REVIEW

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PET and PET/CT imaging: What clinicians need to know

ABSTRACT

Positron emission tomography (PET), once the sole province of academic medical centers, is rapidly being adopted in daily clinical practice in community hospitals and outpatient centers. It can be especially useful in oncology, cardiology, and neurology. We provide an overview of the fundamentals of PET and PET with computed tomography (PET/CT) and discuss their current clinical utility.

KEY POINTS

Whereas CT gives detailed anatomic information, PET gives functional information, and a new type of scan that combines the two (PET/CT) is more useful than either type alone in many oncologic, cardiologic, and neurologic indications.

The tracers used in PET are taken up preferentially in tissues in which metabolism is enhanced, such as tumors compared with normal tissue, or in viable myocardium compared with infarcted myocardium.

A major application of PET is in the workup of indeterminate solitary pulmonary nodules. Other uses of PET in oncology are to diagnose, stage, and restage disease and to assess the effectiveness of chemotherapy in various types of malignancies.

In cardiology, PET can be used to diagnose coronary artery disease and to determine myocardial viability.

In neurology, PET is used to differentiate between tumor recurrence and radiation necrosis in patients who have undergone radiotherapy for brain tumors, to differentiate Alzheimer disease from other dementias, and to locate epileptic foci.

POSITRON EMISSION TOMOGRAPHY (PET) is an exciting innovation in medical imaging. While computed tomography (CT) and magnetic resonance imaging (MRI) provide exquisite anatomic information, PET imaging depicts physiologic processes. This information helps one to make a diagnosis earlier, to determine the stage of the disease more accurately, and to monitor therapy. Recently, PET and CT have been combined in a single scanner; the combination (PET/CT) adds an incremental clinical benefit by simultaneously depicting both functional and morphologic information.

Some of the current applications of PET and PET/CT are in:

- Oncology—identifying and determining the extent of malignant disease and monitoring therapy of numerous cancers
- Cardiology—detecting coronary artery disease and assessing whether dysfunctional myocardial tissue is viable
- Neurology and psychiatry—differentiating between tumor recurrence and radiation necrosis, differentiating Alzheimer disease from other dementias, and locating epileptic foci.

In this review, we review the fundamentals of PET and PET/CT and discuss the current clinical utility of these imaging techniques.

PET: THE FUNDAMENTALS

PET is a noninvasive, three-dimensional, nuclear medicine imaging technique.[1]

*Dr. Brunken has disclosed that he has received research support from the Bracco Diagnostics corporation.

The positron is the antiparticle of the electron: it has the same mass as the electron, but it carries a positive charge instead of a negative charge. The tracers used in PET contain radionuclides that eject a positron from the atomic nucleus when they decay. The emitted positron interacts with adjacent atoms, producing excitations and ionizations that reduce its velocity. As it slows, the positron soon encounters an electron in the surrounding medium. The electron and positron annihilate one another because they are antiparticles. Two photons of 511 kiloelectron volts are released in the annihilation and move in opposite directions (FIGURE 1).

Elements such as fluorine, carbon, oxygen, nitrogen, and iodine have positron-emitting isotopes that can be used for clinical PET imaging. Each PET tracer depicts a specific physiologic process, and the one selected for imaging reflects the information that is desired clinically. For example, tissue utilization of glucose can be visualized using the glucose analogue [18F] fluorodeoxyglucose (FDG). FDG uptake parallels glucose uptake, but unlike glucose, FDG is retained within the tissue and is not metabolized further.

Currently approved indications for FDG-PET include oncologic, cardiac, and neurologic problems

As the tracer accumulates in the targeted tissue, a PET or PET/CT scanner is used to characterize and quantify the physiologic process of interest. PET cameras use circular rings of gamma-ray detectors connected by sophisticated electronic circuitry to detect paired scintillation events. Data from millions of annihilation events are reconstructed and incorporated into three-dimensional images of the tracer distribution in space.

PET vs conventional SPECT imaging

In single-photon emission computed tomography (SPECT), after a radionuclide is injected, single gamma-ray photons that exit the body are captured by a standard gamma-ray camera. The camera sequentially acquires images from multiple projections as it moves over 360- or 180-degree arcs about the body. This raw information is then reconstructed into tomographic image sets.

PET has several advantages over conventional SPECT imaging. Its spatial resolution is about two times better, and it accurately corrects for attenuation (absorption by interposed tissue) of photons emitted from the organ of interest. The attenuation correction process is faster using the PET/CT technique. Because PET images are corrected for attenuation, they more accurately reflect the true activity of the tracer in tissue.

Using the patient's weight (or, in some laboratories, lean body mass), one can calculate the proportion of the injected dose that localizes to the tissue of interest per kilogram of body mass. This measurement, called the *standardized uptake value*, is a normalized measure of the avidity of tracer uptake and has been used to help characterize lesions as benign or malignant and to gauge the efficacy of treatment for malignant neoplasms. However, standardized uptake values should be obtained under controlled conditions and used with caution for these purposes, since a number of technical factors and patient variables can affect this value.

CANCER CELLS USE MORE GLUCOSE

The hallmark of malignancy is uncontrolled proliferation of abnormal cells, which generally metabolize glucose at a high rate.[2] This characteristic is the basis for the use of FDG-PET for diagnosis, staging, and restaging of neoplastic processes.

