The discipline of nuclear medicine consists of radionuclide imaging and radionuclide therapy with the number of patients having radionuclide imaging studies being much greater than those who have radionuclide therapy. The use of radionuclide imaging and therapeutic procedures is increasing because they have an important role in the management of patients with cancer.

Radionuclide imaging is the most often performed procedure in molecular imaging. Nuclear medicine has been performing molecular imaging since the first radionuclide studies that were performed with $^{131}$I sodium iodide for diagnosing and treating thyroid cancer.

To perform radionuclide imaging, a radioactive material (radiopharmaceutical) is administered and the radiation emitted by the radiopharmaceutical detected by sensitive radiation detectors located outside of the patient being studied. Radiopharmaceuticals that provide more sensitive and specific detection of cancers are being developed, and the methods of detecting the radiation are improving.

Radiopharmaceuticals consist of a radionuclide and a molecule that determines the localization. For $^{131}$I sodium iodide, the radionuclide and the molecule are the same. For technetium-$^{99m}$Tc methylene diphosphonate (MDP), the radionuclide is $^{99m}$Tc and the molecule that determines the distribution is MDP. Radiochemists are continuing to improve the ways for radiolabeling new molecules that are developed by basic scientists in molecular biology and pharmacology laboratories.

Radionuclide imaging is commonly separated into single-photon imaging and positron imaging. The devices used for imaging the single-photon-emitting radionuclides are different than those for imaging positron-emitting radionuclides. Single-photon radionuclides emit gamma rays in the energy range of approximately 75 to 360 keV. These radionuclides include $^{99m}$Tc, $^{131}$I, $^{201}$Tl, $^{111}$In, $^{67}$Ga. Devices known as gamma cameras detect these radionuclides, and these devices can perform regional imaging, whole-body imaging, and single-photon emission computed tomography (SPECT) imaging.

Positron-emitting radionuclides such as $^{18}$F, $^{11}$C, $^{13}$N, and $^{15}$O emit a positive electron from the nucleus. The positive electron travels a short distance through tissue and interacts with a free or loosely bound negative electron. The positive electron and negative electron annihilate each other, and their mass is converted to energy. This energy consists of two photons, each of 511 keV, which are given off in opposite directions. The simultaneous detection of the two photons by detectors placed around the body provides a line of response. By obtaining multiple lines of response, the distribution of radioactivity in the body can then be determined. Positron emission tomography (PET) is able to more accurately correct for scatter of the radiation in the body and absorption of the radiation by the body than is SPECT imaging. Furthermore, PET provides higher resolution lesion detection than SPECT imaging.

A major advance that is occurring in radionuclide imaging is the combination of gamma camera and computed tomography (CT) scanners and the combination of PET and CT scanners. The radionuclide images provide excellent information concerning the biology of a process but very little, if any, anatomic information. By combining the high-resolution anatomic information from CT imaging and the biologic information from SPECT and PET imaging, greater diagnostic information is available. Furthermore, the CT scan can provide information concerning the attenuation of the photons in the body, and this attenuation can be corrected for more accurate radionuclide imaging.

This chapter divides radionuclide imaging into the single-photon techniques and positron emission tomography. Radionuclide probe detectors are being increasingly used for the intraoperative localization of radioactivity for such studies as lymphoscintigraphy for the identification of sentinel lymph nodes, but this is not discussed in this chapter.

**SINGLE-PHOTON TECHNIQUES**

Gamma camera imaging is available at every major hospital in the United States. Radiopharmaceuticals are available from central radiopharmacies, which provide the requested radiopharmaceutical on a unit dose basis. Thus, the hospital or outpatient imaging center does not need to compound the radiopharmaceutical on site, but can purchase it in a form that is ready to be administered. The central radiopharmacies are able to provide all the radiopharmaceuticals used in imaging.

In this section, the studies that are performed using single-photon-emitting radionuclides in cancer imaging are addressed.

