeks after radiotherapy. FDG-PET was helpful in differentiating between posttherapeutic changes and residual or recurrent MM manifestations (6). In roughly one third of patients, FDG-PET influenced therapeutic management.

Our group (8) confirmed and extended the results of previous authors using FDG-PET for staging and restaging multiple myeloma and solitary plasmacytoma. In 28 patients with MM and 15 patients with solitary plasmacytoma, we observed focally increased FDG uptake in bone marrow of 38 of 41 patients with known osteolytic bone lesions, resulting in a sensitivity of 93%. In addition, 71 lesions with negative skeletal radiographs were observed. Twenty-six of 71 of these lesions were confirmed by biopsy or other imaging techniques in 20 patients. Clinical management was changed in 14% of all patients examined. Sensitivity and specificity of increased diffuse FDG uptake in bone marrow indicative of active disseminated disease were 84% to 92% and 93% to 100%, respectively (8). Compared with FDG-PET, skeletal radiographs underestimated the extent of disease in 61% of the patients examined (8).

Given the well-known increased synthesis of the monoclonal immunoglobulin in MM, we reasoned that functional imaging of increased amino acid use by MM cells may provide a direct approach for imaging, precise localization, and possibly quantitation of MM mass in vivo. A sixfold increased \(^{[35]S}\)methionine incorporation into CD138\(^+\) plasmacytoma cells, freshly isolated from bone marrow of patients with newly diagnosed untreated MM, compared with normal CD138\(^–\) bone marrow cells confirmed the validity of this novel approach (9). Nineteen patients with MM and ten controls without hematologic diseases were examined with \(^{[11]C}\)methionine and imaged 20 minutes postinjection with PET-CT. The presence and extent of CT-assessed tumor manifestations and \(^{[11]C}\)methionine bone marrow uptake were determined. \(^{[11]C}\)methionine BM uptake in normal controls with no known hematologic disease was homogeneous and low (Fig. 56.1). All patients with MM except one with exclusively extramedullary MM had \(^{[11]C}\)methionine-positive osteolyces (Figs. 56.2 and 56.3). Maximal lesional BM \(^{[11]C}\)methionine SUV\(_{\text{max}}\) was 10.2 ± 3.4 and significantly higher than that of BM of controls (1.8 ± 0.3, p < 0.001). Extramedullary MM was clearly visible in three patients (SUV\(_{\text{max}}\) 7.2 ± 2.4) (Fig. 56.4). Additional \(^{[11]C}\)methionine-positive lesions in normal cancellous bone were found in nearly all patients. Preferentially in pretreated patients, a moderate fraction of osteolyces had no \(^{[11]C}\)methionine uptake.

Based on increased methionine uptake in myeloma cells, active MM could be reliably imaged with \(^{[11]C}\)methionine PET/CT. This novel approach has a high potential for differentiating active MM from inactive scar tissue in radiologically demonstrated osteolyces. In addition, similar to previous findings with FDG-PET (Schirrmeister), there were many focal lesions with increased \(^{[11]C}\)methionine uptake and normal bone structure (Fig. 56.4), suggesting the presence of new, metabolically active lesions developing earlier than structural osteolytic bone changes (9).

In summary, FDG-PET or PET-CT or alternatively \(^{[11]C}\) methionine PET-CT can reliably image both solitary multiple myeloma, nonsecretory myeloma, extramedullary myeloma, and relapsing myeloma. MGUS can be differentiated from
Figure 56.1  Homogenous and low $[^{11}\text{C}]$methionine uptake in a control patient (upper row) compared with diffusely increased $[^{11}\text{C}]$methionine uptake in the whole vertebral spine of a patient with MM.

Figure 56.2  Maximum intensity projection image A, (trunk and head) shows multiple focal lesions with increased $[^{11}\text{C}]$methionine uptake, suggesting widespread disseminated MM. The patient with relapsing MM showed disseminated lesions in right and left ileum and sacrum. (B: computed tomography, C: $[^{11}\text{C}]$methione PET, D: Overlay). Some lesions have intense $[^{11}\text{C}]$methionine uptake whereas others have virtually no $[^{11}\text{C}]$methionine uptake. (See also Case 56).
Chapter 56: PET and PET-CT in Multiple Myeloma

Figure 56.3  Lytic skull lesion shown by CT with highly increased $[^{11}\text{C}]$methionine uptake as typical manifestation of MM. An additional lesion with increased $[^{11}\text{C}]$methionine uptake was diagnosed in the shaft of the left humerus.

Figure 56.4  Extramedullary bilateral MM lesions in the breasts (arrows) and abdominal bulk manifestation A (maximum-intensity projection image). There is intense $[^{11}\text{C}]$methionine uptake in all soft tissue lesions. A further bone lesion (right ileum) without visible change of bone structure in CT. (B: $[^{11}\text{C}]$methionine PET, C: Computed tomography, D: Overlay).
MM. Active MM presents with multiple metabolically highly active lesions, whereas in treated MM many inactive osteolytic lesions suggest scar tissue in a considerable fraction of radiologically detectable bone changes. The presence of metabolically active lesions in structurally unchanged cancellous bone suggests metabolically active lesions preceding radiologically detectable structural bone changes. FDG-PET or better PET-CT has now been implemented into the Salmon/Durie PLUS staging system for myeloma staging (3).

REFERENCES
External beam radiation treatment (EBRT) is delivered most commonly using a linear accelerator system to focus high-energy x-rays on the region of the patient tumor. In most cases, a computed tomography (CT) scan is obtained of the patient’s tumor during the time when a patient is in a device called a treatment simulator. The radiation therapist defines the region of the tumor in relationship to the CT scan, and also identifies normal tissues in the region, which are to be avoided. With the aid of dosimetrists and medical physicists, a radiation treatment plan is implemented, which involves a fraction of repeated doses of radiation to achieve an amount of radiation in the tumor and surrounding normal tissues that can be tolerated by the patient.
Three-dimensional conformal radiation therapy (3D-CRT) represents an approach to improve the local outcome of radiotherapy. The major aim of this method is to decrease the risk of underdosing or missing portions of the tumor. In addition, because of the improved ability to conform the high radiation dose to the target, considerable amounts of normal tissue (such as lung, esophagus, and heart) can be effectively excluded from the high-radiation dose regions. This provides a potential for increasing the tumor dose to levels beyond those feasible with conventional radiotherapy, with a concomitant decrease in the normal tissue complication probability (NTCP).

3D-CRT is accomplished using CT to aid in treatment planning. A clinical tumor volume (CTV) is defined in the axial plane of the CT images. A margin is subsequently added to the CTV to generate the planning target volume (PTV). This margin compensates for tumor motion during treatment caused by breathing, patient movement, and setup error. The treatment beams are subsequently constructed using the beam’s-eye view technique. The optimal radiation beam parameters and orientation are selected by objectively comparing candidate plans using calculations and visual displays. This technique has been used in multiple clinical trials with good efficacy (1,2). Intensity-modulated radiation therapy (IMRT) is a more advanced treatment planning technique than 3D-CRT. It allows escalation to a higher dose of radiation than 3D-CRT. However, there has not been extensive clinical experience in the use of IMRT. Figure 57.1A shows an example of a five-field IMRT prostate plan with the intensity profiles.
shown for each field to reach the desired isodose distribution. Magnetic Resonance Spectroscopic Imaging (Fig. 57.1B,C) has already been used for the first biologically based radiotherapy plans, and PET tracers have the potential of being used for this same purpose (Fig. 57.1D).

Extracranial stereotactic radiosurgery (SRS) is currently being investigated in a number of treatment sites as a potential technique to increase dose to the tumor while limiting the normal tissue around the tumor to low doses of radiation. This can allow for fraction sizes as high as 20 Gy. There have been reports of excellent local control with this technique (3).

Investigators have recently developed a technique known as image-guided radiation therapy (IGRT), which uses imaging while the patient is in the treatment position to verify the accuracy of the treatment. This technique will be especially helpful when high dose per fraction treatments, such as extracranial SRS, are used.

Helical tomotherapy (HT) is an innovative means of delivering IMRT using a device that merges features of a linear accelerator and a helical computed tomography (CT) scanner. The HT unit can generate CT images from the megavoltage radiation it uses for treatment as often as needed during a course of radiation therapy. These megavoltage CT (MVCT) images offer verification of patient position prior to and potentially during radiation therapy (4). Similar technology exists using standard linear accelerators to create MVCTs, as well as using conventional CT imaging via a kilovoltage unit attached to a treatment machine to image patients. In principle these devices could be used to deliver radiation not only to primary tumors but to metastatic tumors deep within the body. Biologic imaging using integrated positron emission tomography (PET) and CT offers the potential to fuse CT images used to define the clinical, gross, and planned target volume in relation to dose-limiting normal tissues with images that may show functional properties of the tumor for refining dose intensification within individual regions.

**FDG-PET STUDIES IN PLANNING AND RESPONSE ASSESSMENT IN RADIOTHERAPY**

Ninety-nine percent of all PET studies today are performed using the radiotracer fluorodeoxyglucose (FDG). This is because of the almost ubiquitous uptake of FDG in all viable cancer cells. FDG-PET imaging appears to have gained a level of general acceptance as having an important role in radiotherapy for staging, treatment planning, treatment monitoring, and detecting recurrence (5). This property has led to its exploratory use for assisting CT in the delineation of radiotherapy margins (6), for the differentiation of viable versus necrotic tissue (7), as well as for potential prognostication of radiotherapy treatment response.

**FDG-PET-CT to Improve Treatment Planning in Lung Cancer**

Surgery remains the primary treatment option for lung cancers that have not metastasized. However, for tumors that are inoperable, either owing to extensive disease or because the patient cannot undergo a surgical procedure, radiation therapy, alone or in conjunction with chemotherapy, is the standard of care. In recent years, evidence has suggested that higher doses of radiation will improve local control of advanced lung cancers (2). Several new radiation techniques have aided in delivering the highest possible radiation dose targeted precisely to the tumor while sparing surrounding healthy tissues and organs.

PET (positron emission tomography) scanning with the tracer FDG ($^{18}$F-2-fluoro-2-deoxy-d-glucose) can be used to augment CT imaging in tumor definition for radiation therapy treatment planning. The extent of many lung tumors is not fully visible on CT scans, and inadequate delineation of the Gross Tumor Volume limits the success of RT. FDG-PET imaging in addition to CT has a higher sensitivity, specificity, and accuracy than CT alone. In a prospective treatment planning study, Erdi et al. (6) combined PET images with CT data for 11 non–small cell lung cancer (NSCLC) patients and reported PTV increases for 7 patients, with an average volume increase of 19%. For the other four patients, PTVs decreased by an average of 18%. Figure 57.2 shows a planning target volume (PTV) that incorporated PET images. Whatever the merits of these and other response findings, perhaps there is clearer evidence when FDG-PET demonstrates patterns of failure post–radiotherapy/chemoradiotherapy as in the study by MacManus et al. (8) for non-small cell lung cancer.

**Optimizing the Use of FDG-PET in EBRT Response Assessment**

In a special circumstance, multiple images can be obtained using PET-FDG during the entire course of the patient’s external beam radiation therapy (Fig. 57.3). An 81-year-old woman was irradiated as primary treatment for her lung cancer. The patient’s radiation treatment consisted of an initial phase of parallel opposed anterior-posterior (AP-PA) fields to 3,420 cGy followed by a cone-down (the treatment field is reduced to provide a boost to a portion of a target volume), consisting of opposed right anterior oblique (RAO) and left posterior oblique (LPO) fields. The AP-PA beams encompassed the entire lesion. However, only the inferior section of the lesion was irradiated by the primary beams of the cone-down plan. The patient received a total of 6,480 cGy to the prescription point in 180-cGy daily fractions using the 6-MV beam of a Varian 2100C (Varian Medical Systems Inc., Palo Alto, Calif.) linear accelerator. A baseline FDG-PET scan was performed 2 weeks prior to EBRT, and treatment response was monitored by imaging on five occasions after completion of each 900-cGy increment of treatment. A follow-up scan
was obtained at 3 weeks after the last treatment was delivered. Several important features of treatment response measurement are illustrated by the patient example shown. A kind of natural history of treatment response in a responding patient is shown (6).

**Timing and Duration of Metabolic Response**
Note that reduction in metabolism occurs relatively early in the course of treatment, so that by the time 1,800 cGy of radiation have been delivered, the metabolic rate for glucose has decreased by one third. This is 10 days into the treatment cycle. Also, the treatment response is progressive, proceeding to less than 10% of the initial activity by the end of treatment. In addition, there appears to be a window of opportunity for assessing the tumor, without major impact by surrounding inflammatory change in the normal lung.

**Importance of Timing of PET-FDG Imaging with Respect to EBRT**
However, within a few weeks of treatment, assessment of the tumor response becomes difficult owing to a major inflammatory response in normal tissue. If tumor response assessment were attempted for the image labeled “post-treatment” in Figure 57.3B, the assessment would be confounded by FDG uptake in the normal tissues.

**Use of Both Qualitative and Quantitative Changes for Tumor Assessment**
In particular, the most valuable quantitative parameters are $SUV_{max}$ and total lesion glycolysis (TLG) (9).

**FDG Uptake in Normal Tissues**
FDG uptake in normal tissues may offer an index to the timing and severity of acute radiation damage. For example, by 900 cGy there was essentially no change in normal tissues. By 1,800 cGy, there was noted increased uptake in the tissues in the back, probably caused by inflammatory change in muscle and soft tissues at the treatment portal. At 2,700 cGy, there is intense uptake in the esophagus associated with clinical esophagitis; by 3,600 cGy, there was absence of uptake in a paratracheal lymph node that was involved by tumor; by 4,500 cGy, there was reduction in uptake of the normal marrow of the thoracic spine; by 5,400 cGy, there was reduction of uptake in the normal marrow of the lumbar spine.

Radiation response in a second patient considered to have progressed during the course of therapy showed a much different FDG-PET uptake profile, with essentially no change in $SUV_{max}$ and TLG during the early treatment, but with increase in both parameters thereafter (6). Preliminary data are also shown for non-small cell lung cancer, in which FDG accurately predicted response of the primary lung cancer to both combination chemoradiation therapy and EBRT (10).

As mentioned earlier, prospective monitoring through the course of EBRT may be the optimum way to determine radiation response in solid tumors. In most cases this is not practical, and we are left with the problem of obtaining a PET scan at an interval posttreatment that may not be optimum for predicting response in tumor or normal tissue. Other examples of the value of FDG-PET in monitoring radiotherapy treatment response are given in Figure 57.4.
Combined Chemoradiation Response in Esophageal Cancer

The value of PET-FDG in monitoring treatment response to combined chemoradiation is clear in esophageal cancers (11–15). Patients were studied at baseline and prior to surgery after combined chemoradiation (Fig. 57.5). Those patients who had a greater than 55% to 59% decline in SUV$_{\text{max}}$ had significantly better progression-free survival than patients with a lesser response (see Chapter 41).

Figure 57.3  A: Radiotherapy patient setup in Styrofoam mold for lung cancer used for PET imaging.  B: Same transaxial slice from repeat FDG-PET scans performed weekly during a course of radiotherapy up to 5,400 cGy.  C: Comparison of different potential PET measures of treatment response: average SUV in the tumor volume, maximum SUV, FDG-avid volume defined by the same 42% of maximum threshold for each PET scan, total lesion glycolysis (TLG) defined as the product of the average SUV with the FDG tumor volume and the TLG normalized by the initial pretreatment TLG value (TLG(t)/TLG).  D–F: Split-screen display of a slice through the center of the lesion pretreatment and posttreatment. Transaxial, coronal, and sagittal planes are shown. From Ref. 6, Erdi et al. 2000). (continued)

Combined Chemoradiation Response in Colorectal Cancer

Early PET studies indicated that FDG uptake would decline after irradiation of colorectal cancers (16). Preliminary data are now available regarding the monitoring of treatment response using FDG-PET imaging in colorectal cancer (17). In this pilot study, patients who did not respond to radiation had an SUV$_{\text{max}}$ and TLG decline of less than 37%, whereas those who did respond had a mean SUV$_{\text{max}}$
Combined Chemoradiation Response in Lymphoma

Because of increasing effectiveness of chemotherapy in lymphoma, radiation is less frequently used as a primary treatment modality of this disorder. Often, radiation and chemotherapy are combined. PET-FDG is commonly used to monitor treatment response in lymphoma, with or without radiation. The persistence of metabolic activity at the disease site is highly suggestive of residual disease. PET imaging is much more effective than CT or other structural imaging modalities in predicting response to either chemotherapy or radiation (18). PET-FDG imaging was introduced clinically in brain tumors, because of the availability of dedicated brain PET scanners (20–22). The differential diagnosis of brain tumor recurrence versus radiation necrosis is a difficult clinical diagnosis, and on cross-sectional imaging there may be significant mass effect that may increase over time and still be owing to radiation necrosis. In this scenario, FDG scanning may be useful in certain situations to detect recurrence versus radiation necrosis. A word of caution is in order, however, in that with gamma knife and other highly focused and intense radiation, the inflammatory response may be greater than with external beam radiotherapy alone. Thus the most reliable outcome on FDG-PET is a mass in the region of the previously positive high-grade glioma, which no longer takes up the radiotracer (Fig. 57.7) (see also Chapter 22).

Head and Neck Cancer

Radiation therapy has become a mainstay of treatment of head and neck cancers (23), and FDG-PET is frequently used in monitoring and detecting recurrence (24–31).
Figure 57.4  A patient with non–small cell lung cancer in the upper lobe and apex of the right lung (Pancoast tumor) before and after radiation therapy. Coronal FDG-PET images before (A) and after (B) therapy. Transaxial CT, PET, and PET/CT fusion images before (left) and after (right) radiation therapy. The images C-H show the top portion of this large lung cancer. Pretreatment, there is inhomogeneous FDG uptake within this lesion, likely indicating partial necrosis of this large tumor. After therapy, there remains a rim of mild FDG uptake around the lesion, likely indicating some degree of residual disease. The images I-N are in the same format as C-H and show the bottom portion of this large lung cancer. Following therapy, the mass is now largely necrotic (lack of FDG uptake), except for a hypermetabolic rim along its lateral border, which indicates residual diseases.
Because of the complex anatomy in the neck, combined PET-CT offers significant advantages in the staging, monitoring of treatment response, and detecting of recurrent disease. In a study by Kubota et al. (31), for example, FDG-PET was performed at a median interval of 4 months after primary therapy when radiation was completed, principally because of residual masses on palpation or on other cross-sectional imaging. FDG-PET performed more accurately in this setting than magnetic resonance imaging (MRI) or CT. Because of the continued presence of inflammation, the sensitivity, specificity, and accuracy of this technique were 70%, 81%, and 70%, respectively. False-positive findings were a problem, but a negative PET excluded disease with a high degree of certainty (negative-predictive value [NPV] 92%). Others have confirmed these findings and have also noted a high accuracy of PET in detecting distant metastases (32,33) (Fig. 57.8) (see also Chapter 34).

**Colorectal Cancer**

In the study of documented pelvic recurrence of rectal cancer after combined chemoradiotherapy, 16 of 19 (84%) documented recurrences were detected, at a minimum of 6 months after treatment. Specificity was 89%, and overall accuracy was 87%. There was a trend toward better accuracy of PET scanning when recurrences occurred more than 12 months after treatment (34) (see also Chapter 44).

**RADIATION BIOLOGY OF TREATMENT RESPONSE**

**Radiobiologic Factors in Radiotherapy**

Several factors affect the radiosensitivity of tumors. These include: intrinsic cellular radiosensitivity (the fraction of cellular inactivation per unit dose), cell cycle phase, dose...
**Figure 57.6** Transaxial CT and FDG-PET images of a patient with rectal cancer, imaged before (A, B) and after (C, D) combined neoadjuvant chemotherapy and radiation therapy. Time difference between imaging studies is 40 days.

**Figure 57.7** Patient with anaplastic glioma, status postresection and adjuvant radiation therapy, now with suspected recurrence on MRI. A transaxial MRI with IV contrast shows rim enhancement around the resection cavity. FDG-PET shows a rim of mild FDG activity, which corresponds to the area of contrast enhancement on MRI. The rim has a ratio of 1.7 times the contralateral white matter, which is consistent with response. (From Ref. 32.)

**Figure 57.8** Carcinoma of right palatine tonsil, extending into the base of tongue (T4). In addition, right level II neck lymph node metastasis. Transaxial CT (A,C) and PET/CT fusion (B,D) images before (A,B) and after (C,D) concurrent chemotherapy and radiation therapy (time difference between imaging studies 5 months). There was complete response, and on follow-up, no residual disease or recurrence is seen.
rate, the growth fraction, cell losses, radiation damage repair, partial oxygen pressure (hypoxia), mode of cell death (mitotic, apoptotic), and so on. Many of these radiobiologic properties have been well characterized for tumor cell lines in vitro and can be found in classic texts on radiobiology (35,36). The characteristic radiation dose response of most tumor cell lines (Fig. 57.9) resemble those of acutely responding normal tissues, and it is this principle that underlies the radiobiologic thinking behind most radiation dosing strategies.

Most radiobiologists group the radiation responsive characteristics into the so-called four “Rs” of radiobiology: Repair, redistribution (within the cell cycle), reoxygenation, and repopulation. Tumors with long potential doubling times (large \( T_{pot} \)) show more curved radiation cell survival curves, that is, small \( \alpha/\beta \) ratios, and as a consequence would result in greater expected changes with fractionation. Rapidly dividing tumors exhibit flatter survival curves and are expected to be less susceptible to changes in the fractionation regimen.

The determination of dose-limiting radiation toxicity for normal organs is considerably more complex and follows different courses depending on whether the organ’s response is acute or chronic. This translates into a variable time of expression of radiation injury in different normal tissues, ranging from a few days in intestine to weeks, months, or even years in slowly proliferating tissues like lung, kidney, and bladder. Also, organs differ in whether they respond as serial (spinal cord) or parallel (lung, liver, kidney) organs. For serial organs, dose to any region of that organ exceeding tolerance will inactivate that organ. In contrast, parallel organs consist of a multiplicity of subunits, the increasing destruction of which leads to the progressive and eventually total loss of organ function.

During the 1970s and 1980s, radiation biologists and physicists were working on attaining the optimum fractionation schedule with which to maximize the tumor to normal tissue damage differential. The concept of nominal standard dose, NSD, proposed by Ellis (37), was the first algorithm that tried to separate the effect of overall time from that of number of fractions. It was developed into a more convenient formulation by Orton and Ellis (38) with the name of time-dose factor (TDF). Later, Thames et al. (39), Fowler (40), and Dale (41) developed the linear-quadratic formulation, which is the common formulation used today. This formalism when applied to tumor and late-responding normal tissues predicts that increasing the dose per fraction increases the tumor cell kill, but that it would also reduce the therapeutic ratio. Consequently, reducing the dose per fraction would increase the therapeutic gain, at least down to dose rates for which cell survival kinetics does not become dominated by tumor cell repopulation. Consideration of such factors, and the experimental radiobiology of the time, led to the adoption of the conventional 1.8- and 2.2-Gy dose per day used in most radiotherapy treatments today. Over the past decade, there has been interest in changing these traditional fractionation regimens by hyperfractionation, in which doses are administered in two or even three fractions per day or hypofractionation in which larger doses are administered over greater time intervals.

**Hyperfractionation** is the practice of reducing the interval between radiation treatments from the conventional single fraction per day. As a consequence, the dose per fraction is reduced and the total dose increased to give improved tumor control without increased late morbidity. Its rationale lies in an improved understanding of cellular radiation repair kinetics. Repeated dosing of the tumor at two or more fractions per day at intervals coinciding with complete repair of the normal tissue (generally 6 hours) at risk may reduce tumor proliferation without additional radiation toxicity. Extensive clinical trials of various hyperfractionation schedules have been performed, and reviews summarizing the clinical results published in head and neck (H&N) cancer (42) and small cell lung carcinoma (43). Typical trial designs involve the use of two 1.8- to 2.0-Gy fractions per day, reducing the overall treatment time to as much as one half. Results for H&N cancers are consistently better than standard fractionation for locoregional control of intermediate to advanced carcinomas without an increase in late toxic effects, yet with inconsistent improvement in patient survival (42).

**Hypofractionation**, the use of accelerated treatment consisting of fewer fractions of higher dose per fraction, was abandoned by the 2 Gy per fraction regimen, owing to the
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much greater chronic normal organ radiation toxicities. There has been a very recent resurgence of interest in hypofractionation for tumors with small α/β ratios such as breast (44,45) and prostate (46,47), where it is thought that equivalent treatment outcomes may be achieved without an increase in radiotoxicity and with significant benefits to patients and physicians resulting from the shorter irradiation schedules. Modest hypofractionation trials are currently ongoing. One such example is the group at Fox Chase Cancer Center, who have compared IMRT for prostate cancer of 76 Gy in conventional 2-Gy fractions to 70.2 Gy in 2.7-Gy fractions. They concluded that hypofractionation at 2.7 Gy per fraction to 70.2 Gy was well tolerated with no increased radiotoxicity. (46)

Other more controversial proposals suggest significant therapeutic gains through the use of a single or few large (>15-Gy) dose fractions. The rationale behinds these regimens does not arise from the classic radiobiologic models, but a new exploratory paradigm of microvascular damage being a significant target and determinant of tumor response to radiation at a range of doses relevant to hypofractionation or single-fraction radiation therapy (48,49). These concepts are being thoroughly explored in preclinical animal models, with human trials being planned.

One potential risk of radiotherapy in a single dose or large dose per fraction is the radioresistance associated with hypoxic cells, known to require up to three times greater doses for inactivation relative to the same cells under normoxic conditions. It is widely believed that fractionation allows reoxygenation of hypoxic tumor cells and maximally exploits the differential repair capacity of normal tissue to tumor cells. Until recently, nuclear medicine had been of little interest to the radiation oncology community. That has changed. With the emergence of the first commercial PET-CT units in 2001, there has been a considerable interest in the radiation oncology community on exploiting this technology, with expectations that it might provide novel information of the tumor radiobiology combined with the anatomic CT information, the foundation of 3D conformal and intensity modulated radiotherapy (50,51).

PET TRACERS FOR RADIATION BIOLOGY

PET offers a noninvasive opportunity of providing information about tumor radiobiology in vivo. Examples of some of the information that could be gleaned using PET tracers of potential interest to radiobiologists are: metabolic viability (FDG), cellular proliferation (iododeoxyuridine, 124I-IUdR; fluorothymidine, 18F-FLT), and hypoxia (19F-MISO, 64Cu-ATSM, 18F-EFS). The locoregional spatial distribution of tumor subvolumes of different tumor cell density, aggressiveness, or resistance might be appropriately targeted using innovative IMRT for so-called dose painting.

Although in general tumors exhibit enhanced FDG uptake because of increased metabolism, there are other influential factors, including blood flow, cellular proliferation and hypoxia (52). The situation may be even more complex during and subsequent to radiotherapy owing to radiation-induced reactive changes in both the tumor and the stroma. Given the heterogeneous nature of human malignancy and the complexity in radiation response of both the tumor and normal tissues, it is possible that the usefulness of FDG-PET is disease specific or even patient specific. Studies designed to indicate optimum time after the initiation of radiotherapy need to be more rigorously conducted. Humm et al. (53) attempted to monitor the changes of FDG uptake in experimental tumors grown in rats by conducting repeated FDG scans during and after a course of ten daily 2-Gy fractions of x-rays. However, changes in FDG uptake measured using the parameter standardized uptake value (SUV) were found of little use as a measure of radiation response. This is perhaps because sterilized “doomed” tumor cells retain their glucose metabolic activity. However, the product of the SUV with the tumor mass, that is, the total lesion glycolysis, was more promising.

FDG may have limitations as a radiation response marker because of the appearance of inflammation and the inability to distinguish clonogenically viable from “living” yet nonviable tumor cells. For this reason, the use of PET tracers that are selectively incorporated into proliferating cells might offer a more useful alternative. What radiobiologists and radiation oncologists would really like to have is a noninvasive imaging assay for proliferating tumor cells. Mankoff et al. (54) proposed using PET to image the incorporation of 11C-thymidine in the tumor DNA. This has proven to be extremely challenging on account of the short 20-minute half-life of 11C and the even shorter metabolic half-life (approximately 3 to 5 minutes) of thymidine. The concept of using thymidine analog iododeoxyuridine 124I-UdR as a nuclear medicine marker of tumor cellular proliferation has been explored in brain tumors by Blasberg et al. (55). The advantage of 124I-iodide is its 4.2-day half-life, allowing images of DNA-incorporated 124I-UdR to be acquired 24 hours postinjection; these images are not confused by blood pool clearance of metabolic radioiodine. However, a weakness of 124I is the low 24% positron yield, resulting in noisy PET images. Shields et al. (56,57), Vesselle et al. (58), and Schwartz et al. (59) have explored the use of a fluorinated thymidine analog called fluorothymidine (18F-FLT), which could overcome the shortcomings of both 11C-thymidine and 124I-UdR. The uptake of 18F-FLT is regulated by cytosolic S-phase–specific thymidine kinase 1 resulting in the tracer’s selective intracellular entrapment in dividing tumor cells. 18F-FLT has been validated as a tumor cell proliferation marker in small cell lung carcinoma where 18F-FLT SUV imaging data were correlated with Ki-67 staining intensity on the surgically resected tumors (59).

Some of the radiotracers that have attracted the greatest interest for evaluating tumor response as well as for potential application in dose painting are the hypoxia markers (60). This is a consequence of the long-held belief that hypoxia is a major cause of treatment failure in radiotherapy, owing to the radio-resistance of cells under low partial...
oxygen pressure. Whether this is true or untrue (because of tumor reoxygenation between treatment fractions), a non-invasive technique to measure tumor hypoxic fraction would allow the role of hypoxia as a therapy outcome prognosticator to be determined.

