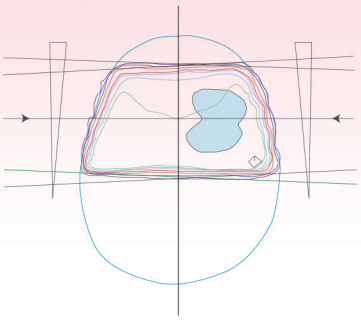
CHAPTER

11 Nuclear Medicine



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Molecular imaging techniques such as nuclear medicine are playing an increasingly important role in oncology. In particular, hybrid imaging modalities such as positron emission tomography/computed tomography (PET/CT) and single photo emission computed tomography/computed tomography (SPECT/CT) frequently provide more accurate initial staging and follow-up in oncology patients. Moreover, metabolic changes to therapy almost always precede anatomic changes, and functional imaging can be useful to assess early response to therapy.

Because CT is used routinely for radiation treatment planning, adding the metabolic information provided by PET or SPECT tracers provides a natural opportunity for selectively targeting tumor subpopulations. Adaptive treatment plans based on PET imaging are currently being investigated.

POSITRON EMISSION TOMOGRAPHY (PET)

Despite the exquisite spatial resolution of CT and magnetic resonance imaging (MRI), the physiologic aspects of disease processes are generally not revealed by these anatomically based modalities. Anatomic modalities also have shortcomings in assessing the early response to treatment and in distinguishing responders from nonresponders.

Over the past half-century, a variety of nuclear medicine probes have been used to evaluate disease processes at the cellular level. Nuclear medicine is the only clinical discipline using intracellular contrast agents in imaging, and it is therefore more sensitive than anatomic modalities in detecting disease processes. The concentration of tracer needed (picomolar levels) for PET imaging is many orders of magnitude less than needed to measure enhancement using MR or CT contrast agents (millimolar levels). On the other hand, nuclear medicine imaging techniques have generally suffered from low specificity and low spatial resolution, the latter being associated with the physics of single-photon-emitting radiotracers. Hybrid imaging (SPECT/CT, PET/CT, PET/MRI) affords the opportunity to combine the strengths of both anatomic and functional imaging.

PET is a nuclear medicine modality that uses positron emitters such as ^{18}F, ^{15}O, ^{13}N, and ^{11}C. The fact that these nuclides are components of common biologic molecules makes PET particularly suitable for visually capturing a wide range of biologic pathways. With the exception of ^{18}F these radionuclides have a relatively short half-life and generally require an on-site cyclotron for availability. The longer half-life (110 min) of ^{18}F has enabled ^{18}F PET tracers to be produced commercially at centralized cyclotron facilities and distributed widely for PET imaging.

Currently, the most widely used PET tracer is the glucose analog 2-deoxy-2-[^{18}F]fluoro-D-glucose (fluorodeoxyglucose [FDG]). FDG-PET has proven applications in staging and restaging a variety of malignancies. Currently, clinical investigations are under way using FDG-PET to evaluate early response to therapy, and some trials are incorporating adaptive treatment strategies based on the metabolic response. Although there is keen interest in developing additional PET tracers, FDG has proven to be a versatile general-purpose radiopharmaceutical and will likely remain a "workhorse" oncology tracer in the foreseeable future.

BASIC PHYSICS OF POSITRON EMISSION TOMOGRAPHY

The radioisotope portion of the molecule used in PET imaging emits a positron (i.e., positively charged electron), which travels a distance of a few millimeters in tissue before it collides with a negatively charged electron. This collision annihilates the entire mass of the positron and electron, generating two photons with energy of 511 KeV each. These two photons travel at the speed of light in exactly opposite directions (i.e., 180 degrees apart). Coincident detection of these two photons by two oppositely positioned detectors in the PET scanner results in images with a much higher resolution compared with the conventional, single-photon nuclear medicine studies.

PET/CT allows metabolic information from PET to be combined with the anatomic information from CT. PET/CT increases the diagnostic accuracy compared with stand-alone PET. In PET/CT, the patient undergoes a CT scan, followed by a PET scan, without changing the patient's position. PET for most oncologic indications is acquired from the base of the skull through the upper thighs. In some instances, such as in melanoma patients, PET is acquired from the vertex of the skull through the toes. The CT portion of PET/CT is acquired within seconds, whereas the PET acquisition time for each bed position (about 15 cm) is several minutes; the total PET acquisition time in newer machines is 15 to 25 minutes.

In addition to delivering anatomic information, the CT portion of PET/CT is used to measure the attenuation of the x-ray photons traveling through the patient to produce the so-called attenuation map and correct the PET data for tissue attenuation. During PET acquisition, photons from structures deep in the abdomen or pelvis are more strongly attenuated than those from superficial structures and the chest. The intensity of uptake in deeper structures is underestimated on nonattenuation-corrected PET images; the intensity of uptake in the deeper structures is normalized to the intensity of uptake in the superficial structures on the attenuation-corrected PET images (Figure 11-1). Attenuation correction of the PET data is also a prerequisite for quantification of radiotracer uptake in PET/CT scans.

Spatial alignment between the PET and CT scans is crucial both for correct anatomic localization and for accurate quantification. Misalignment may be caused by the changed position of a body part (e.g., neck, legs) or physiologic changes in the position of an organ (e.g., respiratory movement) between the CT scan and PET scan. The most commonly encountered problem occurs at the lung bases because CT is obtained over a short time interval and PET images are acquired with the patient quietly breathing. This respiratory misregistration can be minimized by acquiring the CT scan with respiration suspended in quiet end-expiration. Because the degree of misalignment and resulting mislocalization can be significant, the