**BONE SCANNING**

Radionuclide bone imaging is one of the most commonly performed procedures in nuclear medicine (Figure 36h-1). The bone scan has been used for more than 40 years to evaluate patients with suspected metastatic bone disease, primary bone tumors, and primary soft-tissue tumors. Bone scintigraphy with $^{99m}$Tc MDP is very sensitive for detecting bone disease, it is widely available, and it is safe. The radiation dose that the patient receives is comparable to that of conventional radiographic procedures. Because the whole body is included in the imaging, it is an excellent method for evaluating patients with suspected metastatic disease that can occur throughout the skeleton. Abnormal areas of accumulation are seen related to osteoblastic activity. Purely lytic lesions such as multiple myeloma may be missed on the bone scan.

The bone scan can detect an abnormality prior to the radiograph becoming abnormal. Bone scans are quite sensitive for the detection of metastatic disease, but the specificity is lower than the sensitivity. Any process involving bone will result in increased bone turnover and an abnormality on the bone scan. Thus, inflammatory, traumatic, and metabolic abnormalities will result in increased areas of localization on the bone scan. Plain radiographs are frequently needed to correlate with the bone scan to determine the cause of the abnormality on the bone scan. For some lesions, such as sacral abnormalities, CT scanning is particularly helpful for correlation. For other lesions, magnetic resonance imaging (MRI) correlation may be helpful.

Certain primary cancers, such as breast cancer, lung cancer, and prostate cancer, commonly spread to the bone. However, not every patient with these cancers needs a bone scan. The true positive yield in stage 1 and stage 2 breast cancer is very low (< 3%). Thus, these patients should only have preoperative scans when they are symptomatic or have laboratory values worrisome for metastatic disease. The use of prostate-specific antigen (PSA) has helped to clarify the role of bone scanning in the initial evaluation of patients with prostate cancer. Several studies show that bone scanning is not indicated in patients with newly diagnosed prostate cancer if the serum PSA levels are in the lower range of abnormal (10 to 20 mg/mL) and if they do not have bone pain suggestive of metastatic disease.
**Somatostatin Receptor Scintigraphy and Metaiodobenzylguanidine**  
Somatostatin receptors have been identified on cells of neuroendocrine origin, as well as on other cells such as lymphocytes. The development of monoclonal antibodies for imaging cancer has been very difficult. The only monoclonal antibody imaging that is performed in many patients is ProstaScint imaging. The other antibodies approved by the Food and Drug Administration have not proven to have adequate sensitivity and specificity to be useful. The clinical study with ProstaScint has not shown great accuracy, but the studies provide information that is not available from other techniques. For example, in the presurgical staging of prostate cancer, ProstaScint has a sensitivity of 63% for detecting lymph node metastasis at the time of surgery. Bone scans are more sensitive than ProstaScint imaging for detection of osseous metastases. The imaging of ProstaScint is not easy. The antibody is labeled with $^{111}$In, and SPECT and planar imaging are performed 3 to 5 days after injection. Performing the SPECT scans on a SPECT/CT device improves the anatomic information for correlation with the ProstaScint images.

**Gallium Scintigraphy**  
$^{67}$Ga-citrate scintigraphy is useful in the management of lymphoma: staging the extent of the disease, determining the response to therapy, detecting relapse or progression of disease, and predicting outcome. $^{67}$Ga scintigraphy has been used in other cancers such as melanoma, hepatocellular carcinoma, sarcoma, and lung cancer, but its use in cancers other than lymphoma is extremely limited. The primary use of $^{67}$Ga scintigraphy in Hodgkin’s and non-Hodgkin's lymphoma has been to evaluate the response to treatment in assessing a residual mass after therapy. $^{67}$Ga scintigraphy is able to assess the response based on the observation that gallium is a tumor viability agent. Several studies demonstrate that patients who had positive scans at the end of treatment either died or had tumor progression, whereas most patients with negative scans after treatment achieved complete remission.

