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FDG PET and PET/CT Molecular Imaging

CHAPTER HIGHLIGHTS

1. FDG PET provides true molecular and functional imaging.
2. Primary indications for FDG PET/CT imaging include staging, restaging, and monitoring response to therapy.
3. Other important applications for PET/CT include guiding biopsy and selecting biopsy sites, identifying tumor in patients with rising markers, guiding radiation therapy planning, and providing prognostic information.
4. PET/CT is superior to either PET or CT alone or to both modalities evaluated without benefit of fusion of the images.
5. FDG PET can show positive uptake in infection and inflammation. Active granulomatous disease can be a cause of false positive in pulmonary nodules.
6. False-negative results can be caused by hyperglycemia at the time of injection of FDG (*see Case Study*), normal physiologic uptake masking tumor uptake, and low-grade tumors that do not have increased glucose metabolism. Generally, although all tumors are different, FDG PET has reported overall sensitivity and specificity of 84–87% and 88–93%, respectively, and an accuracy of 87–90%, based on a meta-analysis of ~18,000 studies published in 2001 (prior to PET/CT).¹

THE CARE of patients with cancer is a multidisciplinary effort as surgeons, medical oncologists, radiation oncologists, radiologists, nuclear medicine physicians, pathologists, and others confer to determine optimal therapy. Imaging is invaluable throughout the process because it provides pretreatment staging information and allows health care professionals to monitor treatment response and to follow-up for evidence of tumor recurrence. Multi-center, government-sponsored clinical trials place reliance on imaging for noninvasive, objective measures of therapeutic response, as well as for diagnostic and prognostic information. The fusion of positron-emission tomography (PET) and computed axial tomography (CT) provides a powerful combination of functional and anatomic information and is demonstrated to be more sensitive and more accurate than FDG PET and CT performed separately.

Evidence suggests that PET with F-18-fluorodeoxyglucose (FDG, or F-18-fluoro-2-deoxyglucose) improves the accuracy of cancer staging in a cost-effective manner, resulting in up-staging in some cases and down-staging in others. For instance, a patient with a seemingly resectable esophageal cancer may be spared an unnecessary operation if PET shows hypermetabolic lesions in distant locations, such as in the liver. PET's high sensitivity for detecting small-volume disease (e.g., malignant lymph nodes as small as 5 mm) and its ability to differentiate benign reactive lymph nodes from malignant nodal disease have improved both nodal and metastatic staging. Reports suggest that integrated PET/CT improves staging in 30–50% of patients over the results of FDG PET and CT performed separately and evaluated without benefit of image fusion.

Transport of glucose and F-18-FDG across the

FDG and Glucose Kinetics

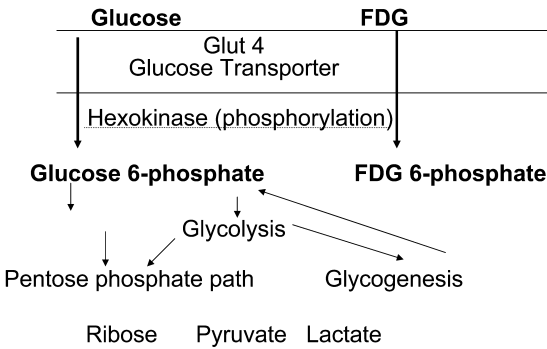


Figure 1.1 PET provides molecular imaging of F-18-FDG as it is metabolized intracellularly. FDG (labeled with F-18) reaches a dead-end after phosphorylation as FDG 6-phosphatase, whereas glucose is further metabolized.

plasma membrane of mammalian cells is facilitated by the family of glucose transporter (GLUT) proteins. Once intracellular, glucose is phosphorylated into glucose 6-phosphate and F-18-FDG into F-18-FDG 6-phosphate by hexokinase; glucose 6-phosphate is then further metabolized via the three pathways depicted in Figure 1.1, but F-18-FDG 6-phosphate is not. It remains trapped intracellularly in that form, providing time for imaging to be accomplished without change or washout of the tracer F-18. Also unlike glucose, FDG is excreted by the kidneys into the urine, that is, it is not reabsorbed by the renal tubules (for more detailed information about F-18-FDG, see the Radiopharmaceutical section below). Normal biodistribution of FDG seen on images includes the brain, myocardium, liver, bone marrow, renal excretory system, stomach, and bowel.