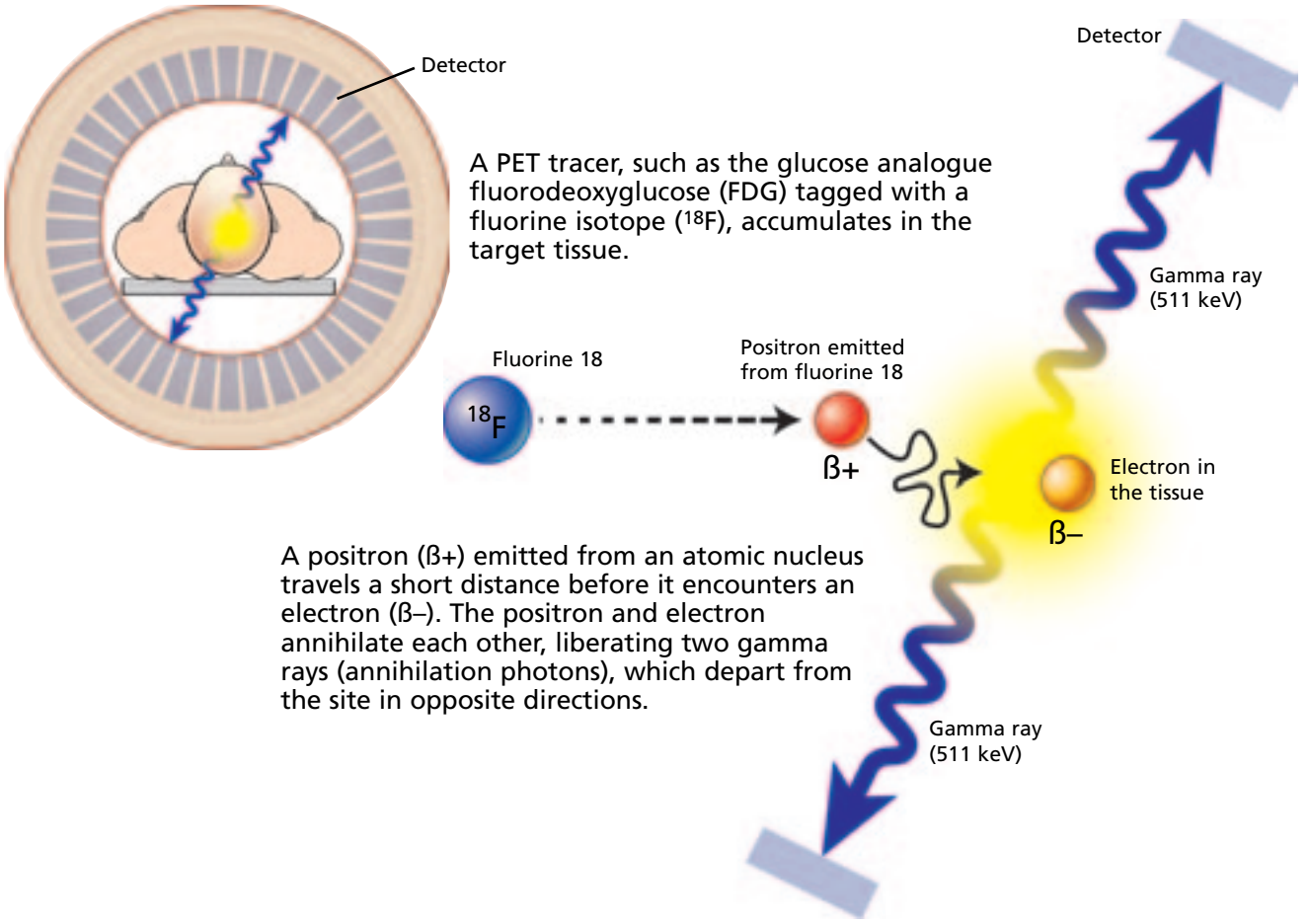
Solitary pulmonary nodules: Benign or malignant?

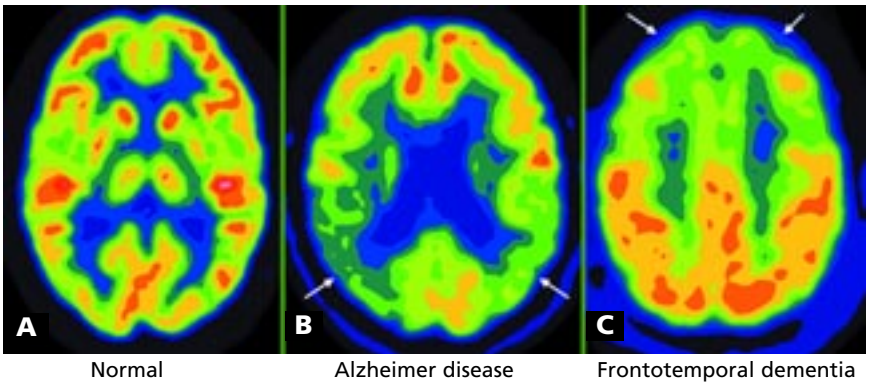
A major application of PET is in the workup of indeterminate solitary pulmonary nodules, defined as noncalcified nodules, 3 cm or smaller, in the lung parenchyma that are found on chest radiography or CT (both of which play vital roles in the diagnosis and management of many pulmonary disorders).

Solitary pulmonary nodules are commonly encountered in clinical practice—about 150,000 new ones are discovered each year in the United States,[3] of which 30% to 50% are malignant.[4] After a standard radiologic evaluation that includes chest radiography and CT, as many as two thirds of cases may be considered indeterminate for malignancy. Up to 70% or 75% of indeterminate cases will prove to be malignant.

PET can help distinguish between benign and malignant nodules, as nearly all malig-

Positron emission tomography (PET)





These FDG-PET images show normal brain (A), focally decreased glucose metabolism in Alzheimer disease in the posterior parietal region (B), and frontotemporal dementia, such as in Pick disease (C).

