

Tumor Imaging With F-18 Fluorodeoxyglucose (FDG)

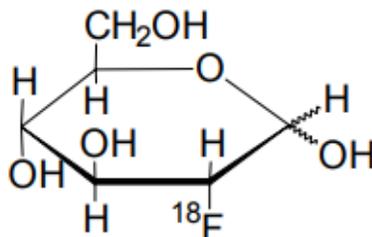
1. OVERVIEW

F-18 Fluorodeoxyglucose Injection is indicated for positron emission tomography (PET) imaging in the following settings:

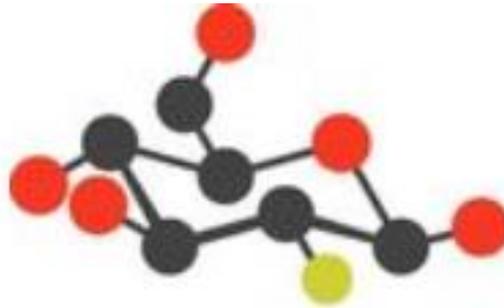
- a) **Oncology:** For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.
- b) **Cardiology:** For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.
- c) **Neurology:** For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures. Also for postoperative evaluation of patients with head and neck cancer

2. RADIOPHARMACEUTICAL UTILIZED

- a) F-18 Fluorodeoxyglucose (FDG) is a positron emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. The active ingredient 2-deoxy-2-[18F]-fluoro-D-glucose has the molecular formula of $C_6H_{11}^{18}FO_5$ with a molecular weight of 181.26, and has the following chemical structure:



b) The structure below illustrates the actual spatial positioning of the atoms in the molecule.



Color code: red = oxygen; black = carbon; yellow = fluorine

c) FDG is provided as either a unit dose in a syringe or as a multidose vial. It is a sterile, pyrogen free, isotonic, clear, colorless citrate buffered solution. Each mL contains between 0.740 to 7.40 GBq (20.0 – 200 mCi). The pH of the solution is between 5.5 to 7.5. The solution contains no preservative.

3. CHARACTERISTICS OF THE RADIONUCLIDE

a) F-18 decays by positron decay (97%) and electron capture (3%) and has a half-life of 109.7 minutes. The principal photons useful for diagnostic imaging are the 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron (Table 1).

Table 1. Principal Emission Data for Fluorine F 18

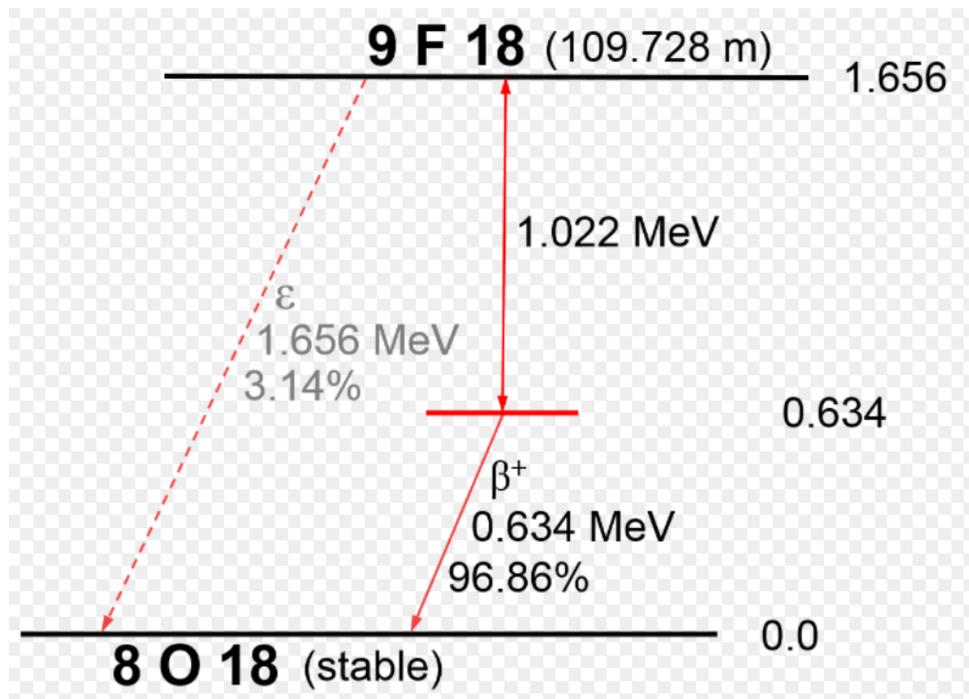
Radiation/Emission	% per Disintegration	Mean Energy
Positron (β^+)	96.73	249.8 keV
Gamma (\pm)*	193.46	511.0 keV