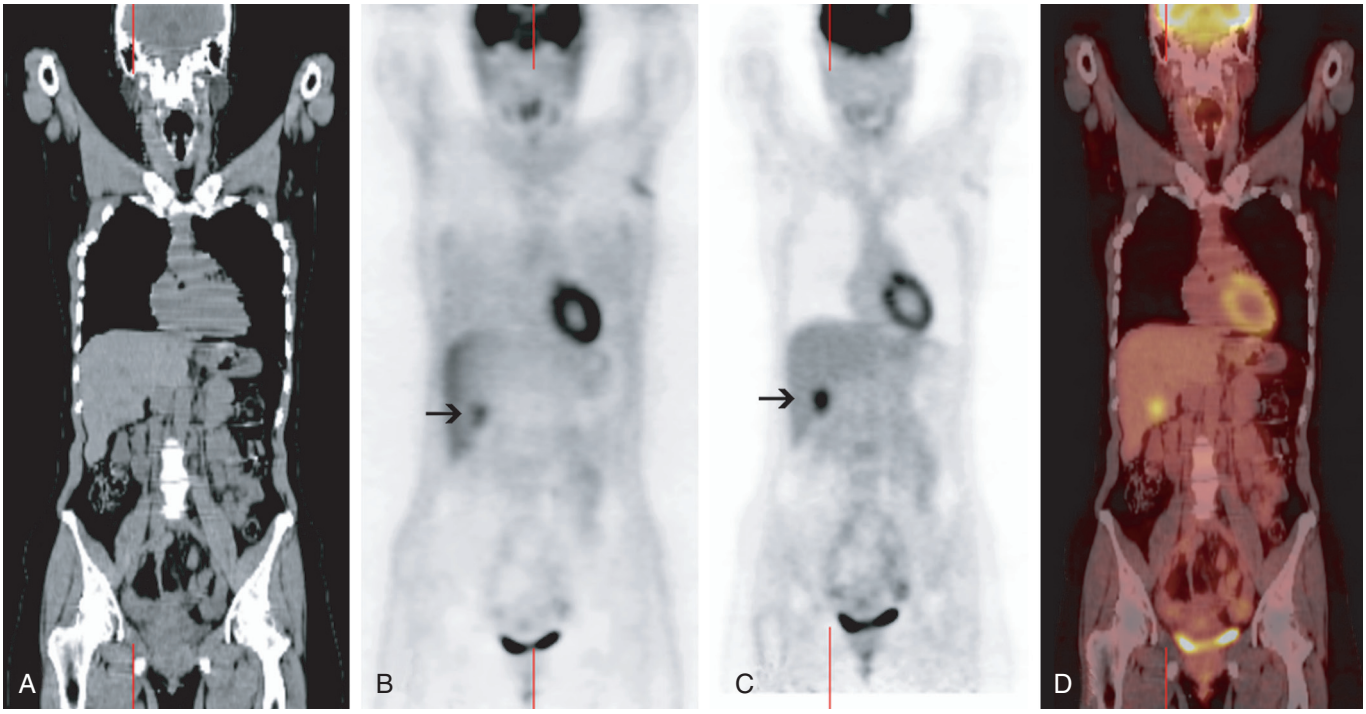

Figure 11-1 CT **(A)** provides diagnostic information (morphology), anatomic localization **(D)**, and photon attenuation data to equalize the intensity of uptake between deeper and superficial structures on the PET scans. In this example, the metastatic liver lesion *(arrow)* is better appreciated on the attenuation-corrected PET image **(C)** than on the nonattenuation-corrected PET image **(B)**.

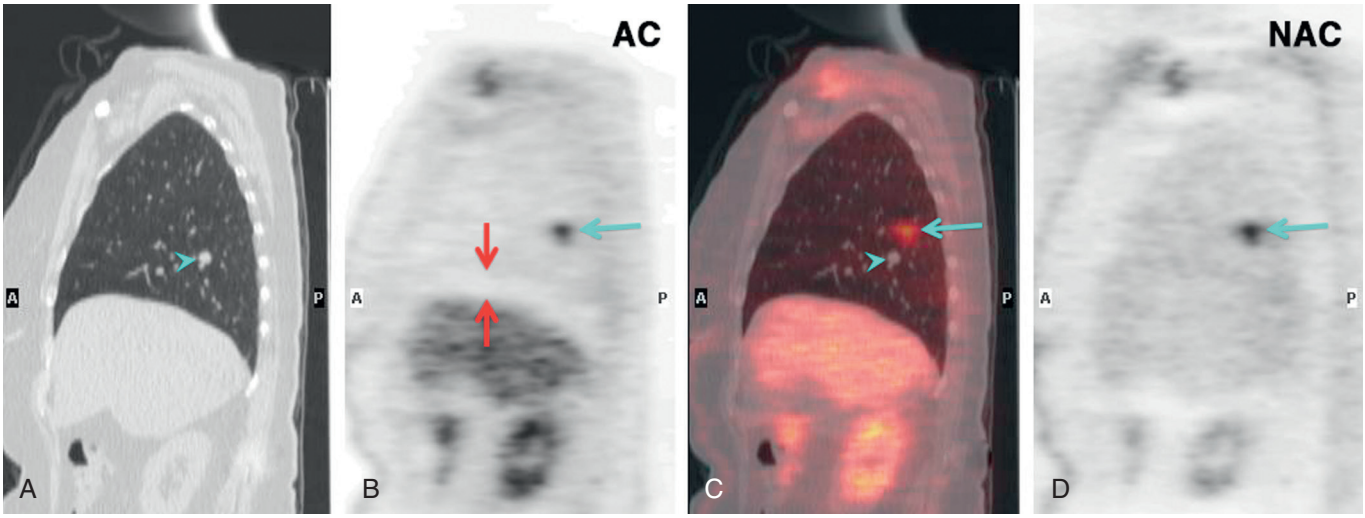

Figure 11-2 Respiratory misregistration. Patient took a full inspiratory breath during the CT scan **(A)**, while FDG-PET imaging (NAC = without attenuation correction) was obtained with the patient quietly breathing **(D)**. Consequently, the lung nodule on CT *(blue arrowhead)* does not correlate with the hypermetabolic focus *(blue arrow)* on PET, as illustrated on the fused PET/CT image **(C)**. On the attenuation-corrected (AC) PET images **(B),** a photopenic rim is noted at the lung base reflecting diaphragmatic misregistration *(red arrows)*. Because the CT scan is used for attenuation correction of the PET images, standardized uptake value (SUV) measurements made on misregistered lesions may not be accurate.

radiologist must be cautious when interpreting or quantifying the attenuation-corrected PET/CT images or using PET/CT images for radiation therapy planning. The magnitude of this misalignment can be assessed by using the fusion display of the nonattenuation-corrected PET images with CT. In case of significant misalignment, the nonattenuation-corrected PET images should be reviewed without fusion with CT, and the metabolic findings on PET should be correlated side by side with the anatomic findings on CT (Figure 11-2).

Current PET/CT scanners are equipped with multidetector CT (MDCT) and have full diagnostic CT capabilities that are equivalent to stand-alone CT scanners. This enables comprehensive PET/CT examinations to be performed that combine PET with fully diagnostic contrast-enhanced CT.[1] MDCT allows reconstruction to be performed using isotropic voxels, enabling multiplanar display of CT images with full spatial resolution. This provides optimal definition of target lesions as well as morphologic characterization and therefore can maximize the diagnostic capabilities of combined PET/CT imaging.

PET-MR has been introduced clinically relatively recently, which offers the ability of obtaining PET images with MRI,

and fusion of that information. MRI provides superior soft-tissue contrast compared to CT. In addition, advanced imaging sequences such as diffusion-weighted imaging (DWI) and dynamic contrast enhancement (DCE-MRI) permit quantitative physiologic information to complement the PET radiotracer information. MRI is also used to calculate attenuation correction for the PET images. Because MRI is limited in its ability to visualize bone and does not use photons, quantification of uptake on PET images may be less accurate compared to PET/CT. However, MRI has diagnostic advantages over CT in evaluating the brain, head and neck, and pelvis, and clinical applications for PET/MRI are currently being developed. Another advantage of MRI is that there is no associated ionizing radiation, so PET/MRI may have additional applications in the pediatric population.

GENERAL ASPECTS OF TUMOR VISUALIZATION ON FDG-PET

FDG is currently the most commonly used radiotracer in clinical PET imaging. Tumor imaging with FDG is based on the principle of increased glucose metabolism of cancer cells, which are more dependent on anaerobic glycolysis (Warburg effect). Like glucose, FDG is taken up by the cancer cells through facilitative glucose transporters (GLUTs). Once in the cell, glucose or FDG is phosphorylated by hexokinase to glucose-6-phospate or FDG-6-phosphate, respectively. Expression of GLUTs and hexokinase, as well as the affinity of hexokinase for phosphorylation of glucose or FDG, is generally higher in cancer cells than in normal cells. Glucose-6-phosphate travels farther down the glycolytic or oxidative pathways to be metabolized, in contrast to FDG-6-phosphate, which cannot be metabolized. In normal cells, glucose-6-phosphate or FDG-6-phosphate can be dephosphorylated and exit the cells. In cancer cells, however, expression of glucose-6-phosphatase is usually significantly decreased, and glucose-6-phosphate or FDG-6-phosphate therefore can become only minimally dephosphorylated and remains in large part within the cell. Because FDG-6-phosphate cannot be metabolized, it is trapped in the cancer cell as a polar metabolite, and it constitutes the basis for tumor visualization on FDG-PET scans.