Several hypoxia radiotracers have been proposed. The first to be extensively studied was fluoro-misonidazole ($^{18}$F-MISO), which was introduced into the clinic by Rasey et al. (61) and has since been continued by Rajendran et al. (62) and others. $^{18}$F-MISO has been shown to acquire good-quality images of tumor in H&N (Fig. 57.10), lung, brain, soft tissue sarcomas, and other tumors (63). It is recognized that such images of hypoxia may be useful in IMRT dose painting. Under the right circumstances, a hypoxic pattern of $^{18}$F-MISO uptake may correlate with reduced radiation treatment response in head and neck cancers (64). One difficulty of $^{18}$F-MISO is associated with the short 110-minute half-life of $^{18}$F, restricting image acquisition to a maximum of about 3 to 4 hours postinjection, and at a time when the hypoxia tissue/blood ratio is only 1.3 to 1.4. As a consequence, $^{18}$F-MISO images are frequently of poor contrast. Other $^{18}$F hypoxia tracers are being explored, with higher octanol/water partition coefficient, with the hope that these will provide greater contrast, for example, $^{18}$F-FETNIM (65) and $^{18}$F-EF5 (66).

Another PET hypoxia tracer that has been extensively investigated in the context of radiotherapy applications is Cu(II)-diacetyl-bis(N4-methylthiosemicarbazone) abbreviated Cu-ATSM, which can be labeled with several positron emitters: $^{62}$Cu ($T_{1/2}$: 9.74 minutes), $^{60}$Cu ($T_{1/2}$: 24.0 minutes), or $^{64}$Cu ($T_{1/2}$: 12.7 hours). The group at Washington University, St. Louis, has shown interesting data suggesting an inverse correlation between the level of $^{60}$Cu-ATSM uptake in tumor and clinical outcome in non–small cell lung cancer, as well as for cervical carcinoma patients (67). This finding provides strong support for the hypothesis that hypoxia is a negative prognostic indicator of radiotherapy outcome. Encouraged by this and the initial data in a rodent model showing a correlation between oxygen electrode measurements and $^{60}$Cu-ATSM accumulation, Chao et al. (68) performed a study to demonstrate the feasibility of biologically based IMRT with the selective targeting of dose to regions of high $^{60}$Cu-ATSM accumulation. Further animal evaluation studies of $^{60}$Cu-ATSM have shown that this agent may not localize in the hypoxic zones of all tumors (69). Nevertheless, this new direction in radiotherapy emerging from a collaboration with nuclear medicine is exciting and holds substantial promise for the future.

**RESPIRATORY MOTION AND RADIOTHERAPY**

Motion of the tumor and of the lung itself during the delivery of each treatment appears to affect the outcome of
Radiotherapy. Lung tumors have been shown to substantially vary in their position during quiet breathing, causing inaccuracies in treatment delivery (70). Underdosage of the clinical target volume may result if the tumor target moves outside of the treatment volume during the administration of radiotherapy. To compensate for this motion, a normal tissue safety margin is typically used to encompass the tumor, which may effectively double the planning target volume. Thus, approaches have been investigated to reduce the intrafraction organ motion and the volume of lung receiving radiation.

Two distinct techniques have been used to reduce the effects of respiratory motion. The first involves confining radiation delivery to a specified phase in the breathing cycle by gating the linear accelerator while the patient breathes freely. Breathing is monitored with devices that trigger radiation delivery during specific phases of the patient’s respiratory cycle (71). In the second approach, breathing is controlled either voluntarily by the patient or by using an occlusion valve. One example of this approach is active breathing control (ABC) developed by Wong et al. (72).

Another example is the deep inspiration breath hold (DIBH) technique. The DIBH technique involves coaching the patient to the same reproducible deep inspiration level during simulation, radiation treatments, and port film verification. This technique has been shown to increase the theoretical maximum safe dose from 69 to 88 Gy (73).

**Respiratory Gated PET-CT for Radiotherapy**

The introduction of combined PET/CT scanners offered the advantage of acquiring a CT and PET in the same imaging session with the expectation of fully automatic coregistration. However, this was soon found not to be true in the thorax, which is subject to respiratory motion as evidenced by some unusual motion artifacts (74,75). Since a CT acquisition of the thorax takes only seconds on a four-slice CT unit (CT raw data acquired at approximately 2 cm/sec), high-quality images are mostly acquired under deep breath hold inspiration. However, it is not feasible to acquire the PET exam under similar respiratory breath-hold conditions, which require minutes even on the highest sensitivity PET scanners. The PET image data represent an average of several complete respiratory cycles, in contrast to deep inspiration, or a fraction of a respiratory cycle acquired by the CT. This difference in acquisition time results in a mismatch between the CT and PET data sets. Such mismatch renders the PET/CT data difficult or impossible for use in radiotherapy planning, which requires tight conformal margins around the tumor volume. The effect of respiratory motion on the PET image is to give rise to tumor image blurring, with the consequences of a degradation in image contrast, overestimation of the lesion volume, and a significant error in the measured SUV (76–78). In CT, respiratory motion may also distort the tumor shape and volume (79,80). The uncertainties resulting from respiratory motion necessitate expansion of the margin around the tumor during radiotherapy planning to ensure adequate dose coverage. When using CT images to correct for attenuation in PET data, the mismatch between PET and CT data sets may compound the quantitative errors in SUV even further (81).

Various respiratory motion–control treatment techniques have been developed to improve the accuracy of determining the tumor location during radiation therapy. These include gating (82), breath holding (83,84) or active breathing control (85,86), respiratory-correlated CT (87,88), and 4D-CT (79). In PET, prospective gated PET (77) and retrospective respiratory-correlated dynamic PET (78) methods have been reported as a possible solution to resolve respiratory artifacts during PET emission scans. When the two are combined, one obtains 4D-PET-CT (89,90).

Current investigations are underway to determine the best way to acquire both PET and CT data in correlation with respiratory motion. Respiratory phase–matched PET-CT data will allow the best target delineation, more accurate attenuation correction in the thorax, and more accurate quantification of PET images, which if perfected would allow IMRT dose painting for lung and other thoracic lesions. For radiation therapy applications, it will be necessary to select the PET counts corresponding to that respiratory phase most suited to treatment, with equivalent gating of the linear accelerator therapy device.

One current implementation of respiratory gated PET-CT for radiotherapy applications is to provide oral training with recorded verbal breathing instructions during radiotherapy simulation (91). These oral instructions act as a metronome to assist the patient to keep a steady breathing rhythm, of vital importance for the PET-CT study. The period of the recorded instructions should be optimized to the comfort level of the patient’s breathing activity. Patient immobilization in the same radiotherapy cast used for therapy is required if the images are to be used for planning. It is necessary to use a motion tracker to record the patient’s phase through the respiratory cycle. Several devices can serve this purpose, for example, the Varian Real-Time Position Management (RPM), designed initially for respiratory gated radiotherapy. Using two infrared markers placed on the patient’s chest, the RPM’s vertical displacement is visualized by an infrared camera, a belt to record the changes in the pressure indicating the degree of chest expansion, a spirometer, nasal thermistor, and so on. Whichever device is used, chest motion is converted into a signal that can be used to track motion. In the case of gated PET, one point in the respiratory cycle is used to trigger the first PET bin, with the PET scanner configured for a cardiac gated PET exam. The respiratory cycle is divided into the desired number of bins for the respiratory cycle according to predefined oral instructions. An alternative approach is to perform either a dynamic scan or a list mode acquisition, in which the frames or events are assigned to the corresponding phase of the respiratory cycle as determined...
from the respiratory motion tracker. A discussion of respiratory-correlated CT exams or 4D CT is beyond the scope of this chapter, and the reader is referred to other sources (79,92,93) (Fig. 57.11).

There are several methods of achieving respiratory phase–correlated PET-CT images for radiotherapy planning. The simplest approach is to use respiratory gated PET, since the image data are already essentially binned into the different respiratory phases and further processing is not required, just reconstruction of each of the individual bins. Alternatively, one can perform a dynamic scan with 1-second frames. This approach allows an analogous handling of the data to 4D CT (94) and allows better handling of irregular amplitude breathing. However, a major limitation is the limit in the number of frames (memory allocation) that is permitted in a dynamic acquisition. Finally, there is list mode data acquisition, which allows complete flexibility in binning the data as desired. The versatility of list mode data has led to considerable research by all three major PET manufacturers for future anticipated respiratory gated solutions. Prior to these solutions, the amount of data processing is prohibitively cumbersome for all but a few research patients.

Figure 57.11  A: Patient setup in the PET scanner with infrared markers placed on the patient’s abdomen. An infrared emitter/camera allows the motion of these markers to be tracked as a function of time and used to model the patient’s respiratory motion. This waveform can be used to trigger the PET camera (similar to an ECG signal) and bin the data into phases of the respiratory cycle. Gated PET images of lung lesions can greatly reduce the amount of motion blurring. If used in conjunction with gated radiotherapy delivery, this would allow a reduction of the radiotherapy planned target volume. The two transaxial images (same window threshold levels) show the same lung lesion acquired from a study first without gating (B; see lesion ROI) and then as one phase of a respiratory gated image (C). (From Ref. 76.)
at the current time. The major advantage of dynamic 4D PET and list mode approaches is that they allow retrospective binning of the data, compared with gated PET, which is a prospective approach only.

Maegert et al. (95) and Nehmeh et al. (89) have measured the extent of lesion motion in patients owing to respiration after matching 4D PET and CT for each specific breathing phase by determining the change in the location of the lesion centroid. These motions can be greater than 1 cm. Volume errors resulting from helical CT scans of a moving lesion can be more than 40% for small lesions. These volume errors compounded with the activity smear- ing have been reported to result in up to 36% errors in the SUV (96). Appropriately correcting such errors will be of great importance for radiotherapy and is consequently attracting considerable interest at the current time.

REFERENCES

Molecular Anatomic Imaging


Clinical PET-CT and SPECT-CT Imaging of Inflammation in the Body

Despite the successes of medical therapy, infectious disease and noninfectious inflammation remain major clinical problems in daily practice. Acute and chronic inflammation in general are characterized by different physiologic alterations that have to be considered when interpreting imaging studies. Vasodilatation, exudation of plasma proteins, and escape of neutrophil granulocytes from blood into parenchyma occur in the acute stage, whereas in chronic inflammation, infiltration with activated macrophages and lymphocytes dominates. Magnetic resonance imaging (MRI) and the various conventional scintigraphic methods detect acute inflammatory changes with high accuracy, whereas specificity is decreased with chronic inflammation.

FDG uptake in PET reflects the increase of glucose metabolism owing to the respiratory burst of activated inflammatory cells and has the potential to demonstrate specifically the grade of inflammation in acute and chronic inflammation. Several papers have appeared over the last few years demonstrating the usefulness of FDG-PET to detect infection and inflammation in various clinical settings. This part of this book summarizes the currently available information on this topic.
Inflammation is described as being acute or chronic depending on its duration. These two phases of an inflammatory process are microscopically characterized by different tissue changes. In acute inflammation, an early vascular response with vasodilatation is found, and exudation of plasma proteins from the peripheral vascular bed owing to damage of the endothelium occurs, which in turn leads to accumulation of edema fluid within the first 10 to 15 minutes. Moreover, increased endothelial permeability allows leukocytes to escape from the blood into tissue parenchyma. Early, these are predominantly neutrophil granulocytes, although a few eosinophils and monocytes emigrate as well. Neutrophils are particularly attracted by bacteria and dying tissue. As acute inflammation subsides after a few days, the number of cells escaping from the blood stream decreases rapidly and the injured tissue returns to normal. Acute infection inflammation does not always resolve, but inflammation may remain active for weeks or months, thereby now becoming chronic inflammation. The clinical character of the inflammation changes

Imaging of septic and sterile inflammation is frequently used in the management of these diseases, be it to decide on the best therapeutic approach or to monitor disease course under therapy. Inflammation can be acute or chronic, the former showing predominantly neutrophil granulocyte infiltrates, whereas in the latter macrophages predominate. Various imaging methods are available for inflammation imaging, most notably magnetic resonance imaging (MRI), which has been used widely because of its excellent soft tissue contrast and its sensitivity to tissue edema and hyperemia, which are hallmarks of acute infection. MRI is less specific in chronic inflammation. Of the various nuclear imaging methods, the most relevant specific methods involve the labeling of granulocytes. Drawbacks are again good suitability for imaging of the acute phase only and a lack of spatial resolution and anatomic detail. The development of combined gamma camera–computed tomography (CT)—that is, single-photon emission computed tomography (SPECT)–CT systems—allows digital image coregistration of anatomic maps with conventional nuclear medicine studies.

Fluorodeoxyglucose (FDG) positron emission tomography (PET) promises to overcome some of the shortcomings of the other methods, and this is owing to the so-called metabolic burst reaction, which granulocytes and macrophages undergo when they are fighting inflammation. This makes FDG-PET potentially useful for acute and chronic inflammation imaging. Furthermore, FDG-PET labels only activated granulocytes, and thus hematopoietic marrow contains little label, making the axial skeleton also accessible to inflammation imaging with PET. The spatial resolution of PET is substantially higher than that of conventional methods. The introduction of anatomic-metabolic imaging with PET-CT has been a great step forward, although the literature is still too limited to make definitive statements on the usefulness of this method in inflammation imaging. Although FDG-PET seems to be very useful in inflammation imaging in general, the logistics of the method make its use easier in chronic than in acute inflammation.
with a decrease of symptoms and episodic fever. In the tissue, the vascular congestion and the interstitial edema are less prominent. The neutrophils in the exudates die or escape back into the blood and are replaced by lymphocytes and macrophages. The inflamed tissue becomes increasingly scarred and fibrotic (1,2).

Inflammation may be septic or aseptic and most frequently involves the musculoskeletal system, the cardiovascular organs, and the lungs, but any organ may be affected. The histologic alterations that occur in the first few hours and days of the inflammatory process change with time, and later more chronic stages of inflammation are considerably different. Since current imaging modalities reflect certain morphologic and functional changes, this dynamic development of an inflammatory process with time has to be kept in mind when interpreting imaging studies.

**DIAGNOSIS**

In most cases, the diagnosis of an inflammatory disorder is a clinical one. The early diagnosis of acute infection is based on signs and symptoms of inflammation (rubor, calor, dolor, edema, functio laesa, raised body temperature, increased white blood cell count [WBC], and C-reactive protein [CRP]). Suspected disorders on certain anatomic sites such as the great vessels or visceral organs cannot be exclusively confirmed by clinical examination and warrant further radiologic workup. Generally, the aim of imaging is to confirm the clinical suspicion, define the grade and extent of inflammation, and detect complications such as abscess or fistula formation in infection.

In cases of chronic inflammatory disorders, the generalized signs of inflammation are frequently masked: the body temperature is normal or only slightly elevated, and hematologic testing (WBC, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]) is highly variable. Imaging represents a particular challenge in these patients, since subsequent treatment is strongly influenced by the imaging results. The main questions, which have to be answered from a clinical point of view, are as follows:

a. Presence of active inflammation versus aseptic non-inflammatory changes, for example, granulation tissue
b. Extension of the inflammation
c. Regional anatomy
d. Development of local complications (abscess, sinus tracts, necrotic tissue)
e. Intensity of inflammation prior/during anti-inflammatory medication (therapy monitoring)

Imaging of inflammation can be accomplished with various imaging techniques. Computed tomography (CT) and magnetic resonance imaging (MRI) are most frequently used and provide anatomic maps with high spatial resolution. A certain degree of functional information can also be obtained by the use of standard x-ray or MR contrast media. MRI in particular has been recognized as a very useful modality for the detection of inflammatory disorders because of its capability to demonstrate anatomic details and pathologic changes of soft tissues and bone marrow with high spatial resolution and contrast. The common criteria used for delineation of inflammatory changes on MRI include the presence of an edema pattern on T2-weighted images and contrast enhancement after intravenous gadolinium application on T1-weighted images. Thus, MRI visualizes accumulation of interstitial fluid, hyperemia, and increased vascular permeability owing to the endothelial damage in inflammation. Vascularized granulation tissue in chronic inflammatory changes exhibits a similar signal and contrast behavior on MRI and cannot be reliably differentiated from noninflammatory aseptic changes after surgical or conservative treatment of any underlying disease (3–5).

**CONVENTIONAL NUCLEAR MEDICINE IMAGING**

Although radiologic techniques provide excellent structural spatial resolution, nuclear medicine procedures can assess the degree of disease activity based on physiologic and metabolic changes caused by underlying pathologies. Radionuclide imaging has proven its usefulness in the evaluation of patients suspected of harboring an infection, although the role varies with the individual and specific setting. The development of integrated single-photon emission computed tomography (SPECT)–computed tomography (CT) cameras has overcome to a certain extent the lack of spatial resolution in conventional nuclear medicine and allows detailed correlation of functional-metabolic information with high-resolution anatomic maps in CT by immediate digital image coregistration and fusion (6). By combining a dual-head gamma camera with low-end and increasingly mid- to high-end CT systems, sequential acquisition of SPECT and CT data has become possible in one session without moving the patient. Inflammation scintigraphy is carried out with radiopharmaceuticals, which all label one of the consecutive steps of the host response to the injury. Defense mechanisms include physical barriers against the penetration of germs, release of cytokines, regulation of adhesion molecules, activation of the complement cascade, and infiltration with inflammatory cells, most notably neutrophil granulocytes, lymphocytes, and macrophages, which undergo a so-called white cell burst reaction when actively fighting inflammation. The choice of the best radiopharmaceutical depends on the grade of inflammation, duration of infection, availability, cost, and radiation exposure. Currently used radiopharmaceuticals comprise the following:

a. $^{99m}$Tc-radiolabeled nanocolloids and human immunoglobulins (HIG)
b. $^{67}$Ga-citrate
foci. 67Ga also binds to lactoferrin, which is present in high concentrations in inflammation. Other mechanisms are uptake into leukocytic lysosomes and endoplasmatic reticulum and direct accumulation by certain bacteria. The normal biodistribution of 67Ga, which can be variable, includes bone, bone marrow, liver, gastrointestinal and genitourinary tracts, and soft tissues. It has been widely replaced by other radiopharmaceuticals because of the unfavorable physical characteristics (high radiation exposure, long examination time, reduced availability, and high energy gamma rays with subsequent low spatial resolution).

Radiolabeled Leukocytes

The development of in vitro radiolabeling of autologous leukocytes was a milestone in the evolution of infection imaging and is commonly performed with the lipophilic compounds 111In-oxyquinoline or 99mTc-HMPAO. Uptake of labeled leukocytes is dependent on intact chemotaxis, the number and types of cells labeled, and the cellular component of a particular inflammatory response. It still represents the gold standard for imaging of infection in nuclear medicine (9). Usually most leukocytes labeled are neutrophils, and hence the procedure is most useful for identifying neutrophil-mediated inflammatory processes, such as bacterial infections. One advantage is the extent of infection in surgical pathology is defined by the delineation of cellular inflammatory infiltrates, which can in principle be accomplished by leucocyte scans. The advantages of 99mTc-labeled leukocytes include a photon energy that is optimal for imaging, a high photon flux because more radioactivity is injected, and the ability to detect abnormalities within a few hours after injection. The instability of the label and the short half-life of 99mTc are disadvantages when delayed 24-hour imaging is needed. This occurs in chronic or low-grade infections for which several hours may be necessary for accumulation of a sufficient quantity of labeled leucocytes. Advantages of 111In are a very stable and constant normal distribution of activity to the liver, spleen, and bone marrow, and the 67-hour physical half-life allows for delayed imaging, which is particularly valuable in chronic musculoskeletal infection. Disadvantages of the 111In label include a low photon flux and the less-than-ideal photon energies.

99mTc-Radiolabeled Murine Monoclonal Antigranulocyte Antibodies (MAB)

Considerable effort has been devoted to developing in vivo methods of labeling leucocytes including antigranulocyte antibodies and antibody fragments. 99mTc-MAB binding to granulocytes shows an in vivo distribution quite similar to that of radiolabeled granulocytes (10,11). With these methods, granulocyte accumulation in the soft tissues and the appendicular skeleton can be imaged. The advantage of 99mTc-MAB is the simplicity of the labelling process of the antibodies with 99mTc and the ensuing in vivo labeling of granulocytes.

Several compounds are available, and one frequently used method makes use of a murine monoclonal antibody that is directed against the myeloid-specific antigen NCA 95 expressed by granulocytes. Another agent that has been investigated is a murine monoclonal antibody fragment of the IgG1 class that binds to normal cross-reactive antigen-90 present on leukocytes. Fanolesomab is an antigranulocyte antibody that is currently evaluated in the United States. It still represents the gold standard for imaging of infection in nuclear medicine (9). Usually most leukocytes labeled are neutrophils, and hence the procedure is most useful for identifying neutrophil-mediated inflammatory processes, such as bacterial infections. One advantage is the extent of infection in surgical pathology is defined by the delineation of cellular inflammatory infiltrates, which can in principle be accomplished by leucocyte scans. The advantages of 99mTc-labeled leukocytes include a photon energy that is optimal for imaging, a high photon flux because more radioactivity is injected, and the ability to detect abnormalities within a few hours after injection. The instability of the label and the short half-life of 99mTc are disadvantages when delayed 24-hour imaging is needed. This occurs in chronic or low-grade infections for which several hours may be necessary for accumulation of a sufficient quantity of labeled leucocytes. Advantages of 111In are a very stable and constant normal distribution of activity to the liver, spleen, and bone marrow, and the 67-hour physical half-life allows for delayed imaging, which is particularly valuable in chronic musculoskeletal infection. Disadvantages of the 111In label include a low photon flux and the less-than-ideal photon energies.

99mTc-Radiolabeled Nanocolloids and Human Immunoglobulins (HIG)

Nanocolloids (NC) are radiolabeled with 99mTc. This radiopharmaceutical has a favorable radiation dosimetry, high availability, and acceptable image resolution. Examination time is short (60 minutes), and the substance is easy to handle because neither time-consuming preparation, nor special facilities, nor technical expertise are needed. The mechanism of uptake in infection is the detection of increased vascular permeability with an interstitial extra-cellular distribution of the nanomolecules. Moreover, since nanocolloids are phagocytized by the reticuloendothelial system (RES), phagocytosis by local and activated macrophages may also contribute to local uptake. Phagocytosis of the reticuloendothelial cells leads to a physiologic uptake in liver, spleen, and bone marrow. The usefulness of NC in suspected acute infection of the extremities is well proven; however, clinical experience documents a limited value in chronic inflammatory infections. Other mechanisms of uptake in infection is the detection of increased vascular permeability with an interstitial extra-cellular distribution of the nanomolecules. Moreover, since nanocolloids are phagocytized by the reticuloendothelial system (RES), phagocytosis by local and activated macrophages may also contribute to local uptake. Phagocytosis of the reticuloendothelial cells leads to a physiologic uptake in liver, spleen, and bone marrow. The usefulness of NC in suspected acute infection of the extremities is well proven; however, clinical experience documents a limited value in chronic inflammatory infections. Other mechanisms are uptake into leukocytic lysosomes and endoplasmatic reticulum and direct accumulation by certain bacteria. The normal biodistribution of 67Ga, which can be variable, includes bone, bone marrow, liver, gastrointestinal and genitourinary tracts, and soft tissues. It has been widely replaced by other radiopharmaceuticals because of the unfavorable physical characteristics (high radiation exposure, long examination time, reduced availability, and high energy gamma rays with subsequent low spatial resolution).

67Ga-Citrate

67Ga-citrate has been used in infection imaging for more than 30 years. Several factors contribute to the uptake of this tracer in infection (8). About 90% of circulating 67Ga is in the plasma and bound to transferrin. Increased blood flow and increased vascular membrane permeability result in increased delivery and accumulation at inflammatory foci. 67Ga also binds to lactoferrin, which is present in high concentrations in inflammation. Other mechanisms are uptake into leukocytic lysosomes and endoplasmatic reticulum and direct accumulation by certain bacteria. The normal biodistribution of 67Ga, which can be variable, includes bone, bone marrow, liver, gastrointestinal and genitourinary tracts, and soft tissues. It has been widely replaced by other radiopharmaceuticals because of the unfavorable physical characteristics (high radiation exposure, long examination time, reduced availability, and high energy gamma rays with subsequent low spatial resolution).
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MAB is the induction of human antimouse antibodies (HAMA) in 3% to 10% of patients, which leads to an altered biodistribution when patients are reinvestigated (14). Other notable problems are similar to those incurred with 99mTc-HMPAO radiolabeled leukocytes. They are as follows:

a. Chronic low-grade infection, which is characterized by decreased granulocyte infiltration as compared with acute septic changes, may be missed and cannot be reliably distinguished from nonpurulent inflammation (15).
b. Postoperative granulation tissue may lead to false-positive scans (16).
c. Anatomic resolution is low in comparison with MRI, frequently leading to diagnostic inaccuracy in the preoperative assessment. The use of modern combined SPECT-CT systems may overcome this problem in the future.
d. The more mature precursor cells of the granulopoietic system as well as the vast nonactivated granulocyte pool residing in the hematopoietic marrow are also labeled, resulting in a noninfection-related uptake of the radio-pharmaceutical in axial skeleton, the liver, and spleen.
e. Unexpected ectopic, hemopoietic active bone marrow may arise in the appendicular skeleton after trauma, for example, at the former fracture sites, and this can give rise to false-positive studies (17).

PET Imaging with FDG

The role of PET has been examined in aseptic inflammatory processes, as well as in a wide variety of infections, and there is growing consensus about its importance in evaluating such disorders (18–24). FDG uptake and metabolism are elevated in activated inflammatory cells such as leukocytes, granulocytes, and macrophages. Visualization of the amount of activated white blood cells represents the parameter to define the grade of inflammation and apparently can be accomplished by FDG-PET. When exposed to certain stimuli, phagocytes (neutrophils, eosinophils, and mononuclear phagocytes) start metabolizing large quantities of glucose by way of the hexose monophosphate shunt, and their rates of oxygen uptake increase greatly, sometimes more than 50-fold (25). This change of the resting cells to activated phagocytes is known as “respiratory burst.” Energy-dependent, interrelated cellular defense mechanisms include migration, generation, and release of microbicidal agents and phagocytosis. The activation of phagocytes leads to the respiratory burst reaction and consequently to an elevated FDG uptake and glucose transporter activity, which can be visualized in clinical PET imaging. Since noninflammatory fibroblast-enriched granulation tissue does not show a significant increase of FDG accumulation (26), the FDG uptake specifically reveals the presence of activated inflammatory cells and reflects the grade of inflammation in acute and chronic inflammation. There are numerous advantages of using FDG-PET for imaging of infection:

a. Much higher spatial resolution in comparison with conventional nuclear medicine modalities
b. Cross-sectional imaging modality with reformatting options in all three imaging planes
c. High target-to-background ratio
d. High sensitivity to detect disease involved areas, particularly in chronic low-grade infections
e. Fast examination time (results available within 2 hours), reducing the degree of inconvenience to the patient and resulting in early reporting
f. No additional scans necessary, all-in-one technique
g. Low bone, bone marrow, and liver uptake, resulting in highly accurate scans in the central skeleton and body trunk
h. Relatively low radiation burden
i. High interobserver agreement
j. PET is an inherently quantitative imaging method, which therefore not only permits disease localization, but potentially also treatment monitoring.

One major drawback of FDG-PET in comparison with MRI has been the lack of anatomic landmarks, which made it sometimes very difficult to assign the lesion to a particular structure. However, the newly developed integrated PET-CT scanners provide the necessary anatomic information on FDG-PET scans with high spatial resolution. High-quality anatomic CT maps and FDG-PET scans are acquired in one study and allow functional-morphologic correlation by immediate digital imaging coregistration (27–32).

At present, other obvious disadvantages are the relatively high cost, the currently limited availability, and the lack of reliable differentiation of inflammation from tumor.

Infection and inflammation imaging with FDG-PET is not widely used yet, but this is not because of the limited diagnostic accuracy. Before proposing an evidence-based role for FDG-PET in daily routine practice, clinical questions have to be answered incorporating knowledge on the role of alternative procedures, and cost-benefit analyses are required today by most health organizations and insurances. Prospective studies in larger patient populations and cost-effectiveness analyses should be awaited. When the high diagnostic yield of FDG-PET is confirmed in larger prospective studies, it may become a cost-effective modality, since the number of noncontributing or additional tests is decreased and the duration of hospitalization may be reduced. Important indications may be fever of unknown origin, suspected focal infection/inflammation, patients with metallic implants, and autoimmune diseases. A substantial limitation will probably be the limited availability in urgent settings, which require immediate clinical decisions, since FDG-PET is not available on an emergency basis in most institutions for logistic reasons. Therefore, subacute or chronic forms of inflammation may be successfully examined by FDG-PET when waiting for 24 to 48 hours for a scan is acceptable. Monitoring of medical therapy is a promising subject of FDG-PET, which identifies therapeutic response earlier than is possible with modern cross-sectional imaging alone. In our experience, immunosuppressive therapy in sterile inflammation results in a fast regression of FDG uptake (33), whereas the effect of antibiotic...
treatment on FDG uptake is less evident and delayed and seems to be more complex (34). In our opinion, available studies and our experience demonstrate a high diagnostic yield of FDG-PET in inflammation imaging. We assume that, with the increasing availability of PET systems and a cost decrease in FDG, FDG-PET will become a competitive and very important imaging modality.

REFERENCES


Soft Tissue Inflammation: PET-CT and SPECT-CT Imaging

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Soft-tissue infections, eluding clinical detection, occur in many settings. Because their therapy depends on the type and extent of the infectious foci, knowing where the infection is located is very important. Imaging can define whether an infection is unifocal or multifocal, whether abscess formation has supervened, and whether soft tissue involvement alone is present or involvement of bones and joints has occurred. Positron emission tomography (PET) and integrated PET–computed tomography (CT) in soft tissue inflammation imaging are likely to become important imaging methods in patients with a suspected infected focus (Fig. 59.1). The current lack of widespread use has to do with the logistics involved: frequently emergency imaging is required, for which PET is not very suitable. Delayed PET imaging after institution of antibiotic therapy may not be very sensitive, so we do not advise the use of PET to detect infection in patients who have been receiving antibiotic therapy. Nevertheless, interesting data have appeared over the last few years on imaging of soft tissues. With increasing use of PET and better availability of fluorodeoxyglucose (FDG), FDG-PET is likely to become available even in emergency situations, and thus its use may increase in the next few years. As in tumors, anatomic location of a lesion is frequently important; thus PET-CT also is believed to be important in PET infection imaging. Experimental studies with FDG-labeled leucocyte PET-CT are promising. The future will show whether the experimental results can be transferred into clinical routine.