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FIGURE 1

PET helps characterize single pulmonary nodules

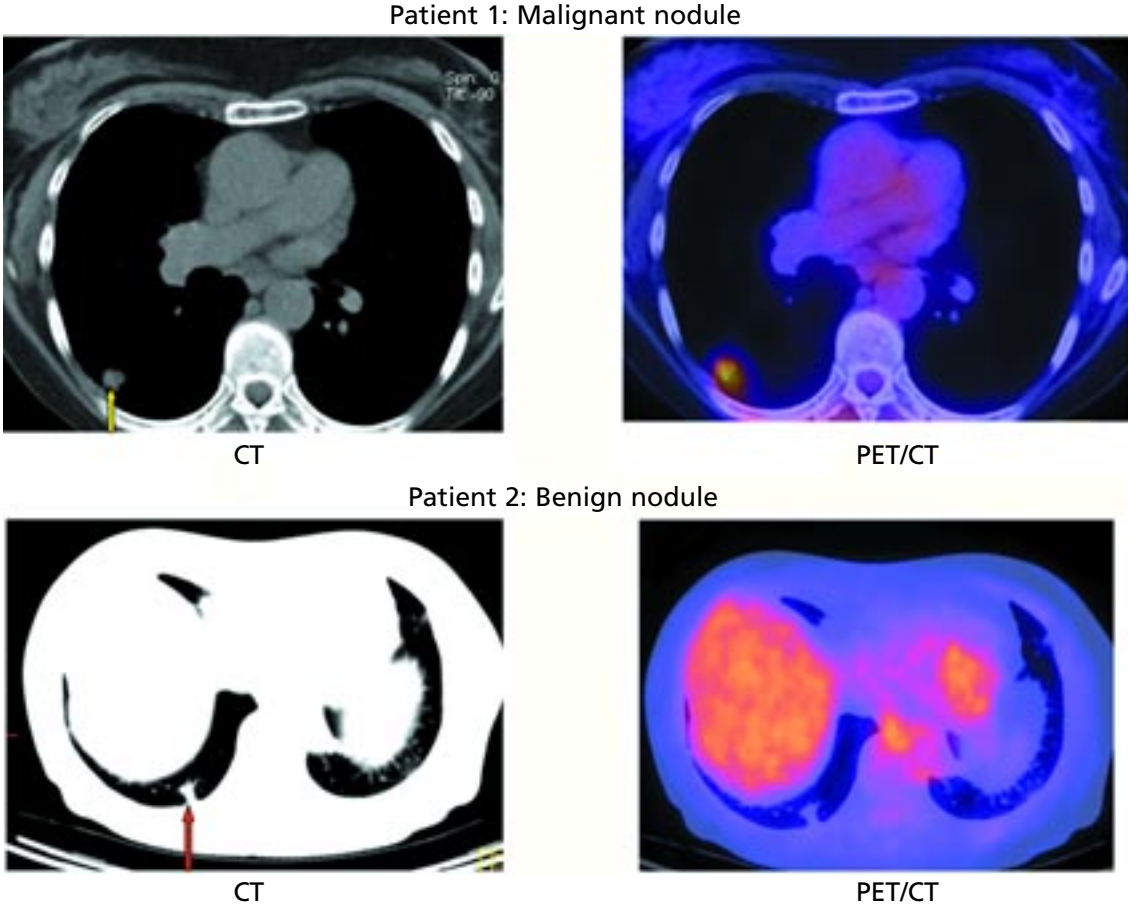

FIGURE 2. Patient 1: (Left) 1.6-cm right lower lobe pulmonary nodule on CT (yellow arrow). (Right) Superimposed FDG PET image shows hypermetabolism (biopsy-proven adenocarcinoma). Patient 2: (Left) 1.3-cm right lower lobe pulmonary nodule (red arrow). (Right) PET/CT does not show increased FDG uptake, which is stable on follow-up CT examinations.

Negative pulmonary nodules on PET/CT should still be followed up

nant tumors have increased glucose metabolism, visible as a focal increase in tissue activity of FDG (FIGURE 2). Initial studies indicated that a standardized uptake value of 2.5 might distinguish benign from malignant processes[5]; however, later studies have shown that there can be some overlap in these values between benign and malignant processes.[6]

The size of the tumor and its avidity for the tracer affect the diagnostic accuracy of FDG-PET. The reported sensitivity of FDG-PET for identifying malignancy in solitary pulmonary nodules ranges from 83% to 100%, and its specificity ranges from 63% to 90%, with a negative predictive value of about 95%.[7–9] Because the spatial resolution of most commercial PET scanners is about 5 to 6 mm, FDG-PET is less accurate for pulmonary nodules smaller than 1 cm.[7]

FDG-PET studies can be falsely positive, primarily due to inflammatory and granulomatous changes, as might be seen in tuberculosis, fungal infections, and sarcoidosis.[10]

Most solitary pulmonary nodules without increased FDG uptake are highly unlikely to be malignant (FIGURE 2). However, FDG-PET scans are occasionally falsely negative in cases of well-differentiated adenocarcinoma, bronchoalveolar cell carcinoma,[11,12] and carcinoid. Thus, most patients with a negative FDG-PET study should still be followed up radiographically (usually by CT) to definitively confirm a benign diagnosis. Typically, those with a low probability of cancer based on the CT findings

alone and those with an intermediate likelihood of malignancy on CT and a negative PET scan should undergo CT in 3 months for follow-up.[3] Although PET is very useful, biopsy may be considered for confirmation if the PET results are incongruous with the other clinical information.

Lung cancer: Has it spread to lymph nodes, other organs?

The most important prognostic indicator in patients with lung cancer, the leading cause of cancer-related deaths worldwide, is the extent of disease at diagnosis.[13] Therefore, once the diagnosis of lung cancer is established, accurate staging is necessary.

An important question in cases of non-small-cell lung cancer, affecting the patient's therapy and prognosis, is whether the cancer has spread to the lymph nodes, and which ones.[14] Locally advanced disease in ipsilateral hilar and mediastinal lymph nodes or in subcarinal nodes may be amenable to surgical resection. In contrast, involvement of the contralateral mediastinal or hilar nodes imparts a worse prognosis and generally indicates that surgery is not feasible.[15,16]

In using CT to assess the lymph nodes, one relies mainly on lymph node size and number to estimate the likelihood of malignancy. CT is approximately 45% sensitive and 85% specific for metastatic disease in the hilar and mediastinal lymph nodes.[17] A major limitation of CT is its inability to characterize the nature of visualized lymph nodes.