Although $^{67}$Ga scintigraphy has been the standard for assessing therapeutic response in lymphoma in many institutions for many years, FDG-PET (2-[18F]-fluorodeoxy-d-glucose–positron emission tomography) imaging is superior to $^{67}$Ga scintigraphy, and PET imaging has replaced gallium imaging in most institutions.

**Thallium-201 and Technetium-99m Methoxyisobutyl Isonitrile**  
$^{201}$Tl was originally described as a myocardial perfusion and viability agent, and has shown some effectiveness in oncology. $^{99m}$Tc methoxyisobutyl isonitrile (MIBI) is now replacing $^{201}$Tl scintigraphy in many nuclear cardiology applications and is being increasingly used in oncologic imaging. $^{201}$Tl chloride behaves similarly to potassium chloride in most biologic systems. Tumors concentrate potassium ions and thallium ions in a similar manner. $^{99m}$Tc MIBI is a lipophilic cation greatly influenced by the negative charges on mitochondria and appears to concentrate related to the increased mitochondrial density in tumors. The washout of MIBI from tumor cells is related to the multidrug-resistant P-glycoprotein system that has MIBI as a substrate. The rapid clearance of MIBI from tumor cells may be a marker of multidrug resistance. $^{201}$Tl and MIBI have been evaluated in several tumors and they have gained limited use in some tumors. Brain tumors, bone and soft-tissue sarcomas, lung cancers, thyroid cancer, and breast cancer accumulate these tracers. However, only in breast cancer has MIBI gained significant use. MIBI breast studies appear to be useful to patients at high risk and who have mammograms that are difficult to interpret. For example, women with dense breasts or who have architectural distortion and are at high risk for having malignant lesions may benefit from MIBI imaging.

**Monoclonal Antibody Imaging**  
The concept of radiolabeling a monoclonal antibody developed to tumors appears very appealing as a “magic bullet.” The development of monoclonal antibodies for imaging cancer has been very difficult. The only monoclonal antibody imaging that is performed in many patients is ProstaScint imaging. The other antibodies approved by the Food and Drug Administration have not proven to have adequate sensitivity and specificity to be useful. The clinical study with ProstaScint has not shown great accuracy, but the studies provide information that is not available from other techniques. For example, in the presurgical staging of prostate cancer, ProstaScint has a sensitivity of 63% for detecting lymph node metastasis at the time of surgery. Bone scans are more sensitive than ProstaScint imaging for detection of osseous metastases. The imaging of ProstaScint is not easy. The antibody is labeled with $^{111}$In, and SPECT and planar imaging are performed 3 to 5 days after injection. Performing the SPECT scans on a SPECT/CT device improves the anatomic information for correlation with the ProstaScint images.

**Positron Emission Tomography**  
The utilization of PET imaging is rapidly increasing in the United States. The radiopharmaceutical used for oncologic PET imaging is FDG. FDG behaves very similarly to glucose. Both FDG and glucose are transported across the cell membrane by glucose transporter proteins,
and both are phosphorylated. Once phosphorylated, the FDG-6-phosphate is not further metabolized in most tissues. However, in the liver, because of the high concentration of phosphatase enzymes, the FDG-phosphate can be dephosphorylated and is transported out of the cell. Malignant cells have an increased glycolytic rate. FDG is concentrated in malignant cells more than in normal tissue.

For a clinical PET study, the FDG is administered to the patient after a 4-h fast. Approximately 1 h after injection of the FDG, the patient is placed in the PET scanner for the imaging. The imaging procedure takes approximately 30 min for the whole-body study.

Medicare first started paying for FDG-PET scans in 1998. In late 2002, Medicare was paying for diagnosis, staging, and restaging of lung cancer.25 PET is very accurate in the characterization of lung nodules that are indeterminate on a CT scan (Figure 36h-3). A meta-analysis of 1,174 focal pulmonary lesions found that PET operates at sensitivity of 96.8% and a specificity of 77.8%.26 False-positive nodules generally relate to granulomatous inflammatory processes.