INTRODUCTION

As noted in the previous chapter, various imaging methods can identify infectious foci in the soft tissues. CT is the mainstay to detect inflammation and infection in the chest, and ultrasonography and magnetic resonance imaging (MRI) are probably used most frequently in patients with soft tissue infections in the musculoskeletal system. Such patients are dealt with in Chapter 60.

The most frequently used nuclear medicine methods to identify soft tissue foci of infection have been gallium imaging, imaging with labeled leukocytes (either with indium [In], technetium [Tc], or with Tc-labeled antibodies against leukocyte surface antigens), colloids, or nonspecific immunoglobulins. All these methods have drawbacks. Gallium (Ga) imaging (1), leukocyte imaging (2), or anti-granulocyte antibody imaging (3) all have a relatively poor spatial resolution; imaging of inflammation in the liver and spleen is difficult because of the normal accumulation of these radiopharmaceuticals in these organs. Nuclear imaging methods with these radiopharmaceuticals are lengthy procedures, typically requiring recurrent imaging over a 24-hour period. Moreover, swallowing of activity from sinus or upper respiratory infections leads to bowel activity in the absence of any intestinal disease. To aid interpretation, additional images of the head and chest as
well as repeated delayed images must be obtained. In patients with sepsis, the leukocytes are activated and migrate physiologically into the margimated pool of the lungs, so that a lobar pneumonia cannot be diagnosed with certainty.

The glucose analog fluorodeoxyglucose (FDG) has been demonstrated to accumulate in various infections (4–6), including abdominal abscess (Fig. 59.1) (7), brain abscess (8), lung abscess (9), lobar pneumonia (10), tuberculosis (11,12), Mycobacterium avium-intracellulare infection (13), mastitis (14), acute enterocolitis (15), and infectious foci in patients with acquired immunodeficiency syndrome (16). Compared with conventional nuclear imaging, FDG positron emission tomography (PET) appears to have several advantages. First, it is a relatively high-resolution tomographic method; second, it demonstrates only activated white cells, as only those take up FDG (see Chapter 58). Hence, infection imaging of the liver and the spleen with good contrast is possible; and third, the examination is relatively brief, providing definitive imaging results 1 to 2 hours after injection of FDG. It is therefore not surprising that a number of articles suggest an important role of PET in soft tissue infection. Furthermore, FDG also appears to be a more specific contrast agent than the extracellular fluid contrast agents used in MRI and computed tomography (CT).

In thoracic inflammatory disease, PET plays a minor role because of the excellent ability of CT to distinguish airspaces from soft tissues. However, recognizing inflammatory disease in the chest as an incidental finding is still relevant. In vascular infections, mycotic aneurysms and graft infections are very interesting indications for PET-CT. In graft infections, care must be taken not to be overly sensitive in image interpretation, because a foreign-body reaction to a graft or stent may cause mild but clinically irrelevant inflammation. Typically, a florid graft infection shows substantial fluorodeoxyglucose (FDG) uptake (Fig. 59.2). The lung is not an organ in

![Figure 59.1](image)

**Figure 59.1** Lesion in the left hemi-abdomen with a very FDG-active rim adjacent to the descending colon. In addition, the descending colon shows segmental FDG activity in coronal PET images (A). Axial PET (B), CT (C), and combined PET/CT (D) images demonstrate the close relationship between the lesion and the descending colon. Intraoperatively, colitis was found with covered perforation and development of an abscess. (See Cases 47 and 49).
which it is usually difficult to diagnose infection, but if lung FDG uptake is noted, it is always important to keep infection on the list of diagnoses. Little experience exists in the genitourinary system, as the renal collecting system contains much FDG, thus not providing good contrast to lesions in the kidneys and bladder. In identifying infected cysts in patients with polycystic kidney disease, FDG-PET/CT may help. Abdominal infectious disease is well diagnosed with PET; however, problems exist in the bowel because of considerable nonspecific uptake of FDG into bowel loops in many patients. The causes are usually not known, but in many instances, the uptake does not seem to reveal relevant pathology. Soft tissue and skin infections are readily recognized on PET images, but frequently these infections are emergency cases, and so few data exist. Finally, infection PET imaging seems to be valuable for the monitoring of disease activity, and few but promising infection PET data exist in patients with acquired immunodeficiency syndrome.

In this and the following two chapters, we deal with soft tissue and bone infections, whereas sterile inflammatory processes of soft tissues in rheumatologic diseases are discussed in Chapter 62. Infections of the brain are dealt with in Chapter 24. Inflammation in children is addressed in Chapter 66.

Our experience with PET-CT tells us that the combination is very useful when the identification of the anatomic location is important (i.e., whether a lesion is in the vessel wall or surrounding a vessel, or whether the lesion is in the soft tissues or adjacent bones). Some soft tissue infections or inflammations may be adequately imaged with single-photon emission computed tomography (SPECT)-CT; however, substantial data are still missing.

INFECTIONS IN THE LUNGS

Imaging diagnosis of lung infections is performed with conventional chest x-rays and CT. PET is excellent in finding infected lung foci, but such foci are currently found incidentally. Therefore, PET is not used for this purpose, and we do not address the use of PET extensively in such patients. The key incidental findings of pulmonary inflammation/infection are in patients with chronic bronchitis and reactive lymph nodes accumulating some FDG as well as FDG uptake into sarcoidosis. Though the former presents typically with spotted foci in the mediastinum, which have to be differentiated from tumorous lymph nodes in bronchial carcinoma (Chapters 38 and 39), the latter condition may be easily recognized in some cases by a "cauli-
flowerlike" biliary uptake pattern that is almost pathognomonic (see Fig. 38.10).

INFECTIONS IN THE CARDIOVASCULAR SYSTEM

FDG-PET infection imaging of the heart has not been explored, as the heart can have intense FDG uptake, thus making it impossible to be certain whether a myocardial accumulation is pathologic. Valvular endocarditis would be difficult to image because of the small structures involved. However, a preliminary report suggests that FDG-PET accurately detects infective endocarditis and may become a useful adjunct to echocardiography (17).

FDG accumulation in vessels and in the wall of the aorta can be observed regularly, and we must call this a normal finding, although some authors believe that such accumulation may correspond to vulnerable plaque formation (18–20) (see also Chapter 33). Activity in the vessels is due to incomplete clearing of FDG from the circulation (see Figs. 33.10 and 33.11), whereas weak aortic wall activity of grade 2 or less (see Fig. 33.9) is less frequently observed, and the reasons for its occurrence are unclear. It is important not to mistake this weak activity for a pathologic condition. Therefore it is suggested that when evaluating PET images with suspected vascular pathology, reading should not be overly sensitive, as sometimes is necessary in PET tumor imaging.

Patients with sterile vascular inflammation such as giant cell arteritis (see Fig. 62.2) or Takayasu arteritis may show FDG uptake at the sites of involvement, which in Takayasu arteritis is typically focal, whereas in giant cell arteritis, it involves extended stretches of the arterial tree rather symmetrically (see Chapter 62).

Mycotic aneurysm of the aorta is a life-threatening disease, especially when rupture occurs. The high mortality rate is due not only to the high rupture rate, but also to sepsis. When mycotic aortic aneurysm is diagnosed, early surgical intervention is mandatory (21). The anatomic location of the aortic infection is one of the main factors determining the surgical strategy (22). Typically, mycotic aneurysms show FDG-uptake in the wall of the aneurysm or in the adjacent inflamed soft tissues (Fig. 59.3). If the inflammatory aneurysm is not the only manifestation of a multifocal infectious disease, PET-CT is, in our experience, a very helpful tool in showing the multifocality (Fig. 59.4). PET may help in the decision-making process of whether to treat the patient with surgery or with antibiotics alone. We usually perform PET in these cases.

![Figure 59.3](image)

**Figure 59.3** A 58-year-old female patient with back pain, fever, and elevated inflammatory blood parameters. FDG-active tissue around an aortic aneurysm is clearly seen on the preoperative PET/CT images (A–D). Blood cultures were positive for pneumococcus. PET/CT follow-up examination 1 month after implantation of an aortic stent graft and antibiotic treatment shows complete regression of the FDG uptake (E–H). Patient had normal C-reactive protein at this time. (See also Case 54).
in combination with a CT angiography on a 16-slice or 64-slice CT scanner to provide the vascular surgeon with all informations that he or she needs for therapeutic decision making. CT angiograms are necessary to describe the localization, size, and extension of the aneurysm and the relationship to important structures such as the renal arteries or the intestine. Complications like infarctions (kidney, spleen), covered perforation, or dissections are visible with contrast-enhanced diagnostic CT imaging. Fusion of PET information with volume-rendered CT angiograms (Fig. 59.4) are very helpful for the vascular surgeon for operation planning. This “one-stop shop” approach might be the best way to image vessel infections, which need the combination of PET with a modern multidetector-CT.

The second important topic concerns vessel graft infection. Vascular or perivascular infections occur after trauma, after intravascular procedures, but mainly after implantation of vascular grafts, in which the foreign body implanted represents an increased risk for infection. Implantation of aortic endoprosthesis is increasing. Graft infection is a potentially life-threatening problem. Patients treated with extra-anatomic bypass grafting and aortic graft removal have an overall treatment-related mortality of 19% and an overall survival of 56% (23).

Conventional scintigraphy with \(^{99m}\text{Tc}\)-HMPAO-labeled leukocytes showed good results in detection of graft infections (24–26). CT alone is reported to be also very diagnostic (sensitivity 94%, specificity 85%) if findings such as ectopic gas, perigraft fluid, and increased soft tissue are taken into account (27). In some patients, CT-guided aspiration of fluid is necessary to confirm the diagnosis and to find the appropriate antibiotics. Although the clinical presentation may be typical and diagnostic in one patient, even MRI (28) and CT (27) may be misleading in another patient, delaying correct diagnosis and immediate treatment. Angiography is rarely useful to diagnose vascular infection; however, it may help to plan anticipated vascular distal reconstruction. Patients with vascular stents or grafts can exhibit a substantial inflammatory reaction in the graft or stent region, which results in FDG accumulation (Fig. 59.5). The FDG uptake noted in the entirety of this patient’s aortoiliac graft persisted over many months, as evidenced by a repeat scan. The moderate FDG accumulation is likely to be an expression of sterile inflammation generated by the implanted foreign body. Although this finding is not normal in the strict sense, such FDG accumulation does not represent infection. The two ways to avoid misdiagnosis are that one should not be overly...
sensitive in calling such accumulations positive, and involvement of the entire graft rather than focal uptake should make one suspicious that this is inflammatory disease rather than infection. The literature on the subject is largely anecdotal. In a study performed by our group (29), PET successfully excluded a suspected graft infection in five of seven cases and identified the two cases with infection. Although FDG-PET seems to be more specific than the other imaging modalities in this setting, the differentiation between a low-grade infection and physiologic foreign body reactions remains difficult, and reporting should take all the patient's clinical data into account such as age and material of the graft, symptoms, and laboratory findings. The PET-CT angiogram provides the vascular surgeon rather quickly with much more of the information he or she needs for therapy planning.

A pathologic vascular lesion should exhibit substantial FDG accumulation. On our arbitrary grading scale (0, background; 1, comparable to soft tissue accumulation; 2, comparable to liver uptake; 3, between liver and brain; 4, comparable to brain, see header of Part V), this would mean that FDG uptake must be distinctly higher than liver uptake on cross-sectional images and approach an uptake of 3 or more to be pathologic. It is important to understand what vascular disease the patient is suspected to have, because FDG accumulation noted after graft implantation may still represent a “normal” reaction, whereas in a patient with vasculitis, the FDG accumulation is pathologic. Because the vessel walls are relatively thin when compared with the resolution of even the best clinical PET scanners available, partial volume effect–induced reduction of FDG also may be present and thereby make the lesion appear less FDG active (see Chapter 33). Conversely, absence of FDG accumulation in a suspected infected graft also appears to be useful, as it strongly suggests that no infection is present.

FDG-PET/CT is promising and may play a role in better characterizing lesions in the vascular system suggestive of infection. The precise value of FDG-PET/CT (angiography) in this setting is not yet defined. Only case reports and no prospective study are available so far (30,31).

**Figure 59.5** Patient with a 1-year-old infrarenal aortoiliac graft. The patient was initially scanned for a right Pancoast tumor (A: PET-CT). This image shows an infrarenal vascular graft with moderate FDG uptake. The maximum-intensity projection (MIP) image (B) 6 months later shows successful tumor therapy, but FDG activity in the graft in its entire length persists. Proximal sections of the aorta are not seen. This represents moderate inflammatory reaction of uncertain significance induced by a foreign body. The transaxial PET image shows moderate circular activity (C), whereas on CT the aneurysmatically dilated aorta appears partly calcified (D). From comparing the images, it is likely that the inflammatory process involves tissue between the aortic wall and the implanted graft.
INFECTIONS OF THE GENITOURINARY SYSTEM

Only rare reports are available regarding infections of the genitourinary system because FDG accumulates in the kidneys and is partly excreted through the renal collecting system. Thus, distinction of a pathologic focus from normal FDG accumulation in these structures is not possible and makes FDG-PET not very useful. There is some spurious experience in patients with autosomal dominant polycystic kidney disease. These patients frequently have infections of one or some of the cysts, which is a serious complication. Neither MRI nor CT is perfect at pinpointing the infected cysts among the many noninfected ones that contain fluid or debris. A cyst taking up substantial amounts of FDG, even within it, may turn out to be the culprit lesion (32). Some of these patients have concomitant hepatic cysts, which can be infected as well. Bleeker-Rovers (33) described the detection of infected hepatic and kidney cysts in three patients.

INFECTIONS OF THE GASTROINTESTINAL SYSTEM

Infection detection in the gastrointestinal system by PET may have considerable value in some situations, but there can be very substantial FDG accumulation in normal bowel. FDG-PET imaging of inflammatory bowel disease may be sensitive, but a lack of specificity makes it probably less useful than initial reports have suggested (see Chapter 62). Acute enterocolitis has been reported to be detectable by PET (15,34,35). Colitis was confirmed in five of six patients with a segmental pattern of high FDG uptake in a study of Tatlidil (36). CT information can help in the diagnosis of inflammation: wall thickening, fluid collections, and stranding in the mesenteric fatty tissue are CT signs that are not 100% specific but suggestive in addition to the PET findings (Fig. 59.6).

We are very careful when calling bowel activity pathologic. When lesions are focal and can be clearly located to the bowel, which is much easier with PET/CT, this may represent pathology such as a colorectal carcinoma and we recommend endoscopy in all cases (see Chapter 44). In a study performed by our group, 13 (19%) and 29 (42%) of 69 patients with incidental FDG accumulations in the gastrointestinal tract were harboring cancerous and precancerous lesions, respectively. In 12 (17%) and 6 (9%) patients, inflammatory and benign gastrointestinal (GI) lesions were detected. According to our study, focally increased FDG uptake seems to be predictive of relevant pathologic findings on colonoscopy as 90% of the cancerous and precancerous findings and 50% of the benign findings were
characterized by focally increased FDG uptake ($p = 0.001$) (37).

Israel et al. (38) found 58 cases with incidental focal GI uptake in FDG-PET/CT of which two turned out as inflammation (one sigmoid abscess, one gastritis). If extended segments of bowel are involved with increased FDG uptake—which would be typical of inflammatory bowel disease—a specific diagnosis is often difficult to make. The activity may represent normal uptake into bowel, where “normal” is not further specified, as such uptake may well represent some subclinical bowel infection or inflammation.

Limited data exist on inflammatory changes in other organs and structures of the upper abdomen. We often see gastric uptake in the region of the cardia in asymptomatic patients and think that this finding is physiologic in most cases. Gastric FDG uptake can also be caused by infection, for example, with Helicobacter pylori (39). One article discussed the usefulness of detecting abdominal abscesses with FDG-PET (7). We detected an inflamed fistula between stomach and abdominal wall in a patient with a FDG-active “street” in the upper abdomen, indicating that FDG-PET is able to image fistulas (Fig. 59.7).

Suspected infectious disease of the liver may be a good indication for FDG-PET imaging. Reuter et al. (40) showed in 12 inoperable patients with Echinococcus multilocularis (the fox tapeworm) that PET may prove valuable in assessing disease activity. It was suggested that a positive FDG-PET scan may reflect parasite vitality in vivo and thus may potentially be used to decide on stopping long-term benzimidazole therapy in some inoperable cases. Parasitic viability in patients infected with E. multilocularis has proven to be difficult to assess by MRI and CT. Patients receive chemotherapy for very extended periods, and FDG-PET may be the method of choice to monitor disease activity, as one might expect that medication can be discontinued when FDG activity in the lesion is no longer visible. However, a second study by Reuter et al. (41) discourages the discontinuation of benzimidazole treatment in inoperable E. multilocularis patients even after many years of treatment, as 53% (8 of 15) of their patients had recurrent disease after 18 months. Our (yet unpublished) data confirm and complement these results. Figure 59.8 shows images of a patient with extensive affliction of the liver with E. multilocularis, and FDG activity on the perimeter of the polylobular cystic lesion suggests that further therapy is needed.

Bacterial infections of the liver and the biliary tree may well be identified on FDG-PET, but no literature exists on these diseases. Viral hepatitis have not been examined and are diagnosed on the basis of laboratory findings. Although FDG-PET is certainly not used to diagnose cholecystitis, this may be an incidental finding on an examination performed for other reasons (see Fig. 42.5). Splenic abscesses also can be visualized in PET, but in most
instances, FDG-PET of the liver and spleen provides no information beyond that obtained with MRI, which is very sensitive and relatively specific.

INFECTIONS OF THE SKIN AND CONNECTIVE TISSUES

Infections of the skin and the underlying connective tissue, the muscles, and bones are well recognized with FDG-PET. As musculoskeletal infection is a very important topic in itself, Chapter 60 is devoted to FDG-PET imaging in this disease group.

Most frequently, infections of the skin and underlying connective tissues do not require imaging, and if imaging is used, it is usually MRI. Because hyperemia/edema can occur without infection or in the vicinity of infection, PET and PET-CT imaging may be excellent in the planning of a therapeutic intervention in acute soft tissue infections. Depending on the depth of involvement, the therapeutic approach is very different. Unfortunately, few data exist, and for good reasons. Infections of skin and soft tissues are often acutely dangerous, and treatment must be instituted as soon as possible. Conversely, few institutions have the luxury of availability of FDG almost around the clock to permit emergency scanning as is available by CT and MRI. Thus, although FDG-PET may be an excellent method, the formidable logistics currently prevent its widespread use in this setting.

FDG-LABELLED LEUCOCYTES

A promising new method seems to be PET-CT imaging with FDG-labeled leucocytes. This approach combines cell-bound radionuclide trafficking from the blood pool compartment to the infection with the high image quality of PET-CT. Osman and Danpure (42) and Forstrom et al. (43) showed the feasibility of FDG labeling of autologous leucocytes successfully. Recently published data on rat models showed better results for $^{18}$F-FDG-leucocytes compared with $^{18}$F-FDG (44). This method needs further evaluation in prospective patient series.

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Musculoskeletal Infections: PET-CT and SPECT-CT Imaging

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Infections of bones and joints are severe diseases that can result in debilitating joint destruction, joint fusion, or bone and soft tissue defects. Early diagnosis is the key to successful therapy and prevention of complications. Commonly, infection is not limited to one compartment. Osteomyelitis and septic arthritis may be associated with soft tissue infections including cellulites, abscess formation, or fasciitis. Conversely, soft tissue infections may involve bones and joints. A good example is diabetic foot, which typically starts as soft tissue infection and then proceeds to bone and joint infection. The ideal imaging method should not only be sensitive and specific in the diagnosis of infection but also be topographically precise.

For assessment of soft tissue abnormalities, ultrasound and magnetic resonance imaging (MRI) are commonly used; for joints standard radiographs, ultrasound, and MR imaging; and for bones, standard radiographs and MR imaging. Both ultrasound and MRI are excellent in identifying effusion and soft tissue abscess formation. The cited imaging methods have many advantages, including topographic information, early detection of disease (MR imaging), or extent of bone destruction (standard radiographs). However, these methods tend to be nonspecific, and it may be difficult to differentiate infection from nonspecific edema, trauma, or neoplasm.

In this situation, radionuclide imaging can play an important role. Bone scans are sensitive in diagnosing bone and joint infections. Many institutions use labeled leucocytes as the standard of reference to identify infectious foci in the musculoskeletal system. Major weaknesses of this method are in imaging chronic infections and the axial skeleton (see Chapter 58). Similarly, antigranulocyte antibody imaging has a definitive role in imaging osteomyelitis of the peripheral skeleton. Integrated single-photon computed tomography (SPECT) and computed tomography (CT) may assist in the differentiation of increased uptake by using image coregistration. This is particularly promising in skeletal imaging.

Fluorodeoxyglucose (FDG) positron emission tomography (PET) has shown encouraging results for diagnosing both acute and chronic infection of the trunk and the extremities and seems to be more accurate in detecting chronic osteomyelitis than conventional functional imaging, including bone scan, antigranulocyte antibody imaging, and labeled leucocyte imaging (see Fig. 60.1). Whether PET has the potential to replace conventional scintigraphy completely depends on several factors, including cost and availability. FDG-PET makes use of the fact that there is no physiologic FDG accumulation in white blood cells not actively fighting inflammation. Therefore, granulocytes residing in the hematopoietic marrow do not demonstrate activity, which permits imaging of the axial skeleton. FDG-PET may be superior to MRI in distinguishing disc space infection from erosive osteochondrosis. Data with FDG-PET/CT concerning osteomyelitis in diabetic foot are controversial.

Experience with FDG-PET-CT and SPECT-CT in the musculoskeletal system is still limited, and more data have to be gathered before a definitive role in the imaging algorithms for infection can be assigned to them. Combined PET-CT improves the limited anatomic information of FDG-PET.
Musculoskeletal infections can be divided into infections occurring in the axial and the peripheral skeleton. Infections of the axial skeleton include sternal osteomyelitis, disc-space infection, and vertebral osteomyelitis. Osteomyelitis of the long bones and of the foot, for example, in patients with diabetic pedal ulcers belong to the group of peripheral musculoskeletal infections. Some patients with musculoskeletal infections have undergone osteosynthesis or have metallic prostheses. As presentation on positron emission tomography (PET) scans of these patients is somewhat special, there is a separate discussion of this topic in Chapter 61.

In children, involvement of the bones and joints of the peripheral skeleton is frequent (see Chapter 66). In adults, peripheral musculoskeletal infections occur frequently in patients with trauma and diabetes, but infections of the vertebral column become more common. Bone infections are typically hematogenous, but may also be caused by surgery, penetrating trauma, or by continuity, for instance, in ulcers found in diabetic feet.

Triple-phase bone scintigraphy is sensitive in the early diagnosis of infection. In addition, $^{67}$Ga, leucocytes and monoclonal antibodies are used to increase the specificity in cases of positive bone scintigrams (1). However, the need to use multiple tracers and to perform imaging at multiple times adds complexity to the procedure and is an inconvenience to patients.

A single imaging method, equally sensitive and specific, would be preferable. Magnetic resonance imaging (MRI) is accurate in the detection of musculoskeletal infections and is currently the most widely used imaging method in the workup of musculoskeletal diseases. MRI provides at the same time anatomic details and abnormalities of bone marrow, joints, and surrounding soft tissues with high sensitivity (2). It provides adequate spatial resolution and tomographic capabilities, which are required to distinguish between bone and soft tissue infection. Computed tomography (CT) has proven to be a useful adjunct to MRI in the detection of bone sequestration and identifies even small devitalized bony fragments. In this regard, CT is superior to MRI (2).

Recent publications on the use of fluorodeoxyglucose (FDG) positron emission tomography (PET) in chronic musculoskeletal infections suggest that this method is promising (3–5). In contrast to conventional nuclear infection scanning, PET results are obtained with a single scan obtained 40 to 60 minutes after injection of the radiopharmaceutical. Recently introduced combined PET-CT imaging may even be superior in musculoskeletal infection. PET is sensitive in demonstrating disease activity. CT demonstrates the precise anatomic location of the finding and alterations of bone structure. Similar aspects may be true for SPECT-CT cameras. However, the spatial resolution might be a limiting factor for the detection of small infectious lesions such as ulceration in diabetic feet.

**GENERAL REMARKS**

**MUSCULOSKELETAL INFECTION: PERIPHERAL SKELETON**

**Acute and Chronic Osteomyelitis of the Long Bones**

Osteomyelitis is a serious health problem that can result in severe morbidity and loss of function. Conventional radiographs may not be diagnostic because bone destruction and periosteal new bone formation in acute hematogenous osteomyelitis is typically noted only after approximately 2 weeks after disease onset, although acute infection may present earlier with subtle signs of abnormality such as periostial reaction or obliteration of fat planes between compartments.

Conventional scintigraphy is sensitive in detecting osteomyelitis. Three-phase bone scan is the procedure of choice if the suspected osteomyelitis is not superimposed on another disease causing bone remodeling. This means that standard radiographs should be normal. If the suspected osteomyelitis is superimposed on another disease associated with bone remodeling, leukocyte or granulocyte-antibody imaging is the procedure of choice in the nonhematopoietic marrow-containing skeleton, and leukocyte imaging and bone marrow scintigraphy are the procedures of choice in the hematopoietic marrow-containing skeleton (6).

Osteomyelitis may be classified as acute, subacute, and chronic. Acute osteomyelitis becomes chronic in 15% to 30% of cases. In contrast to acute osteomyelitis, subacute or chronic osteomyelitis is more difficult to diagnose with imaging. Subacute and chronic osteomyelitis with extensive tissue destruction is one of the most severe complications, which can occur after trauma with open fractures and orthopedic surgical interventions. Patients may present with relatively subtle symptoms for a long time. In contrast to acute osteomyelitis, inflammatory parameters such as C-reactive protein, erythrocyte sedimentation rate, and white cell count rate lack sensitivity, especially in the assessment of low-grade infections. MRI assists in the management of these patients, but it is of limited value for discriminating between active residual infection and simple postoperative changes. In addition, the image quality of MRI is severely affected by the presence of metallic implants in these patients (7) (See Chapter 61).

Because edematous and infected tissues are not readily distinguished on MRI, determination of the true extent of the infection is not easy. Edema surrounding active infection easily leads to overestimation of the extent of disease, potentially leading to medical overtreatment or to more extensive surgical intervention than absolutely necessary. Ledermann et al. (7) reported about 100% sensitivity but five false-positive findings with MR in 17 investigated regions in patients with proven chronic posttraumatic osteomyelitis. In patients with chronic osteomyelitis, CT may play an important role because it may demonstrate sequestration, fistulation extending into bone, and bone...
defects potentially important for surgical planning and stability of bone.

FDG-PET imaging is increasingly used in the diagnosis of acute osteomyelitis of the peripheral skeleton and may also be suitable in suspected chronic infection. In this diagnosis, PET may be useful because FDG is avidly taken up by activated macrophages, which are the predominant inflammatory cells in the chronic phases of infection.

In acute and subacute bone and soft tissue infections, FDG-PET is sensitive and specific. We found a sensitivity of 100% and specificities between 83% and 99% in bone infection (n = 18) (8). In the diagnosis of chronic osteomyelitis, FDG-PET seems to be comparably sensitive and specific. In a study by de Winter et al. (9), sensitivity, specificity, and accuracy in suspected chronic musculoskeletal infection of the peripheral skeleton (27 patients) were 100%, 86%, and 93%, respectively. Similar results were found in a study by Guhlmann et al. (10,11) and by Kälicke et al. (12) in patients with chronic osteomyelitis in the axial and peripheral skeleton. Zhuang et al. (13) demonstrated a sensitivity of 100% and a specificity of 87.5% with two false-positive findings in 22 patients. One of the false-positive patients had a tibial nonunion and the other had an osteotomy. It is well known that postoperative reparative tissue may present with increased FDG uptake. However, when wound healing proceeds properly, fibroblasts predominate and FDG accumulation quickly subsides (14). FDG-PET has a relatively high spatial resolution compared with other nuclear imaging techniques, but the anatomic information available in PET is still limited. PET/CT solves this problem and adds valuable anatomic information (Figs. 60.1 and 60.2).

Figure 60.1 PET-CT obtained several years after motorcycle accident with recurrent and increasing pain in the left lower leg and soft tissue tenderness over the tibia (A–D). PET demonstrates increased uptake in the soft tissue as well as in the bone marrow cavity of the tibia, suggesting the diagnosis of osteomyelitis, which was confirmed surgically.

Figure 60.2 Patient with left lower limb amputation and suspected chronic osteomyelitis in the distal part of the stump. Contrast-enhanced T1-weighted fat-suppressed MRI of the left distal bone stump shows moderate contrast media enhancement in the bone marrow (A). CT shows marked left leg atrophy (B). Coregistered PET-CT shows no FDG accumulation in the patient’s femoral stump (C). The clinical follow-up confirmed absence of osteomyelitis.
Osteomyelitis in Patients with Diabetic Foot Ulcers

Ulceration is the most common complication of the diabetic forefoot and accompanies more than 90% of cases of osteomyelitis of the foot (15). Early diagnosis of osteomyelitis in patients with diabetic foot ulcers is important because prompt antibiotic treatment has been shown to decrease the amputation rate. Clinical diagnosis is inadequate, as only 32% of the cases of underlying osteomyelitis in diabetic foot ulcers were detected clinically (16). Differentiation between diabetic osteoarthropathy (neuropathic or Charcot joint) and osteomyelitis is challenging for the clinician and radiologist. Even MRI may not be successful (17). Bone marrow edema and contrast enhancement on MRI is not specific for osteomyelitis. The standard of reference for this diagnosis is bone biopsy, which obviously is an invasive technique. The radionuclide study of choice for diagnosing osteomyelitis associated with diabetic feet is labeled leukocyte imaging. The reported accuracy is about 80% (18). New studies regarding PET/CT in osteomyelitis of the foot in diabetic patients are controversial. Keidar et al. (19) investigated 14 patients with clinical suspicion of osteomyelitis of the foot. 18F-FDG PET was highly accurate in their investigation. PET/CT accurately differentiated between osteomyelitis and soft tissue infection. They concluded that FDG PET/CT can be used for diagnosis of diabetes-related infection. Hopfner et al. (20) compared PET and MRI preoperatively in diabetic patients. PET was superior in differentiation between Charcot neuroarthropathy and osteomyelitis and also between infection and nonspecific inflammation of soft tissue. We have not been able to confirm these excellent results, however. We compared FDG-PET with antigranulocyte antibody scintigraphy and MRI in diabetic patients with chronic ulcers without clinical suspicion for osteomyelitis. FDG-PET was performed in 12 patients and FDG PET/CT in 8 patients. In seven patients, osteomyelitis was histologically proven. PET/CT and antigranulocyte antibody scintigraphy were positive in only two of seven patients with osteomyelitis. MRI made the correct diagnosis in all cases (21). Diagnostic accuracy was limited by motion artifacts and limited spatial resolution in relation to the size of the small structures on the forefoot. In addition, the quality of FDG-PET is affected by the level of circulating glucose and insulin. Measurement of blood glucose is important before scanning. Elevated glucose levels decrease FDG uptake because FDG and glucose compete for transporters. Insulin decreases blood glucose levels and increases skeletal muscle uptake of glucose and FDG. This may result in decreased uptake of FDG by activated leukocytes. Currently, FDG-PET/CT cannot be recommended as a routine imaging method in diabetic patients with suspicion for pedal osteomyelitis although it may contribute to the diagnosis. In Figure 60.3, PET/CT diagnosed osteomyelitis of the fourth toe and excluded this diagnosis in the fifth toe where MR imaging also suspected infection. In this case, the PET/CT diagnoses were confirmed by biopsy.