This is the molecular imaging being used in today’s clinical practice setting. The field of molecular imaging is advancing into genomics and proteomics, and in the future, we may be imaging radiolabeled reporter genes or radiolabeled antisense molecules for assessments of gene function. In vivo imaging with current radionuclide imaging techniques will be supplemented by imaging techniques including optics, MRI, and ultrasound.

Primary Clinical Indications for PET/CT

In 1999, the Health Care Financing Administration (HCFA) approved reimbursement for diagnostic FDG imaging for the management of patients with

recurrent colorectal cancer, for staging of lung cancer, for evaluation of the solitary pulmonary nodule seen on CT scanning, and for staging of lymphoma and recurrent melanoma. More recently, the Centers for Medicare and Medicaid Services (CMS) expanded reimbursement for 13 indications (Table 1.1) in malignant disease. Patients with malignancies falling outside these indications can still receive reimbursement by Medicare if the referring physician and the imaging physician report the patient’s medical and scan information to a database (NOPR—National Oncologic PET Registry) initiated by CMS and agree to provide follow-up data (see Chapter 20, Comparative Costs of Diagnostic Procedures). In general, indications for PET or PET/CT include the following:

- Staging, restaging, and monitoring response to therapy for many tumors.
- Distinguishing tumor recurrence or residual from post-therapy changes (fibrosis, necrosis) in masses seen on CT.
- Clarifying the nature of uncertain findings on CT.
- Guiding biopsy by (1) identifying the metabolically active part of a mass or (2) identifying less invasive sites for biopsy not evident on CT (e.g., adrenals, supraclavicular, or other accessible lymph nodes that show increased glucose metabolism on images).
- Identifying sites of tumor in patients with increasing tumor markers.
- Providing information about prognosis, including the level of FDG uptake (for many tumors, higher levels of FDG uptake correlate with poorer prognosis) and the extent of tumor spread and tumor burden.

In addition, the role of PET in planning radiation therapy is expanding and under investigation.

Patient Preparation

Patient preparation is predicated on evaluating hydrated patients with basal blood glucose and insulin levels; therefore, patients should fast (not including water) at least 6 hours prior to imaging to decrease physiologic changes in serum glucose and insulin concentrations. Furthermore, it is important to remember to discontinue dextrose-containing intravenous fluids and parenteral feedings for inpatients 6 hours prior to injection of F-18-FDG. Any medications administered in the hours prior to the study should be prepared in saline and not in a dextrose-containing solution.

Blood glucose levels will be checked prior to intravenous injection of F-18-FDG. If the patient is

Table 1.1
Indications Qualifying for Reimbursement for FDG PET by the CMS

Clinical Condition	Coverage
FDG PET	
Breast cancer	Staging, restaging, and monitoring response to therapy
Colorectal cancer	Diagnosis, staging, and restaging
Esophageal cancer	Diagnosis, staging, and restaging
Head and neck cancers (excluding CNS and thyroid)	Diagnosis, staging, and restaging
Lung cancer (non–small cell)	Diagnosis, staging, and restaging
Lymphoma	Diagnosis, staging, and restaging
Melanoma (excludes evaluation of regional nodes)	Diagnosis, staging, and restaging
Myocardial viability	Primary or initial diagnosis or following an inconclusive SPECT prior to revascularization
Refractory seizures	Covered for presurgical evaluation only
Solitary pulmonary nodule	Characterization of indeterminate single pulmonary nodule
Thyroid cancer	Restaging
Cervical cancer	Staging as an adjunct to conventional imaging
Dementia	Differential diagnosis of fronto-temporal dementia (FTD) and Alzheimer's disease (AD) or CMS-approved practical clinical trial
Non-FDG PET	
Perfusion of the heart using rubidium-82 tracer	Covered for noninvasive imaging of the perfusion of the heart
Perfusion of the heart using ammonia N-13 tracer	Covered for noninvasive imaging of the perfusion of the heart