*Produced by positron annihilation

From: Kocher, D.C. "Radioactive Decay Tables" DOE/TIC-11026, 89 (1981).

b) The specific gamma ray constant for F-18 is 6.0 R/hr/mCi at 1cm. The half-value layer (HVL) for the 511 keV photons is 4.1 mm lead (Pb). The interposition of an 8.2 mm thickness of Pb, representing 2 half-value layers, will decrease the external radiation by 75%. The tenth-value layer (TVL) for the 511 keV photons is 17 mm of lead

c) **Decay Scheme of F-18**



4. **DRUG AVAILABILITY**

- a) F-18 FDG is readily available all over the US from most Central Radiopharmacies as well as PETNET, IBA, and other PET drug manufacturing facilities.

5. **DRUG PREPARATION**

- a) None required on part of the technologist. The patient dose should be measured in a suitable dose calibration system immediately prior to administration.

6. **RADIOCHROMATOGRAPHIC QUALITY CONTROL PROCEDURES**

- a) Not required in the Hot Lab- performed by Central Pharmacy.
- b) May be performed at the production facility by either thin layer chromatography or by HPLC.

7. CLINICAL PHARMACOLOGY

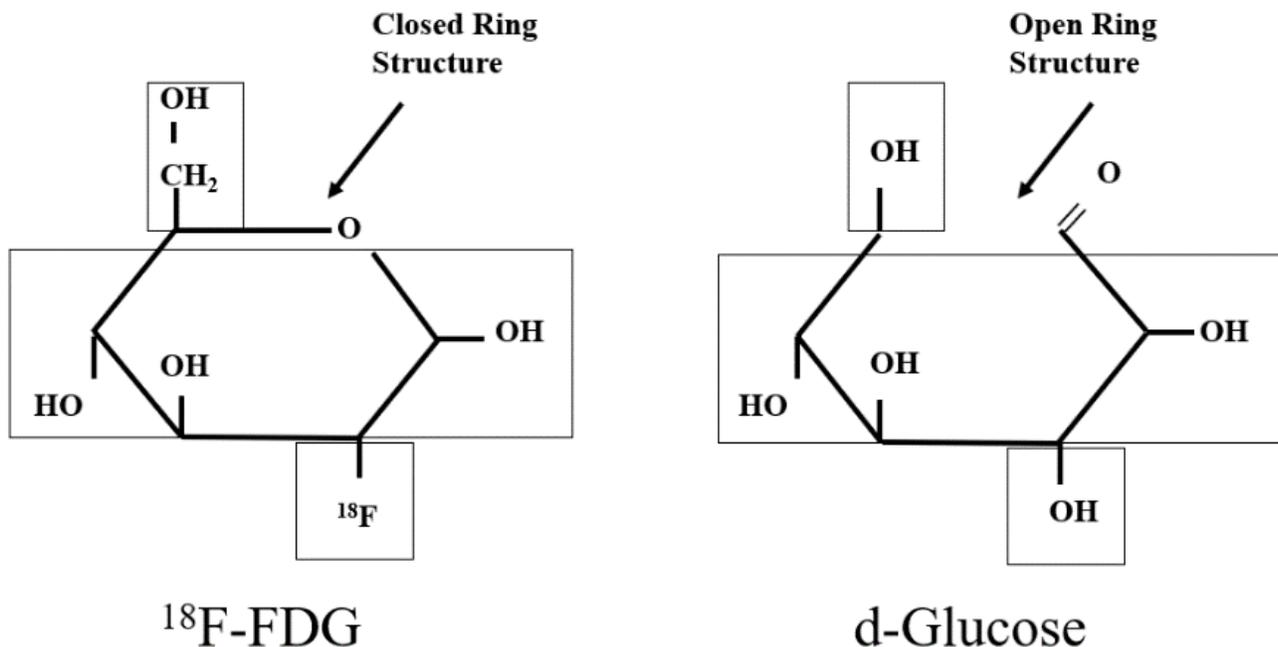
- a) F-18 FDG is a glucose analog that concentrates in cells that rely upon glucose as an energy source, or in cells whose dependence on glucose increases under pathophysiological conditions. It is transported through the cell membrane by facilitative glucose transporter proteins and is phosphorylated within the cell to [18F] FDG-6- phosphate by the enzyme hexokinase. Once phosphorylated it cannot exit until it is dephosphorylated by glucose-6-phosphatase.
- b) Therefore, within a given tissue or pathophysiological process, the retention and clearance of F-18 FDG reflect a balance involving glucose transporter, hexokinase and glucose-6-phosphatase activities. When allowance is made for the kinetic differences between glucose and F-18 FDG transport and phosphorylation (expressed as the “lumped constant” ratio), F-18 FDG is used to assess glucose metabolism.
- c) In comparison to background activity of the specific organ or tissue type, regions of decreased or absent uptake of F-18 FDG reflect the decrease or absence of glucose metabolism. Regions of increased uptake of F-18 FDG reflect greater than normal rates of glucose metabolism.
- d) F-18 FDG Injection is rapidly distributed to all organs of the body after intravenous administration. After background clearance of F-18 FDG Injection, optimal PET imaging is generally achieved between 30 to 40 minutes after administration.
- e) F-18 FDG is cleared from most tissues within 24 hours and can be eliminated from the body unchanged in the urine.
- f) In cancer, the cells are generally characterized by enhanced glucose metabolism partially due to (1) an increase in the activity of glucose transporters, (2) an increased rate of phosphorylation activity, (3) a reduction of phosphatase activity or, (4) a dynamic alteration in the balance among all these processes. However, glucose metabolism of cancer as reflected by F-18 FDG accumulation shows considerable variability. Depending on tumor type, stage, and location, F-18 FDG accumulation may be increased, normal, or decreased. Also, inflammatory cells can have the same variability of uptake of F-18 FDG.
- g) In the heart, under normal aerobic conditions, the myocardium meets the bulk of its energy requirements by oxidizing free fatty acids. Most of the exogenous glucose taken up by the myocyte is converted into glycogen. However, under ischemic conditions, the oxidation of free fatty acids decreases, exogenous glucose becomes the preferred myocardial substrate, glycolysis is stimulated, and glucose taken up by the myocyte is metabolized immediately instead of being converted into glycogen. Under these conditions, phosphorylated F-18 FDG accumulates in the myocyte and can be detected with PET imaging.