Soft Tissue and Joint Infections

Soft tissue infections may be caused by penetrating trauma or through ulcers such as those occurring in diabetes. Direct implantation of infectious agents may also occur after injections and after surgery. Hematogenous routes of infection may also occur, especially in immunocompromised patients. Different types of soft tissue infections can be found—cellulites, fasciitis, myositis, as well as diffuse forms—versus abscess formation. Characteristic clinical signs of soft tissue infections are swelling, redness owing to hyperemia, and tenderness.

To differentiate between soft tissue infection and osteomyelitis, three-phase bone scanning showing increased perfusion and blood pool activity may help. This distinction is difficult to make in 67Ga or leucocyte scintigraphy. Scintigraphic imaging suffers from comparably poor spatial resolution. This may produce problems in distinguishing the involved compartments, particularly in body regions with complicated anatomy such as the hands and feet.

FDG-PET is superior to conventional scintigraphic methods in distinguishing between soft tissue and bone infection owing to its better spatial resolution compared with standard scintigraphic techniques and owing to its tomographic capabilities. Guhmann et al. (11) demonstrated that differentiation between bone infection and infection of surrounding soft tissues was possible with PET in patients with suspected chronic osteomyelitis, for both the axial and peripheral skeleton. PET appears to be useful in the localization of an intramuscular abscess, which appears as a ringlike increased uptake of FDG (13). PET/CT adds precise anatomic information and thus improves the ability of PET to differentiate soft tissue from bone infection. An example is shown in Fig. 60.4 in a patient with suspected posttraumatic osteomyelitis of the right femur. In this case, MRI was equivocal because of metallic artifacts. PET/CT excluded osteomyelitis and identified soft tissue infection.

Septic arthritis may develop after joint aspiration or surgery, in association with osteomyelitis or by hematogenous spreading of infectious agents. Typically, septic arthritis is monoarticular. Polyarticular involvement may occur, especially in elderly patients. Early standard radiographs demonstrate joint effusion, followed by joint-related osteopenia and, if untreated, joint space loss owing to rapid destruction of articular cartilage. Ultrasonography can detect joint effusion and synovitis very sensitively. In addition, this method is useful in guiding fluid aspiration for bacteriologic examinations. MRI with intravenous contrast administration reliably demonstrates the abnormalities associated with septic arthritis (22), including joint effusion, synovial hyperemia and proliferation, reactive bone marrow and soft tissue edema, secondary
osteomyelitis, tendon abnormalities, and soft tissue abscesses. Bone scanning is a simple method to demonstrate all involved joints in suspected multilocular disease. Bone scans become abnormal within hours to days after the onset of joint infection and days to weeks before the disease becomes manifest on conventional radiographs. Some investigators have indicated that bone scans are relatively insensitive and nonspecific in the diagnosis of septic arthritis. \(^\text{67}\) Gallium may improve sensitivity to greater than 50%, which is still relatively modest. Combined studies of bone scintigraphy and \(^{67}\) gallium increased the sensitivity in diagnosing septic arthritis to 84% (23). The early and delayed phases of bone scintigraphy may demonstrate photopenia of bones adjacent to the infected joint. This typically occurs in the femoral head, indicating impaired blood flow caused by increased intraarticular pressure.

Although PET has the potential to detect septic arthritis (see Fig. 60.4), it may be too costly for use in septic arthritis, which mainly requires joint aspiration for identification of the infectious agent and later standard radiographs and MRI for demonstration of complications and structural damage. PET may instead have a role in evaluating and monitoring sterile inflammatory joint disease such as rheumatoid arthritis (see Chapter 62).

**MUSCULOSKELETAL INFECTION: AXIAL SKELETON**

Infections of the axial skeleton differ from peripheral infections in several respects, including age distribution, differential diagnosis, anatomic details, and type of bone marrow. Patients with disc space infection tend to be older than those with peripheral infection. Infections of the axial skeleton may occur by hematogenous route, after surgery, after injections, or by continuity, similarly to peripheral infections. The differential diagnosis may include inflammatory diseases typically associated with the central skeleton, such as ankylosing spondylitis with its typical localization to the sacroiliac joints and spine as well as SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis), typically found in the sternoclavicular region. The sternoclavicular, in part the acromioclavicular, and the sacroiliac joints, the pubic symphysis, and the connection between ribs and sternum as well as the intervertebral spaces do not have a classic...
joint space lined with articular cartilage and a synovial membrane, but represent a synchondrosis with fibrocartilage (or intervertebral disk, respectively). Such anatomic details influence the imaging appearance of inflammation.

In adults, peripheral bone marrow is predominantly fatty, contrary to the central skeleton where relevant amounts of hematopoietic marrow influences imaging appearance typically on MRI and in many scintigraphic methods. Finally, several of the central structures are not easily imaged because they tend to be localized far apart and may suffer from respiratory motion artifacts, influencing MRI.

Disc space infection typically starts with infection of the end plates of the vertebral bodies, but quickly extends into both the intervertebral disk and the adjacent soft tissue. The early diagnosis of disc space infection is important because this is a severe disease that may even lead to death if untreated and has a tendency for complications including abscess formation and deformity. In disc space infection, the current imaging method of choice is contrast enhanced MRI (24). However, MRI may be equivocal in early phases of disc space infection because this disease may resemble active changes associated with degenerative disease of the intervertebral space (so-called Modic I abnormalities). Both abnormalities are hypointense in comparison with normal bone marrow on T1-weighted images with signal increase on T2-weighted images, and enhancement after intravenous injection of gadopentetate can sometimes not distinguish degenerative end plate abnormalities (25, 26).

The lumbar spine is the most typical site of involvement (see Fig. 60.4). Nuclear medicine studies are reserved for those situations in which MRI cannot be performed or is not diagnostic. Standard bone scans do not reliably differentiate degenerative end plate abnormalities from infection. Modic
Figure 60.5 Patient with biopsy-proven disc space infection at level L5/S1. MR showed disc space narrowing on sagittal T1-weighted fast spin-echo (FSE) images (A) and signal increase at both end plates at L5/S1 intervertebral disc level. In addition, centrally located increased signal intensity is seen within the disc at level L5/S1 on sagittal T2-weighted FSE images (B). Sagittal T1-weighted fat-suppressed image shows contrast enhancement around the intervertebral disc at L5/S1 and adjacent bone marrow (C). Sagittal PET scan (D) demonstrates a focus of intense FDG uptake in the inferior aspect of L5 vertebral body. (See also Cases 44 and 50).

Figure 60.6 A 70-year-old patient with biopsy-proven colon cancer. PET/CT in prone position for radiotherapy planning. A: Sagittal PET image shows the FDG-active primary tumor of the colon (short arrow) and an FDG active lesion in the spine at level TH 7/8 (long arrow). B: Axial bone window of the CT image (C) and axial PET/CT fusion image show FDG activity in the vertebral body with osteolysis (long arrow) and FDG-active paravertebral soft tissue (short arrows). CT-guided biopsy made the diagnosis of clinically unsuspected disc space infection.
et al. (27) found a sensitivity and specificity of 90% and 78% for bone scans and 96% and 92% for MRI, respectively. The detection of chronic osteomyelitis in the axial skeleton with white blood cell imaging has sensitivities only in the range from 53% to 76% (specificity 56%–100%). The diagnostic performance is not better because of the physiologic radiotracer accumulation in hematopoietic bone marrow and frequently occurring photopenic areas of fatty marrow in the axial skeleton (28–30). Palestro et al. (31) have reported an accuracy of only 66% for 111indium-leucocyte imaging in vertebral infection. Compared with other radionuclide studies, FDG-PET appears to be superior in the detection of disc space infection. In 30 patients with substantial end plate abnormalities of the lumbar spine in MRI, FDG-PET was always negative in degenerative and always positive in infectious end plate abnormalities (4). Therefore, FDG-PET may be useful for excluding disc space infection in equivocal MR cases. The potential dilemma in the differentiation of degenerative end plate abnormalities from early disc space infection is demonstrated in Figure 60.5, where end plate abnormalities and disc hyperintensity on T2-weighted MR images without much contrast enhancement are present. The good performance of FDG-PET in differentiating degenerative from infectious end plate abnormalities is probably explained by the fact that granulocytes and macrophages are not prominent in degenerative disc disease, resulting in no or little FDG uptake. In infection, large numbers of polymorphonuclear leucocytes are present (32). Schmitz et al. (33) found that FDG-PET is sensitive in the detection of disc space infection and may depict paravertebral soft tissue involvement. Because of the compromised immune response of tumor patients, neoplastic and infectious lesions can occur in the same patient. Occasionally, infections are not suspected clinically because of atypical symptoms. Figure 60.6 demonstrates a clinically not suspected, histologically confirmed disc space infection in a patient investigated with PET/CT for staging of a rectal cancer.

Another diagnostic problem that may be solved is subacute osteomyelitis in patients with cardiothoracic surgery. The diagnosis may be delayed as the signs of the infection are masked by concomitant tissue injury. Radiographic techniques are often not conclusive, and cross-sectional anatomic imaging with CT and MR may be hampered by the artifacts caused by sternal wires. PET may be useful in suspected sternal osteomyelitis (Figure 60.7), although low-grade infection and reparative changes can be difficult to differentiate for many months after surgery, and we have become cautious in making the call of an sternal infection. SPECT/CT may be used alternatively for differentiation between deep and superficial sternal infections (34).

**SPECT/CT**

Alternatively, a combination of SPECT and CT may increase the specificity in detecting bone infection. Horger et al. (35) used immunoscintigraphy with 99mtechnetium-labeled antigranulocyte antibodies (AGA) to evaluate the value of SPECT/CT. SPECT/CT enabled differentiation between soft tissue infection, septic arthritis, and osteomyelitis, as well as between cortical, corticomedullary, and subperiosteal foci. Sensitivity was identical for SPECT and SPECT/CT (100%), whereas specificity improved from 78% to 89% by the use of SPECT/CT.

**SUMMARY**

PET promises to be a helpful imaging modality in bone, joint, and soft tissue infections because it is able to visualize infection both in the peripheral and axial skeleton and adjacent soft tissues without much interference by other FDG accumulations. FDG-PET is useful in both acute and chronic infection because FDG-accumulating granulocytes and macrophages are typically present in both forms of infection. FDG-PET may become the radionuclide procedure of choice of musculoskeletal infection in the future. Comparative studies are needed to evaluate in which indications PET is superior to MRI.
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The diagnosis of musculoskeletal infections in patients with metallic implants still remains a major challenge. Most imaging methods suffer from one or more limitations such as low sensitivity in detecting bone or soft tissue abnormalities and low specificity in differentiating infection from reparative tissue as well as implant-associated artifacts.

Radionuclide studies currently represent imaging methods of choice in patients with suspected infection in the presence of metallic implants. However, nonspecific tissue uptake of imaging agents and limited spatial resolution restrict their usefulness. Because of these problems, the diagnosis of implant-associated infection may be delayed. Revision surgery may have to be planned without definitive diagnosis. The interest in advanced imaging methods is, therefore, considerable. Fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging is both sensitive and specific in the diagnosis of implant-associated infections in trauma patients because FDG is taken up into activated white cells only. PET–computed tomography (CT) offers additional information as it provides precise anatomic information (see Fig. 61.1) and can identify sequestered bone fragments, which is relevant for surgical planning. Whether single-photon emission computed tomography (SPECT)–CT can replace PET-CT in institutions without PET-CT remains to be seen.

In contrast to use in patients with implants used for trauma surgery, PET and PET-CT may not be as useful in the diagnosis of infection in patients with hip and knee prostheses.

**GENERAL REMARKS**

The diagnosis of implant-associated infections in trauma and orthopedic surgery is difficult (1,2). Clinical signs and laboratory parameters may be uncharacteristic or even normal in so-called low-grade infections. Standard radiographs may demonstrate implant loosening, periosteal reaction, osteopenia, osteolysis, osteosclerosis, or sequester formation, depending on the stage of infection. However, in early and low-grade infection and in the diagnosis of abnormalities related to soft tissue, these signs may not be diagnostic. Ultrasound has its value in diagnosing abnormalities of bone surfaces and soft tissues, but is not useful in diagnosing intraosseous changes. Magnetic resonance imaging (MRI) and computed tomography (CT) tend to have degraded image quality in the presence of metallic...
implants owing to susceptibility and beam-hardening artifacts, respectively. Even when metallic devices are removed, small residual metallic particles can lead to susceptibility artifacts that can limit the interpretation of MR images.

In light of these considerations, nuclear medicine studies play an important role. Radionuclide imaging may be the most useful imaging modality for evaluating painful prosthesis, although the differentiation of aseptically loosened from infected joint prosthesis is not always possible. Standard bone scintigraphy represents an initial screening test. A normal bone scan rules out both septic and aseptic loosening. Bone scintigraphy is more sensitive than plain radiographs or arthrography (3,4) in the diagnosis of loosening. $^{67}$Gallium ($^{67}$Ga) imaging combined with bone scans was originally suggested for suspected implant-associated infection. Because of different radiotracer characteristics of $^{67}$Ga citrate imaging and bone scintigraphy, each study provides complementary information (5). However, the use of gallium has substantial limitations in this setting: as uptake also is found in postoperative reactive changes, which may be difficult to differentiate from postoperative osteomyelitis. $^{111}$Indium ($^{111}$In)-labeled white blood cells in combination with $^{99m}$technetium ($^{99m}$Tc) sulfur colloid marrow imaging has become the method of choice to assess infection in total joint replacement, as it allows correction for the abnormal leukocyte accumulation that may occur because of either displacement of marrow at the time of surgical implantation of the prosthesis or stimulation of the conversion of yellow to red marrow. Noncongruent radionuclide uptake in leukocyte and marrow scintigraphy with absent bone marrow uptake and accumulation of leukocytes is the most accepted criterion of infection (6–8).

Labeled leukocyte imaging alone has improved specificity in comparison with other imaging methods (9). However, leukocyte imaging cannot distinguish between the leukocytes of normal hematopoietic bone marrow and activated white cells. The diagnosis of osteomyelitis may be difficult in the axial and to a lesser degree in the peripheral skeleton. Labeled leukocyte imaging combined with bone scanning or bone marrow scanning is helpful in this setting, and the combination demonstrates higher sensitivities and specificities than leukocyte imaging alone (10). Fluorodeoxyglucose (FDG) positron emission tomography (PET) also has been shown to be very promising in this setting (Fig. 61.1), particularly in patients in whom bone anatomy has been altered because of the presence of posttraumatic bone deformity and in chronic infection (11–14). However, currently no tracer is equally satisfactory for all types of infections in the musculoskeletal system.

The use of FDG-PET in this setting has the potential advantage of being a single-step procedure with imaging 1 hour after the injection; other advantages are rapid loss of radioactivity from the patient and a radiation dose comparable with that of leukocyte-imaging techniques. Initial studies indicate that FDG-PET detects both loosening and infection and differentiates between them in both hip and knee prostheses. However, recent data are inconsistent and less encouraging (8,15–21). Metallic artifacts and foreign

![Image](A) ![Image](B) ![Image](C) ![Image](D)

**Figure 61.1** Images obtained two years after lumbar decompression and spondylodesis of the lumbar spine suspected of having a low-grade infection. Sagittal coregistered PET/CT scan shows activity in the region of the L1/2 intervertebral disc level (A). Axial unenhanced CT image shows artifacts in the region of the screws in the L1 vertebral body. In addition, bone destruction is noted (B). Axial PET shows two foci of increased FDG uptake on the right side of a lumbar vertebra (C). Axial combined PET/CT scan with increased FDG uptake in the region of the right cranial screw in the L1 vertebral body corresponding to osseous infection (D).
body reactions influence PET image interpretation in patients with prostheses (see also Chapter 59, e.g., Fig. 59.5).

METALLIC IMPLANT-ASSOCIATED INFECTIONS IN TRAUMA PATIENTS

In traumatology, osteomyelitis is a rare but serious complication after fracture stabilization with metallic implants. Despite important advances in surgical and long-term antibiotic treatment, osteomyelitis often remains refractory to therapy, leading to chronic illness. Infection is responsible for 5% to 10% of nonunions after fractures. Particularly in patients with nonunited fractures who have previously undergone surgery, the distinction between fracture instability and implant-associated infection may not be possible with the currently available imaging modalities (1,2).

Standard radiographs may demonstrate nonunion, sequestered bone, intraosseous abscess formation, and bone resorption at implant–bone interfaces in infection. They are not useful, however, for the diagnosis of early or low-grade infection. MRI sensitively demonstrates abnormalities of bone marrow and soft tissue if not hampered by susceptibility artifacts caused by metallic implants. However, reparative and infected tissue may be impossible to differentiate. This is also true for ultrasound, which is also limited to bone surfaces and soft tissue. CT more precisely demonstrates fragments and sequesters than standard radiographs, but is inferior to MRI in soft tissue and bone marrow assessment. CT also suffers from beam-hardening artifacts at the level of implants. Modified imaging techniques and protocols in MRI and CT decrease artifacts in the vicinity of metallic instrumentation (22–24), but do not provide perfect images.

In conventional nuclear medicine, the three-phase bone scan has been the accepted examination for the initial evaluation of osteomyelitis, but findings are affected by previous surgery and trauma and are often not specific. The limitations of spatial resolution are a relevant problem. Specificities of this combined technique, however, still vary between less than 50% and 100% (1,2,5,25). In labeled leukocyte combined with 99mTc methylene diphosphonate scintigraphy has been the method of choice for posttraumatic infection imaging at fracture nonunion sites (1). Sensitivities of 84% and specificities of 97% have been reported in the detection of osteomyelitis (26,27). This combined method improves the specificity of In-labeled leukocyte imaging alone by differentiating between soft tissue infection and bone infection at the fracture site.

In the last decade, In-labeled leukocyte combined with 99mTc bone marrow scintigraphy have been shown to be highly accurate for the diagnosis of various musculoskeletal infections that could alter distribution of bone marrow with sensitivities and specificities of 100% and 94%, respectively (10).

FDG-PET appears to have a sensitivity superior to that of combined leukocyte–bone marrow scintigraphy, particularly in chronic infections of the axial skeleton. FDG-PET also has practical advantages as FDG accumulates within 1 hour in the lesions, contrary to other infection-specific nuclear medicine modalities requiring multiple scans and imaging over a period of up to 24 hours because of the slow accumulation kinetics of these radiotracers. Furthermore, PET is a tomographic technique with substantially better spatial resolution than that of other scintigraphic techniques. FDG-PET may also provide a different type of imaging characteristics, as uptake of FDG in bone and bone marrow is relatively low. The available data suggest that FDG-PET better distinguishes between osseous and soft tissue infection than other techniques. This is relevant for the surgeon, as the operative approach differs greatly when osteomyelitis is present. Unlike MRI and CT (Fig. 61.2) (28,29), FDG-PET images do not show substantial implant-associated artifacts or tissue edema, which can interfere with image interpretation in patients with osteosynthetic metallic implants. These contrast with the findings in patients with hip and knee prostheses, as is discussed in the next section.

Published data of FDG-PET demonstrate a sensitivity of nearly 100% and a specificity in the range of 88% to 93% in the diagnosis of chronic musculoskeletal infections, including patients with and without metallic implants or prosthetic replacements (11–13). De Winter et al. (12) analyzed the use of FDG-PET in the diagnosis of chronic musculoskeletal infections in 60 patients. Thirty-four patients had metallic implants at the time of scanning. The overall sensitivity, specificity, and accuracy were 100%, 88%, and 93%, respectively. In two of four false-positive findings, surgery had been performed 6 months before the PET examination. It has been reported that postoperative inflammatory changes may show increased FDG uptake within the first 6 months (30). Lesions in the peripheral as well as in the axial skeleton were correctly identified with FDG-PET. Similar results were found by Guhlmann et al. (11), who examined six patients with suspected metallic implant-associated infection of a group of 31 patients with suspected chronic osteomyelitis. These authors reported an overall sensitivity, specificity, and accuracy of 100%, 92%, and 97%, respectively. The only false-positive finding was a patient with a soft tissue infection, which in PET was assigned to bone because of missing anatomic landmarks. Kälicke et al. (31) examined seven patients with acute osteomyelitis and eight patients with chronic osteomyelitis; FDG-PET was true-positive in all cases. FDG-PET was not affected by metal-like implants used for fixation of fractures. However, these authors reported a seemingly limited value of FDG-PET in the early postoperative phase because of unspecific tracer uptake. In concordance with these results, our own data demonstrated a sensitivity of 100% and a specificity of 93% with FDG-PET in the diagnosis of metallic implant-associated chronic infections in trauma patients (13). There was only a single false-positive finding.
in the soft tissue of a patient 6 weeks after surgery. No false-positive findings were seen because of metallic artifacts. In addition, in this study, the surgeons retrospectively assessed the influence of FDG-PET on their treatment decisions. They found that PET influenced the clinical decision-making process in almost two thirds of the patients.

A general limitation of FDG-PET is that the available anatomic information is limited. PET/CT imaging may further enhance the use of PET in trauma patients with suspected metallic osteosynthetic implant-associated infections in both the axial and peripheral skeleton. Preliminary experience of our group is promising, but larger series of patients are needed before the clinical use of this method can be recommended.

In addition, SPECT/CT may be a useful new imaging modality in trauma patients, which improves the limited anatomic information of planar scintigraphy alone. Infection was adequately detected in a patient with a lower spine osteosynthesis (Fig. 61.3).

**INFECTION IMAGING IN PATIENTS WITH HIP AND KNEE PROSTHESSES**

Infection is a serious complication of prosthetic joint surgery and can occur in up to 4% of patients (32,33). Therapeutic management of infected prostheses differs substantially from those with aseptic loosening. Patients with an aseptic prosthetic loosening frequently require...
only a single hospitalization with a revision arthroplasty, whereas infected prostheses may require multiple revision surgeries with additional antimicrobial therapy.

The diagnosis of prosthetic joint infection is usually made on the basis of the clinical findings, laboratory abnormalities, and radiologic findings. Unfortunately, no sensitive and specific test exists for the differentiation of aseptic loosening from infection in patients with arthroplasty. Inflammation parameters (e.g., erythrocyte sedimentation rate and C-reactive protein) may be elevated in both loosening and infection (34). Joint aspiration lacks sensitivity (35). Morphologic changes seen on standard radiographs are neither sensitive nor specific.

In nuclear medicine, three-phase bone scintigraphy is very sensitive and provides a high negative-predictive value. A normal bone scan virtually rules out septic or aseptic loosening. The type of prosthesis (cemented or cementless) may affect the degree and the site of radionuclide uptake. Although generally described as focal, the changes on the bone scan may be diffuse or focal in an aseptically loosened prosthesis. Diffuse uptake also may be seen with infection. Therefore, an additional test is required. To improve specificity of bone scintigraphy, a combination of bone and gallium scanning is often performed. This combination provides better results than bone scintigraphy alone, with an accuracy between 70% and 80% (36,37). Because bone and gallium uptake can be found both in infection and in nonspecific inflammation, the success rate of this combined technique is still relatively low. Specificities less than 80% have been reported (3,35).

Combined marrow scintigraphy with 111In-leukocyte and 99mTc-sulfur colloid provide the best results regarding sensitivities and specificities, which are between 86% and 100% and 89% and 94%, respectively (8,10). However, the accuracy of this technique varies considerably, and there are significant inconsistencies between reports. Scher et al. (38) described positive- and negative-predictive values of 54% and 95%, respectively.

The role of FDG-PET in the evaluation of painful hip and knee prostheses has been investigated extensively. As FDG-PET seems to be a sensitive and specific method for infection imaging, its use to differentiate between septic and aseptic loosening seems obvious. However, although initial reports suggested that FDG-PET could accurately identify the infected joint prosthesis, more recent studies are less convincing. In a study by Zhuang et al. (15), FDG-PET appears to be sensitive (90%) and specific (89%) in the diagnosis of infected lower-limb prostheses. A total of 74 prostheses (36 knee prostheses and 38 hip prostheses)
were examined. PET was more accurate for detecting infections in patients with hip prostheses than in patients with knee prostheses. PET images were interpreted as positive for infection if the tracer uptake was increased at the bone-prosthesis interface. Two false-negative findings were seen. In contrast, 10 false-positive results, mostly in patients with knee prostheses, were found. The reasons for these false-positive findings could not be explained. The interval between surgery and PET was at least 1 year, and postsurgical increased FDG uptake would no longer be expected. However, in another study by Zhuang et al. (39), activity around asymptomatic hip replacements can persist for several years after implantation, possibly owing to postoperative inflammation; these data are not reproduced by other studies (21). Chacko et al. (18) reviewed the results of 167 FDG-PET scans in patients suspected of having various, but mostly orthopaedic, infections. Accuracy of FDG-PET in 97 cases of suspected complicated orthopaedic hardware was 96% for hip prostheses, 81% for knee prostheses, and 100% for other orthopaedic devices. Several studies (18,19,21) have shown that FDG uptake as a sole criterion for diagnosing infection will result in false-positive findings in this setting because uptake in loosening can be as high as or even higher than uptake in infection.

Manthey et al. (17) suggested that PET is not only a useful tool for differentiating loosening from infected orthopaedic prostheses, but also is valuable in detecting inflammatory processes such as synovitis as they often found highly increased synovial FDG uptake around a knee arthroplasty, which was considered to be the cause of pain following arthroplasty. This also could explain the false-positive findings in patients with suspected infected prostheses. According to our own results (yet unpublished), increased FDG uptake in the synovial membrane was found in all patients except one patient with a painful total knee arthroplasty independent of the clinical diagnosis. In this study, PET/CT helped to demonstrate precisely if FDG uptake was located in the synovial membrane or in an extrasynovial location (Fig. 61.4). In agreement with the results of other studies (8), our data indicate that periprosthetic uptake is associated not only with infection. Extrasynovial focal uptake in our series was mostly found in patients with severe internal femoral malrotation. However, we had only three infections in our study. Moreover, FDG uptake was not related to pain location.

Findings of van Acker et al. (40) comparing FDG-PET, $^{99m}$Tc-hexamethyl-propylenediamine oxime (HMPAO), white blood cell SPECT, and bone scintigraphy confirm the high sensitivity of FDG-PET in patients with suspected infected knee arthroplasties. Focal uptake at the bone–prosthesis interface was used as the criterion for infection in PET. False-positive focal FDG uptake was seen in three patients with septic loosening and in another patient because of synovitis adjacent to the bone–prosthesis interface. The authors reported that FDG-PET offers no additional value to the highly specific combined $^{99m}$Tc-HMPAO white cell/bone scintigraphy in the detection of infected knee prostheses.

Data of de Winter et al. (12), Love et al. (8,20), and of our group (21) indicate that it is questionable whether FDG-PET is able to differentiate between aseptic and septic loosening. The largest series of patients with surgical confirmation of final diagnoses in patients with failed prosthetic joints was performed by Love et al. (8) who examined 59 patients (40 hip and 19 knee) with FDG-PET using a coincidence detection system and combined $^{111}$indium-labeled leucocyte and $^{99m}$Tc-sulfur colloid marrow imaging. The accuracy of FDG-PET for diagnosing...
prosthetic joint infection in this series was very low. Its range varied between 47% and 71% depending on different criteria used to evaluate the images. These results are similar to the 69% accuracy we obtained in our study in patients with suspected infected total hip prostheses (21). Combined $^{115}$In-labeled leucocyte and $^{99m}$Tc-sulfur colloid marrow imaging was more accurate (95%) than FDG-PET for diagnosing infection of the failed prosthetic joint. The difficulty in differentiating between aseptic and septic prothetic loosening can be explained by the remarkably similar histopathology of these entities, as the inflammatory reaction accompanying the infected prosthesis is identical to that present in aseptic loosening. The only difference compared with infection is that neutrophils are present in less than 10% of loosening-associated inflammation. We compared FDG-PET, standard radiographs, and three-phase bone scintigraphy in 35 patients suspected of having infection in their total hip replacements (21). We found that standard radiographs seem to be more sensitive but less specific with respect to infection, compared with three-phase bone scintigraphy and FDG-PET. FDG-PET was unable to differentiate between aseptic loosening and infection. An example is shown in Figure 61.5 in a patient with suspected low-grade infection of a right hip prosthesis. The standard radiograph shows a broken acetabular ring, but PET demonstrates circularly increased FDG uptake around the head and neck of the prosthesis. Histopathologic results demonstrated aseptical loosening with giant cells resulting from a foreign body reaction. In our investigation, localization of uptake was not used for the differentiation of infection. New data by Reinartz et al. (19) indicate that soft tissue uptake should be considered in the evaluation of infected hip prostheses.