hyperglycemic (>200 mg/dl), the procedure will be rescheduled, because tumor uptake of FDG is reduced when serum glucose levels are elevated (see Figure 1.1). Exogenous insulin may be used pharmacologically to lower blood glucose levels prior to imaging, but a 1- to 2-hour or more wait period is necessary prior to FDG injection, depending on type and route of insulin used.

Standard barium-containing oral contrast is usually administered 2 hours prior to imaging to distinguish normal GI tract from other normal and abnormal structures on images.

What to Tell the Patient

The patient should be informed of the reason for the study, of how to prepare for it (previous section), and about avoiding physical exercise 12–24 hours prior to the test since skeletal muscle uptake of FDG may be quite high and thereby decrease

the sensitivity of the scan. Patients should know that after the FDG administration, they will rest for 60 minutes in a quiet room for an “equilibration period,” which gives the F-18-FDG time to distribute throughout the body. Specifically for head and neck imaging, the patient should not be chewing, vocalizing, or straining neck muscles during the equilibration period, for these activities may increase FDG activity in normal structures.

The patient should be told that this study will provide the doctors with pictures that show the tumor(s) in his/her body. It will tell the doctors how extensive the tumor is, which is important in “staging” the tumor. The PET scan will also show exactly where the tumor is located. It may provide information on the likely behavior of the tumor based on its level of metabolic activity, and it may indicate whether or not a good response to therapy can be expected if the scan is done following therapy.

Furthermore, patients should have a basic understanding of how FDG PET works. They should

be made aware of the strengths and limitations of this modality—that it is neither 100% sensitive or specific and that small, partially treated, or metabolically weak tumors may not enhance, whereas nontumor inflammation can enhance. They should also be informed that their treating physicians may obtain other imaging because PET imaging (with or without non-contrast CT) does not provide adequate anatomic imaging to plan for an operation.

How the Procedure Is Performed

Approximately 45–60 minutes after intravenous injection of 6–20 mCi (depending on instrumentation) of F-18-FDG, imaging is performed on a PET, PET/CT, or coincidence (hybrid, SPECT/PET) camera or scanner. (See Appendix 1 for further discussion of instrumentation.) Lower activities are injected for coincidence imaging because of the camera's limitations in imaging the increased numbers of events related to higher activity levels.

The 45–60 minutes between injection and imaging is called the equilibration or uptake phase, during which FDG localizes within tumor cells wherever they may be in the body. During this time, FDG is excreted, primarily through the kidneys but also through the bowel and liver.

In PET/CT, procedures differ vis a vis contrast administration, oral and intravenous. Contrast on the CT scan assists in distinguishing vascular and gastrointestinal structures that serve as landmarks and can be confused with tumor tissue if unmarked. The PET scan is fused with the CT scan so that all landmarks and structures identified on CT are also identified on the PET.

The Report

The report will describe the clinical indication for the test, the procedure, and the image findings. The interpreter will characterize the findings as normal physiologic uptake or will comment on the abnormal uptake and whether it likely represents tumor, inflammation, or either. The report will provide a semi-quantitative index of FDG uptake, known as the standardized uptake value (SUV), in the lesions identified. The SUV indicates the degree of glucose hypermetabolism in the lesion by representing the relative radioactivity, corrected for attenuation and normalized for the injected dose and body weight (or lean body mass or body surface area). Typically, tumors have SUVs that are higher than for normal tissues. For many tumors,

high SUVs also correlate with tumor growth and patient prognosis. Although these values vary from institution to institution depending on the timing of imaging relative to injection, the size of the lesion, the partial volume effects, the patient's serum glucose level at the time of injection, the methods of reconstruction and attenuation correction, and other factors, general guidelines accept that SUVs lower than ~2.5 correlate with benignity and that higher SUVs align with malignancy. These values may vary, however, depending on all of the above-mentioned factors as well as the particular tumor type. Inflammation or infection can also demonstrate increased glucose metabolism and FDG uptake, and it may not be possible to distinguish between the two conditions without tissue biopsy or interval follow-up.