The intensity of a malignant tumor on PET is dependent on the histology and number of malignant cells in the tumor mass. Hodgkin lymphoma and melanoma are markedly intense on FDG-PET, whereas other tumors such as bronchioloalveolar lung cancer, mucinous adenocarcinomas, or mucosal-associated lymphoid tissue (MALT) lymphomas may have only modest FDG activity. In addition, FDG is also taken up in benign processes such as infection and inflammation because white blood cells and fibroblasts are highly avid for FDG. The major causes for false positive and false-negative FDG-PET activity are summarized in Box 11-1.

Radiation therapy can elicit a chronic accumulation of metabolically active macrophages that are avid on FDG-PET scans. The time course is variable and is dependent on the tumor site, but FDG activity may persist for months in the radiation treatment field. An example of evolving postradiation therapy changes in lung cancer is shown in Figure 11-3. Interestingly, FDG-PET may be obtained during chemoradiation therapy to evaluate early response in patients with non–small-cell lung cancer, suggesting that this inflammatory activity may be delayed until some time after therapy.[2,3] In contrast, radiation therapy may result in false-positive FDG activity when evaluating early response to neoadjuvant therapy in esophageal cancer, and FDG-PET is typically used to evaluate early response to the chemotherapy alone prior to adding radiation therapy.

BOX 11-1 Potential Pitfalls in Oncologic Imaging with FDG-PET

I. FALSE-POSITIVE UPTAKE

1. Variant physiologic activity
   a. Cardiac
   b. Thyroid
   c. Gastrointestinal tract
   d. Genitourinary tract
   e. Brown fat, muscle
2. Nonmalignant conditions
   a. Inflammation, particularly chronic
   b. Atypical infection, including fungal
   c. Granulomatous diseases, sarcoidosis
   d. Pneumoconioses
   e. Benign neoplasms (adenomas)
   f. Reactive lymph nodes
3. Posttreatment changes
   a. Prior radiation therapy
   b. Talc pleurodesis
   c. Postsurgical

II. FALSE-NEGATIVE UPTAKE

1. Variable FDG metabolism
   a. Prostate adenocarcinoma
   b. Renal cell carcinoma
   c. Neuroendocrine tumors, carcinoid
   d. Adenocarcinoma in situ (bronchoalveolar)
   e. Lobular breast cancer
   f. Mucinous neoplasms
   g. Mucosa-associated lymphoid tissue lymphoma (MALT)
   h. Hepatocellular carcinoma
   i. Sclerotic osseous metastases
   j. Necrotic tumors and nodes
   k. Small or superficial lesions
   l. Sentinel lymph nodes
2. High adjacent FDG background activity
   a. Cerebral cortex
   b. Gastrointestinal tract
   c. Genitourinary tract
   d. Cardiac

PATIENT PREPARATION FOR FDG-PET

To minimize FDG uptake in the muscle while maximizing its uptake in tumor, patients are instructed to fast for at least 4 hours and avoid excessive physical activity for 24 hours before the PET appointment. Glucose-containing drinks and intravenous glucose should be avoided at least 4 hours before FDG injection. The fasting state lowers the serum level of glucose so that FDG has less competition for uptake by the tumor, whereas muscle uptake is minimized by fasting (by lowering the serum insulin level) and by avoiding excessive physical activity; low FDG uptake in the muscles improves the tumor-to-background ratio and the image quality.

High glucose levels in diabetic patients can decrease the image quality. Although a normal glucose level in diabetic patients before FDG injection is desirable, it often cannot be achieved. Most institutions perform PET for diabetics after one or two attempts to reduce the serum glucose level below an empirically set level of 200 to 250 mg/dL. Although the positive predictive value of the findings on such a scan remains high, the negative predictive value may be reduced. In patients with diabetes, the image quality (i.e., muscle and soft-tissue uptake) should be assessed before interpretation and mentioned in the report.

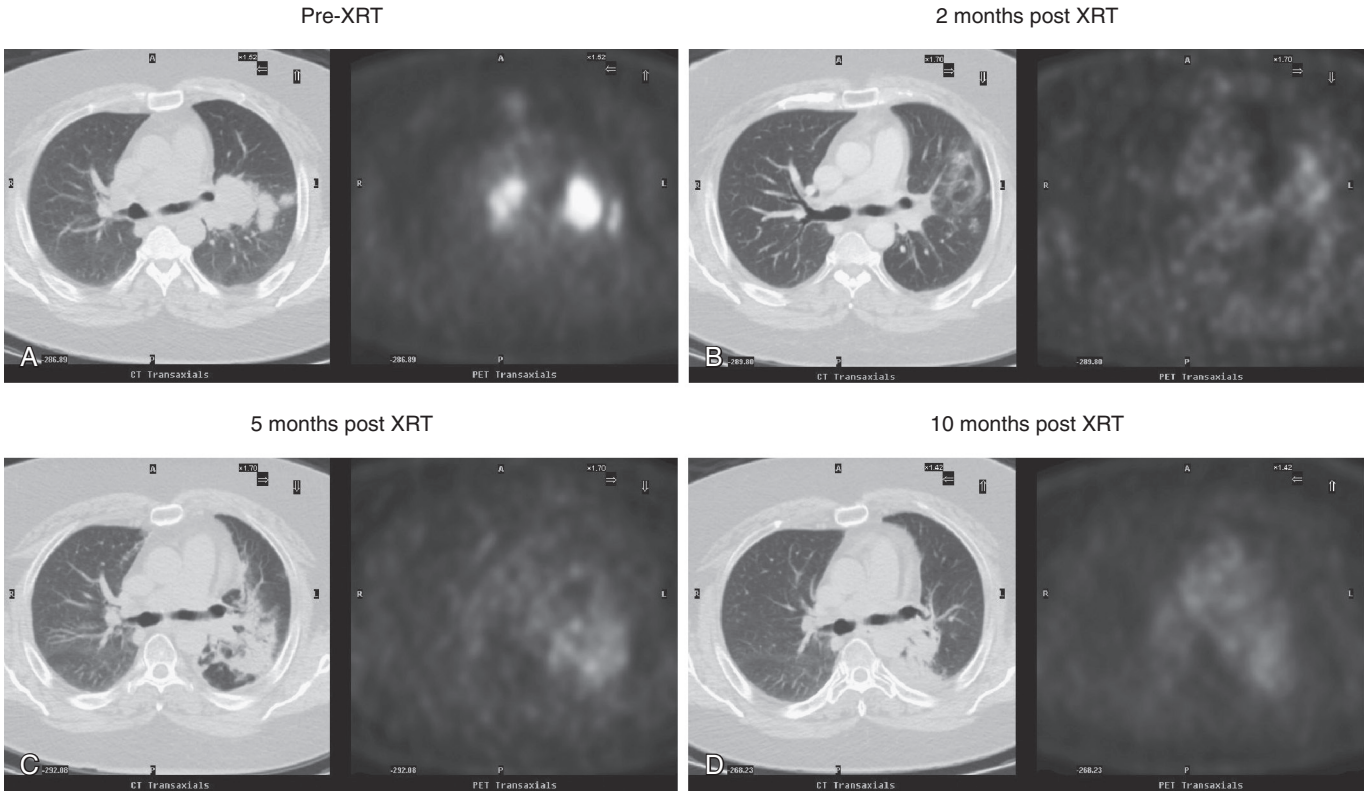

Figure 11-3 Evolution of posttreatment changes in the lung following radiation therapy. Pretherapy PET/CT scan **(A)** demonstrates bilateral hilar masses, predominantly on the left. PET/CT at 2, 5, and 10 months following radiation therapy **(B-D)** include evolving atelectasis and bronchiectasis on CT, with associated mild homogeneous FDG accumulation. The geographic distribution and absence of focal FDG accumulation are characteristic of expected postradiation changes.

FDG uptake in the brown fat in the neck and supraclavicular regions may obscure pathologic findings in these areas. FDG uptake in brown fat is even more extensive in pediatric patients, and it can be seen in the mediastinum, paraspinal region, and upper abdomen. Diazepam administration can reduce the FDG uptake in brown fat.