The reason for the increased FDG uptake around the prosthesis in aseptic loosening is likely an inflammatory immune reaction to the prosthetic material. This reaction may in turn contribute to aseptic loosening. Mononuclear white cells exhibit a respiratory burst when fighting inflammation, which explains why increased FDG uptake is found in patients with septic as well as aseptic prosthetic loosening. Three of the five false-positive findings in our study had a loosened prosthesis at surgery, a foreign body reaction with macrophages and giant cells. Both types of cells accumulate FDG.

Image interpretation in patients with hip or knee prostheses seems to be more strongly affected by attenuation-correction–induced artifacts (see Chapters 7, 8, and 33) than in patients with osteosynthetic materials. When evaluating PET scans of hip or knee prostheses, it is therefore mandatory to include the unattenuated scans in these patients, as they exhibit fewer reconstruction artifacts (41). We found an apparently increased FDG uptake around the neck of hip prostheses in the attenuation-corrected images in regions where the prostheses were not surrounded by bone. Most likely the more noticeable artifacts in patients with arthroplastic metallic implants are the result of the different sizes of materials used when compared with the more slender and lighter materials and the frequent external fixations used in trauma patients (13). Heiba et al. (16) also found attenuation-induced artifacts in FDG-PET in two patients with total knee replacement. The artifacts were located in the joint space. Knowledge of these artifacts is important. Increased FDG uptake around a metallic implant should be verified in the nonattenuated images (Figs. 61.5 and 33.5). The artifacts are not less severe when using CT data for attenuation correction in PET/CT. Thus the value of PET/CT in such patients may be limited. Further PET studies in larger numbers of

**Figure 61.5** Patient with pain in the right hip, which turned out to be a loosened hip prosthesis rather than an infection. The sedimentation rate was slightly increased. AP radiograph of the pelvis shows a broken acetabular ring and a cranial migration of the prosthesis (A). Corrected (B) and and non–attenuation-corrected PET scans (C) show highly increased FDG uptake around the head, the neck, and the proximal shaft of the prosthesis. See also Case 45.
patients are necessary to clarify the value of FDG-PET in patients with prosthetic joint replacements.

SUMMARY

FDG-PET is an excellent method for the detection of metallic-implant–associated infections in trauma patients in both the axial and the peripheral skeleton. Differentiation between osteomyelitis and infection of the adjacent soft tissues may be better achieved with FDG-PET than with CT or MRI, because of better lesion-to-background contrast and because of prominent artifacts arising from metallic implants in CT and MRI. To assess the clinical impact of FDG-PET in this setting, prospective studies also evaluating the impact on the surgical strategy, including combined PET/CT scanning and larger patient populations, are needed.

Despite its limitations, combined leukocyte-marrow scintigraphy remains the imaging modality of choice for the diagnosis of infected joint replacements. SPECT-CT adds value in these examinations because it provides exact localization of the radiotracer accumulations. Although the current literature suggests that FDG-PET will assume increased importance in the detection of musculoskeletal infections, this technique will probably be of limited value in the differentiation of septic and septic loosened prostheses, as both disease entities show uptake of FDG.

Artifacts owing to the metallic implants mimicking infection are more prominent in arthroplastic joint replacements, which are typically larger and heavier than their counterparts used in trauma surgery. Artifacts are prominent independent of whether conventional or CT attenuation correction is used, and image interpretation in these patients requires mandatory analysis of the non–attenuation-corrected scans as well, because these scans show less-prominent artifacts.

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Because fluorodeoxyglucose (FDG) is taken up into activated granulocytes, lymphocytes, and macrophages, positron emission tomography (PET) has the potential to visualize not only infectious but also sterile inflammations that are present in active rheumatologic diseases. So far, the impact of PET on the diagnosis and follow-up of rheumatologic diseases is not yet defined. Promising results have been reported for large-vessel vasculitis. PET demonstrates increased uptake within large artery walls involved in vasculitis in patients with fever of unknown origin (see Fig. 62.1). If vasculitis is clinically suspected, PET may be superior in the evaluation of the extent and grade of activity of the disease compared with other imaging methods, including magnetic resonance imaging (MRI). PET combined with computed tomography (CT) angiography offers a “one-stop shop” approach that demonstrates not only the classical PET signs of vasculitis but also complications that have been classical indications for CT, including stenosis, aneurysm, or dissection. Physiological and atherosclerotic vessel uptake should be considered as differential diagnoses if vasculitis is suspected. Coregistered CT angiography can show atherosclerotic plaques, which helps to solve interpretation problems.

Rheumatoid arthritis is a common, chronic, and progressive disease. It has the highest incidence of all autoimmune diseases. Although some studies dealing with the use of PET in this disease have been done, further studies are needed to evaluate whether metabolic imaging with PET plays a substantial role in the imaging of these patients. PET has been discussed for the initial diagnosis and “staging” of the inflammatory process. Another potential application of PET relates to the monitoring of therapy when expensive new types of medication are being considered.

PET may also occasionally be useful in the differentiation of inflammatory abnormalities potentially mimicking other diseases, such as pulmonary nodules and lymphadenopathy. Experience with PET in systemic lupus erythematosus (SLE), ankylosing spondylitis, and Behçet syndrome is still very limited.

Bone scintigraphy, widely used for imaging patients with various types of arthritis, is very sensitive but unspecific in the diagnosis of inflammatory disease. In comparison with standard bone scintigraphy, single-photon emission computed tomography (SPECT) increases image contrast and improves lesion detection and localization. Evaluation of hot spots with multi-slice CT in the same session increases the specificity and can provide additional important information, such as the extent of bone destruction.
Vasculitis includes different diseases presenting with inflammation of the arterial wall. The 1992 Chapel-Hill consensus conference defined the vasculitides according to their pathological features and the size of the involved arteries (1). Conventional scintigraphy is not accurate in detecting vessel wall inflammation (2). The most important entities for imaging with PET are the large-vessel arteritides: giant cell arteritis (GCA) and Takayasu arteritis (TA). The diagnosis relies mostly on symptoms, laboratory tests, ultrasound, MRI, invasive pathologic and angiographic investigations, and clinical outcome after treatment. GCA affects patients older than 50 years and presents with new headache and elevation of erythrocyte sedimentation rate. Patients with TA usually present at younger age (younger than 40 years), often with a difference in systolic blood pressure between the arms and bruits over the subclavian arteries or the aorta as a result of stenosis (3–5). Polymyalgia rheumatica (PR) is a common illness in elderly persons presenting with proximal muscle pain and stiffness. There is clear evidence that vasculitis of medium-size and large arteries play an important role in PR. Positron emission tomography (PET) studies confirm the suspicion that in many patients PR is associated with subclinical large-vessel vasculitis. Moosig investigated 13 untreated patients with active PR and found increased fluorodeoxyglucose (FDG) activity of the aorta and its major branches in 12 patients (6). Patients with large-cell vasculitis may initially present with untypical and unspecific symptoms, like fever of unknown origin (Fig. 62.1). Diagnosis of vasculitis can be confirmed by typical abnormalities in a temporal artery biopsy, but temporal artery biopsy in vasculitis patients can be falsely negative (Fig. 62.2). An imaging method providing an overview such as PET is important, because the extent of extracranial vessel involvement in GCA is often clinically underestimated and may only be confirmed by autopsy results. Complications of large-vessel inflammation, including stroke, ruptured aneurysm, dissection, and infarction (kidney, heart), are rare but potentially life-threatening (7). Metabolic imaging with FDG-PET has the potential to confirm the diagnosis by visualization of the inflammatory process within the vessel wall. In decreasing order, GCA involves the aorta, the carotid arteries, and the upper and lower limb arteries. TA typically affects the aortic arch and descending aorta, the subclavian arteries, and the pulmonary arteries.

Large-vessel vasculitis has to be differentiated from physiological vessel activity. Mild FDG activity is commonly found within the wall of large vessels, most pronounced in the thoracic aorta of elderly patients (8). Active atherosclerosis is an important differential diagnosis for vasculitis. Atherosclerotic plaques are said to accumulate FDG (9). The pattern and grade of vascular FDG uptake has to be evaluated. FDG accumulation in active atherosclerosis appears to be more focally distributed, to be of mild grade, and to affect the upper and lower legs predominantly. Visualization of calcified plaques in low-dose computed tomography (CT) or soft plaques in CT angiography
in the area of vessel wall FDG activity make the diagnosis more likely. Intense, symmetric FDG uptake involving the large cervical and thoracic vessels is highly suspicious for a vasculitic process.

FDG-PET can be used in monitoring of therapy response. Apparently, there is a good correlation between inflammatory blood parameters and FDG activity in the vessel wall (10). Unlike in GCA, the inflammation parameters in TA do not necessarily reflect disease activity (11). In comparison to standard imaging modalities such as ultrasound or magnetic resonance imaging (MRI), FDG-PET has a number of advantages, including that it may detect vasculitis earlier than MRI (12). In addition, PET demonstrates the entire extent of vascular involvement during a single imaging session. PET is also investigator independent and therefore more reproducible than ultrasound. If it is combined with CT angiography performed with intravenous iodine contrast media, potential complications of vasculitis, including aneurysm, dissection, and stenosis, can be detected in a “one-stop shop” imaging approach.

The main indication of FDG-PET is an atypical presentation of large-vessel vasculitis, and it is also used to monitor response to anti-inflammatory treatment. It has the potential to reduce the time to diagnosis and to detect clinically and radiologically unsuspected but potentially life-threatening vascular involvement. Especially when it is used in combination with CT angiography, the number of conventional invasive angiograms may be reduced. PET can help to determine the most accurate location for biopsy.

Moderate vascular uptake should be interpreted cautiously, especially in elderly patients with atherosclerosis. All published studies concerning imaging in vasculitis have the limitation of lacking a standard of reference, because biopsy of large vessels and histopathological correlation is not practical in most cases.

PET IN RHEUMATOID ARTHRITIS

Rheumatoid arthritis has a high prevalence. It is a multisystemic often chronic progressive disease characterized by synovitis. FDG-PET as a metabolic imaging method seems to be ideal and promising for imaging patients with rheumatoid arthritis. Inflammatory joint activity is the most important clinical parameter that defines the clinical approach. Because patients are treated with expensive and potentially toxic medication, an accurate assessment to detect and quantify the activity and extent of synovial inflammation initially and during therapy is of great value. The possibility of multiplanar tomographic reconstruction of the whole-body PET scan and the relatively high spatial and excellent contrast resolution permit detection of synovial inflammation not only of peripheral joints but also of small vertebral articulations such as the atlantodental joint (Fig. 62.3) as well as bursae and tendons (Fig. 62.4). One major advantage of PET compared with other cross-sectional imaging methods and particularly MRI is its inherent whole-body imaging capability. Further, its ability to quantify metabolic activity suggests a future role for PET...
in the follow-up of patients, particularly the evaluation of response to therapy and disease recurrence (Fig. 62.5). Palmer et al. quantified inflammation in the wrist with gadolinium-enhanced MRI and FDG-PET in 12 patients receiving anti-inflammatory therapy (13). The volume of enhancing pannus in MRI and FDG uptake (SUV) were strongly associated with clinical findings in wrists ($p < .002$) but not with treatment outcomes ($p > .05$) (13,14). The potential clinical utility of these measures remains to be defined.

Extraskeletal manifestations in rheumatologic diseases can lead to interpretation problems due to the nonspecificity of PET: pulmonary rheumatoid nodules may be characterized by mild FDG uptake. Exclusion of coincidental malignancies, such as mildly active malignant lung cancers, by biopsy or resection is required (15).

Besides FDG, other tracers have been evaluated: first reports about the use of carbon 11 ($^{11}$C) choline are promising for quantitative imaging of proliferative arthritis (16).

**Figure 62.3** $^{18}$F-FDG-PET in rheumatoid arthritis. Synovitis of the atlantodental joint with increased $^{18}$F-FDG uptake (arrows).

**Figure 62.4** Rheumatoid arthritis. Polyarticular synovitis with tenovaginitis of the tibialis posterior tendon shown on MIP FDG-PET (A) and sagittal PET-CT (B–D). In addition, there is insertion tendinopathy of the Achilles tendon (E–G).

**OTHER RHEUMATOLOGIC DISEASES**

Experience with PET in systemic lupus erythematosus (SLE), ankylosing spondylitis, and Behcet syndrome is still limited. Nowak et al. observed increased FDG uptake in lymph nodes of patients with active SLE and patients with inactive SLE and concluded that immunologic activity may be enhanced not only in active but also in clinically quiescent disease (17). Thymic uptake was observed only in patients with active disease, suggesting that the
Figure 62.5  $^{18}$F-FDG-PET in rheumatoid arthritis. Polyarticular synovitis (arrows) and tenovaginitis (arrowhead) with increased FDG uptake (A–C). The patient underwent anti-inflammatory therapy. $^{18}$F-FDG-PET imaging was repeated 2 months later. Inflammatory activity was clinically reduced, reflected by a decrease in FDG uptake (D–F).

Figure 62.6  A 55-year-old female patient with lumbar back pain, polyarthralgia, and slightly elevated inflammatory blood parameters. MIP PET (A) and PET-CT show FDG activity in sternoclavicular (B–D), acromioclavicular, and lumbar facet joints (E–F). Findings are suspicious for SAPHO syndrome. Bone scintigraphy with SPECT-CT (G–N) confirmed these findings. (See Case 52.)
thymus plays an important role during periods of disease activity.

Whole-body MRI opens up new opportunities for imaging of multifocal musculoskeletal diseases and appears to be becoming a strong competitor to other whole-body imaging tools such as PET. Whole-body “staging” of patients with ankylosing spondylitis with MRI seems to be a promising method of detecting inflammatory changes, especially in the iliosacral joints and spine, at an early stage (18–23). Case reports show that identification of inflammatory lesions and follow-up during anti-inflammatory therapy with PET are possible. At present, to our knowledge, no studies comparing PET with MRI have yet been published (22).

Our own experience with PET in SAPHO syndrome is limited to a case where typical changes, including arthritis of the sternoclavicular joint, were detected incidentally during oncologic staging (Fig. 62.6). Whether PET can provide more information than bone scintigraphy in SAPHO syndrome has not been evaluated (24,25). Publications concerning PET in Behçet syndrome are limited to the brain (23).

Our experience with PET in inflammatory muscle diseases, including dermatomyositis, polymyositis, and inclusion body myositis, is limited to sporadic cases in which FDG uptake could be seen in inflamed muscles. It is conceivable that PET could assist in “staging” the extent of the inflammatory muscles and could guide any muscle biopsy required to confirm the diagnosis. It is well known that the risk of cancer is increased in patients with dermatomyositis and polymyositis (26,27). Associated cancers could also be detected with the help of PET.

Nevertheless, subsequent prospective studies with larger numbers of patients are necessary to correlate the findings on PET imaging with state-of-the-art MRI, ultrasound, and bone scanning to determine whether PET can improve the management of patients with rheumatologic disease.

SPECT-CT IN RHEUMATOLOGIC DISEASE

Bone scintigraphy is widely used in rheumatologic patients today to evaluate the extent and activity of inflamed joints (28). The differentiation between inflammatory processes, osteoarthritis, and tumor manifestations is still difficult due to the high sensitivity but low specificity of the method. Therefore, additional radiological studies are regularly needed following bone scintigraphy. The hybrid SPECT-CT cameras offer the opportunity to correlate functional information with morphology in one session (see Fig. 62.6H).

Figure 62.7 A 64-year-old patient with T4N2 breast cancer. A: Bone scintigraphy performed for tumor staging shows a hot spot in the lumbar spine. B: With the help of SPECT-CT, the hot spot can be localized exactly in the right L5-S1 facet joint. CT additionally shows typical degenerative changes associated with osteoarthritis (osteophytes, sclerosis, joint space narrowing). (See also Case 53.)
SPECT of the bone is the second most frequently performed SPECT examination in routine nuclear medicine practice, with cardiac SPECT being the most frequent. Compared with planar scintigraphy, SPECT increases image contrast and improves lesion detection and localization. Studies have documented the important additional diagnostic information provided by SPECT and SPECT-CT, particularly for avascular necrosis of the femoral head (29), for back pain (Fig. 62.7) (30), and for the differential diagnosis between malignant and benign vertebral lesions (31,32). In addition to an improved diagnostic accuracy, SPECT-CT considerably shortens data acquisition and provides the clinician with important additional information. Prospective studies are needed to define the therapeutic impact of SPECT-CT in rheumatologic patients.

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Clinical PET-CT and SPECT-CT: Miscellaneous and Pediatric Applications

The last part of this book is concerned with miscellaneous applications, which include some single-photon computed tomography (SPECT) and integrated positron emission tomography and computed tomography (PET-CT) applications that do not fit under a standard heading and warrant some discussion by themselves. Malignant disease is discussed in Part V, and this part covers benign disease conditions, but there is some overlap. Notably, benign thyroid and parathyroid disease as well as benign bone tumors are discussed here, but the reader should also refer to Chapter 37 on thyroid tumors and Chapter 51 on bone tumors, as imaging of benign conditions and imaging of malignant ones have similarities. There is a short (and admittedly inconclusive) note on SPECT-CT applications in the diagnosis of pulmonary thromboembolism, and the book ends with a discussion of pediatric applications, which overlap applications discussed in other chapters. It was decided to separate the pediatric part because many special
considerations arise when dealing with children. As SPECT, PET, and CT use ionizing radiation, the application of these modalities in imaging children has to be done with even more diligence than when evaluating adults, and alternative imaging modalities such as magnetic resonance imaging and ultrasonography need to be considered carefully.

As the applications of SPECT-CT and PET-CT will evolve and mature, some of these last chapters may be integrated into other chapters in future editions or be expanded or omitted. The approach chosen here is a reflection of the fact that SPECT-CT and PET-CT are still very fast evolving technologies.
INTRODUCTION

The thyroid gland normally is located in the anterior lower neck. Substernal extension into the superior mediastinum may occur. Nuclear scintigraphy provides functional information about the gland, whereas cross-sectional imaging, including ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), provide predominantly anatomic information. The commonly used radiotracers for scintigraphic studies are technetium 99m \(^{99mTc}\) pertechnetate, iodine 123 \(^{123I}\), and iodine 131 \(^{131I}\) (1,2). Planar thyroid scintigraphy is a very commonly used technique in nuclear medicine in the workup of thyroid disease, while single-photon emission computed tomography (SPECT) is utilized infrequently for this purpose. The application of thyroid scintigraphy SPECT is mainly restricted to thyroid volume estimation.

SPECT and PET in Benign Thyroid and Parathyroid Disease

Ujwal N. Bhure  Daniela B. Husarik

The role of integrated single-photon computed tomography (SPECT) and integrated positron emission tomography (PET-CT) in imaging thyroid and parathyroid disease is still largely undefined. SPECT and SPECT-CT in thyroid disease may play a role in dosimetry prior to radioiodine therapy, but dosimetry is more relevant in malignant thyroid disease, which is treated in Chapter 37. While PET and PET-CT have no role in thyroid disease per se, incidental fluorodeoxyglucose (FDG) uptake is occasionally noted on PET and PET-CT scans performed for oncology staging. Focal disease represents a malignancy in almost 50% of cases (see Fig. 63.1) and therefore requires invasive diagnosis, while diffuse disease indicates thyroiditis, which has to be worked up according to standard clinical practice.

Parathyroid imaging with SPECT and SPECT-CT is a relevant imaging modality, particularly in the identification of parathyroid adenomas in recurrent parathyroid disease. SPECT provides better localization and better differentiation from thyroid tissue and therefore is evolving into a standard imaging procedure. Whether the anatomic information provided by SPECT-CT adds clinical value has not yet been determined. There have been reports that imaging performed with carbon 11 \(^{11C}\)methionine is useful for identifying parathyroid adenomas and may be superior to standard radionuclide imaging. Unfortunately, this seems not to be the case with fluorine 18 \(^{18F}\)ethyl tyrosine, another PET amino acid uptake and metabolism tracer.

THYROID VOLUME ESTIMATION WITH SPECT AND SPECT-CT

Thyroid volumetry is used for dose estimations for thyroid therapy. Although morphological methods permit excellent volumetry of anatomic volume, thyroid therapy with...
radioiodine requires functioning iodine volume. Hence, there is some value in using SPECT or SPECT-CT for this purpose. SPECT as planar scintigraphy typically uses a single intravenous administration of 120 MBq of \[^{99m}Tc\]pertechnetate. With the patient in supine position, a 180 degree anterior rotation (starting from the 270 degree position) is completed, with 32 azimuths at 25 seconds per azimuth. It is advantageous to use transmission correction either with transmission sources such as gadolinium 153 (\[^{153}Gd\]) transmission line sources or CT when a SPECT-CT camera is used. Transmission scans are reconstructed using filtered back-projection and are corrected for downscatter of \[^{99m}Tc\] into the \[^{153}Gd\] window. For the emission scan, an iterative maximum likelihood reconstruction algorithm with attenuation correction and window-based scatter correction as well as resolution recovery is typically used. For noise reduction, a 3-D edge-preserving 3 × 3 × 3-point median filter is applied (3).

Various algorithms for identifying the thyroid volume on SPECT have been utilized. One established method is to use the largest transaxial cross-section of the thyroid and then draw a region of interest (ROI) of 4 × 4 pixels in the center of the larger thyroid lobe. If both lobes appear equally large, the right lobe is chosen. Within this ROI of maximum activity, the average pixel value is calculated. A threshold of 45% of this value is used for the segmentation of the thyroid gland. This threshold has been established in patient studies using a minimal mean squared error method (3).

A similar procedure can be used with SPECT-CT, but the anatomic information provided by the CT data will allow for much more precise edge detection. Because iodine dose is dependent on many factors besides thyroid uptake, the additional precision of volumetry of functioning thyroid tissue may not be relevant clinically for dose determination, and so the additional effort expended on dosimetry with this method in benign disease is mainly of scientific interest, while in malignant disease the clinical relevance may be higher (see Chapter 37).

**THYROID PET**

Although a benign disease of the thyroid is not an indication for PET per se, FDG partial- or whole-body PET performed for tumor staging in other diseases does sometimes detect incidental thyroid lesions. Metabolic activity detected on PET is not, however, specific for malignancy but also demonstrates infectious and inflammatory disorders (4). The mechanism of FDG uptake in the thyroid gland is not known. Lymphocytic infiltration is a histologic characteristic of chronic thyroiditis. It has been reported in conditions with activated lymphoid tissue, such as sarcoidosis, Warthin tumor, and reactive lymphadenitis, and the same mechanism may be at work in chronic thyroiditis (5,6). The identification of such diffuse uptake should prompt further assessment of the thyroid. The growing number of PET examinations will likely lead to detection of an increased number of incidental thyroid lesions in patients without clinical symptoms. Concurrent with the etiology of thyroid disease, the FDG uptake may be focal or diffuse.

**Focal FDG Uptake in the Thyroid**

Incidental thyroid nodules identified in routine FDG-PET for benign or malignant disease were reported to be present in about 2.3% of 4,525 PET studies of patients with no prior history of thyroid disease. Biopsy of 15 of the 102 positive patients revealed thyroid cancer in 7 patients (47%), and 6 patients (40%) had nodular hyperplasia (Fig. 63.1) (7). Consequently, such an incidental finding requires further workup. Gain-of-function mutations of the thyrotopin receptor (TSHR) gene have been invoked as one of the major causes of toxic thyroid adenomas. \[^{18}F\]FDG uptake was higher in these cases. Focal autonomous nodules are associated with focally enhanced glucose metabolism. Disseminated autonomous goiters show various patterns of focal or global hypermetabolism. Autonomous thyroid tissue caused by constitutive mutations of the TSH receptor is characterized by simultaneous increases in glucose and iodine metabolism (8).
Hence, the differential diagnoses for focal disease include a thyroid malignancy, a metastasis to the thyroid, and a benign nodular thyroid condition. Diagnosis can typically be made with fine needle aspiration.

**Diffuse FDG Uptake in the Thyroid**

While focal disease is more likely to be tumorous, diffuse disease is more suggestive of an inflammatory thyroid affection. Diffuse FDG uptake can be an indicator of thyroiditis such as Hashimoto or de Quervains thyroiditis. Obviously, because of its painless nature and the frequent initial lack of significant other symptoms, Hashimoto thyroiditis is more likely to be incidentally diagnosed by FDG-PET. FDG-PET is also positive in Graves disease and has been used to measure glucose metabolism in thyroid glands thus affected. FDG uptake was seen to be significantly higher in Graves disease patients than in controls. In these patients, FDG uptake increased with increasing antithyroid antibodies and shorter radiiodine half-life. Glucose metabolism is enhanced in the thyroid of Graves disease patients due not only to enhanced fractional blood volume but also to enhanced utilization. Whether lymphocytes present or thyroid epithelial cells utilize this surplus of glucose cannot be determined using in vivo PET measurements in humans. Still, the correlation of radiiodine half-life and glucose hypermetabolism suggests direct or indirect connections between glucose metabolism and hormone synthesis in thyroid cells (9).

Symmetrically increased uptake of FDG in the skeletal muscles and thymus is a clue for the diagnosis of Graves disease. The uptake of FDG in skeletal muscles is more specific in the psoas and rectus abdominis muscles. An increment of muscle FDG uptake may be responsible for the high peripheral glucose utilization seen in Graves disease (10). The enhancement of metabolic rate by thyroid hormone in target tissues is accompanied by increased glucose utilization, which in skeletal muscle and many other tissues is regulated at the level of membrane transport. Thyroid hormone may be an important regulator of the muscle/fat glucose transporter in skeletal muscle (11).

As diffuse thyroid uptake noted on PET is unlikely to be malignant, a workup of the finding usually does not require biopsy. Sonography and laboratory tests are adequate diagnostic tools in these patients (5,12,13).

**SPECT AND SPECT-CT IN PARATHYROID DISEASE**

Primary hyperparathyroidism (PHP) is a condition characterized by the overproduction of parathyroid hormone. It is a common endocrine disorder that occurs in about 1 in every 500 women and 1 in every 2,000 men over the age of 40 years (14). In the majority of patients (85%), a solitary adenoma is the underlying cause (15). Multiple adenomas and parathyroid hyperplasia are much less common, present in 4% and 10% of patients, respectively (16). Other rare causes include parathyroid carcinoma and parathyroid cysts. Only about 1% of cases of hyperparathyroidism are related to parathyroid carcinoma (17,18). There is general consensus that surgical excision is the treatment of choice for most cases of symptomatic and asymptomatic primary hyperparathyroidism, with a reported success rate of 90% to 95% (19). For successful surgery, exact localization of the lesion is considered to be increasingly important, particularly with advances in minimally invasive surgery, where accurate preoperative localization of the hyperfunctioning parathyroid tissue is essential for successful surgical treatment. The onus of identifying this hyperfunctioning parathyroid tissue falls on imaging techniques such as high-resolution ultrasound, radionuclide imaging, CT, and MRI. Radionuclide scintigraphy has proved to be a reasonably accurate method for locating parathyroid adenoma or hyperplasia (20), but the choice of method depends on the patient's state. As all imaging modalities have a relatively low sensitivity for the detection of parathyroid adenomas (21), the major use of imaging is still in cases recurrent disease, and many advocate using only ultrasonography when a patient presents with the first manifestation of hyperparathyroidism. Scintigraphic methods are unequivocally advocated in recurrent hyperparathyroidism for two reasons: there is a higher complication rate in reoperation, demanding accurate preoperative localization, and morphological imaging is compromised by scarring (22).

**Ectopic Parathyroid Glands**

Parathyroid glands located in an ectopic site (EPGs) account for 4% to 10% of cases of hyperparathyroidism. The prevalence of ectopic adenomas can be as high as 20% (23), and this condition represents one of the most frequent causes of surgical failure. Ectopic inferior parathyroid tissue is a well-established entity responsible for 10% to 13% of all cases of hyperparathyroidism (24,25). Such tissue can result from the carotid bifurcation at the angle of the mandible to the base of the heart according to the developmental and migratory aberrations. Rare sites include the carotid sheath, vagus nerve, thyroid, retroesophageal region, thymus, thyrothymic ligament, mediastinum, aortopulmonary window, and pericardium (17). When routine exploration for parathyroid disease yields inconclusive results, a thorough search must be conducted along the line of descent of the inferior parathyroids, with possible excision of the thymus and thyroid.

**Radionuclide Parathyroid Imaging**

Subtraction techniques using $^{[99mTc]}$sestamibi and $^{[99mTc]}$per technetate or $^{123I}$ show a sensitivity in the localization of parathyroid adenomas from 68% to over 90% (26). The dual-phase (single-tracer) technique using $^{[99mTc]}$sestamibi (27) proved to be reliably accurate and easy to perform. Its reported sensitivity in the preoperative localization
of parathyroid lesions is 89% to 95% (28–30). The simplicity of performance and high accuracy of the double-phase technique have made it the predominant technique used in clinical nuclear medicine for this condition.

Sestamibi is a cationic, lipophilic isonitrile derivative that was first used for myocardial scintigraphy (see Chapter 29). 

Sestamibi scintigraphy has the following advantages over thallium–technetium subtraction scintigraphy: simplified handling of a single radiotracer, short half-life, good imaging quality, low risk of irradiation (31), dual-phase acquisition capability, and capability for 3-D assessment with SPECT (27,32,33). However, it has some limitations. It does not allow the specific evaluation of the thyroid gland. R. Tailliefer, the technique inventor, himself realized these problems and soon suggested complementing the delayed images with optional thyroid imaging with 

In a meta-analysis by Castellani et al. (34) of data for 1,297 patients from over 25 studies with PHP, the sensitivity for the detection of parathyroid adenoma was 78% (range, 53% to 94%) with a thallium–technetium scan, 82% (range, 74% to 94%) with a dual-phase 

The addition of CT to radionuclide scintigraphy has been proven to exhibit enhanced sensitivity and accuracy in locating abnormal glands (35,36). Any improvement in preoperative localization procedures can decrease the risk of missing enlarged parathyroid glands. MIBI-CT image fusion has a sensitivity of 93% and a specificity of 99% in correctly detecting the position of enlarged parathyroid glands (37). MIBI-SPECT-CT image fusion had higher overall accuracy (p < 0.0001) than MIBI-SPECT. MIBI-SPECT-CT image fusion also had higher sensitivity and specificity (p < .001) in predicting the site and side than MIBI-SPECT (37).