PET imaging provides metabolic information in addition to these anatomic findings and offers a more accurate means of delineating the nodal spread. For mediastinal nodes, sensitivities of 80% to 90% and specificities of 85% to 100% have been reported for FDG-PET.[17] In a meta-analysis,[18] the sensitivity and specificity of positive hilar nodes by PET (83% and 92%, respectively) were significantly higher than with CT alone (59% and 78%).

Therefore, PET enables more accurate assessment of regional lymph nodes in patients with early-stage non-small-cell lung cancer, significantly reducing unnecessary mediastinoscopy and thoracotomy procedures. Conversely, in approximately one third of cases of lung cancer initially staged with CT, the disease is found to be more extensive on PET imaging (FIGURE 3).

Distant metastases typically preclude a surgical cure. Evaluation for metastatic disease with conventional imaging generally requires several studies, including CT, MRI, and skeletal scintigraphy. FDG-PET is an alternative means of evaluating for metastatic disease, and it complements these conventional imaging techniques. Weder et al[19] reported that FDG-PET established a more advanced disease stage in 20% of their cases.

Advantages of PET/CT in staging lung cancer

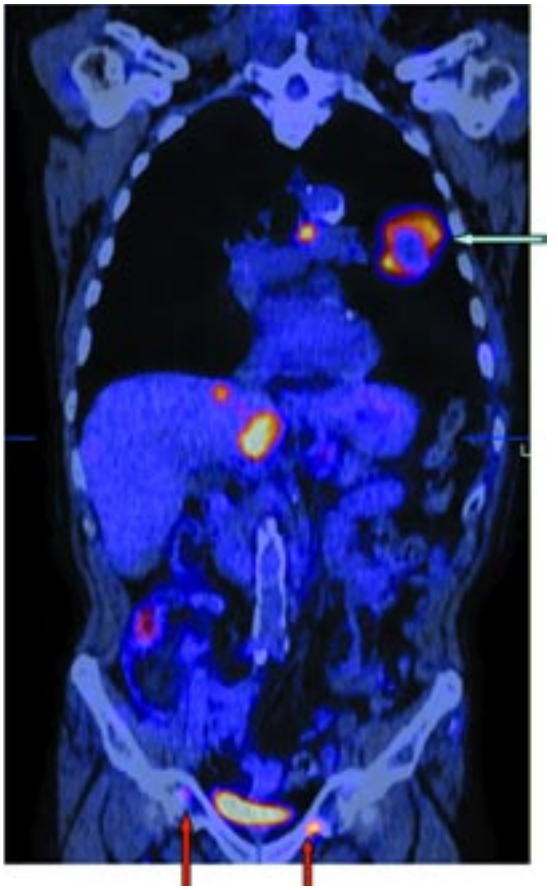

FIGURE 3. Coronal slice of a PET/CT scan demonstrating a large left lung mass showing peripheral hypermetabolism with central necrosis (olive arrow), positive mediastinal disease, two liver lesions, and previously unsuspected pelvic bone metastases (red arrows). The presence of distant metastases changes the treatment options for the patient.

PET/CT is more sensitive for positive lymph nodes than CT alone

Restaging of colorectal cancer

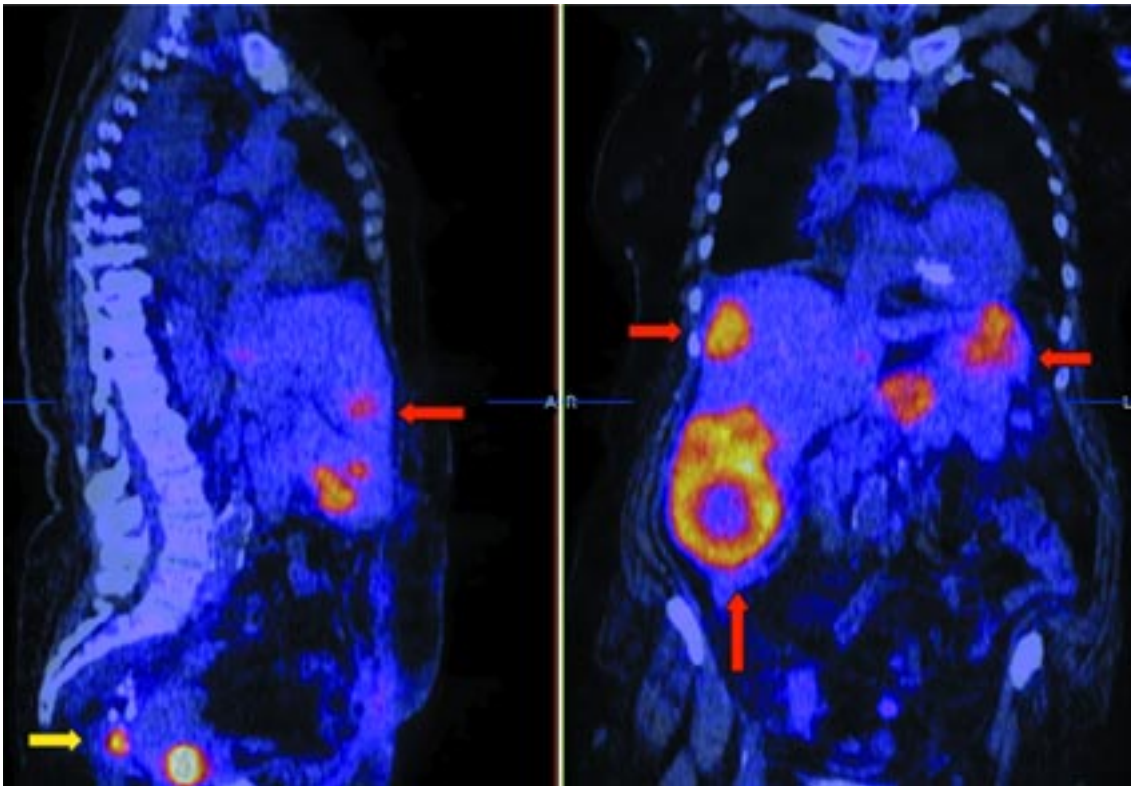

FIGURE 4. Sagittal (left) and coronal (right) PET/CT slices of patient with prior surgery and increasing carcinoembryonic antigen show increased FDG uptake in multiple liver lesions (red arrows), as well as recurrence of local disease in the presacral space (yellow arrow).