SUVs may vary by tumor type. Typically, in lung cancer for example, SUVs exceed 2.5, but small pulmonary nodules (<1 cm) may have lower SUVs and still be malignant. Adenocarcinomas typically have lower SUVs than squamous cell cancers (SUVs can range from 2.5 to 20 or higher). Bronchioalveolar cancer is notorious for false-negative results, simulating normal tissue.

If the study was performed as a PET/CT exam, the report may describe that the CT was performed for purposes of attenuation correction and anatomic localization and was not of diagnostic quality. Under those circumstances, a low mA setting is used (minimizing radiation to the patient), and oral rather than intravenous contrast is administered. Finally, the report should indicate the extent of the study; most PET scans are performed from the base of the brain to the mid-thighs, however, whole-body scans are necessary for patients with high-risk melanoma.

The Radiopharmaceutical

PET scanners image high-energy coincident photons of positron-emitting radionuclides. Using positron emitters (e.g., F-18, C-11, O-15, N-13), radiopharmaceuticals that closely mimic endogenous molecules, leading to true “molecular imaging,” can be produced. F-18-fluoro-2-deoxyglucose (FDG) is the only FDA-approved radiopharmaceutical for oncologic PET imaging and permits in vivo evaluation of glucose metabolism. N-13 is easily incorporated into amino acids, and C-11, into carbon-based molecules. Many positron emitters have a short half-life (seconds to minutes), but F-18 has a relatively long physical half-life of 110 minutes. This longer half-life allows time for this radiopharmaceutical to be

shipped from cyclotron-containing facilities to imaging centers without cyclotrons. There are sufficient numbers of commercial radiopharmacies with cyclotrons dedicated to the manufacturing of F-18 located throughout the United States.

The effective radiation dose to patients from an F-18-FDG PET scan is about 0.7–1.4 rem or 7.03–14.06 mSv (based on an administered dose of 10–20 mCi or 370–740 MBq). The organ that receives the largest radiation dose is the bladder, 0.59 rad per mCi or 0.16 mGy per MBq administered. These levels are similar to other diagnostic imaging exams that utilize ionizing radiation, such as CT.

In children, radiation doses are higher due to smaller body size and relatively larger organ-to-body size ratio. Administered FDG doses in children are 0.15–0.30 mCi/kg or 5.55–11 MBq/kg, and consequent effective radiation doses are 0.18 rem per mCi or 0.050 mSv per MBq.

Pitfalls of Pet Scanning

Background Genitourinary Tract Activity

FDG is excreted by the kidneys into the bladder. Bladder activity may interfere with the evaluation of a pelvic mass, and some centers place an irrigating catheter to minimize this problem when indicated.

Background Gastrointestinal Activity

There may be prominent uptake in the cecum as well as activity in the esophagus, stomach, and intestine; occasionally, gut activity can present a problem in interpretation. Many reports suggest that increased focal activity in the gastrointestinal tract should not be ignored as likely to be physiologic but should be followed with an endoscopic exam.

Muscle Activity

Muscle tension, hyperventilation with increased diaphragmatic exertion, and stress-induced tension in the trapezius and paraspinal muscles may result in increased FDG uptake in the active muscle groups. In anxious patients, a muscle relaxant such as diazepam may improve results.

Brown Fat

Fused CT images assist in identifying increased FDG uptake as localized within fat. At times, this result

can be problematic for image interpretation since the brown fat uptake may mask true tumor uptake. Brown fat uptake can be minimized by having the patient equilibrate in a warm room or with blankets. Interestingly, centers in warm climates see less brown fat uptake than those in cold climates.