A solitary focus of increased tracer uptake with delayed washout in late images is characteristic of a parathyroid adenoma (Fig. 63.2). The presence of more than one such focus of increased tracer uptake favors the diagnosis of hyperplasia or multiple adenomas, for either of which unilateral neck exploration is unsuitable. SPECT is useful for lesions not well demonstrated with the conventional technique and for patients undergoing reoperation. There are several nonparathyroid entities that take up 

The positivity of scintigraphy does not simply depend on adenoma size or serum PTH levels but is also related to the number of oxyphilic cells that are rich in mitochondria (34). Parathyroid hyperplasia, multi-site parathyroid disease, and concomitant thyroid and parathyroid disease remain potential hurdles for this scintigraphic technique (17).

**SPECT-CT**

The addition of CT to radionuclide scintigraphy has been proven to exhibit enhanced sensitivity and accuracy in locating abnormal glands (35,36). Any improvement in preoperative localization procedures can decrease the risk of missing enlarged parathyroid glands. MIBI-CT image fusion has a sensitivity of 93% and a specificity of 99% in correctly detecting the position of enlarged parathyroid glands (37). MIBI-SPECT-CT image fusion had higher overall accuracy (p < 0.0001) than MIBI-SPECT. MIBI-SPECT-CT image fusion also had higher sensitivity and specificity (p < .001) in predicting the site and side than MIBI-SPECT (37).

**Image Interpretation**

A solitary focus of increased tracer uptake with delayed washout in late images is characteristic of a parathyroid adenoma (Fig. 63.2). The presence of more than one such focus of increased tracer uptake favors the diagnosis of hyperplasia or multiple adenomas, for either of which unilateral neck exploration is unsuitable. SPECT is useful for lesions not well demonstrated with the conventional technique and for patients undergoing reoperation. There are several nonparathyroid entities that take up 

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**Conclusion**

Scintigraphy plays an important role in the investigation of primary hyperparathyroidism. Preoperative localization is essential for the safety and efficacy of surgery, particularly in the present era of minimally invasive surgery. There is sufficient evidence that SPECT and SPECT-CT with 

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PARATHYROID PET

Additional imaging information would be desirable in patients with primary hyperparathyroidism if conventional scintigraphy and ultrasound failed to locate hyperfunctional tissue and in patients with secondary or tertiary hyperparathyroidism. The PET radiopharmaceutical [11C]methionine appears to be accumulated intensely in parathyroid adenomas (42–46). It was observed by autoradiographical methods that methionine accumulated in calcium-depleted rat parathyroids and that this accumulation was related to active incorporation of this amino acid into parathyroid hormone (47). Hellman et al. (46) reported that in 15 patients undergoing parathyroid reoperation, true-positive localizations were obtained with [1-methyl-11C]-methionine-PET in 87% of the cases. In a study by Otto, Boerner et al. (42), more than 70% of all lesions in secondary or tertiary hyperparathyroidism were detected with [11C]methionine, whereas the detection rate with 99mTc-MIBI was below 50%. [11C]methionine PET has correctly localized abnormal parathyroid glands in most patients with recurrent hyperparathyroidism in whom conventional nuclear medicine techniques had been unsuccessful (44). PET offers advantages over single-photon imaging, including greater spatial resolution, the incorporation of tomography as a routine, and the use of labeled, naturally occurring substances that are more likely than analogs to behave physiologically. However, due to its limited availability, [11C]methionine PET does not have an established role in routine imaging for hyperparathyroidism. FDG does not accumulate in parathyroid adenomas, and in addition, in our experience, F-ethyl tyrosine, which can serve as a substitute for [11C]methionine as an amino acid analog in many diseases, also does not seem to accumulate in parathyroid adenomas.

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Integrated SPECT-CT Imaging in Pulmonary Thromboembolism

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Over the last years, the use of pulmonary ventilation–perfusion scanning with nuclear methods has been superseded in part by multi-detector computed tomography (CT) pulmonary angiography, in which pulmonary emboli can be demonstrated directly. With the advent of integrated single-photon emission computed tomography (SPECT)-CT, the complementary information obtained by CT angiography and perfusion SPECT may be relevant, because defects in the perfusion scan may readily point to anatomic emboli on CT. To what extent the combined approach will be useful has not been explored.

CLINICAL AND IMAGING WORKUP OF PULMONARY THROMBOEMBOLISM

Pulmonary thromboembolism (PE) is an important cause of mortality. Therefore, early and accurate diagnosis and treatment of PE is mandatory. However, the diagnosis of PE is often delayed or the problem even remains unrecognized. Although anticoagulation is an effective therapy, risks of the treatment are well known. Because of the difficulty of diagnosing PE on the basis of clinical signs, laboratory tests and imaging studies play an important diagnostic role in the evaluation of patients with suspected PE. Traditionally, ventilation–perfusion imaging in combination with a negative chest x-ray has been used for diagnosing PE. Most PEs do not result in radiographic changes. Chest x-ray is used to exclude other thoracic abnormalities that mimic PE clinically and can produce ventilation–perfusion abnormalities. In case of an abnormal chest x-ray, nowadays multi-detector computed tomography (CT) angiography of the pulmonary vessels is performed as the first imaging technique in many institutions. It has been recognized that ventilation–perfusion scanning is not cost-effective, as it is nondiagnostic in many cases if the chest x-ray is abnormal. Therefore, multi-detector CT has become an important part of the diagnostic workup for PE (1).

In most cases, multiple pulmonary emboli occur rather than a single embolus. The emboli usually resolve after lysis, and the involved vessels return to normal. However, in some patients the emboli do not fully resolve. After repeated PE, the patient may develop secondary pulmonary artery hypertension (PAH). PAH can be caused by several different mechanisms. However, in some cases the cause remains unknown. It is important to understand the underlying cause of PAH in order to choose the appropriate treatment. The treatment of patients with primary PAH consists of supportive medical therapy and lung transplantation. In patients with secondary PAH, if the organized thrombi are present at the level of the main or lobar arteries or at the origin of the segmental vessels, pulmonary thromboendarterectomy (PTE) is a potential curative treatment (2).

Chronic thromboembolic pulmonary hypertension (CTEPH) is more common than previously thought, with a cumulative incidence of 3.8% (3). CTEPH can be associated with a poor prognosis, depending on the severity of
pulmonary hypertension. If the mean pulmonary artery pressure (PAP) exceeds 30 mm Hg, the 5-year survival rate is only 30% (4). Because of the unspecific clinical symptoms of CTEPH, the different imaging modalities play a crucial role in the diagnosis. The traditional imaging techniques used to differentiate between primary PAH and chronic CTEPH are ventilation–perfusion imaging and pulmonary angiography (5). Recently, the potential of multi-detector CT in the workup has been recognized. Multi-detector CT enables recognition of chronically obstructed vessels and can also be used to exclude competing diagnoses and to confirm surgical accessibility of obstructed vessels (6).

**SPECT-CT IN PULMONARY THROMBOEMBOLISM**

In our experience, the combination of functional and anatomic imaging in patients with PAH can provide a noninvasive one-stop shop for the evaluation of disease. Image fusion of ventilation–perfusion single-photon emission computed tomography (SPECT) and high-resolution CT, including CT angiography, provides information that is necessary for treatment decisions and cannot be obtained by perfusion scintigraphy alone (Fig. 64.1). The thrombi can easily be depicted by CT angiography. The perfusion defects in the perfusion SPECT offer hints as to which areas should be closely evaluated with CT. The CT finding of enlarged bronchial and nonbronchial systemic arteries can support the diagnosis of CTEPH, since these vessels are more often found in CTEPH than in other etiologies of pulmonary hypertension (7). Other important findings can be depicted by CT in a combined examination, such as venous occlusive disease. The roles of integrated SPECT-CT in the diagnostic algorithm for PE are currently evolving.

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PET-CT and SPECT-CT of Benign Bone Tumors

Abbas Yousefi-Koma  Klaus Strobel

Benign bone tumors are commonly noted in children and young adults. They can be classified into bone-forming, cartilage-forming, connective tissue, and vascular lesions. Plain films often suffice for the characterization of nonaggressive benign bone lesions, and additional imaging and biopsy is superfluous. Discrimination between benign and malignant bone tumors is crucial because treatment is completely different: in most benign bone tumors, often no treatment or only follow-up imaging is performed; malignant bone tumors are treated with surgery, chemotherapy, radiation, or combined therapies. Unnecessary bone biopsies of benign lesions should be avoided.

Data on the use of positron emission tomography (PET), integrated PET–computed tomography (CT), and integrated single-photon emission computed tomography (SPECT)-CT in this field are very limited. Increased fluorine 18 fluorodeoxyglucose (18F-FDG) uptake in benign bone tumors, such as giant cell tumor or fibrous dysplasia (see Fig. 65.1), can lead to misinterpretation and a diagnosis of malignancy. Although FDG-PET-CT can be useful for distinguishing benign from malignant bone tumors and for assessing the grade of musculoskeletal sarcomas (see Chapter 51), there is a considerable overlap of standard uptake values (SUVRs) between the two groups. If the CT part of PET-CT studies is performed with a high-resolution technique on multi-slice scanners, the information obtained can be of great help in localizing and characterizing bone lesions. A special background in musculoskeletal radiology is useful for reaching the correct conclusions. In some situations, additional imaging with MRI should be considered.

SPECT and SPECT-CT have increased sensitivity and specificity compared with planar scintigraphy in conventional bone scanning. For the detection of osteoid osteoma or osteoblastoma, SPECT-CT seems to be the ideal imaging method.

GENERAL CONSIDERATIONS

Besides hemangiomas of the spine, osteochondromas, and enchondromas, most benign bone tumors are very rare. The primary aim of imaging bone lesions should be to reach a specific diagnosis in order to decide whether biopsy, surgery, or only observation is the best option for further management. Plain radiography is still the most important first-step imaging method in the diagnosis of bone tumors. In many locations with complex anatomy, like the spine or the pelvis, conventional radiographs fail to show the whole extension of a bone lesion. Multi-slice CT provides exact anatomic information about the center of a bone lesion (medullary, cortical, periosteal, parosteal), periosteal changes, sclerotic reactions, and cortical alterations (remodeling, endosteal scalloping, focal penetration).

PET-CT IMAGING

PET-CT is a promising tool for evaluating the biological behavior and histopathological grade of primary bone lesions in a noninvasive manner (1–3). Little is known about FDG-PET-CT in benign bone tumors and tumor-like lesions. It is very important for reporting PET-CT studies to know that there are benign PET-positive bone tumors: fibrous dysplasia, giant cell tumors, chondroblastoma, sarcoidosis, Langerhans cell histiocytosis, aneurysmal bone
cysts, and nonossifying fibromas (4–8). It seems that, in particular, histiocytic and giant cell–containing lesions often have SUVs greater than 2.0. Although FDG-PET-CT can be useful for distinguishing benign from malignant bone tumors and for assessing the grade of musculoskeletal sarcomas (Chapter 51), there is a considerable overlap of standard uptake values (SUVs) between the two groups (4,9,10). First results show that PET cannot overcome the clinical problem of discriminating between benign enchondromas and low-grade chondrosarcomas.

Dehdashti et al. evaluated 20 intraosseous lesions with FDG-PET and correctly diagnosed 14 of 15 malignant and 4 of 5 benign lesions with a cutoff value of 2.0 SUV. Thirteen of the malignant lesions were metastatic carcinomas. Aoki et al. investigated 52 primary bone lesions with FDG-PET and observed a statistically significant difference in SUV between benign and malignant bone tumors overall. However, a significant overlap of SUVs was observed in the two groups. SUVs greater than 2.0 were noted in all five giant cell tumors, all three chondroblastomas, three of six fibrous dysplasias, one sarcoidosis, one Langerhans cell histiocytosis, and one of three nonossifying fibromas. Schulte et al. investigated 202 bone lesions (70 high-grade sarcomas, 21 low-grade sarcomas, 40 benign tumors, 47 tumorlike lesions, 6 osseous lymphomas, 6 plasmacytomas, and 12 metastases of an unknown primary tumor). All lesions were biopsied. Using a tumor-to-background ratio cutoff level for malignancy of 3.0, the sensitivity of FDG-PET was 93.0%, the specificity was 66.7%, and the accuracy was 81.7% (1 1). Most cases of primary bone lymphomas, Ewing sarcomas, and osteosarcomas show a high uptake in FDG-PET. Chondrosarcomas are characterized by lower SUVs than possessed by other bone sarcomas. In general, cartilaginous tissue has a tendency to be hypovascular or avascular.

Cartilage tumors include enchondromas, osteochondromas, and chondrosarcomas. Histopathologic grades correlate well with the clinical outcome of the patients (12). Lee et al. evaluated 35 cartilage tumors preoperatively with FDG-PET. The mean SUV_{max} values were 1.1 for benign tumors, 0.9 for grade I chondrosarcomas, and 6.9 for high-grade chondrosarcomas (grades II and III). The authors calculated a positive predictive value of 82% and a negative predictive value of 96% for high-grade sarcomas with a cutoff SUV of 2.4 (13).

The role of PET or PET-CT in guiding the biopsy to the representative hypermetabolic foci of inhomogeneous bone lesions must be evaluated in further studies.
Giant Cell Tumors

Giant cell tumor is an aggressive benign tumor frequently showing local recurrence (in up to 50% of patients). The clinical presentation of the tumor is variable, and the progression of the disease is difficult to predict. Tubbs et al. evaluated 475 patients with giant cell tumors and found lung metastases in 13 (3%) (14). The overall mortality rate attributable to giant cell tumor was 23%. Strauss et al. evaluated 18F-FDG kinetics and gene expression in 19 patients with histologically confirmed giant cell tumor (15). All 19 giant cell tumors showed significant 18F-FDG uptake. The mean SUV was 4.6 (range, 1.8 to 9.4). The authors concluded that increased 18F-FDG uptake is mainly attributable to an enhanced vascular fraction and increased 18F-FDG transport. There was a close association between FDG uptake and the expression of genes responsible for angiogenesis. Aoki et al. measured an SUV of 4.64 ± 1.05 in 5 patients with proven giant cell tumors.

Fibrous Dysplasia

Fibrous dysplasia is a benign developmental disorder in which normal bone marrow is replaced by fibro-osseous tissue. Patients are often asymptomatic, and fibrous dysplasia is detected incidentally with the help of its distinctive radiography, CT, and bone scintigraphy findings. Fibrous dysplasia can lead to complications like deformity, pathologic fractures, and, rarely, malignant transformation. It can occur as monostotic or polyostotic disease. Polyostotic fibrous dysplasia is a component of McCune-Albright syndrome (16–19).

Aoki et al. found increased FDG uptake (SUVmax greater than 2.0) in three of six patients with fibrous dysplasia. There was no statistically significant difference in SUV between fibrous dysplasia \((n = 6, \text{SUV}_{\text{max}} = 2.05 \pm 0.98)\), osteosarcoma \((n = 6, \text{SUV}_{\text{max}} = 3.07 \pm 0.96)\), and chondrosarcoma \((n = 7, \text{SUV}_{\text{max}} = 2.23 \pm 0.74)\) (4). In another publication, the authors presented the case of a female patient with breast cancer in which the bone scan showed multiple focal uptakes due to polyostotic fibrous dysplasia. Figure 65.1 shows an interesting case in which a patient had sarcoma of the pulmonary artery and an incidentally detected FDG-positive \((\text{SUV}_{\text{max}} = 2.9)\) fibrous dysplasia of the proximal femur. The fibrous dysplasia was confirmed histologically to exclude metastasis of the sarcoma. All of the lesions were PET negative (20). Toba et al. described the case of a patient with fibrous dysplasia in the craniofacial bone without increased FDG uptake (21). One explanation for the different grades of

Figure 65.2  A 30-year-old man with chronic pain in the right shoulder since 1 year. A: On planar whole-body bone scintigraphy, the hot spot (arrow) is difficult to detect. B–D: On SPECT-CT images, the hot spot is easily visible and can be located exactly in the posterior part of the scapula. E: On a high-resolution axial CT image, the nidus of an osteoid osteoma is nicely demonstrated. The patient was treated successfully with resection of the lesion.
FDG metabolism of fibrous dysplasia may be that the turnover of the remodeling process may have various velocities in different patients at different stages. Fibroblasts are the predominant proliferating cells in fibrous dysplasia lesions, and the difference in SUV in fibrous dysplasia may be due to the difference in the amount of proliferating fibroblasts.

Tsuyuguchi et al. reported two cases of fibrous dysplasia in the bone of the skull base with mild accumulations (SUVs of about 2.0) of 11C-methyl-L-methionine (11C-Met) on PET (22). They speculated that the mechanism of 11C-Met is due to increased metabolism and active transport of this amino acid because of the increased density of spindle cells.

Fibrous dysplasia shows malignant transformation in 4% to 10% of cases. PET may reveal increasing accumulation in cases of malignant transformation of fibrous dysplasia, but this hypothesis has not been confirmed yet.

**Benign Cartilaginous Tumors of Bone**

Cartilage tumors such as enchondromas and chondrosarcomas are the most common skeletal neoplasms. Histopathologic grades correlate well with clinical outcome (12). Bone scan changes reveal osteoblastic activity or increased local blood flow in the affected regions.

Lee et al. studied 35 biopsy-proven cartilaginous tumors in 27 patients (13). The mean SUV_{max} figures were 1.147 ± 0.751 in the benign tumors, 0.898 ± 0.908 in the grade I chondrosarcomas, and 6.903 ± 5.581 in the high-grade chondrosarcomas. They concluded that PET may not be the appropriate initial screening tool for cartilaginous tumors. However, it may be helpful for distinguishing grades II and III chondrosarcoma from benign chondroid lesions and grade I chondrosarcoma. Döbert et al. reported on a woman who was referred for FDG-PET for the staging of a malignant melanoma (6). Although no signs of metastatic melanoma were evident on the whole-body scan, focally increased uptake within the femoral metaphysis was noted. Radiographic and MRI examinations revealed an enchondroma as the cause of the increased uptake. The histopathologic diagnosis was actively proliferating enchondroma. Enchondromas may be responsible for focally increased FDG uptake in bone lesions and must be considered when FDG-PET scans are obtained in cancer staging.

**Other Tumors**

There are a few reports of increased FDG uptake in other benign bone lesions, such as aneurysmal bone cyst of the rib (8) and ischial chondroblastoma (7).

**SPECT-CT OF BENIGN BONE TUMORS**

Bone scintigraphy is still widely used to evaluate bone lesions. The recently introduced hybrid cameras combin-


Special Considerations in Pediatric PET-CT and SPECT-CT Imaging

Lise Borgwardt  Annika Loft  Liselotte Højgaard

Children are not just small adults. They differ in their psychology, normal physiology, and pathophysiology, and various issues specific to pediatric patients should be considered when planning a positron emission tomography (PET) scan, a PET–computed tomography (CT) scan, a single-photon emission computed tomography (SPECT) scan, or a SPECT-CT scan. SPECT studies have been used for more than 2 decades in pediatric patients, and different protocols and regimes have been presented. PET imaging of children is a relatively new but growing area, and it presents challenges common in pediatric nuclear medicine but not pertinent to the imaging of adult patients. These include dealing with children, dosimetry, organization within the pediatric department and with other departments, and preparation of the child. Further, informing the child and parents on the fasting procedure, the imaging procedure, and the tracer injection is extremely important, and there is a need for proper positioning, sedation, and bladder emptying. Finally, there are various pitfalls in the performance and interpretation of pediatric PET scans that must be avoided to ensure both proper interpretation and the safety and comfort of the patients.

Both PET and conventional nuclear medicine have recently added hybrid scanners with integrated CTs for better anatomic referencing. These scanners raise new considerations, including the increased radiation dose and which indications justify the increased radiation exposure.

INTRODUCTION

Positron emission tomography (PET) is a well-established diagnostic imaging technique used in oncology, infection imaging, neurology, and cardiology in adults. The technique is used less often in children, but recent advances have improved the imaging quality and shortened the length of the imaging procedure (1), making pediatric PET scanning increasingly relevant. Single-photon emission computed tomography (SPECT) has been used for more than 2 decades in pediatric patients, and different protocols and regimes have been presented (2,3).

Nuclear medical and PET examinations in children are very rewarding, especially when the staff understand the requirements of the child and parent. A successful examination can be defined as one in which a high-quality study is achieved and the child and parents feel that their emotional needs are met (4).

DEALING WITH CHILDREN

*Children are very special persons who need to be treated with caution and care and whose integrity must be
respected” (5). In nuclear medicine, dealing with children is very different from dealing with adults. Children are not just small adults. They differ in their psychology, normal physiology, and pathophysiology, and various special issues need to be considered when planning a PET or a SPECT scan for a child. Everybody involved must enjoy working with children, and the scans should be performed by a child-oriented staff. Patience, flexibility, imagination, and truthfulness are crucial qualities when dealing with children.

Children have parents, and the parents are just as worried as the children, often even more so. In each case, the parents’ anxiety affects the child and hence the entire examination, but the parents also are able to offer the child the best comfort and security. This is why dealing with children also means dealing with the parents, and this is done successfully through communication and understanding and by figuring out how best to use their potential as contributors to the imaging process.

**DOSIMETRY IN PET**

An important principle in diagnostic imaging in general is to limit the use of radiation, especially in children and in those with chronic diseases (see Chapter 9). The tracer most frequently used for clinical studies is fluorodeoxyglucose (FDG) (Fig. 66.1). The injected activity is 3 MBq per kilogram of body weight for brain studies (effective dose equivalent \( \sim 4 \) mSv) and 6 MBq per kilogram of body weight for whole-body scans (effective dose equivalent \( \sim 6 \) mSv). The dose to the brain is 0.24 ± 0.05. The target organ (the organ receiving the highest radiation dose), the bladder wall, receives 1.03 ± 2.10 MBq. This can be reduced by good hydration and rapid drainage of radioactive urine. The heart wall is estimated to receive 0.89 ± 0.26 MBq. These figures are from a study that demonstrated that FDG-PET studies in newborns resulted in radiation doses lower than in adults and lower than infants who underwent conventional scintigraphy with technetium 99m (\(^{99m}\)Tc)-DTPA or \(^{99m}\)Tc-MDP (6).

**DOSIMETRY IN SPECT**

The amount of activity administered to an adult can be reduced for children by one of the following methods: body weight/70 kg, body surface area/1.73 m², or height/174 cm (7). The pediatric task group of the European Association of Nuclear Medicine (EANM) has published a dose schedule (8) (Table 66.1). Furthermore, the child should be well hydrated, since frequent micturition reduces the radiation to gonads.

**ORGANIZATION**

Organization and good communication are important in the nuclear medicine and the PET departments, especially between the camera and laboratory staffs. Equally important is comprehensive contact with the pediatric departments. This is not easily done, because nuclear medicine examinations are only some of many different examinations for which pediatric patients are referred, and they are definitely among the most complicated to prepare for. It is beneficial to give lectures in the pediatric departments not only for the physicians but most importantly for the staff nurses and also to have a contact person in each department for every specific examination (9). This will generally be the nurse taking care of the child, as these complicated examinations necessitate special arrangements. The technologist who is to perform the examination has to make the arrangements with the pediatric department, and all communications concerning a specific examination should be written on the referral in case another technologist has to take over. Good cooperation with the team of anesthesiologists is essential, as it takes flexibility to assist a nuclear medicine and PET department in performing pediatric scans. It saves time if both staffs are familiar with one another’s procedures during the examination in order to minimize the time spent.
<table>
<thead>
<tr>
<th>Fraction of Adult Administered Activity</th>
<th>3 kg</th>
<th>4 kg</th>
<th>6 kg</th>
<th>8 kg</th>
<th>10 kg</th>
<th>12 kg</th>
<th>14 kg</th>
<th>16 kg</th>
<th>18 kg</th>
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</tr>
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<tbody>
<tr>
<td></td>
<td>0.1</td>
<td>0.14</td>
<td>0.19</td>
<td>0.23</td>
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<td>36 kg</td>
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<tr>
<td></td>
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<td>0.53</td>
<td>0.56</td>
<td>0.58</td>
<td>0.62</td>
<td>0.65</td>
<td>0.68</td>
<td>0.71</td>
<td>0.73</td>
<td>0.76</td>
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<tr>
<td></td>
<td>42 kg</td>
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<td>56 kg</td>
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<td></td>
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<td>0.82</td>
<td>0.85</td>
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<td>0.90</td>
<td>0.92</td>
<td>0.96</td>
<td>0.98</td>
<td>0.99</td>
</tr>
</tbody>
</table>

This card summarizes the views of the Paediatric Committee of the European Association of Nuclear Medicine. It should be taken in the context of “good practice” of nuclear medicine and local regulation.

**Recommended Adult and Minimum Amounts in MBq**

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Adult</th>
<th>Minimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tc99m DTPA (Kidney)</td>
<td>200</td>
<td>20</td>
</tr>
<tr>
<td>Tc99m DMSA</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>Tc99m MAG3</td>
<td>70</td>
<td>15</td>
</tr>
<tr>
<td>Tc99m Pertechnetate (Cystography)</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Tc99m MDP</td>
<td>500</td>
<td>40</td>
</tr>
<tr>
<td>Tc99m COLLOID (Liver/Spleen)</td>
<td>80</td>
<td>15</td>
</tr>
<tr>
<td>Tc99m COLLOID (Marrow)</td>
<td>300</td>
<td>20</td>
</tr>
<tr>
<td>Tc99m SPLEEN (Denatured R B C)</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Tc99m R B C (Blood Pool)</td>
<td>800</td>
<td>80</td>
</tr>
<tr>
<td>Tc99m ALBUMIN (Cardiac)</td>
<td>800</td>
<td>80</td>
</tr>
<tr>
<td>Tc99m Pertechnetate (First Pass)</td>
<td>500</td>
<td>80</td>
</tr>
<tr>
<td>Tc99m MAA/Microspheres</td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>Tc99m Pertechnetate (Ectopic Gastric)</td>
<td>150</td>
<td>20</td>
</tr>
<tr>
<td>Tc99m Colloid (Gastric Reflux)</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Tc99m IDA (Biliary)</td>
<td>150</td>
<td>20</td>
</tr>
<tr>
<td>Tc99m Pertechnetate (Thyroid)</td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>Tc99m HMPAO (Brain)</td>
<td>740</td>
<td>100</td>
</tr>
<tr>
<td>Tc99m HMPAO (W B C)</td>
<td>500</td>
<td>40</td>
</tr>
<tr>
<td>I–123 HIIPURAN</td>
<td>75</td>
<td>10</td>
</tr>
<tr>
<td>I–123 (Thyroid)</td>
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<td>3</td>
</tr>
<tr>
<td>I–123 Amphetamine (Brain)</td>
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<td>I–123 mBG</td>
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</tr>
<tr>
<td>I–131 mBG</td>
<td>80</td>
<td>35</td>
</tr>
<tr>
<td>GALLIUM 67</td>
<td>80</td>
<td>10</td>
</tr>
</tbody>
</table>

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INFORMATION

Information on planned examinations should be given both verbally and in writing. Good information will help to ensure compliance and keep the child’s anxiety at a minimum. The information leaflets for children should be specific for the different age groups, and pictures can be used for children who cannot read but are old enough to discuss the pictures.

SPECIAL CONSIDERATIONS IN PET

Preparation for PET

Children, like adults, should fast for 6 hours (4 hours in the case of infants) before the FDG injection so as to establish the optimal target–background ratio. Fasting reduces the physiological utilization of glucose and brings down serum levels of insulin to near basal values, thereby minimizing the uptake of unspecific tracer into various organs. Infants may be fed 30 minutes after the tracer injection, when most of the FDG uptake period has passed. When other PET tracers are used, such as H215O, carbon 11 [11C]methionine, and nitrogen 13 [13N]ammonia, fasting is not necessary.

Activity Administration in PET

It is essential that the child and parents be informed about and understand the estimated time the procedure will take so that impatience does not impair the chances of obtaining a high-quality study. To ensure optimal conditions, the staff should not show signs of stress, and if it can be arranged, the child should be the first patient on the program in order to eliminate any delay on the camera.

To provide some quietness during the imaging procedure, the staff at the other cameras should be informed that a pediatric examination is underway via signs posted on the relevant doors in the department. The signs might say, “QUIET, CHILDREN’S EXAMINATION.” If possible, the child should be the only patient in the preparation room.

Before the FDG injection, the fasting child must rest for 30 minutes with eyes blindfolded for a brain scan and for 10 to 15 minutes without a blindfold for a whole-body scan, since it is important to minimize environmental effects on the distribution of glucose consumption in the brain. A pair of eyeshades can be used, and most children

Figure 66.2 Children in PET. A comfortable environment is of great benefit.

Figure 66.3 Children in PET. Even a toddler can sleep if handled properly!
Positioning in the PET Scanner

To ensure the optimal position in the scanner and to avoid movement artifacts, all patients should be comfortably immobilized during study acquisition with Velcro straps, tape, or cushions. Younger children can be successfully immobilized by placing them on a special cushion filled with small plastic balls that fits the body contour by vacuum extraction (see Fig. 66.3).

The child and the parents should be told when scanning is about to start, how long it will take, and whether it is with or without noise, although the PET scanner is much less noisy than the MRI scanner. Parents and/or a nurse with whom the child is familiar should be encouraged to remain in the room during the scanning procedure, as this will reassure the child. The child can be offered a choice of music, storytelling, or, if this does not interfere with the scan, a favorite videotape to watch.

If possible, only one technologist and one physician should be involved in the examination in order to provide a quiet atmosphere and to establish the best contact possible with the child and parents. Empathy in this situation is important in order to avoid misunderstandings and to prevent the child and, just as essential, the parents from feeling anxiety. After the scanning, the child returns to the pediatric department. Note that the results of the PET scan should always be provided by the referring pediatrician and never by the PET department staff.

Sedation in Pediatric PET Imaging

If one wants to limit the use of sedation, it is necessary to spend the extra time it takes in order to perform the examination without sedation. A quiet environment, small gifts, and the parents’ participation are important if sedation is to be avoided. But because of the length of the imaging procedure and the need for patients to remain still during imaging, sedation is sometimes required, most often in the case of young children. It is seldom necessary with children less than 1 year old if the scan can be fitted into with a normal sleep period.