PET QUANTIFICATION

As previously mentioned, one of the advantages of PET imaging with attenuation correction is the ability to measure activity within target lesions. The standardized uptake value (SUV) is a semiquantitative measure of the tracer uptake in a region of interest that normalizes the lesion activity to the injected activity and a measure of the volume of distribution (usually total body weight or lean body mass). For FDG-PET, it is generally accepted that SUV alone is not reliable to differentiate malignant from benign processes and that other factors, including lesion location, size, CT morphology, pattern of contrast enhancement, and symmetry contribute to this evaluation. In addition, there are many technical and biological factors that can influence the observed SUV, such as the patient's serum glucose, the time between tracer injection and image acquisition, the detector technology of the PET scanner, attenuation-correction map, imaging field of view, and the image reconstruction parameters.[4] Nonetheless, SUV may be useful as a measure to follow the metabolic activity of a tumor over time within the same patient and to compare different subjects within a research study under defined conditions. For FDG-PET, the magnitude of early response to therapy varies with tumor histology. Most malignancies responding to therapy exhibit a 20% to 35% reduction in SUV early in the course of therapy, and these changes have prognostic significance.[5] On the other hand, Hodgkin lymphoma and gastrointestinal stromal tumors (GIST) have a dramatic response on FDG-PET soon after initiation of therapy, which can be assessed visually. Several clinical trials are investigating the ability of PET to direct therapy based on metabolic response early in the course of therapy. Currently, SUV measurements are not sufficiently standardized between PET/CT scanners, and the baseline and follow-up scans should be performed on the same PET/CT scanner for reliable assessment of early response to therapy.

MOST COMMON INDICATIONS FOR FDG-PET/CT IN ONCOLOGY

Lung Cancer

FDG-PET/CT (referred to hereafter as PET) has an overall sensitivity higher than 90% and specificity of about 85% for diagnosing malignancy in primary and metastatic lung lesions; the sensitivity and specificity of PET for small cell lung cancer are similar. The sensitivity of PET for bronchioloalveolar lung cancer and carcinoid of the lung is about 60%, and the specificity of PET for lung cancer is lower in areas with a high prevalence of granulomatous lung disease. PET is particularly useful in patients with a low (5% to 20%) or intermediate (20% to 70%) risk of lung cancer, as determined by an evaluation of symptoms, risk factors, and radiographic appearance. In these cases, PET is helpful in moving the patient to the very-low-risk (<5%) or high-risk (>70%) category.[6] It is expected that the use of PET for diagnosing malignancy in indeterminate lung nodules will continue to grow as more patients are diagnosed

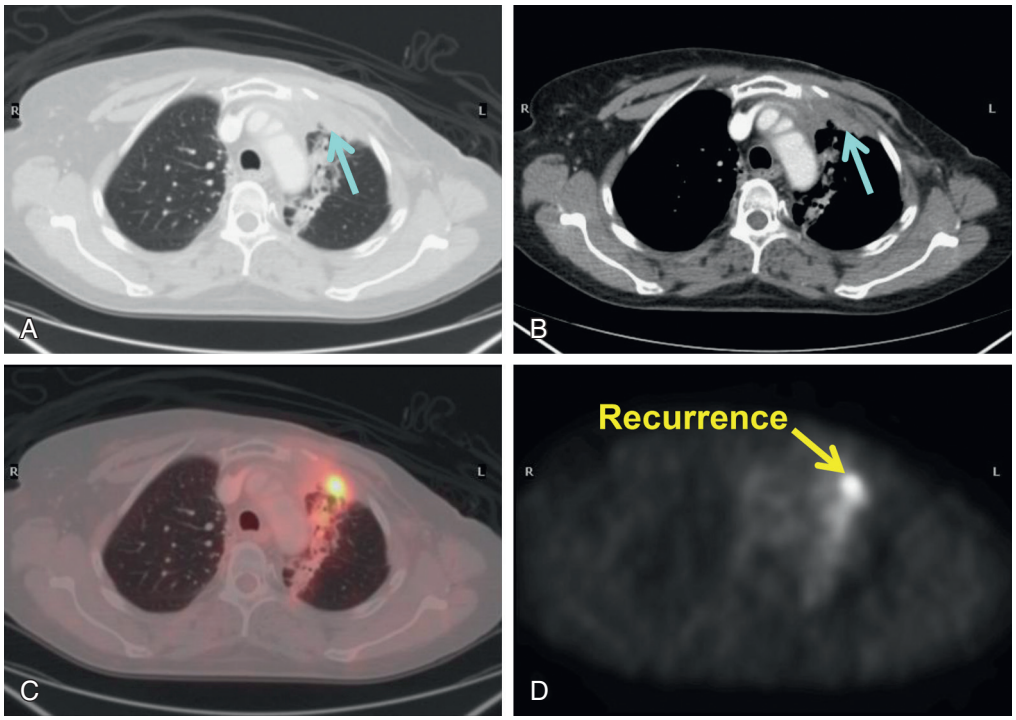

Figure 11-4 Recurrence following radiation therapy. Contrast-enhanced CT (with lung **(A)** and soft-tissue **(B)** windows) demonstrates opacity in the left upper lung in a geographic distribution consistent with postradiation therapy changes. Fused PET/CT **(C)** and PET **(D)** images reveals expected mild activity within the radiation treatment field, but superimposed focal activity *(arrow)* on FDG-PET corresponding to a focal area of nodular pleural thickening on CT *(light blue arrows)* which was subsequently shown to represent recurrent tumor.

with nodules on CT performed for other indications or as a screening test. Most of the current PET scanners are capable of detecting lung lesions as small as 4 to 5 mm.

In mediastinal staging of non–small cell lung cancer (NSCLC), patients with clinical stage I and II disease have by definition a radiographically negative mediastinum. However, in patients with central tumors, adenocarcinoma, or N1 lymph node enlargement, the false-negative rate of CT for mediastinal involvement is 20% to 25%. It is unclear whether PET should be used instead of mediastinoscopy in staging the disease of these patients. In mediastinal staging of clinical stage III tumors, positive results of PET need to be confirmed by tissue diagnosis because of a relatively high false-positive rate (15% to 20%). The false-negative rate of PET and mediastinoscopy in assessing enlarged mediastinal lymph nodes is 5% to 10%, and some authorities therefore do not pursue biopsy in the case of a negative PET result for disease in the mediastinum, whereas others argue that mediastinoscopy can detect "microscopic" metastases, and they are not comfortable accepting a negative PET result.[7] Practically, in larger centers, patients with stage III tumors undergo both PET to assess for distant metastases, and mediastinoscopy, but a strong argument for staging of the mediastinum with PET can be made in communities without an experienced mediastinoscopy service. In any case, it should be noted that the term *microscopic* is not well defined, and that routine pathologic tissue processing may be a limiting factor in detecting microscopic disease.

For patients with clinical stage I peripheral tumors, most authorities do not request mediastinoscopy before surgery because the rate of mediastinal or systemic involvement is very low (about 5%). Among patients with clinical stage II tumors, the rate of metastatic disease is higher, and there is a debate about whether PET is warranted in these patients to assess for systemic disease. For stage III tumors, the false-negative rate of clinical evaluation for systemic disease is about 15% to 30%, and PET therefore is justified instead of a battery of other tests (e.g., bone scan, CT, MRI) to assess for distant metastases.[7] According to the most recent recommendations of the American College of Chest Physicians, in patients with a normal clinical evaluation and no suspicious extrathoracic abnormalities on chest CT who are being considered for curative-intent treatment, PET is recommended to evaluate for metastases.[8] PET is more sensitive (90% versus 80%) and more specific (90% versus 70%) than bone scan in detecting bone metastases from NSCLC; PET has a sensitivity and specificity of greater than 90% in detecting adrenal metastases from NSCLC. Brain CT or MRI is still needed because PET cannot reliably detect brain metastases because of physiologically intense brain uptake of FDG. For patients with stage IV tumors, PET can potentially indicate the best accessible site for biopsy.