PET can find the primary site in up to half of cases of carcinoma of unknown primary

Benign adrenal nodules are a common CT finding and frequently pose a diagnostic challenge when conventional imaging alone is used. FDG-PET reliably differentiates between benign adrenal nodules and adrenal metastases, with a reported sensitivity of 100% and specificity of 80%.[20] Blake et al[21] reported that PET/CT increases the specificity to over 90%.

Carcinoma of unknown primary: Where is the primary tumor?

About 0.5% to 5% of patients with newly diagnosed cancer have an occult primary tumor, the site of which remains undetected in the patient's lifetime.[22] These patients have varied outcomes depending upon the tumor's histopathologic features and on the efficacy of therapy. However, the overall prognosis is poor, with a mean survival of 3 to 6 months.[23]

Clinical studies indicate that PET can identify the primary tumor site in 6% to 55% of these patients, most of whom have adenocarcinoma and, less commonly, undifferentiated carcinomas and squamous cell carcinomas.[23,24] In a prospective study,[22] FDG-PET was able to locate the primary tumor in 25% of cases of carcinoma of unknown primary in patients who already had had an exhaustive work-up. Larger clinical studies are currently under way to better define the role of PET and PET/CT imaging in patients with carcinoma of unknown primary.

PET does have limitations when used for this purpose: it is less sensitive in detecting small neoplasms owing to its limited spatial resolution; some tumors are less avid for FDG, owing to low metabolic activity; and occasionally, the primary tumor spontaneously regresses before PET is performed.[25]

Restaging cancer: Was treatment effective? Is cancer recurring?

The goal of restaging is to detect residual or recurrent disease after treatment. Follow-up

Assessment of treatment response of lymphoma with PET

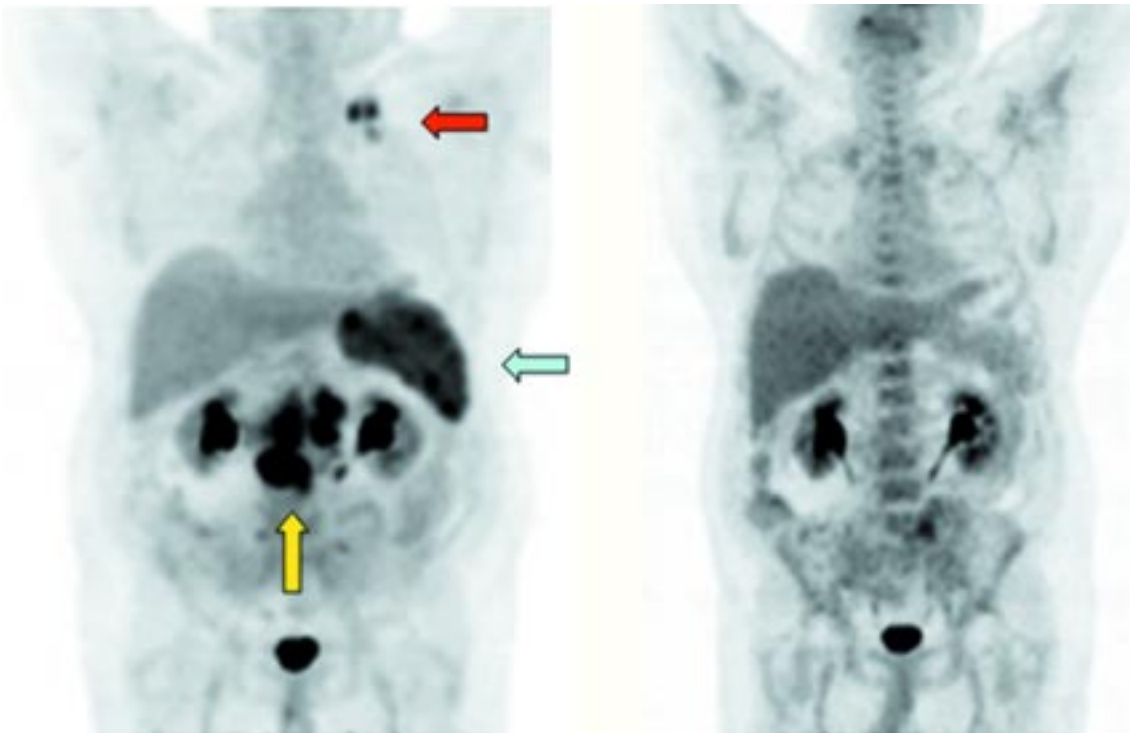

FIGURE 5. Images of pre- and post-therapy PET scans in a lymphoma patient treated with chemotherapy. The pretherapy image (left) shows increased FDG uptake in the left supraclavicular region (red arrow), mesentery, retroperitoneum (yellow arrow), and spleen (olive arrow). The post-therapy image (right) shows no residual disease, with a bone marrow activation commonly seen after chemotherapy and which can be seen with other treatments such as granulocyte colony-stimulating factor.

PET can assess the efficacy of chemotherapy as early as 24 hours after the first dose

PET imaging can be considered in two groups of patients: those in whom other imaging or laboratory studies raise the concern of relapse, and those in whom the response to treatment needs to be gauged.

Not all patients with recurrent neoplasms benefit from PET imaging, but PET/CT has proven advantageous in several situations.