Inflammation

Inflammation or infection can be associated with increased FDG uptake, particularly problematic for solitary pulmonary nodule interpretation when there is granulomatous inflammation such as tuberculosis, sarcoid, histoplasmosis, and aspergillosis. Uptake can be intense enough to be confused with tumor. For this reason, FDG imaging usually is delayed for several days after minor surgical trauma or biopsy procedures to give the inflammation time to dissipate. After major surgery or radiation therapy, PET scanning should be delayed by up to 3 months for optimal results.

Poorly Controlled Diabetics

These patients present challenges for FDG PET imaging since their serum glucose levels must be sufficiently low so that tumor uptake does not compete with circulating glucose for F-18-FDG entry into tumor cells. They cannot be given insulin immediately prior to injection with FDG because high blood insulin will drive the FDG into muscles, resulting in very poor images for tumor identification. The best results have been obtained by scheduling these patients in late morning, at least 4 hours following their morning insulin administration (not long acting) and their routine breakfast.

On the Horizon

PET/CT protocols and the use of CT for attenuation correction and anatomic localization, including using contrast materials, are evolving. Corrections for respiratory motion to minimize artifacts have been developed, including respiratory gating for PET or CT or both and re-registration of images. Also, new radiopharmaceuticals for more specific tumor imaging are being tested.

New instrumentation will extend PET fusions to MR imaging. New imaging protocols, such as dual timepoint imaging, are being used to distinguish tumor from infection. Clarifications of the reliability and timing of FDG PET imaging to determine

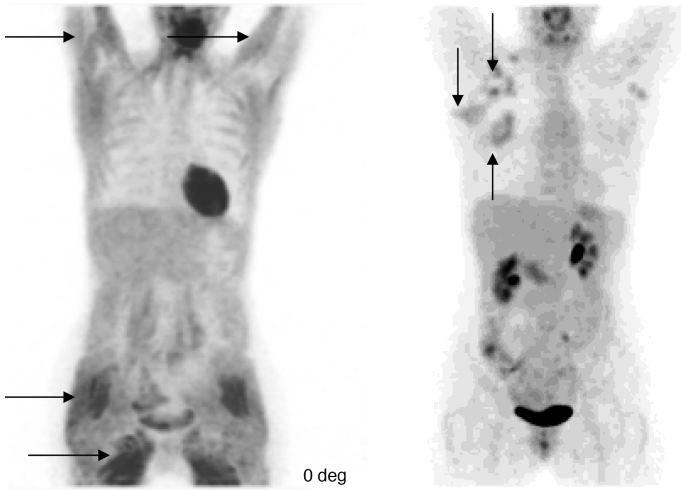


Figure 1.2 High serum glucose causes false-negative FDG PET results. At the time of the PET scan on the left, the patient's serum glucose was 225 mg/dL. There is excessive gluteal and other muscle uptake (*horizontal arrows*). The scan on the right, performed on the same patient within 2 days and with serum glucose at 120 mg/dL, shows no excessive muscle uptake and evident tumor uptake (not seen on the scan on the left) in the right breast and axilla (*vertical arrows*). (Case provided by Alan Waxman, MD)

when chemotherapy should be changed because the tumor is not responding are being established.

The role of PET in planning radiation therapy is getting more attention. Outcome data are currently lacking. PET offers advantages for tumor delineation, but its applicability in every tumor type will likely be different.

Using PET in planning biopsy site selection and PET/CT to guide biopsy to the most metabolically active part of a lesion is not yet widely practiced in clinical arenas but is on the horizon.

Case Study

A 50-year-old woman with a history of breast cancer is administered F-18-FDG even though her blood glucose measured 225 mg/dl. The resulting scan is shown in Figure 1.2 (*left*). Note the excessive uptake in the gluteus muscles around the hips bilaterally. No tumor uptake is identified. The study is repeated 48 hours later with blood glucose measuring 120 mg/dl (Figure 1.2, *right*). Note the absence of muscle uptake around the hips and the abnormal uptake in the right axilla and right breast. This case demonstrates the importance of low blood glucose (and low insulin levels) for FDG PET tumor imaging.

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Further Reading

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