PET is also useful in restaging NSCLC. In particular, PET appears to be more sensitive than CT in differentiating postirradiation change from local recurrence, although differentiating these two entities remains a challenge. The postirradiation change in the chest can remain intense on PET for up to several years. In differentiating local recurrence from postirradiation change, the intensity of uptake and its shape should be taken into account (Figures 11-3 and 11-4).

Head and Neck Cancers

Most patients with head and neck cancers present for PET with a known diagnosis. However, cervical lymph node metastases from an unknown primary constitute about 5% of newly diagnosed head and neck cancer cases; CT and MRI can identify up to 50% of the primary tumors in patients with no findings on physical examination. The overall PET detection

rate in patients with negative results of physical examination, CT or MRI, and endoscopy is about 25%. However, this number is probably higher if PET is performed before endoscopy. In one prospective study, patients underwent PET prior to endoscopy but the results were first not revealed to surgeons performing the procedure under anesthesia. The surgeons were able to find the primary site of the disease in only 5 out of 20 patients. When PET information was revealed to the surgeons during the procedure, they were able to find the primary site of the disease in another 6 patients, which improved the detection rate to a total of 11 out of 20 patients.[9] It should be noted that knowledge of the variable benign and physiologic uptake patterns in the head and neck region is essential to minimize false-positive interpretations.

In initial staging of head and neck tumors, PET has a sensitivity and specificity of about 90% for nodal staging, and PET therefore is more sensitive and specific than CT or MRI. A weakness of PET is its low sensitivity (30%) for nodal disease in patients with clinically N0 necks. Given the high specificity of PET in nodal staging, it appears reasonable to perform neck dissection in patients with a positive PET result, whereas those with a negative PET result may be able to undergo sentinel node localization and biopsy.[10] In addition to local staging, PET can detect synchronous malignancies and distant metastases. In initial staging of head and neck malignancies, a PET scan is overall most helpful in patients with locally advanced disease because these patients have a risk of 10% or greater for distant disease. Furthermore, PET has been playing an increasingly important role in planning of radiation treatment in patients with head and neck cancers because it helps to better delineate the primary tumor from surrounding tissue and differentiate between metastatic and benign lymph nodes.

For restaging of head and neck tumors after radiation therapy, PET is highly sensitive but should be performed at least 3 months after irradiation to avoid false-positive findings. Patients with a negative scan at 3 months after irradiation can be followed without intervention (i.e., high negative predictive value), but those with a positive scan need to undergo further evaluation and probably biopsy.[10] For follow-up of the patients with a negative FDG-PET 3 months after completion of radiation therapy, there are currently no definitive data to indicate the time interval and total duration of the follow-up, and this should depend on the patient's individual risk factors.

Lymphoma

Hodgkin disease and high-grade non-Hodgkin lymphoma are mostly markedly avid for FDG and almost always visible on PET, whereas low-grade non-Hodgkin lymphoma may be only mildly intense and, in rare cases, completely invisible on PET. FDG-PET is superior to CT in staging of lymphoma and is recommended by the International Harmonization Project (IHP) for staging of Hodgkin lymphoma and aggressive non-Hodgkin lymphoma because of their consistent FDG avidity and potential curability. Furthermore, it is reasonable to use FDG-PET in all lymphomas except chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), marginal zone lymphoma (MZL), and some peripheral T-cell lymphoma (PTCL)[11]; however, there is no definite evidence that PET changes the initial management in a significant number of patients with lymphoma. Other controversial issues related to the initial stating of lymphomas with PET include the sequence of imaging tests to avoid redundant testing and the routine use of contrasted CT after PET/CT. Contrasted CT is definitely helpful to better delineate intraabdominal disease and for reliable measurement of lymph node size.[11]

The normal spleen shows mild uptake, whereas the uptake of the normal bone marrow can be variably intense. Intense spleen uptake (i.e., more intense than the liver) before chemotherapy is a reliable indicator of its involvement, but spleen involvement by lymphoma cannot be excluded with normal uptake. PET can be used to identify areas of bone marrow involvement although the impact of this on the overall staging is unclear because most patients with clearly visible marrow involvement on PET have other sign of stage IV disease. The relevance of PET in this setting remains controversial. Activation of hematopoiesis after chemotherapy or by bone marrow stimulating factors can cause intense uptake in the bone marrow, spleen, or thymus, which can persist for a while after the termination of the chemotherapy or stimulating factors.

The most promising role of PET in lymphoma management appears to be in therapy monitoring: early prediction of response to chemotherapy (i.e., interim or midway PET) and evaluation of a residual mass for active lymphoma at the completion of chemotherapy (i.e., end-of-treatment PET). The decrease of uptake associated with effective chemotherapy seen on interim PET precedes the anatomic changes seen on CT by weeks to months. At the completion of chemotherapy, CT demonstrates a residual mass at the initial site of disease in as many as 50% of patients. On the end-of-treatment PET, these patients demonstrate increased FDG uptake in the area of residual lymphoma in contrast to those without active lymphoma. The positive predictive value of residual uptake at the completion of chemotherapy is more than 90%. The negative predictive value is likely lower and associated with microscopic remnant disease. Generally, patients with non-Hodgkin lymphoma and stages III and IV Hodgkin disease and negative PET results at the completion of chemotherapy should undergo repeat PET at least once at about 6 weeks after the last cycle of chemotherapy.

In follow-up of patients in remission, PET is more sensitive than CT in detecting recurrent disease. However, there are no guidelines as how often follow-up PET scans should be performed. Follow-up PET scans are often performed, depending on the individual risk factors, as frequently as every 3 months.

Colorectal Cancer

PET plays no role in the screening or diagnosing of colorectal cancer, and neither the depth of the tumor nor the local lymph nodes status can be assessed by PET. However, PET is highly sensitive in detecting distant hepatic and extrahepatic metastases. A meta-analysis of the literature on detection of hepatic metastases from colorectal, gastric, and esophageal cancers by ultrasound, CT, MRI, and PET found that in studies with a specificity higher than 85%, the mean weighted sensitivity was 55% for ultrasound, 72% for CT, 76% for MRI, and 90% for PET. Results of pairwise comparison between imaging modalities demonstrated a greater sensitivity of PET than ultrasound ($p = 0.001$), CT ($p = 0.017$), and MRI ($p = 0.055$). The conclusion was that at equivalent specificity, PET is the most sensitive noninvasive imaging modality for the diagnosis of hepatic metastases from colorectal, gastric, and esophageal cancers.[12] Considering the higher sensitivity of PET in detecting distant metastases and the introduction of intravenous contrast to the CT portion of fused PET/CT, it is conceivable to use PET/CT in preoperative staging of colorectal cancer; the contrast-enhanced CT portion of PET/CT can be used instead of conventional CT or MRI for evaluation of anatomic resectability of liver metastases. PET plays an important role in restaging of colorectal cancer. PET can visualize the site of the local and distant disease when recurrence is suspected based on the clinical findings, findings on other imaging modalities, or an increasing carcinoembryonic antigen level with sensitivity and specificity higher than 90% (Figure 11-5).