In colorectal cancer, carcinoembryonic antigen levels and CT have conventionally been used to monitor for tumor recurrence. However, CT often does not reliably distinguish postsurgical changes from tumor recurrence or identify metastatic sites. PET (FIGURE 4) has a significant clinical impact on the management of these patients.[26]

A meta-analysis[27] indicated that in detecting hepatic metastases, FDG-PET has a sensitivity of 95%, significantly higher than that of CT (65%) or MRI (76%). Sensitivity, specificity, and identification of remote metastases are expected to be even better using PET/CT.[28,29]

In head and neck tumors, recurrences often are challenging to detect by CT or MRI alone, as surgery or radiation therapy can significantly distort the normal anatomic landmarks. Although PET by itself accurately detects tumor recurrence, PET/CT more precisely delineates the enhanced FDG uptake, making it easier to differentiate between recurrent neoplasm and inflammatory or physiologic uptake.[28,30]

Is chemotherapy working?

The efficacy of cancer chemotherapy has conventionally been assessed by monitoring the size of the tumor. In 2000, a multinational committee proposed that a 30% decrease in the largest diameter of the tumor be used as evidence of chemotherapeutic success.[31]

PET evaluation of coronary artery disease

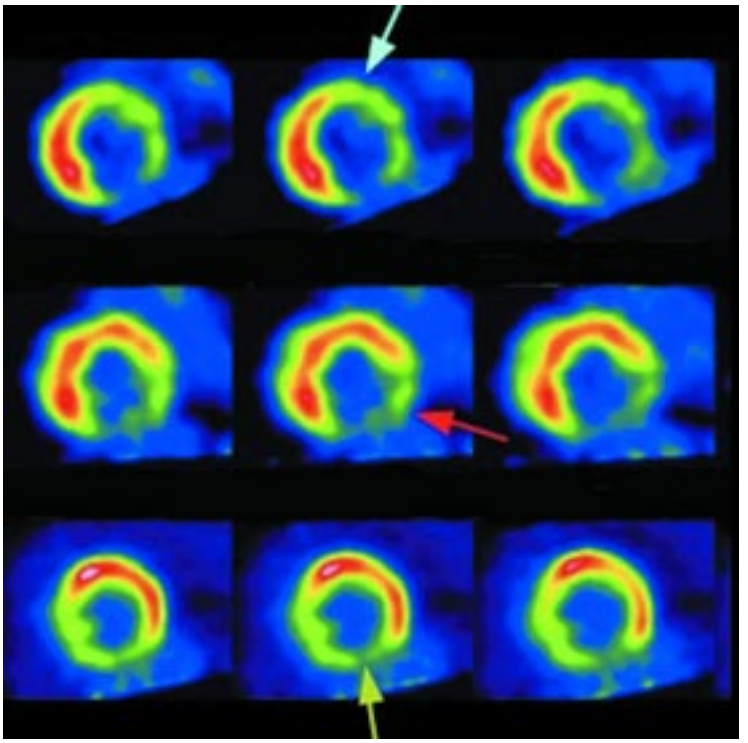

FIGURE 6. Short-axis cardiac PET images obtained at several left ventricular levels in a patient with ischemic cardiomyopathy using stress/rest rubidium-82 perfusion and FDG metabolic imaging. A reversible perfusion defect indicative of pharmacologic stress-induced ischemia is noted in the anterior and anterolateral areas (blue arrow). A fixed perfusion defect with enhanced tissue glucose metabolism consistent with myocardial hibernation is noted in the inferolateral region (red arrow), while matching perfusion and metabolic defects consistent with scar are identified in the inferior region (olive arrow).

However, gauging the success of therapy in this manner can take months.

Because PET provides functional information, it can be used to assess therapeutic efficacy as early as 24 hours after the initial dose of chemotherapy.[32] Ineffective, toxic, and costly therapies can be stopped and replaced promptly with alternative treatments.

In patients with solid tumors, a reduction in the standardized uptake value of 25% to 60% from the baseline value is highly predictive of a positive therapeutic response and a favorable prognosis.[33–36]

In lymphoma patients, residual tissue masses can be detected by anatomic imaging in as many as 65% of cases after therapy is completed.[37] The mass may reflect viable tumor or posttreatment scarring and fibrosis, and it is often not possible for CT to distinguish between the two.

On PET, a decrease in the standardized uptake value of 60% or more 10 days after the third cycle of treatment is highly predictive of a favorable response and can be used clinically (**FIGURE 5**; see also **www.ccjm.org/PET/cancer.htm** to view a three-dimensional video).[38] On the other hand, FDG uptake in the mass after therapy is a relatively specific sign of viable tumor and denotes a poor prognosis.[39] Enhanced FDG uptake 4 to 6 weeks after chemotherapy is highly predictive of tumor recurrence. If FDG uptake is not observed, the progression-free survival rate at 20 years is 85%.[40]

Post-radiotherapy PET assessment in the appropriate patient population can be very useful. However, FDG uptake may persist as long as 3 to 4 months after radiotherapy is completed.[41]

PET IN CORONARY DISEASE

Is there a perfusion defect with stress?

Myocardial perfusion imaging depicts the pattern of blood flow to the cardiac muscle. The PET tracers used most frequently for perfusion imaging are rubidium-82, [13N]-ammonia, and [15O]-water.

During the procedure, myocardial perfusion is imaged at rest and again during pharmacologic stress with intravenous dipyridamole or adenosine. The hallmark of stress-induced ischemia is a reversible perfusion defect, ie, a defect present on the stress perfusion images but absent on rest perfusion images (**FIGURE 6**; see also **www.ccjm.org/PET/cardiac.htm** to view a cine loop). The location and extent of the perfusion defect is used to infer which of the three major coronary vessels is diseased. The severity of the stress-induced ischemia is gauged by the relative tracer concentration within the stress perfusion defect. The lower the relative tracer concentration, the more profound the ischemia.