Many sedatives affect the cerebral blood flow and metabolism, and thus for studies of the cerebral function it is recommended that sedation be postponed until 30 minutes after the tracer injection, when most of the FDG uptake has occurred (13). At some institutions, 50 mg/kg of chloral hydrate in a gel solution administered rectally is used for sedation following a monitoring procedure designed by a team of anesthesiologists (14), along with pulse oximetry and with ventilatory equipment at hand. If chloral hydrate is not effective, the anesthesiologists can administer a general anesthesia. The sedative and general anesthesia should only be administered during the scanning period.

Bladder Emptying

As the bladder is a target organ, the radiation dose can be reduced by good hydration and rapid drainage of the radioactive urine. This can be done by offering the child water before the PET scan (if the tracer is FDG) and their favorite drink after the scan. Bladder catheters are not generally recommended but in special cases are optional for tracers like FDG with renal excretion. Catheterization may be relevant in patients with a dilated or distorted urinary tract, where excessive accumulation of tracer will impair evaluation of the related regions, or where the primary lesion is suspected of being close to the urinary tract (13). But even in such cases, voluntary emptying of the bladder before the scan should be encouraged, because catheterization does increase the risk of infection. If the scan is performed in a PET scanner and not in a hybrid PET-CT, the transmission scan is performed from brain to bottom and the emission scan from bottom to brain to ensure a minimum of time in between the two scans over the bladder region.

Study Interpretation and Pitfalls in PET and PET-CT

In a startup process, when experience is still limited, it is important to have access to specialized knowledge, training, and the chance of a second opinion. In PET scanning of children, a helping hand is mandatory owing to the many pitfalls (Figs. 66.4 and 66.5 and Table 66.2) (9), but the use of PET-CT instead of PET alone reduces many interpretation problems. In brain scanning, the alteration in the FDG/glucose metabolism of the brain with age causes dramatic changes in the pattern of the brain glucose utilization during the first year of life (Fig. 66.6) (15,16). The literature on pitfalls in pediatric PET-CT scanning is still missing, and current views on the issues are based on adult data (17).

The small anatomical parts in children may complicate image interpretation. The CT component of PET-CT certainly aids in assessing the small sites of avidity, but small anatomical parts and lack of retroperitoneal fat in many young children continue to complicate image interpretation (18). The use of intravenous and oral contrast materials can often aid in assessing these small retroperitoneal structures (18). Another potential pitfall of imaging performed using a hybrid PET-CT scanner, not only in pediatric patients, is related to differences in breathing patterns between the CT and the PET scans. Although CT scans can...
be acquired during a breath-hold, PET acquisitions are taken during tidal breathing and represent an average position of the thoracic cage over 3 to 5 minutes. This may lead to misregistration of pulmonary nodules between the two modalities, particularly in the peripheries and at the bases of the lungs. Misregistration may be minimized by performing CT during normal respiration (19).

In a learning process, it is important to set up a database as a reference for complicated scans. It can be used for “atypical” phenomena, which when studied through the database might turn out to be less atypical than first thought.

**PET-CT IN PEDIATRIC PATIENTS**

Because of the improvements achieved by implementing diagnostic PET-CT for adults as compared with PET alone, including the increased accuracy of scan interpretation, it seems obvious that this new modality should also be applied to the pediatric population (20).

Fortunately, cancer is a relatively rare disease in children. This means, however, that acquiring experience in oncopediatric PET is difficult and that the literature is scarce, mainly due to difficulties in collecting sufficient numbers of patients for clinical trials. Therefore, the knowledge from adult PET-CT (21) is applied to pediatric PET-CT, just as occurred when PET alone was first used with children. The knowledge from PET combined with CT in adults would logically seem to give good results in pediatrics as well (18,22).

The practical issues that arise with pediatric PET, including fasting, FDG dosage, serum glucose levels, and sedation, are the same as arise with the combined scan, and these have been discussed above. For the CT part of PET-CT, it is recommended that the guidelines of the local radiology department be followed concerning voltage (kV), ampere (mA) and scanning time, which of course depend on the weight and length of the child, as well as the use of intravenous and oral contrast media. The flavoring added to the oral contrast should be sugar-free. Just as in adult PET-CT, the intravenous contrast is given mainly to define blood vessels and adjacent lymph nodes, but it also helps to image tumors that do not take up FDG. Intravenous contrast can improve the PET-CT images when evaluating small children with limited retroperitoneal fat and when evaluating the mediastinum and neck (18).

PET-CT scanning of children raises special concerns, because it exposes them to a higher radiation dose than that given for a PET scan (the whole-body PET dose = 6 to 8 mSv) (23). Consequently, the need for PET-CT instead of PET must be carefully evaluated. It should be taken into account that the radiation dose from PET-CT is not additive to the dose from the PET scan, but that the dose from the CT scan is additive to that from PET imaging.

**Figure 66.4** FDG uptake in the Waldeyer ring (arrow) in a 5-year-old child with rhinitis (A: axial; B: coronal; C: sagittal).

**Figure 66.5** Physiological FDG uptake in the muscles of mastication in a newborn. (A: axial; B: coronal; C: sagittal).
TABLE 66.2

UNIQUE FEATURES OF NORMAL FDG DISTRIBUTION AND PITFALLS IN PEDIATRIC PET

The thymus gland
- The thymus is of maximal size and function at the time of birth.
- FDG uptake in the thymus is a common finding in children and young adults.
- The thymus normally appears as an upside-down V.
- Thymus hyperplasia after chemotherapy is a common finding.

Waldeyer ring
- Prominent FDG uptake often occurs in the naso-/oropharyngeal region and in the neck area, caused by normal symmetric lymphoid tissue in the Waldeyer ring (see Fig. 66.4).

Muscles of mastication
- Muscles of mastication may become visible in babies who suck pacifiers or are fed within 30 minutes following the tracer injection (see Fig. 66.5).

Bone and bone marrow
- High FDG uptake is often seen symmetrically in the epiphyseal plates of the long bones.
- Physiological regenerating processes in bone marrow and/or growth plates after chemotherapy and/or irradiation may affect the FDG uptake in different ways. The FDG uptake can be elevated, reduced, or abolished in these regions, and a change of one of these types must not automatically be taken to be a symptom of malignancy.

Developmental changes in cerebral glucose metabolism (see Fig. 66.6)
- In newborns, the sensorimotor cortex, thalamus, brainstem, and cerebellar vermis are the most metabolically active areas of the brain.
- At 2 to 3 months, the parietal, temporal, and primary visual cortex mature.
- At 6 to 12 months, the frontal cortex matures.
- At 1 year, FDG distribution is the same as the typical adult distribution.
- At 2 to 3 years, FDG distribution is the same as the typical adult distribution, but if quantified, glucose metabolism increases to above the adult level.
- At 8 to 10 years, FDG distribution is the same as the typical adult distribution, and glucose metabolism starts to decrease toward the adult level.
- At 16 to 18 years, FDG distribution is the same as the typical adult distribution, and glucose metabolism is at the adult level.

See also Chapter 33.

consideration that the information obtained from a PET-CT scan often is much more useful than from separate PET and CT scans and that the radiation dose to the child is the same whether the scans are combined or not.

PET-CT scanning of children also involves the radiologist and technologist in specific technical aspects of the setup. The radiation dose is tailored for each individual child, unlike in the case of adults, for whom a standard setup is used. This makes the process more time consuming. Furthermore, the interpretation of the PET-CT scans needs to be performed by specialists qualified in radiology and nuclear medicine, followed by a simultaneous reading of all three images (the CT image, the PET image, and the fused image).

PET-CT in pediatrics seems to be valuable for diagnosing malignant lymphoma, both Hodgkin and non-Hodgkin (24,25) (see Chapter 55); for diagnosing sarcoma, as PET-CT is more sensitive than bone scintigraphy in detecting osseous metastases of Ewing sarcoma (26); and especially for biopsy guidance, since sarcomas may have very heterogeneous FDG uptake (Chapter 53). Hence it must be remembered that low-grade sarcomas may not be FDG avid (27). More clinical trials are needed to verify these applications of PET-CT in the pediatric population (28).

Finally, PET-CT is useful in radiation planning, where it can be helpful in the delineation of the tumor. No pediatric publications concerning this application are available as yet.

SPECIAL CONSIDERATIONS IN PEDIATRIC SPECT

Pediatric nuclear medicine is mostly performed in departments mainly for adults, but insight into this specific field has been developing for more than 2 decades. Guidelines for specific scintigraphies in pediatric nuclear medicine now exist: for bone scintigraphy (29), for $^{99m}$Tc-DMSA scintigraphy (30), for glomerular filtration rate determination (31), for indirect radionuclide cystography (32), and for standard and diuretic renograms (33). The approved
guidelines are published under the auspices of bodies of the EANM and are available at www.eanm.org. Problems in pediatric studies are largely related to the dosage of radionuclide; patient cooperation; motion artifacts in long studies; different tracer distribution, as in increased uptake in growth plates; and the resolution of the camera, due to the small size of the anatomic parts of children.

Preparation in SPECT: Injection Technique

Since in most nuclear medicine departments venous puncture is part of the examination, an anesthetic cream is applied to the skin an hour before injection. Thereafter, a catheter (1 mm) is placed in a cubital vein and fitted with a three-way stopcock. A test injection with saline is done. The dose is injected immediately, followed by a saline flush (10 mL). The stopcock is discarded and a new one is fitted. Blood samples can be taken through the same catheter after 0.5 mL of "waste," preferably before tracer injection.

Imaging Procedure in SPECT

Positioning and Immobilization
Small children need to have someone close during imaging, and an ordinary examination table is sometimes too large. A custom-made small table adapted directly to the head of the camera is the best option, and Plexiglas is a suitable material for this purpose. Placing the child directly on the collimator also minimizes scattering material between the child and the camera and results in a better resolution. The custom-made table is useful, especially when oblique views are needed, but one should have the distance in mind so as not to compromise the resolution. When studying small objects, such as the bones of the foot, wrist, hip, and spine, the pinhole collimation should be used to optimize the resolution. In order to minimize movements, a deflatable "vacuum" cushion, sand bags, or straps are used.

Sedation
The principles are the same in PET and SPECT studies, but the traditions are somewhat different (2,3). Midazolam, applied as a nasal spray, has been used in several studies with good efficacy, and it is easily applied (5). The dose of Midazolam nasally administered is 0.2 mg/kg.

Bladder Emptying
The child should be well hydrated, since frequent micturitions reduce the radiation to gonads. The bladder should always be emptied before pelvic images.

Study Interpretation and Pitfalls in SPECT and SPECT-CT

Commonly encountered patient-related pitfalls include artifacts caused by attenuation, contamination artifacts, and artifacts caused by intravenous lines, tubes, and...
catheters. Less commonly, artifacts arise because of the use of multiple isotopes, the presence of fistulas or surgically altered anatomy, and the interference of pharmaceuticals and other substances with expected radiopharmaceutical uptake and distribution. The diagnostic accuracy of nuclear medicine reporting can be improved by awareness of these patient-related artifacts. If increased focal uptake is observed, one should always exclude contamination and acquire data in two projections. If decreased focal uptake is observed, one should exclude attenuation from coins or belt buckles, since children can have an unknown number of things in their pockets even after having emptied them. The pitfalls related to the specific radiotracer used are not discussed in this chapter, but there are several changes specific to children, such as the well-known increased uptake in growth plates on bone scintigraphy of younger children. To assist in interpreting pediatric bone scans, “Scintigraphy of the Paediatric Skeleton” (www.medical-atlas.org) is suggested as a reference.

SPECT-CT IN PEDIATRIC PATIENTS

There are many publications on SPECT-CT in adults (34,35), but so far no publications on SPECT-CT in children exist, which is why current thinking is again based on adults. In pediatric studies, whole-body SPECT has been combined with MRI by using scan coregistration (36). Pediatric brain SPECT studies coregistered to MRI (SISCOM) is well established in the diagnostic evaluation of epilepsy (37, 38).

SPECT-CT scanning of children demands special considerations, because it exposes the child to a higher radiation dose than a SPECT scan alone.

CONCLUSION

Working with children is challenging, rewarding, and unpredictable, and thus when the staff and environment are child oriented, the chances of achieving a high-quality study are markedly increased. Successful nuclear medicine and PET scans in children require good communication and collaboration with the children and parents, between all the relevant departments and their staffs, and, last but not least, across the involved professions.

REFERENCES

INTRODUCTION

Childhood cancer is rare, accounting for only 2% to 3% of all cancers, but cancer is second only to trauma as a cause of childhood death in the United States and Europe. In the Western world, the cancer incidence is 12 to 14 per 100,000 children under 15 years per year (1). During the last decades, the treatment of pediatric malignancies has been greatly improved, so the overall survival rate is more than 75% (2–4).

The neoplasms affecting children differ from those commonly found in adults, and several types of cancers are virtually unique to childhood. Neuroblastoma, Wilms tumor,
rhabdomyosarcoma, and retinoblastoma are predominantly or exclusively pediatric cancers (5). In addition, leukemias, lymphomas, central nervous system (CNS) tumors, and primary bone malignancies are of relatively greater importance in children than in adults. The most frequent malignancies in childhood are brain tumors, followed by neuroblastoma, osseous sarcoma, and lymphoma. Carcinomas of the lung, breast, stomach, large bowel, and prostate are extremely rare among children (6).

Experience with positron emission tomography (PET) and integrated PET–computed tomography (CT) has accumulated more slowly in pediatric than in adult cancers. The initial studies of PET applications in children have focused on disorders of the brain and congenital heart disorders. PET is rapidly becoming more widely available, and the clinical value of PET for childhood tumors is currently under investigation. PET has gained a dominant position within the nuclear medicine applications in pediatric oncology (7), but single-photon emission computed tomography (SPECT) and SPECT-CT play an important role in the management of certain pediatric tumors. Regarding both PET-CT and SPECT-CT, most of the available body of evidence still derives from studies of adult cancer patients. Very few data exist on the application of PET-CT and SPECT-CT in infectious and inflammatory diseases. However, a number of case reports indicate that the methods have a high value in these diseases.

**CENTRAL NERVOUS SYSTEM TUMORS IN CHILDHOOD**

CNS tumors are the most common solid tumor in childhood (8), accounting for 20% to 25% of all cancers (see also Chapters 22 and 23). Although the prognosis has improved considerably over the last 2 decades, the overall cure rate today is approximately 60% (9), with the best prognosis for benign astrocytoma localized to the cerebellum (almost 100%) and the worst for brainstem gliomas (5% to 10%) (9). Brain tumors are the leading cause of cancer mortality in children (8). Descriptive classification by histological examination is crucial for the appropriate management of CNS tumors. Theoretically, all types might develop in children. However, the tumor types of special importance in childhood are significantly fewer than in adults and are dominated by medulloblastoma, pilocytic astrocytoma, diffuse astrocytoma, ependymoma, and cranioopharyngioma (8).

Tumors localized centrally can rarely be totally resected without severe neurological deficits, and even biopsies can be a major risk. Thus, the burden of late effects is troublesome (9,10). Survivors of childhood CNS tumors often have severe neurological, neurocognitive, and psychosocial sequelae (10–14), either due to the tumor or the treatment necessary to control it.

Diagnostic imaging with CT and MRI (with MRI as the first priority) is generally used to monitor the effect of treatment on tumor and recurrence, but the image interpretation is impaired by changes in the brain tissue related to surgery, glucocorticosteroids, radiotherapy, and chemotherapy leading to non-tumor-associated post-treatment contrast enhancement. Thus, other noninvasive diagnostic modalities, as PET and SPECT (15) and MR spectroscopy (MRS) (16), are suggested for monitoring treatment effect and recurrence, as they add functional dimensions to brain scanning (Fig. 67.1).

**PET Imaging**

FDG is widely used for PET studies of brain lesion metabolism. The use of PET to grade tumor malignancy is based on the assumption that malignant tumors have high FDG uptake and benign tumors have reduced FDG uptake (17) compared with the average value of brain FDG uptake. FDG demonstrates enhanced uptake in the majority of malignant tumors, and the uptake is positively correlated with tumor malignancy in childhood CNS tumors (18–20). The diagnostic value of FDG-PET for grading malignancy in adults has previously been investigated (21–25). The studies showed that the specificity for malignancy grading was not sufficient, as a great deal of overlap between high-grade and low-grade tumors existed; however, PET-MRI coregistration and image fusion was shown to improve the accuracy of malignancy grading with FDG-PET (26,27).

A limited number of PET studies on CNS tumors in children have been published (18–20,24,28–35). Four small retrospective pre- and post-therapeutic studies (19,20,32,33) and two with a pretherapeutic prospective design (18,34) all reported a potential clinical diagnostic value for FDG-PET. Four of these studies were of malignancy grading (18–20,34), and they found a correlation between FDG and tumor malignancy, but with an overlap making malignancy grading difficult. One of these studies systematically combined PET with MRI coregistration and image fusion and showed an improved diagnostic value for FDG-PET in malignancy grading. Digitally performed coregistration and image fusion of PET with MRI was shown to increase the specificity in 90% of cases in terms of tumor location, tumor extent, and of heterogeneity (Figs. 67.2 and 67.3) (18). However, the remaining problem to be solved is still the hypermetabolic benign tumor (31).

The significant physiological FDG uptake in normal gray matter is a potential source of error in the interpretation of FDG-PET studies. Therefore, other tracers with higher tumor-to-background contrast, such as labeled amino acids, have been proposed as alternatives in preoperative malignancy grading, but the amino acids seem more useful for differentiation between low-grade neoplastic and nonneoplastic lesions than for tumor grading (34–36).

FDG-PET has also been proposed as a tool to improve the quality of biopsies from brain tumors in adults (37) and in children (30), but the delineation of tumor is difficult in the cerebral cortex. Carbon 11 [11C]methionine (MET) PET provides additional information in terms of
delineation of tumor extent for local management of pediatric brain tumors (34,38). Recently O-\(2-\)\([18\text{F}]\)fluorooethy1-L-tyrosine (FET) PET has been found useful for biopsy guidance in adults (39). No pediatric publications concerning this issue are yet available.

FDG-PET has been used to differentiate post-treatment contrast enhancement on MRI from recurrent tumor (40–44). Some studies in adults report a high accuracy (40,41,45–47), whereas others report that PET is neither sensitive enough nor specific enough to be used routinely (48,49). FDG-PET has also been used to describe the metabolic effects of various therapies on brain tumor metabolism (17,50–53) in adults, and a number of small clinical adult trials have indicated that quantification of changes in FDG uptake may provide an early and sensitive dynamic marker of the effect of chemotherapy and radiotherapy (50). Only a few studies have investigated the possible value of FDG-PET in the monitoring and diagnosing of...
recurrent disease in childhood tumors. Plowman et al. found FDG-PET to be useful in the distinction of active tumor from post-treatment sequel in ten young patients with different brain tumors (33). In a study by Holthoff et al. that included 15 children and young adults (range, 0.5 to 26.0 years of age) with histologically confirmed brain tumors, FDG-PET was found to be useful for evaluating the metabolic activity of pediatric brain tumors over time and for assessing the response to treatment (20). Borgwardt et al. found FDG-PET with MRI coregistration to be useful for monitoring hypermetabolic childhood brain tumors (54).

MET-PET was found to be useful for evaluating post-treatment contrast enhancement in childhood CNS tumors in general (34,35). However, this tracer has considerable nonprotein metabolism, since a significant fraction seems to be incorporated into phospholipids through the S-adenyl-methionine pathway and to generate substantial amounts of nonprotein metabolites. This makes quantification of protein synthesis difficult if required (55). Other amino acids, such as [11C]tyrosine and [14C]leucine, have been proposed as better protein synthesis rate imaging agents, but clinical experience with these radiotracers is still limited. Carbon 11–labeling is a limiting factor for routine clinical use and for regional distribution, because of the shorter half-life. Tyrosine can also be labeled with 18F, with high yields and specific activity, and 18F-ethyl-tyrosine appears promising as replacement for MET and as a complement for FDG in tumor diagnosis.

Recent studies have shown the potential usefulness of [14C]choline in brain tumors (56,57); it may be helpful in discriminating between benign and malignant brain tumors (58). Choline analogs are phospholipid precursors and have been shown by MRS to be present in increased concentrations in brain tumors, particularly high-grade lesions, probably representing the activation of choline uptake and phosphorylation in tumor cells. Choline metabolism in tumor cells is directed primarily toward membrane synthesis, de novo synthesis of choline is negligible in tumor cells, and the cell membranes are duplicated at the same rate as cell duplication. The recently developed [18F]choline is believed to be superior to 11C-labeled choline because of its longer half-life and shorter positron range (59), making synthesis and patient handling much easier. No pediatric studies are yet available.

In addition, studies have begun evaluating tumor proliferation imaging with radiolabeled nucleoside analogs that measure DNA synthesis and thereby tumor cell proliferation as a noninvasive means of assessing tumor growth potential and grade of malignancy and of identifying the most rapidly proliferating regions of the tumor. The radiolabeled nucleoside analogs [18F]-3′-fluoro-thymidine (60) and the [2′-deoxy-2′-[18F]fluoro-beta-D-arabinofuranosyl nucleosides (61) seem promising, but studies on the use of these tracers for human brain tumor imaging have not yet been published.

Most of the interest in PET lies in the labeling of specific molecules such as drugs. An example is [11C]tegafur, whose differential uptake in tumor and uninvolved brain can be determined over time as a way to assess regional kinetics (62). These studies suggest that PET has the potential to improve the clinical outcome of childhood brain tumors even more at different stages of the disease by increasing the accuracy of the choice or targeting of therapy. This becomes more important as the range of available tracers evolves.

**SPECT Imaging**

SPECT scans generally have poorer resolution than PET, but the use of this modality expands with the number of tracers available and hence with the targets that can be probed.
LYMPHOMA

The lymphomas belong to a heterogeneous group of diseases with two main types: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) (see also Chapter 55). HL and NHL account for approximately 15% of all cancers in children, with NHL being slightly more frequent in childhood than HL. The incidence of NHL increases steadily throughout life, but a peak occurs between the ages of 5 and 9 years. The clinical presentation of NHL in children varies and depends on the localization and extent of tumor as well as on the histologic subtype. HD has a characteristically bimodal incidence curve, with the first peak occurring during adolescence and young adulthood (6). In both NHL and HL, a quick diagnosis is essential, because the lymphomas often grow very rapidly and the tumor burden is the most important pretreatment determinant of outcome (74). The initial treatment strategy in NHL and HL is largely determined by the disease stage, so an accurate determination of the extent of disease is essential (75). After induction therapy, reliable response monitoring is crucial, since the response to therapy guides treatment modifications. The management of childhood lymphoma involves multidrug chemotherapy and radiotherapy. The overall cure rate is very high in HL (95%) and somewhat lower in NHL (4).

The conventional staging and monitoring of lymphomas, both NHLs and HLs, are based on computed tomography (CT) scanning of the chest, abdomen, and pelvis and, in certain patients, additional magnetic resonance imaging (MRI) or ultrasound imaging (76). In children with bone complaints or in those with an unexplained elevation of serum alkaline phosphatase, bone scintigraphy may be helpful. Gallium 67 [67Ga]citrate scintigraphy has long been considered useful for staging and treatment monitoring of lymphomas because of its tendency to concentrate in viable lymphoma cells. It is still used in some centers for staging, therapy response monitoring, and the evaluation of residual masses (77). However, the procedure is costly and laborious, and the spatial resolution is rather low. It has now largely been replaced by FDG-PET or FDG-PET-CT where available (78,79).

The usefulness of FDG-PET for staging of adult lymphomas has been thoroughly established; in particular, it has higher diagnostic and staging accuracy than conventional staging methods and contributes to changes in the clinical stage in 40% and changes in treatment in up to 25% of patients (80–87). FDG-PET generally identifies more disease sites than conventional imaging methods and allocates more patients to more advanced treatment than to less advanced treatment. Recent studies have assessed the value of FDG-PET-CT and have shown it to be higher than that of FDG-PET, especially in the deep nodal regions. In the monitoring of early therapy response and residual masses, FDG-PET has proven to be capable of playing an important role in adult lymphoma populations (88–90). FDG-PET performed during or after completion of therapy has a strong predictive value, superior to that of gallium scintigraphy (91).

The body of evidence concerning FDG-PET and FDG-PET-CT in pediatric lymphomas is more limited. Shulkin et al. performed FDG-PET scanning in four pediatric lymphoma patients. In three of the four patients, FDG-PET and gallium scintigraphy showed corresponding lesions. In all the lesions, FDG uptake was substantial, and image resolution was superior to that of gallium scintigraphy. In the fourth patient, studied within 1 week after initiation of chemotherapy, no FDG uptake was noticed (92). O’Hara et al. also found FDG-PET to be useful in cases of pediatric lymphoma and suggested that FDG-PET could be an effective problem-solving technique when diagnostic dilemmas or inconsistencies are encountered (93). Montravers et al. performed 42 FDG-PET examinations on pediatric lymphoma patients and found a high staging sensitivity and substantial upstaging rate (50%) compared with conventional staging procedures. FDG-PET was also found to be useful.
highly accurate for monitoring therapy response and evaluating residual masses after treatment (94). Wickmann et al. analyzed FDG-PET findings in 106 children managed using the Society for Pediatric Oncology and Hematology protocol for Hodgkin lymphoma treatment (GPOH-HD 95) and found a high concordance with conventional methods of primary staging (95). When used for treatment monitoring, a negative FDG-PET could reliably exclude later relapse of the disease, but the positive predictive value was low, since only a small fraction of FDG-PET–positive children later relapsed. In a retrospective study of 28 lymphoma children, Depas et al. confirmed the high accuracy of FDG-PET for staging and the high negative predictive value during and after therapy for the prediction of subsequent progressive disease (96). FDG accumulation in the thymus is a common finding in children (Figs. 66.1 and 67.4) and occasionally can also be observed in young adults after chemotherapy (97). When reading FDG-PET scans of pediatric lymphoma patients, it is important to be familiar with the characteristics of a typical retrosternal lymphoma mass. FDG-PET is not suitable for evaluating lymphomatous involvement of the thymus.

Although there are still no large systematic prospective studies available concerning FDG-PET in childhood lymphoma, the current body of evidence indicates that FDG-PET is just as valuable in children with lymphoma as in adults. The method is already incorporated into routine management in many centers. In the most recent Society for Pediatric Oncology and Hematology protocol for Hodgkin lymphoma treatment (GPOH-HD 2003), children with localized disease are given additional radiotherapy only if FDG-PET is positive after two cycles of chemotherapy (98). The role of FDG-PET-CT has not been established. However, the relative advantage of fusion imaging is likely to be important in children, since disease-mimicking physiological FDG uptake in normal structures is more common in children than in adults (Fig. 67.4). FDG-PET and FDG-PET-CT will probably play an increasingly important role in staging, response monitoring, planning of radiotherapy fields, and monitoring after

Figure 67.4  FDG-PET-CT images of a 5-year-old child with newly diagnosed stage II Hodgkin lymphoma. There is involvement of both sides of the neck and supraclavicular regions (B,D). Diffuse physiological uptake is seen in the thymus (B,E). In the right lower abdomen, there is a small area of suspect FDG uptake (F), which on PET alone might be interpreted as lymphoma manifestation. On PET-CT, it is identified as normal uptake in the lumen of the large bowel (D, arrow, G). After one cycle of combination chemotherapy, this child still had large tumor masses on both sides of the neck, but FDG-PET was completely normalized.
therapy in childhood lymphoma. New more tumor specific tracers are likely to be introduced, but no studies have so far been performed on pediatric populations.

MUSCULOSKELETAL TUMORS

General Aspects of FDG-PET and SPECT in Musculoskeletal Sarcomas

Musculoskeletal sarcomas are relatively rare tumors in the adult population, but they account for a substantial number of the malignant extracranial solid tumors in children (see also Chapters 51 and 53). Osteosarcoma and Ewing sarcoma are the two most common malignant bone tumors in children. Soft-tissue sarcomas comprise a multitude of entities with heterogeneous biologic behavior, and the different types of soft-tissue sarcomas exhibit different age distributions (6).

The value of FDG-PET in the management of osseous and soft-tissue sarcomas has been investigated in several series, mainly in adults. The few reports on the use of FDG-PET in pediatric sarcomas include rather small series of patients (99). In musculoskeletal tumors, the pretreatment planning depends on histologic type and grade. Biopsy remains the most specific method for diagnosis, but sampling errors occur, especially in large heterogeneous tumors. The quantitative determination of the tumor metabolic rate for FDG correlates strongly with histologic tumor grade and may therefore be used in the pretreatment tumor grading (100). The distribution pattern of FDG in the tumor may be useful for performing biopsy of the most malignant areas of the tumor (Fig. 67.5) (101), and combined PET-CT or fused PET and MRI may facilitate biopsy sampling (Fig. 67.6). Accurate staging at presentation is essential, as metastatic disease, most often to the lungs, is present in 10% to 25% of patients and affects both treatment and prognosis. An initial whole-body FDG-PET with thoracic CT has been shown to identify most sites of metastatic disease, and through use of combined PET-CT, the patient can have the staging done in just one examination, which perhaps is even more important for children. Studies have also shown that FDG-PET can provide information about response to therapy and prognosis in adults (102,103) as well as in children (104). However, FDG uptake was also noticed in benign, reactive tissue both within and adjacent to treated tumors, and this finding should be taken into consideration when interpreting the FDG-PET studies. High FDG accumulation also may occur in benign bone tumors and tumor-like lesions, especially histiocytic and giant cell–containing lesions (105). The role of PET in treatment evaluation is not established for sarcomas, although for primary diagnosis in adults, PET seems promising, and the published data concerning children tend to support its potential usefulness (104).

Many different radioisotopes have been used to evaluate bone and soft-tissue tumors, including $^{201}$Tl, $^{67}$Ga, technetium
99mTc-sestamibi, 99mTc-pertechnetate, 99mTc-dimercaptosuccinic acid (DMSA)-V, 99mTc-MIBI, and 99mTc-tetrofosmin (5, 106). Bone scintigraphy with 99mTc-MDP has low specificity for the assessment of response due to its uptake in tissue-repairing areas. No reports concerning SPECT-CT are yet available, but the advantages of fusing metabolic and anatomic information seem quite obvious.