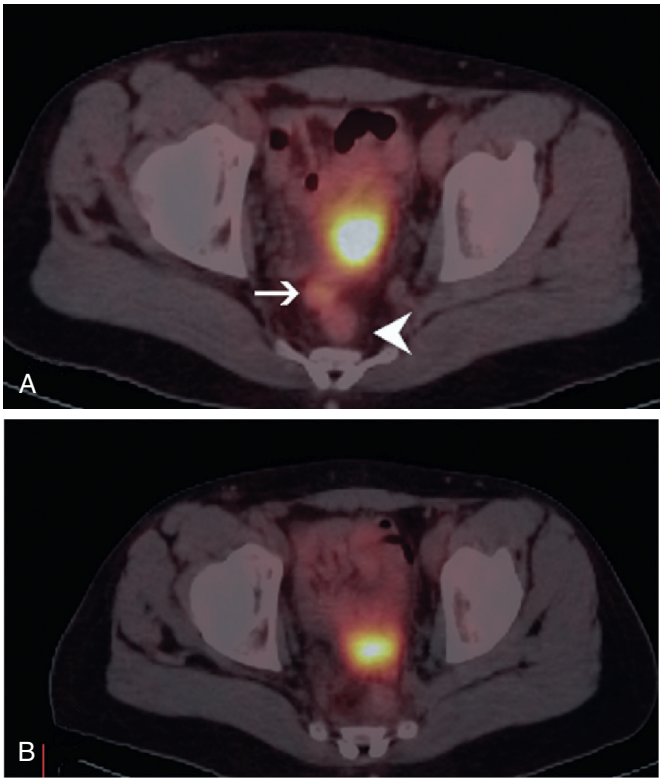

Figure 11-5 PET/CT for differentiating local recurrent from scar in a patient with colon cancer, status after low anterior resection. Recurrent disease was suspected based on increasing carcinoembryonic antigen (CEA) level. CT is not able to differentiate between scar and local recurrence. **A,** FDG-PET indicated an intense focus *(arrow)* suspicious for malignancy. A second mild focus was interpreted as scar *(arrowhead)*. **B,** The diagnosis was confirmed surgically and the recurrent tumor was removed.

Breast Cancer

PET can increase the detectability of small primary breast cancers and may be useful especially in evaluating patients with dense breasts. In evaluating the axillary lymph nodes, PET does not play any role because of its low sensitivity (60%) despite relatively high specificity (80%).[13] In contrast, PET is relatively sensitive (85%) and specific (90%), and it is superior to CT (sensitivity of 54%, specificity of 85%) in evaluation of the internal mammary chain lymph node for metastases. The main role of PET in breast cancer lies in the investigation of distant metastases and response monitoring. Compared with CT, PET has a higher sensitivity (90% versus 40%) but lower specificity (80% versus 95%) in detecting metastatic disease. Overall, PET has the same sensitivity as bone scan in detecting bone metastases (both about 90%), but PET appears to be somewhat more sensitive than bone scan for osteolytic lesions and somewhat less sensitive than bone scan for osteoblastic lesions. PET has a higher specificity than bone scan in detecting bone metastases (95% versus 80%). This may be explained by the fact that PET captures the metabolic activity of the tumor cells independently of changes in the bone, whereas bone remodeling seen on bone scan can result from metastatic disease and benign causes. Overall, priority should be given to FDG-PET over ^{99m}Tc bone scan for staging purposes not only because FDG-PET can detect both bone and soft-tissue metastases.

In patients with advanced breast cancer undergoing neoadjuvant chemotherapy, PET differentiates responders from nonresponders as early as after the first cycle of therapy. This may help improve patient management by avoiding ineffective chemotherapy and supporting the decision to continue dose-intensive preoperative chemotherapy in responding patients although universal criteria for assessing response have not been established. PET has great efficacy in cases of suspected recurrence and surpasses conventional imaging (including bone scan) for whole body evaluation.

FDG-PET/CT Applications in Other Malignancies

In esophageal and gastric cancer, PET is useful to assess for distant disease. In esophageal cancer, PET has the potential to be used for monitoring the effect of neoadjuvant therapy. In ovarian, uterine, and cervical cancer, PET is used to assess for recurrent disease. In cases of cervical cancer, because of its greater sensitivity than CT and MRI for detecting paraaortic nodes, PET plays an important role in nodal staging and radiotherapy planning. In malignant melanoma, PET is used to evaluate the presence of distant metastases at the time of initial diagnosis and to assess for recurrent disease after initial treatment in high-risk patients. In sarcoma, the most intense areas on PET have usually the highest grade and should be considered for biopsy.

Targeted Imaging in Nuclear Medicine

From its inception, nuclear medicine has used specific physiologic and biophysical targets for imaging and therapy.

Because nuclear imaging techniques have had high sensitivities with known lower specificities, agents with greater specificity are being developed. Even though there may be some trade-off in sensitivity compared with other nuclear modalities, they have proved to be better than general radiologic modalities for many indications, and in some cases, they can be used for targeted radionuclide therapies. Newer imaging technologies have been developed that greatly enhance molecular imaging.

Traditionally, nuclear imaging involves planar imaging using single photon emitters, such as technetium-99m (^{99m}Tc), indium-111 (^{111}In), iodine-123 (^{123}I), among many others. However, it is also possible to do tomographic—or SPECT—imaging of radiotracers, providing overall greater accuracy of lesion diagnosis and detection. Compared to PET imaging, SPECT imaging has lower resolution, and can be further limited in large patients because of inherent attenuation. In the last few years, however, there have been substantial advances using concurrent CT imaging—as in PET/CT—for both attenuation correction as well as anatomic localization. The result has been the development of SPECT/CT that has provided a great leap forward in disease evaluation and the continued development of molecular imaging independent of PET/CT.

In the realm of radiopharmaceutical development, some agents rely on targeting using antibodies or their fragments, peptides, or are receptor or even gene specific. Although established procedures like FDG-PET imaging are clearly superior to most of these newer methods at the present time, they remain clinically important in sites where PET may not be available. Nevertheless, radiopharmaceutical development in both the PET and SPECT side show promise in the evaluation of disease, and the evolution of molecular imaging.

Bone Scanning

Bone scanning is the most basic oncologic imaging procedure in nuclear medicine. Its utility has long been proven in multiple diseases in both detection of osseous metastases and in follow-up. Traditionally, the study is done using planar whole

body studies using ^{99m}Tc-labeled bisphosphonates, most commonly methyl diphosphonate (MDP) and hydroxyethylene diphosphonate (HDP). Multiple additional limited planar or SPECT views can also be obtained by focusing in on the body part of interest. The procedure allows a rapid skeletal survey and an overall assessment of disease.

There are drawbacks to this modality. MDP and HDP accumulation is related to the osteoblastic phase of bone remodeling, so planar bone scintigraphy is relatively insensitive for the detection of lytic lesions. In addition, bone remodeling occurs in many conditions, including arthritis, inflammation, trauma, benign and malignant neoplasms, and metastatic disease, reducing the specificity of the study. SPECT and SPECT/CT imaging can improve both the sensitivity and specificity of the study; however, a single SPECT acquisition can take 15 to 30 minutes and only covers a selected area of the body. Some have advocated whole-body SPECT studies, which could take more than 90 minutes of scan time.

^{18}F-sodium fluoride (NaF) was one of the first radiopharmaceuticals used for skeletal scintigraphy, but it fell out of favor with the development of ^{99m}Tc tracers and improved gamma camera technology. However, there is now renewed interest in bone imaging with NaF utilizing PET/CT technology.[14] Additional advantages of NaF-PET/CT compared to ^{99m}Tc bone scans include shorter uptake time (1 hour versus 2 to 4 hours) and the ability to obtain diagnostic contrast-enhanced CT scans along with the NaF-PET images. Although NaF is FDA approved, NaF PET scanning is currently being evaluated by CMS at the time of writing this manuscript for potential reimbursement as a routine clinical procedure.