Studies of SPECT myocardial perfusion imaging indicate that the risk of cardiac events in patients increases nonlinearly as the anatomic extent and severity of stress-induced ischemia increases.[42]

The utility of PET perfusion imaging for detecting coronary stenoses has been addressed in eight clinical studies involving a total of 791 patients.[43] The average sensitivity was 93%, and average specificity 92%.

In differing patient populations matched for multiple variables, PET had greater sensitivity, specificity, and diagnostic accuracy than SPECT imaging.[44] In a meta-analysis of clinical studies in which PET and SPECT perfusion imaging were performed in the same patients, Go and colleagues[45] reported that PET had a significantly higher sensitivity (93% vs 85%, $P < .005$), specificity (82% vs 67%, $P < .05$), and diagnostic accuracy (91% vs 81%, $P < .001$).

Current practice guidelines[46] indicate that PET perfusion imaging during stress and at rest is appropriate for detecting coronary stenoses in patients with an intermediate likelihood of coronary disease, and for risk stratification in patients with an intermediate or high likelihood of disease in whom a pharmacologic SPECT study is equivocal for diagnostic or risk-stratification purposes (class I recommendation).

PET perfusion imaging is also appropriate as the initial diagnostic test in patients who cannot exercise (class IIa recommendation) or who can exercise but who have left bundle branch block or an electronically paced rhythm (class IIa recommendation).

Is the heart muscle dead, or merely hibernating?

FDG-PET is used to find out if myocardium is viable in patients with coronary artery disease with left ventricular dysfunction.

Although a regional wall motion abnormality (on a variety of imaging techniques) may indicate a myocardial scar, nearly half of coronary patients with a reduced left ventricular ejection fractions actually have a clinically important amount of viable tissue in the dysfunctional regions.[47] Neither the resting electrocardiogram nor the severity of the associated wall motion abnormality reliably distinguishes between completed infarction and viable but dysfunctional tissue in these areas. This distinction is crucial for optimal management because those with viable tissue will benefit functionally and prognostically if coronary revascularization can be performed.

In a meta-analysis of clinical studies involving 3,088 patients with coronary artery disease and left ventricular dysfunction (mean left ventricular ejection fraction 32% ± 8%), Allman et al[48] reported that patients with viable myocardium on noninvasive imaging who underwent coronary revascularization had an 80% lower rate of annual mortality compared with those treated medically (3.2% vs 16%, $P < .0001$). In the patients with viable myocardium, coronary revascularization provided the greatest survival benefit to those with the most depressed ejection fraction before surgery. In contrast, annual mortality rates in patients with nonviable myocardium were comparable regardless of whether they were treated surgically or medically (7.7% vs 6.2%, P = NS).

In coronary patients with a reduced left ventricular ejection fraction, FDG-PET imaging has been used for nearly 2 decades to identify those who might benefit from revascularization. A resting perfusion defect can represent either scar or a reversible state of muscle dysfunction known as myocardial hibernation. In hibernating myocardium, perfusion and function are low, but glucose metabolism is preserved, resulting in a "perfusion-metabolism mismatch" (**FIGURE 6**). These areas improve in function after revascularization. In contrast, hypoperfused areas with completed scar are metabolically inactive, and therefore demonstrate matching defects on PET perfusion and FDG metabolic images and typically do not improve functionally after revascularization.

A persistent defect on SPECT does not rule out viability on PET

A persistent defect on SPECT thallium-201 redistribution/re-injection perfusion images does not preclude metabolic viability on PET imaging, as about 20% of segments with severe thallium-201 defects show preserved glucose metabolism on PET imaging. PET imaging is more sensitive (88% vs 84%) but slightly less specific (73% vs 81%) than low-dose dobutamine echocardiography for predicting recovery of regional function after revascularization. Limited clinical data are available comparing MRI with late enhancement and FDG-PET, but a recent study by Knuesel et al[49] suggests that the two tests may provide complementary information.

TABLE 1

Medicare-accepted indications for positron emission tomography (PET)

INDICATION	PURPOSE
Alzheimer disease	Differential diagnosis
Breast cancer	Staging, restaging, evaluating treatment response
Cardiac perfusion	If single-photon emission CT examination is equivocal
Colorectal cancer	Diagnosis, staging, restaging
Esophageal cancer	Diagnosis, staging, restaging
Head and neck cancer	Diagnosis, staging, restaging
Lung cancer	Diagnosis, staging, restaging
Lymphoma	Diagnosis, staging, restaging
Melanoma	Diagnosis, staging, restaging
Myocardial viability	Evaluation
Refractory seizures	Presurgical evaluation
Solitary pulmonary nodules	Characterization
Thyroid cancer	Restaging (with negative iodine-131 scan and positive thyroglobulin)

Current practice guidelines indicate that PET metabolic imaging is appropriate for defining myocardial regions that will benefit functionally from revascularization (class I recommendation), for identifying patients with coronary artery disease in whom revascularization is anticipated to improve heart failure symptoms (class IIa recommendation), and for identifying those likely to derive a survival benefit from revascularization (class I recommendation).

PET IN NEUROLOGY: TUMORS, EPILEPSY, DEMENTIA

PET is useful in many neurologic disorders. Glucose metabolism imaging with FDG evaluates the functional integrity of the brain and complements the information obtained from CT and MRI.

Brain tumors. In patients who have undergone radiation therapy for a brain tumor, it is often difficult to differentiate radiation necrosis from tumor recurrence when one finds an enhancing lesion on MRI. By assessing the metabolic activity of the enhancing lesions, PET helps differentiate radiation necrosis from tumor recurrence. Recurrent tumors typically exhibit increased uptake, while radiation necrosis is metabolically inactive.

On the other hand, FDG-PET has a limited role in detecting brain metastases and certain primary brain tumors, owing to high background uptake in normal gray matter and to PET's lesser resolution compared with MRI, which is the preferred imaging study for these indications.