PET is more accurate than CT in staging the mediastinum. In patients who have had conventional imaging for evaluation of metastatic disease, PET will identify previously undetected metastatic disease in 10% to 15% of patients (Figure 36h-4). PET is also very accurate in monitoring the effects of treatment.

**Lung Cancer**  The most common use of FDG-PET imaging is in diagnosis, staging, and restaging of lung cancer.25 PET is very accurate in the characterization of lung nodules that are indeterminate on a CT scan (Figure 36h-3). A meta-analysis of 1,174 focal pulmonary lesions found that PET operates at sensitivity of 96.8% and a specificity of 77.8%.26 False-positive nodules generally relate to granulomatous inflammatory processes.

PET is more accurate than CT in staging the mediastinum. In patients who have had conventional imaging for evaluation of metastatic disease, PET will identify previously undetected metastatic disease in 10% to 15% of patients (Figure 36h-4). PET is also very accurate in monitoring the effects of treatment.

**Colorectal Carcinoma**  PET is not frequently used for the diagnosis and initial staging of patients with colorectal cancer. It is used in the initial staging of high-risk patients for whom surgery could be avoided if metastasis could be identified.27

FDG-PET in colorectal cancer patients is primarily used for the detection of recurrent or metastatic disease. PET is more accurate than CT for staging recurrent cancer. The sensitivity of FDG-PET imaging is lower for mucinous adenocarcinoma than nonmucinous adenocarcinoma. PET is useful in evaluating patients who have a history of colorectal cancer, rising carcinoembryonic antigen (CEA), and negative CT. Approximately 70% of these patients will have the cause of the rising CEA detected on the FDG-PET scan.

**Malignant Melanoma**  PET imaging does not replace lymphoscintigraphy in identification of regional nodal disease. Patients with intermediate or high-risk tumors benefit from having a PET scan because of the prevalence of regional or distant disease at presentation in these patients.28 Several studies show that PET is more sensitive than conventional imaging in staging metastatic melanoma. In some institutions, PET is being used as a surveillance procedure in high-risk patients. In patients with recurrent tumor, FDG-PET can identify the distribution of tumor. Unsuspected distant metastases are identified in approximately 15% of patients, which changes the patient from surgical to nonsurgical therapy.

**Lymphoma**  PET is used in lymphoma for pre-treatment staging, posttreatment detection of residual disease, prediction of treatment effect, and diagnosis of recurrent tumor.28 FDG-PET is very accurate in staging Hodgkin’s disease and high-grade non-Hodgkin’s lymphoma. FDG-PET is more accurate in staging patients than gallium or CT scanning.7,8

Many studies demonstrate the ability of FDG-PET to differentiate viable tumor from fibrosis in a residual posttreatment mass. PET is superior to gallium scintigraphy in making this differentiation. Even early during the course of therapy, FDG-PET imaging can predict eventual...
than PET and/or CT scanning in detection of paraesophageal lymph nodes, but PET is more accurate in the detection of distant disease. PET is also used in evaluating response to therapy of the esophageal cancer, and in assessing recurrent esophageal cancer after therapy.

**BREAST CANCER**  FDG-PET at this time does not play a role in diagnosis of breast cancer\(^{30}\) nor is it accurate enough to replace lymphoscintigraphy in the evaluation of axillary lymph nodes. FDG-PET is accurate in staging breast cancer and in detection of metastatic disease. Furthermore, PET can predict early during a course of therapy whether or not the patient will respond to the therapy.

**CONCLUSION**

Radionuclide imaging in cancer medicine consists of standard imaging techniques and new methods. PET imaging is playing an increasingly important role in diagnosis, staging, and restaging of many cancer patients. New radiopharmaceuticals will be available that will improve the ability to diagnose and stage cancer.

**REFERENCES**