**Osseous Sarcomas**

Osteosarcoma is one of the most common bone tumors in children (see also Chapter 51). It occurs in infants and throughout adulthood, but its incidence peaks between the ages of 10 and 20 years. The annual incidence in the United States has been reported as 1.6 to 2.8 per million in children younger than 15 years (6). Osteosarcomas commonly occur in the metaphyseal region of the long bones, especially the femur. A definite diagnosis can be made only by biopsy, but as metastatic disease influences the prognosis and management, plain radiography, CT, MRI, and bone scanning are routinely used in the diagnostic workup. FDG-PET is more sensitive than bone scanning and MRI in detecting bone metastases and also reveals soft-tissue involvement. However, due to false-positive findings on PET, the specificity is higher for MRI (107). The false-positive rate is expected to decrease with PET-CT, but no data are yet available to confirm this (Fig. 67.7). Response to neoadjuvant chemotherapy is a significant prognostic factor for osteosarcoma, but...
conventional imaging does not discriminate between responding and nonresponding osseous tumors. The change in SUV during treatment correlates with histopathologic assessment of response and seems to have prognostic value for these patients (108–110), and when MRI is equivocal, adding PET information to MRI helps to distinguish viable tumor tissue from tissue changes due to therapy (111). PET-MRI fusion is cumbersome and time consuming, but it can be helpful for biopsy guidance (see Figs. 67.5 and 67.6).

**Ewing Sarcoma**

Ewing sarcoma accounts for 10% to 15% of all primary malignant bone tumors (see also Chapter 51). The annual incidence is 0.6 per million. It is usually situated in the lower extremities and more seldom affects flat bones (i.e., the ribs, scapula, vertebrae, and pelvis). As opposed to osteosarcoma, Ewing sarcoma in the long bones arises from the diaphysis. The peak incidence is between 10 and 15 years, and Ewing sarcoma is very rare in children younger than 5 years. The diagnosis can be established with plain radiography and biopsy. MRI is so far the best procedure for delineating the soft-tissue extent of the primary tumor and bone marrow involvement. Bone scintigraphy is used routinely in the search for bone metastases. The most important differential diagnosis with Ewing sarcoma is osteomyelitis.

The usefulness of FDG-PET in children with Ewing sarcoma for staging and treatment monitoring corresponds to that of osteosarcomas, described above (99,101,108). High FDG accumulation in the region of the primary tumor has been shown to correspond to MRI findings (107). Being able to reveal soft-tissue involvement as well, the use of PET for a more precise staging of Ewing sarcoma might be helpful, and combined PET-CT is probably better yet (99) (Fig. 51.2).

An important differential diagnosis for Ewing sarcoma is eosinophilic granuloma, which is frequently observed in histiocytosis X. Eosinophilic granulomas show a clear uptake of FDG, originating from the bone marrow and increasing toward the periphery of the lesion, and this finding also resembles Ewing sarcoma on plain radiographic imaging. The correct diagnosis is determined from a biopsy. In contrast, osteochondromas have characteristically low peripheral FDG accumulation.

Skeletal scintigraphy is used to evaluate the primary tumor and can also depict bone metastases. The therapeutic response can be assessed using thallium and 99mTc-MIBI scintigraphy (5). SPECT-CT for these patients would seem to be a useful tool, but this has not yet been documented.

**Rhabdomyosarcomas**

Rhabdomyosarcoma (RMS) accounts for approximately 4% to 5% of all childhood malignancy. Classically RMS is divided in two major forms according to histology, the embryonic type and the alveolar type, comprising approximately 80% and 15% to 20% of all RMSs, respectively. The peak incidence is seen in early childhood, with a median age at diagnosis of about 5 years. RMS is encountered in almost all regions of the body, although the head and neck and genitourinary locations are the most common primary sites. Diagnosis and staging investigations include routine adequate imaging of the primary site with CT or MRI and biopsy. The treatment of RMS is based on surgical resection, multi-agent chemotherapy, and radiotherapy. The overall 5-year progression-free survival rate is approximately 65% (2).

These tumors exhibit various levels of biologic activity and FDG uptake. High FDG uptake in residual tumor and FDG uptake. High FDG uptake in residual tumor and FNAC showing no viable tumor tissue from tissue changes due to therapy (111). PET-MRI fusion is cumbersome and time consuming, but it can be helpful for biopsy guidance (see Figs. 67.5 and 67.6).

In conclusion, the use of PET and PET-CT in childhood sarcomas is not established, but studies are emerging. PET must now be regarded as a supplement to conventional diagnosis and follow-up, very much as in the adult patient group.

**Neuroblastoma**

Neuroblastoma (NB) is the most common extracranial solid malignant tumor in children. The annual incidence of NB is 10.5 per million children younger than 15 years, and it accounts for 15% of all childhood cancer deaths (112). Seventy-five percent of all neuroblastoma cases are found in children under 4 years of age, and the disease is extremely rare in older children. NB primary tumors may arise at any location, coinciding with normal sympathetic nervous system structures. About 25% of the primaries are found in the thorax or neck, 70% in the abdomen, and 5% in the pelvis. The clinical manifestations of NB are extremely varied and depend on the site of the primary tumor and whether there is metastatic disease. The disease has the greatest diversity in clinical behavior of all pediatric solid tumors, with some tumors regressing spontaneously, some curable by chemotherapy, and others resistant to therapy. Metastatic NB in children younger than 1 year is associated with the worst prognosis of all malignancies in childhood. Depending on the pretreatment staging, the therapeutic strategies include surgical resection, chemotherapy, radiation treatment, and eventually consolidation with myeloablative therapy with hematopoietic stem cell support.

Because of its neuroendocrine origin and capacity to accumulate catecholamine-like agents, NB has been extensively studied by nuclear medicine techniques, including planar and SPECT scintigraphy with 131I- and 123I-labeled metaiodobenzylguanidine (MIBG). 131I-MIBG was introduced in the management of neuroblastoma in the 1980s (113), and several studies have shown 131I-MIBG scintigraphy to have a high sensitivity (80% to 90%) and specificity (90% to 100%) in the diagnosis and staging of neuroblastoma (114–116). 131I-MIBG scintigraphy is a valuable tool for treatment response monitoring and early detection of recurrence (117). Due to its high specificity, 131I-MIBG scintigraphy is useful in the differential diagnosis of childhood tumors of unknown origin (118). More recently, 123I-MIBG was introduced in the management of neuroblastoma. Because of its properties,
123I-MIBG delivers images of a better quality than 131I-MIBG, and some authors argue that 123I-MIBG is better suited for SPECT studies than 131I-MIBG (119). Tang et al. showed that the fusion 131I-MIBG SPECT-CT provides improved tumor localization and enhanced MIBG uptake measurement (120).

The great majority of NBs accumulate FDG. The characteristics of FDG uptake in neuroblastomas were investigated by Shulkin et al. in 17 pediatric patients with known or suspected NB (121). All the patients underwent conventional 123I-MIBG scintigraphy. In 7 patients examined before systemic therapy, the primary tumors were readily visualized on FDG-PET scans. Most of the primary tumors demonstrated intense FDG accumulation, with SUVRs ranging from 2.0 to −4.0, with mean SD of 2.8 ± 0.7. In 2 of the 7 patients, FDG scans were considered superior to the MIBG scans; in another 2, the scans were considered equivalent; and the MIBG scans were considered superior to the FDG scans in the remaining 3 patients. For most patients examined at various times during and after therapy when residual or recurrent disease was suspected, tumor FDG uptake tended to be lower in patients after treatment, and MIBG was judged superior for depicting lesions, but FDG accumulation not seen on MIBG imaging was also noticed. In a few patients, FDG-PET failed to visualize foci depicted on MIBG scintigraphy, predominantly when lesions were situated in the skull or brain. Kushner et al. studied the role of FDG-PET for monitoring in 51 patients (median age, 8 years) with high-risk NB after initial treatment. All patients underwent conventional diagnostic procedures, including MIBG scintigraphy, bone scintigraphy, CT and/or MRI, and bilateral bone marrow examination. The results indicated that FDG-PET and bone marrow examination suffice for monitoring high-risk NB in the absence or after resolution of cranial vault lesions and once the primary tumor is resected (122).

[11C]hydroxyephedrine (HED) and [11C]epinephrine (EPI) are newly developed radiotracer probes of sympathetic neuronal activity. HED is a norepinephrine analog, and it is the first PET tracer of the sympathetic nervous system suitable for human use. The ability of HED to map sympathetic innervation in the heart and depict pheochromocytoma was previously described (123). Similarly for NBs, uptake and retention of HED is high, allowing imaging within minutes after tracer injection (124). HED reflects the type 1 catecholamine uptake system, and as opposed to FDG, it serves as a specific metabolic marker of cells related to the sympathetic nervous system and thereby of NB. The role of HED-PET imaging in the clinical evaluation of NB is still uncertain. EPI is a true tracer of catecholamine physiology and is stored largely in the intracellular storage vesicles. High uptake and retention of this agent have been demonstrated in pheochromocytoma, and preliminary results have demonstrated high uptake in NB (125). A more recent animal study by Lee et al. demonstrated that the functional norepinephrine analog [11C]fluoropropyl-benzylguanidin has binding properties for adrenal tissues similar to those of 123I-MIBG, and this PET tracer could be of importance in the future (126). A recent case was reported presenting the value of fusion PET-CT in the HED imaging of NB (127), but no systematic studies of the added value of PET-CT in NB have yet been performed. 123I-MIBG SPECT and SPECT-CT are recommended as the methods of choice for the diagnosis and follow-up in NB. The role of PET and PET-CT with FDG and more specific tracers still remains to be established.

**Nephroblastoma (Wilms Tumor)**

Accounting for 90% of renal cancer in children, nephroblastoma (Wilms tumor) is the most common renal tumor in this age group (6). Wilms tumor covers a large spectrum of special variants that differ in morphologic features and in their prognosis. The most common initial manifestation of Wilms tumor is an asymptomatic abdominal mass, with typical findings on CT, ultrasound, and MRI. The diagnosis is verified by biopsy or excision. In the past, functional imaging with traditional nuclear medicine techniques such as bone and renal scintigraphy has been used for the evaluation of skeletal metastases or renal function in selected cases.

Diseases of the kidneys pose a special challenge for FDG-PET assessment because a large quantity of FDG is normally excreted through the kidneys. Increased FDG uptake in Wilms tumor was reported by Shulkin et al. (128). They examined three pediatric patients with known or suspected Wilms tumor—one patient had unilateral disease and two had bilateral tumors—and found increased FDG accumulation in all but one of the tumors. The latter was present in one of the patients with bilateral disease, where the left-side tumor lacked FDG uptake and the rightside had increased uptake. The reason for this difference was unclear but might be related to the pathologic heterogeneity of Wilms tumor. The results indicate that FDG uptake clearly represents active neoplasm but that the lack of tracer accumulation cannot exclude viable tumor. PET-CT might gain a role in the diagnosis of Wilms tumor in the future, especially for smaller tumors that otherwise could be difficult to discriminate from FDG excretion in the normal kidney tissue.

**INFECTION AND INFLAMMATION**

Ultrasound, CT, and MRI are often essential in the diagnosis and localization of infectious and inflammatory processes, but in difficult patients with structural alterations (e.g., after surgery), the precise diagnosis is sometimes very hard to obtain. Functional imaging with nuclear medicine procedures can often help localize such processes. [67Ga]citrate three-phase bone scans and indium 111 ([11In]-labeled or 99mTc-labeled WBC scintigraphy are available, together with more experimental methods, including avidin-mediated imaging (129,130) and imaging using radiolabeled chemotactic peptides (131), radiolabeled liposomes (132), and radiolabeled antibodies.
In adults, the use of FDG-PET can be very helpful in the detection of infection and inflammation (134). Several studies have shown the usefulness of [99mTc]dimer-captosuccinic acid (DMSA) SPECT in the diagnosis and monitoring of upper urinary tract infections in children (135,136). SPECT with [99mTc]labeled bisphosphonates has been reported of high value in septic arthritis of a lumbar facet joint in a 4-year-old child (137). SPECT with [111In]labeled white blood cells (WBCs) is useful for a range of infections indications. For skeletal infections, including postoperative infections in children, dual-tracer SPECT with [111In]labeled WBCs and [99mTc]labeled bisphosphonates is of high diagnostic value (138). Combined SPECT-CT offers improved anatomical localization of disease foci. This is likely to be of high clinical value in a number of pediatric clinical conditions. However, the value of SPECT-CT in pediatric infections and inflammation has not yet been thoroughly investigated.

Because neutrophils, activated macrophages, and other inflammatory cells have increased glycolytic activity, these cells show increased FDG uptake at sites of inflammation or infection (139). The value of FDG-PET for the diagnosis of infection or inflammation is almost exclusively based on studies in adults. Only a few reports have been published on the clinical value of FDG-PET in pediatric infectious diseases. Dreyer et al. evaluated the role of whole-body FDG-PET in pediatric patients (140). Ten patients (age range, 1 to 15 years; mean, 6 years) were referred to FDG-PET because of fever of unknown origin. All patients had previously undergone conventional diagnostic procedures for visualizing potential infectious foci, but the results had been negative or inconclusive. PET revealed pathologic uptake in 11 of 13 studies. One patient with a true-positive scan was an infant with an abscess in the heart after surgery that could not be diagnosed by any other modality. At second look, the abscess was found in the atrial wall. Franzius et al. reported a case where FDG-PET showed pulmonary aspergillosis in a 3-month-old girl with chronic granulomatous disease. FDG-PET was useful for staging and therapy monitoring during antimycotic treatment (141). Other case reports have demonstrated the ability of FDG-PET to detect infectious foci in children, including infectious mononucleosis (142) and occult infection in a child with acute myeloid leukemia (143). A recent case was reported where FDG-PET showed unexpected infectious colitis in a child who had a fever of unknown origin after receiving cardiac surgery (144). No systematic comparisons of FDG-PET and WBC scintigraphy are available in children, but a recent case with a 16-year-old girl with Lemierre syndrome (postanginal sepsis with abscesses) was positive on FDG-PET but negative on WBC scintigraphy performed with [111In]labeled granuloocytes (145).

Skehan et al. investigated 25 children aged 7 to 18 years with suspected inflammatory bowel disease (IBD) with FDG-PET as well as colonoscopy, including multiple biopsies. They found FDG-PET useful, with a sensitivity of 81% and a specificity of 85% for detection of IBD. FDG-PET also proved valuable in determining which segments of the bowel had active disease at the time of the investigation (146). The diagnostic and therapeutic impact of whole-body FDG-PET in children with chronic granulomatous disease has been examined. This X-linked or autosomal recessively inherited primary immunodeficiency disease with complete absence or malfunction of

**Figure 67.8** A 25-year-old man with chronic granulomatous disease and known furuncles. PET-CT scan was performed to screen for infectious lesions. MIP image (A) demonstrates focal increased FDG activity in both axillae and in the left lower lobe of the left lung corresponding to the furuncles and a left lower lobe pneumonia. Transaxial CT sections (B,D) and corresponding PET-CT sections (C,E) demonstrate bilateral axillary furuncles and also an uninfected cavity with an air-fluid level in the right upper lobe.
phagocytes results in defective killing of catalase-positive bac-
teria and fungi. Consecutive recurrent bacterial and fungal
infections are the major clinical manifestations. Identification of
inflammatory active granulomas and also differentiation of
active from inactive chronic lesions are important in the cli-
cal handling of the disease, especially before bone marrow
transplantation. CT is an established method of localizing the
site and extent of infective foci but is often unreliable in dis-
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demonstrated that PET was a useful supplement (147) (Fig. 67.8).

Experience with the use of SPECT-CT and PET-CT in
inflammation and infection is limited, but this number has
seemed very promising in a number of cases. PET can
be used to supplement (147) (Fig. 67.8).

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PET-CT and SPECT-CT
in Non-Neoplastic, Noninflammatory Pediatric Diseases

Liselotte Højgaard  Lise Borgwardt

With the recent availability of combined single-photon emission computed tomography (SPECT) and computed tomography (CT), along with the advent of high-performance CT, it is anticipated that this modality will be used for imaging benign pediatric diseases, for example, in lung scintigraphy for the imaging of congenital malformation and cystic fibrosis and for the workup for lung transplantations. In Kawasaki disease and complicating aneurisms of the coronary arteries, a "one-stop shop" 64-slice CT combined with cardiac SPECT might be useful. SPECT-CT will probably be useful in Meckel’s diverticulum scintigraphy and perhaps also in cholecsintigraphy of the newborn with jaundice. In benign pediatric diseases of the bones, recent reports are available on the beneficial use of SPECT-CT, especially for the spine. In the brain, positron emission tomography (PET)-CT and SPECT-CT are useful for the diagnosis of epilepsy but also in rarer diseases such as Sturge-Weber syndrome, Rett syndrome, neurofibromatosis, tuberous sclerosis, sickle cell encephalopathy, and traumatic brain injury. PET has been evaluated, and PET-CT might be play a role in pediatric imaging in the future.

INTRODUCTION

Combined single-photon emission computed tomography (SPECT)–computed tomography (CT) cameras have been available with low-dose CT for a number of years, and recently new scanners with high-performance CT with up to 64 slices have been introduced. Combined positron emission tomography (PET)-CT scanners have been commercially available since 2001. In children, SPECT-CT with low-dose CT has been used increasingly for iodine 123 (123I)-MIBG (meta-iodobenzylguanidine) scintigraphy for neuroblastoma, for indications for octreotide scintigraphy, and for indium 111 (111In) white blood cell (WBC) scintigraphy for infections. In the case of non-tumor and non-infection indications, the availability of SPECT-CT with multi-slice CT will probably lead to more widespread use of this modality for a variety of indications in pediatric nuclear medicine.

SPECT-CT AND PET-CT IN BENIGN PEDIATRIC DISEASES OF THE BRAIN

In pediatric non-neoplastic neurology, PET and SPECT are regarded as accurate and noninvasive modalities for studying brain activity, elucidating the complexities of the
developing brain, and understanding disease processes (1). The maturational changes relevant for pediatric neurological interpretation were described by Chugani et al. (2) using PET (Fig. 66.6). Muller et al. (3) studied brain organization for language in children, adolescents, and adults with left hemispheric lesions. They found enhanced postlesional plasticity in childhood.

A simplified quantification method for measuring cerebral glucose utilization in early infancy was published by Suhonen-Polvi et al. (4). If blood samples cannot be obtained, SUV represents an alternative for estimation of cerebral glucose uptake and thus for interindividual comparison of patients.

The majority of publications discussing pediatric brain PET and SPECT in clinical neurology are concerned with the diagnosis of epilepsy (Fig. 68.1). PET and SPECT are used in combination with clinical findings, neurophysiologic evaluation, electroencephalography monitoring, and magnetic resonance imaging (MRI) studies, and they have proven very useful for exact preoperative localization of the epileptogenic focus. However, authors of comparative localization studies have come to divergent conclusions regarding the priority of the different methods. The International League against Epilepsy (ILAE) commission report recommends the priority of the different examinations (5).

Nearly all results of PET in children with epilepsy have been obtained using interictal studies because of the very complicated operational problems associated with ictal PET studies and the long period of tracer uptake in fluoro-deoxyglucose (FDG) PET (see also Chapter 25). Nevertheless, some favorable results have been reported employing ictal PET in patients with continuous or frequent seizures (6).

In addition to PET with FDG, other tracers, such as carbon 11 [11C]flumazenil (FMT), have been used in children with epilepsy (7). The authors of these studies concluded that PET with other tracers is significantly more sensitive than FDG-PET for the detection of cortical regions of seizure onset with frequent spiking in patients with extratemporal epilepsy, whereas PET with both FDG and [11C]flumazenil shows only limited sensitivity in the detection of cortical areas with rapid seizure spread. Alpha-[11C]-methyl-L-tryptophan (AMT) was found to be a promising diagnostic tool for localization of epileptogenic areas in patients with tuberous sclerosis (8).

Ictal–interictal SPECT maps cerebral perfusion during and shortly after single seizures, compared with the interictal state. Often in unilateral mesial temporal lobe epilepsy–hippocampus sclerosis (MTLE-HS), the retention of interictal technetium 99m (Tc)–HMPAO (hexamethylpropyleneamine oxime) or 99mTc-ECD (ethyl cysteinate dimer) is mildly or moderately decreased in the anterior temporal lobe ipsilaterally, but false lateralization of interictal temporal lobe hypoperfusion occurs in perhaps 10% of patients. When the radioligand is injected during a complex partial seizure, the temporal lobe of ictal onset usually shows a great increase in radioligand uptake.
retention, and false lateralization is quite rare when using coregistered ictal versus interictal temporal lobe perfusion maps, the subtraction ictal SPECT coregistered to MRI (SISCOM) (Fig. 68.2).

Peri-ictal SPECT studies of temporal lobe epilepsy have shown a characteristic evolution in the regional perfusion, as the region of ictal hyperperfusion declines to severe hypoperfusion for several minutes postictally, and then within 20 minutes perfusion increases back to a milder degree of interictal hypoperfusion. This phenomenon has been called "postictal switch" and can cause false lateralization when interictal scans are compared with early postictal scans that are mistakenly considered to represent an ictal scan. Ictal–interictal SPECT studies require considerable expertise in the timing of the radioligand injection, which must be performed with continuous EEG. Thus it appears likely that ictal SPECT maps are areas of ictal onset and of most intense seizure propagation.

FDG-PET studies in term newborns with hypoxic-ischemic encephalopathy have shown that during the subacute period after perinatal asphyxia, cerebral glucose metabolism correlates well with the severity of encephalopathy and short-term clinical outcome (9,10). SPECT studies have also been used in studying perinatal asphyxia (11).

A summary of functional imaging of neuropsychiatric disorders in childhood was published by O'Tuama et al. (12). The focus has primarily been on attention deficit hyperactivity disorder (13,14), anorexia nervosa (15), bulimia nervosa (16), and obsessive–compulsive disorder (17).

FDG-PET has also been used to investigate different types of inflammatory neurological diseases in infants, such as Rasmussen encephalitis (18,19) (Fig. 25.6), and to study HIV-1–infected children born to seropositive mothers (20).

In addition, PET and SPECT have been used to study the pathophysiology of many other childhood brain disorders, such as Sturge-Weber syndrome (21–25), Rett syndrome (26,27), neurofibromatosis (28), tuberous sclerosis (8), sickle cell encephalopathy (29,30), and traumatic brain injury (31).

**SPECT-CT AND PET-CT IN BENIGN PEDIATRIC DISEASES OF THE THORAX**

For a variety of indications in pediatric nuclear medicine, lung perfusion scintigraphy with $^{99m}$Tc-MAA and lung ventilation scintigraphy with $^{99m}$Tc-Technegas or krypton 81m employ a planar acquisition technique, with SPECT as a supplement to the planar acquisitions. The introduction of SPECT-CT is anticipated to lead to increased use of this modality combination. In children with lung emboli due to coagulopathies, chemotherapy, or radiation therapy or with complications due to Port-a-Cath catheters or interventional lines, combined SPECT-CT lung perfusion and ventilation scintigraphy will probably yield much higher sensitivity and specificity than the present planar scintigraphy. However, no studies are available yet.

In children with structural and functional abnormalities of the lung, including congenital malformations such as bronchopulmonary dysplasia, it is also assumed that the planar lung ventilation scintigraphy and lung perfusion scintigraphy can be improved through the use of SPECT-CT. For cystic fibrosis, lung scintigraphy is frequently used in cases of exacerbations. For workup for lung transplantation and for follow-up after lung transplantation, lung perfusion scintigraphy and ventilation scintigraphy are also used. SPECT-CT can be used in the future, but the radiation burden due to repeated CT studies may limit its use. In children who have swallowed foreign objects such as coins or peanuts, where conventional x-ray or bronchoscopy cannot identify the foreign object, lung scintigraphy is sometimes useful. SPECT may improve the chances of finding the foreign object, with CT as an attractive supplement. In children with shunts where echo Doppler cardiography is not sufficient, lung scintigraphy may add valuable information.

In children with lung problems due to, for example, pulmonary fibrosis following graft-versus-host reactions after bone marrow transplants, lung scintigraphy may also be improved with SPECT, with CT used in doubtful cases. The combined use of functional and anatomical imaging will yield better diagnostic power in patients with complicated anatomy.

Myocardial scintigraphy with SPECT is used in children as follow-up after heart transplantation, where CT might be used for low-dose attenuation correction (32). A full diagnostic CT is not recommended due to the radiation burden, as follow-up will entail investigations every year.
SPECT-CT AND PET-CT IN BENIGN PEDIATRIC DISEASES OF THE ABDOMEN

In children with gastrointestinal bleeding and a suspected Meckel diverticulum, $^{99m}$Tc-pertechnetate scintigraphy is performed. The traditional planar images can be difficult to interpret, and a supplementary SPECT-CT scan might be useful. In patients with a negative investigation, a SPECT-CT scan should not be added. In children who have profuse bleeding and for whom a bleeding scintigraphy is indicated, the planar image acquisition may also benefit from SPECT-CT if the bleeding is found and the anatomical localization is difficult.

Scintigraphy of the spleen is performed on rare occasions for the diagnosis of accessory spleens after splenectomy due to thrombocytopenia. In patients for whom surgery or radiotherapy planning is necessary, an additional SPECT-CT might improve the anatomical localization.

Cholescintigraphy in the newborn baby with jaundice is the method of choice for the diagnosis of biliary atresia with $^{99m}$Tc-mebrofenin. Whether a SPECT-CT with high diagnostic quality 64-slice CT and biliary contrast agents will increase sensitivity and specificity has not been determined, but future trials might be warranted.

SPECT-CT AND PET-CT IN BENIGN PEDIATRIC DISEASES OF THE KIDNEYS

Urinary tract infections are frequent in infants and are often complicated by several relapses. The radiation burden due to investigations is therefore important to consider. In patients with acute pyelonephritis, the investigation of choice is ultrasound for dilatations and $^{99m}$Tc-DMSA for renal scars. No studies report on the diagnostic impact of SPECT-CT compared with planar images alone for $^{99m}$Tc-DMSA, but in cases where a CT scan is planned, it seems wise to perform an image fusion study with simultaneous acquisition of SPECT and CT images.

For traditional dynamic renal scans with $^{99m}$Tc-MAG3 used to establish right and left renal function, perform a post-transplantation evaluation, check for renal hypertension, or assess drainage of the pelvis, use of SPECT-CT does not seem justified (35).

SPECT-CT AND PET-CT IN BENIGN PEDIATRIC DISEASES OF BONE

Avascular necrosis of the femoral head may occur in adolescence after steroid therapy, with diagnosis made by bone scintigraphy. Whether CT will add diagnostic information is not known at present, but the promising results from 64-slice CT with contrast agents may lead to the use of SPECT-CT for bone scintigraphy as part of a “one-stop shop” investigation. The same goes for a variety of other indications for bone scintigraphy, including dissecting osteochondritis and Calve-Legg-Perthe disease with osteonecrosis of the proximal femoral head.

In “battered child syndrome,” whole-body bone scintigraphy might also benefit from supplemental SPECT-CT scanning.

Lesions of the spine, especially the lumbar spine, are at present investigated by SPECT bone scintigraphy for a variety of conditions in which the improved anatomical localization obtained by SPECT would be useful. With the growing use of multi-slice CT with contrast agents, SPECT-CT may be relevant, for example, for low-back pain, discitis, small fractures, and spondylolysis, for which recent reports on the use of SPECT-CT are now available (36–38).

In children with congenital malformations of the facial skeleton and skull, such as Apert-Cruzon syndrome, bone scintigraphy with SPECT-CT might be useful, with 3-D images for surgical reconstructions and also for follow-up. In these patients, brain FDG-PET-CT or FDG-PET-MRI is used for monitoring brain development.

In patients with mandibular congenital malformations and in children with growth dysplasia of the mandible, bone scintigraphy with quantitative ratio calculations over the joints is used at present. SPECT-CT may be advantageous here. In patients where scintigraphy is used to assess bite dysfunction, especially where repeat investigations are needed for a relatively benign condition, the use of supplementary CT seems unjustified.

In sports injuries, bone scintigraphy is often indicated, along with the use of SPECT for a variety of conditions. The use of CT as a supplement will depend on the problem. In children with metatarsal or navicular necrosis, such as Osgood-Schlatter disease, or generalized growth disorders, CT is probably not necessary as part of a routine.

SPECT-CT AND PET-CT IN SYSTEMIC BENIGN DISEASES OF THE CHILD

In children with Takayasu arteritis, PET-CT with FDG might be useful for the diagnosis of vascular involvement (39). In children with Langhans cell histiocytosis, MR diagnosis is often supplemented with FDG-PET-CT and indium 111 $^{111}$In-octreotide scintigraphy to ensure that all lesions are diagnosed (40). If the child has many clear lesions, planar scintigraphy will probably be sufficient, but if the diagnosis
is unclear, SPECT-CT might increase the diagnostic sensitivity and specificity.

**CONCLUSION**

In children with non-tumor and non-infectious indications, an increase in the use of SPECT-CT is anticipated in the future. SPECT may be used as a supplement to planar acquisitions in a number of investigations, along with very low dose CT for attenuation correction or diagnostic quality contrast-enhanced CT as part of the routine diagnostic workup. In selected cases, CT might be used as a supplement if the extra radiation burden to the child is justified. Especially in lung scintigraphy; bone scintigraphy; and specific gastrointestinal studies as Meckel diverticulum scintigraphy, bleeding scintigraphy, and cholecist scintigraphy for biliary atresia, the use of SPECT-CT might increase in the future. As in adults, PET-CT will take over from PET alone, also with due consideration given to the radiation dose. Image fusion, especially in combined scanners, will lead to more accurate localization of pathology, which is especially important where there is complex anatomy, such as congenital malformations. For follow-up and treatment evaluation, combined functional imaging (SPECT or PET) and anatomical imaging (CT) will have special advantages in growing children, as changes in function can be difficult to evaluate due to the growth of organs.

For minimally invasive surgery and radiotherapy planning (Chapter 57), accurate lesion description is especially necessary, and here also combined functional and anatomical imaging will be of benefit.

The large studies needed for evidence-based medicine are difficult to achieve in the case of children and adolescents, especially studies of rarer diseases. A pediatric nuclear medicine network that incorporates telemedicine and increases the opportunities for a second opinion is therefore an attractive possibility.

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