Epilepsy. In conjunction with MRI and electroencephalography, PET is helpful for locating the focus of seizures before epilepsy surgery by detecting regional decreased glucose metabolism, which is often associated with the site of seizure onset.

Dementia. By detecting characteristic patterns of regional decreased glucose metabolism (FIGURE 1), PET also appears to be the best imaging tool for the differential diagnosis of dementia. PET can detect regional abnormal glucose metabolism in patients with mild cognitive impairment before the overt clinical manifestations of dementia appear and is considered the most sensitive and specific diagnostic tool for Alzheimer disease and frontotemporal dementia.[50]

Experimental uses. In preliminary studies, PET appeared promising for other neurologic applications. It may be a good tool for predicting prognosis and monitoring neuronal protective intervention in stroke patients and may be useful for monitoring the effectiveness of deep brain stimulation in movement disorders.

Currently, FDG is the main tracer used for clinical cerebral imaging, but a number of promising new tracers under investigation[51,52] depict information about neurotransmitters and their receptors (dopamine, serotonin, acetylcholine, gamma-aminobutyric acid, adenosine, opioid), synapses, and even genetics.

DOES INSURANCE COVER PET IMAGING?

The Centers for Medicare and Medicaid Services (CMS) issued an initial indication in January 1998 providing reimbursement for

PET imaging for the characterization of indeterminate solitary pulmonary nodules and for the staging of lung cancer.[53,54]

Over the ensuing years, the list of reimbursable indications has expanded considerably, so that many conditions are now covered (TABLE 1). Specific billing codes for PET/CT were published in November 2004 in the Federal Register. Private payers tend to follow CMS indications, but reimbursement policies vary from company to company. There is also significant regional variability in payments. Patients or physicians would need to contact their payers or Medicare for the specific cost of their studies. Although FDG PET/CT imaging is more expensive than "conventional" imaging alone (CT, MRI), preliminary data suggest that in many processes, particularly cancer, using PET in the workup may be more cost-effective than using conventional imaging alone by avoiding needless studies or procedures.[55]

In oncology, CMS has initiated a National Oncologic PET Registry project, which will likely increase the number of covered indications in the future. At present, imaging for many "noncovered" oncologic indications will be reimbursed as part of the registry project if the referring physician completes brief data-collection forms. Further details are available at **www.cancerpetregistry.org**.

In cardiology, Medicare began reimbursing for cardiac PET imaging with rubidium-82 in 1995 and more recently with [13N]-ammonia. In selected patients, current Medicare guidelines permit reimbursement for FDG-PET imaging for the determination of myocardial viability.

In neurology, Medicare currently provides coverage for PET for presurgical localization of seizures.

Medicare has also approved coverage of FDG-PET for the differential diagnosis of dementia. However, it limits coverage of the study to patients with certain qualifying characteristics. The physician must provide documentation of the following before the patient is considered for coverage:

- Date of onset of symptoms (at least a 6-month history of cognitive decline)
- Mini-Mental Status Examination or similar test score
- Report from any neuropsychological testing performed
- Diagnosis of the clinical syndrome (eg, possible, probable, or uncertain Alzheimer disease)
- Results of structural imaging (MRI or CT)
- Relevant laboratory tests (vitamin B_{12}, thyroid hormones)
- Prescribed medications.

More detailed information can be found at **www.cms.hhs.gov**.

TABLE 2

PET tracers and examples of their future uses

[18F] Fluorodeoxyglucose (FDG)	Glucose metabolism
[18F] Fluoride	Bone imaging
[11C] Methionine	Amino acid metabolism
[11C] Tyrosine	Amino acid transport
[11C] Acetate	Fatty acid synthesis
[18F] Fluorothymidine	Cell proliferation
[18F] Arginine glycine aspartic acid	Angiogenesis
[18F] Annexin V	Apoptosis
[18F] Fluoromisonidazole	Tissue hypoxia
[18F] Fluoroestradiol	Estrogen receptor status
[18F] Fluorodopa	CNS agent dopamine
[11C] Raclopride	CNS agent dopamine
[11C] Methylspiperone	CNS agent dopamine
Iodine 124	Thyroid metabolism
Technetium 94m	Potential label for amyloid plaque

FUTURE OF PET/CT

The uses of PET and PET/CT imaging have rapidly grown over the last decade: previously available only at academic centers, they are now offered at community hospitals and outpatient facilities. Mobile services have brought PET to areas that do not have a fixed site. About 1 million PET procedures were performed in 2004. Although FDG-PET imaging now plays a major role in the clinical manage-

ment of many oncologic and cardiologic and some neurologic disorders, its full clinical potential has yet to be realized. Additional improvements in the technical and instrumentational aspects of PET in the future are expected.

However, the field that is evolving most rapidly is radiopharmaceutical development. New tracers (TABLE 2), depicting amino acid metabolism, receptor density, neurotransmitter activity, blood flow, tissue hypoxia, angiogenesis, and apoptosis, have been developed and may eventually find even wider clinical use than FDG. Use of these tracers could prove particularly valuable in cancers that are not typically FDG-avid, such as those of the prostate and renal cells. Use of PET imaging in drug discovery and development (for example, anticancer drugs) is feasible and can be tested in small animal models using smaller PET imaging devices before clinical trials.

Evaluation of gene expression and cell transplantation therapy also appear likely in the future. Recent animal studies indicate that PET imaging can be used to noninvasively monitor gene expression over time and to gauge the success of cell transplantation.

As the list of commercially available tracers continues to expand, the physiologic information provided to the clinician will increase. This will improve our ability to diagnose disease and to noninvasively monitor the response to treatment. As such, the use of PET imaging to characterize disease at the molecular level will help translate the fundamental knowledge of disease pathophysiology obtained at the laboratory bench to the bedside care of the patient, improving the quality of care for many.

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