Antibody-Based Imaging Agents

One of the more successful antibody-based agents is ProstaScint (capromab pendetide), an antibody against prostate membrane surface antigen, a type II membrane glycoprotein strongly associated with prostate cancer. The usual indication is a rising prostate-specific antigen (PSA) level in a patient who has had a prostatectomy but who has no obvious location for a metastatic focus as determined by CT or MRI. These modalities have sensitivities of disease detection of only 5% to 20%, although they have much higher specificities. The accuracies for capromab imaging are about 70%, although it is much less sensitive than bone scan for skeletal metastases. Absence of extrapelvic disease on capromab and other studies may allow for radiotherapy to the pelvis.

Carcinoembryonic antigen scans use a labeled murine antibody fragment (^{99m}Tc-arcitumomab) to detect recurrent colorectal and breast cancer. OncoScint (^{111}In-satumomab pendetide) is another antibody also used for detection of recurrent colorectal and ovarian carcinomas. The sensitivity of extrahepatic disease recurrence detection for satumomab is 97%, whereas for CT scan it is 72% for colorectal malignancy. For liver metastases CT is better, but when the two modalities are combined, the sensitivity is approximately 90%.[15] Although FDG-PET outperforms these modalities and is the scan of choice, the antibodies may be of clinical value if FDG-PET is not available.

Clear cell renal cell carcinomas can constitute up to ~55% to 60% of histologies of incidentally discovered renal masses, and methods to identify this aggressive malignancy early and preoperatively could be useful. A recently developed agent—^{124}I-cG250 (Girentuximab)—a radiolabeled chimeric antibody against the carbonic anhydrase IX (CA IX), is reactive in >95% in immunohistochemical assays on fresh frozen tissues and can be used with PET/CT imaging. A phase I trial for this agent showed more than 90% accuracy for the detection of primary clear cell renal carcinoma, although the accuracy for metastatic disease detection was not studied.[16] This agent is still undergoing review for clinical approval as an imaging agent.

Cellular Imaging

Various agents being developed build on the newer understanding of cellular physiology, including angiogenesis, apoptosis, and other ideas. Some are routinely used clinically, but others show potential for future development and may revolutionize the way cancer is approached.

^{18}F-fluorothymidine (^{18}F-FLT) is a thymidine analog and a PET tracer, which is phosphorylated by thymidine kinase-1 (TK1) to FLT-monophosphate. FLT uptake correlates with TK1 activity and cellular proliferation. FLT may be more suitable than FDG to monitor the effect of chemotherapy and radiation therapy. Another important area of current PET tracer research concerns cell-cell and cell-matrix interaction. Tracers such as ^{18}F-galacto-GRD (glycosylated Arg-Gly-Asp) enable the noninvasive determination of integrin $\alpha_v\beta_3$ expression and are being evaluated for use in assessing angiogenesis and metastatic potential of tumors.

Annexin-V shows great promise for evaluating apoptosis, and it is available as a single-photon and PET agent. Highly apoptotic areas in tumors may be more likely to be sensitive to irradiation or chemotherapy, and there is the potential for evaluating therapy response or overall disease prognosis with such agents. Similarly, the field of tumor hypoxia is central to the understanding of tumor response to irradiation. PET agents such as ^{18}F-fluoromisonidazole (^{18}F-MISO) and Cu-labeled diacetyl-bis (*N*(4)-methylthiosemicarbazone (Cu-ATSM) can be used to detect intratumoral hypoxia. Although still in the evaluation phase, these agents could potentially be used to evaluate areas of hypoxia for targeting radiation delivery.[17]

Recently, ^{11}C-choline has obtained clinical approval in the United States for imaging prostate cancer. Tumor cells produce abundant quantities of choline because it is a precursor of phosphatidylcholine, a major constituent of membrane lipids, which along with proteins, are synthesized during cell proliferation. Choline kinase is upregulated in malignancy, which leads to incorporation and trapping of choline into lecithin. The limitation for this tracer is that its use requires proximity to a cyclotron given its short half-life. A recent study showed an accuracy of 99% when ^{11}C-choline PET is used in a hybrid PET-MRI scanner.[18] ^{18}F-fluorocholine (FCh)[19] and ^{18}F-FACBC (1-amino-3-fluorine 18-fluorocyclobutane-1-carboxylic acid)[20] are also being evaluated for evaluating prostate cancer, and will also likely benefit from the combination of PET/MRI.

Neuroendocrine Tumor Imaging

^{111}In-octreotide is a peptide that is routinely indicated for neuroendocrine tumors, including carcinoids, tumors associated with the multiple endocrine neoplasias, meningiomas, and lymphomas (i.e., Hodgkin disease and non-Hodgkin lymphoma). Increased activity can be seen in benign disease such as sarcoidosis and other inflammatory processes. ^{111}In-octreotide has the highest affinity for somatostatin receptor (SSTR) subtypes 2 and 5, with weaker affinities for others. This agent is still relevant in the era of PET because many of the well-differentiated lesions will not take up FDG. Even so, many diseases do not have appropriate receptor expression and therefore have limited detection on such scans. A similar agent, ^{99m}Tc-depreotide, has greater affinities for SSTR 2, 3, and 5 and therefore has the potential for greater sensitivities for tumors with various SSTR expressions and uptake in a broader number of malignancies, including lung cancers.

Routine imaging of neuroblastoma and pheochromocytomas involves metaiodobenzylguanidine (MIBG), a

norepinephrine analog taken up by the uptake 1 mechanism in receptors. It has uptake in many of the same malignancies as octreotide, although not with the same frequency. For imaging, MIBG may be labeled with ^{131}I, ^{123}I, or ^{124}I, a positron emitter. The sensitivity for lesion detection can exceed 90%, and specificity approaches almost 100% for single photon imaging.[21] Nevertheless, as tumors de-differentiate or metastasize to other sites, specifically the bones, MIBG becomes less sensitive in detecting disease, in which case a bone scan is useful. With the advent of ^{124}I-MIBG used in PET/CT, it is unknown whether the increased resolution will allow better detection of disease, obviating the need for bone scans.

There is growing interest in being able to use newer tracers such as 3,4-dihydroxy-6-^{18}F-fluoro-phenylalanine (^{18}F-FDOPA) and PET in neuroendocrine imaging, which use neurohumoral pathways of uptake, and trapping similar in concept to that of FDG to concentrate in relevant areas. Many studies show that this tracer has far greater accuracy for disease detection than either octreotide analogs or MIBG.[22] Unlike the SPECT counterparts, the PET imaging can be done within an hour after injection, with PET quality images. Still, ^{18}F-FDOPA is most useful in the well-moderately differentiated tumors, with FDG being superior for the more poorly differentiated ones. Additionally, octreotide based positron tracers labeled with ^{68}Ga—such as [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid]-1-Nal3-octreotide (^{68}Ga-DOTANOC), and others—are undergoing review, with at least one of these forms expected to be approved in the near future for imaging.[23]

Other Modalities

Breast-specific gamma imaging (BSGI) is gaining interest in breast imaging. The limitations and controversies surrounding mammography are well known. Single photon gamma devices have now been developed for specifically imaging breast. These use ^{99m}Tc-Hexakis (2-methoxy-2-methylpropylisonitrile), also known as sestamibi, a tracer which has been used for imaging in malignancies before the rise of FDG PET or where PET was not readily available. The modality may be particularly useful in denser breasts where traditional mammographic evaluation is more limited. Recent publications have shown good ability to evaluate lesions, with an overall accuracy of about 91%.[24]

Positron emission mammography (PEM) similarly uses breast-specific PET imaging technology with FDG. Again, this holds promise in mammography, demonstrating significant improvement in diagnostic accuracy. Studies have demonstrated a similar performance as compared to breast MRI, providing complementary information in the evaluation of breast cancer. Still, even combining these modalities show some limitations in the initial surgical management of disease.[25]

TARGETED RADIONUCLIDE THERAPY

Imaging agents are valued more for their sensitivity, but for targeted therapy, it is the specificity that is essential. Many imaging agents are specific enough for therapeutic purposes. Treatment of well-differentiated thyroid cancer, radioimmunotherapy, and bone metastases pain palliation are discussed elsewhere in this text. The following sections provide examples of selected therapies used in other clinical settings that show promise for development in the near future.

Thyroid Diseases

Thyroid diseases are the most successful clinically relevant application of targeted therapy. The thyroid's unique ability to metabolize elemental iodine to synthesize thyroid hormones is fortuitous because it is a highly specific but easily targeted process with radioactive iodine. Treatment is effective, is virtually definitive, and has minimal side effects. There are practically no long-term sequelae from appropriate radioactive iodine administration for benign thyroid disease. Generally, radioactive iodine treatment in benign disease is reserved for hyperthyroid conditions, such as Graves disease or toxic and multinodular goiters. Radioactive iodine is used when the disease cannot be controlled medically, and it is often a first-line option in clinically hyperthyroid patients. Surgery is reserved for instances in which radioactive iodine may be contraindicated (e.g., pregnancy, marrow suppression, etc.) or when there may be compressive findings of the enlarged thyroid on critical structures, such as the trachea.

Patients with thyroid cancer have traditionally undergone 4 to 6 weeks of L-thyroxine withdrawal before radioiodine scanning and treatment to stimulate tumors to take up iodine. The introduction of recombinant human thyroid stimulating hormone (rhTSH) has revolutionized thyroid malignancy evaluation. rhTSH is injected intramuscularly to stimulate residual thyroid cells to take up radioiodine. This avoids the prolonged hypothyroid state that patients traditionally had to go through, and can be used in those who would otherwise be unable to tolerate hormone withdrawal. When used before therapeutic radioiodine in post-surgical remnant thyroid ablation for low-risk disease groups, prospective studies show equivalent efficacy in short-term outcomes.[26] Retrospective studies show similar efficacy between hormone withdrawal and rhTSH in longer-term outcomes in even moderate-higher risk patients.[27]

Octreotide Derivatives in Neuroendocrine Malignancies

A novel application is to use octreotide in targeted radionuclide therapy. ^{111}In-octreotide has been used in clinical trials and initial results were encouraging, although objective response rates were a meager 0% to 8%, with 42% to 81% with stable disease and 12% to 38% showing disease progression. The octreotide molecule has subsequently been modified to increase its specificity for tumor targeting, decrease its affinity for nontargeting areas in other organs, and in an effort to improve its toxicity profile. ^{111}In-octreotide has been altered to create [^{90}Y-DOTA^{0}]- Tyr^{3}-octreotide (DOTATOC) and [^{177}Lu-DOTA^{0}]-Tyr^{3}-otreotate (DOTATATE), with some improvement in their target to nontarget ratios. The DOTATOC trials showed improved objective responses ranging from 7% to 33%, stable disease in 52% to 81%, and disease progression in 9% to 19%. Trials with DOTATATE also showed similar objective response rates. Aside from marrow toxicity and myelodysplasia, nephrotoxicity was the other most significant long-term sequela, which could be decreased with infusion of amino acids before therapy. As in most targeted therapies for solid tumors, hematotoxicity was seen in these patients.[28]

The success of DOTATOC and DOTATATE likely results from their better targeting of tumor compared with octreotide. The radiobiology of the beta emitters ^{90}Y and ^{177}Lu appears to be superior to the Auger emitter ^{111}In. The newer trifunctional, somatostatin-based derivatives have prolonged cell retention, and they are internalized into the cell nucleus, making them optimal for Auger therapy, such as ^{111}In.[29] Future trials with such compounds are of great interest in developing targeted radionuclide modalities.

Metaiodobenzylguanidine Therapy in Neuroendocrine Malignancies

MIBG has been used therapeutically as ^{131}I-MIBG in neuroblastomas in children and pheochromocytomas. Objective

responses have ranged from 47% to 80% as a single agent in neuroblastoma. The main toxicity was hematologic, and subsequent trials are being conducted with autologous stem cell reconstitution. Studies have also been conducted combining MIBG with chemoradiotherapy.[30]

Other Targeted Radionuclide Therapies

Polycythemia vera was frequently treated with ^{32}P-phosphorous in the past, but with the advent of modern chemotherapy, this has become uncommon. Although the median survival was improved, there was an increase in the incidence of secondary blood dyscrasias. This therapy is used in patients who cannot tolerate hydroxyurea and other treatments, or who have symptoms that do not respond to other therapeutic maneuvers.

Radiocolloids such as ^{198}Au-gold colloid or chromic phosphates labeled with ^{32}P or ^{90}Y have been used as palliative regimens in malignant ascites in ovarian carcinoma, pleurodesis for pleural effusions, intracavitary injections for cystic brain tumors, and even for radiosynovectomies in benign inflammatory arthritic diseases. Other therapies have included using ^{35}S-thiouracil for ocular melanoma. Despite being effective treatments, they have been replaced by modern medical management, although they are still rarely used when other therapies fail. Interest in radiosynovectomy is growing as an alternate to surgical management, or delaying surgery when medical management is no longer adequate.

Some newer therapies involve using microspheres embedded with ^{90}Y for palliation in hepatocellular carcinoma, as well as other malignancies such as colorectal carcinoma and neuroendocrine malignancies that have metastasized to the liver. Following arterial access by an interventional radiologist, the ^{90}Y microspheres are injected selectively into the hepatic artery to the site of diseased liver, where they will reside in the vascular space, delivering lethal radiation doses locally. Because the product is not systemically delivered, side effects are well tolerated and less severe than other therapeutic options. Palliative benefits are clear, and some initial evidence suggests promising survival time compared to systemic options.[31,32] Its role compared to bland embolization or chemoembolization is not well defined. Similarly, ^{131}I-Lipiodol is also emerging as a candidate for similar indications, and has undergone trials with cisplatin showing a well tolerated toxicity profile.[33] In the future, newer therapies may use liposomes to deliver therapeutic radionuclides to micrometastases in various other malignancies to complement antibody mediated therapies.[34]

Therapy-Enhancing Strategies

Therapy enhancement basically relies on trying to boost radionuclide uptake and prolong its cellular retention for improving efficacy, or improving tumor sensitivity to make them more susceptible to the effects of targeted radiation. In thyroid cancer, lithium has been shown to have a modest increase in free iodine retention and raising the dose delivery to tissue.[35] There is some evidence to suggest that medications like rosiglitazone, SAHA and others may improve radioiodine uptake in tumors with decreasing ability to take it up, but no clear clinical benefit has yet been demonstrated.[36] Whereas newer agents—such as sorafenib and sunitinib—have demonstrated some activity against tumors independent of radioiodine, no studies have been done to see whether combined modality therapies are any more effective in the treatment of advanced thyroid cancer.

Conversely, the addition of gemcitabine to an yttrium-90 radiolabeled antibody—^{90}Y-hPAM4—has shown some promise in pancreatic cancer in improving therapeutic efficacy of targeted therapy, presumably by acting as a radiosensitizer.[37] Currently, a Phase III trial is under way in evaluating this combination as a potential future clinical therapy.

Some of the newer antibody therapies use genetically engineered antibodies or altered pharmaceuticals and attach radionuclides with more favorable characteristics to improve tumor-specific targeting and possibly therapeutic efficacy. Other methods employ multistep targeting, all of which are experimental, but they hold promise. Such results have prompted their use in conjunction with external beam therapy and chemotherapy. This could help to bring targeted radionuclide therapy into general clinical practice.

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