- h) Normally, the brain relies on anaerobic metabolism. In epilepsy, the glucose metabolism varies. Generally, during a seizure glucose metabolism increases. Interictally, the seizure focus tends to be hypometabolic.

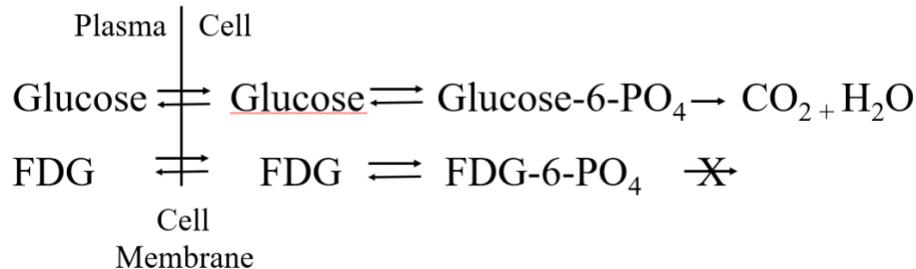
8. MECHANISM OF LOCALIZATION

- a) **Mechanism of localization** is referred to as **Metabolic trapping**. Radiolabeled sugar analog may be trapped by cells for cell metabolism. Tumors, with their higher-than-normal metabolic rate, are able to take up and retain more molecules per gram than normal tissue, resulting in an accumulation of the radioisotope in the tumor.
- b) **Comparison:** Structures of FDG and Glucose. Note the similarities.

Comparison: Structures of FDG and Glucose



- c) **Metabolism of Glucose and FDG.** both glucose and FDG can penetrate the cell membrane and migrate into the cell interior. In addition, both can be phosphorylated. However, FDG can only do so one time and is trapped in the cell since it can not be metabolized; glucose undergoes multiple phosphorylation steps and is ultimately metabolized into CO₂ and H₂O. Refer to diagram below.



9. NORMAL DISTRIBUTION OF DRUG

Normal Biodistribution

(Source: Mettler FA & Guilberteau MJ. Essentials of Nuclear Imaging. 6th ed. Saunders, 2012)

- 20-40% into urine by 2nd hour
- 7% into brain
- 4.5% into liver
- 3.3% into heart
- 1.7% into red bone marrow
- 1.3% into kidneys
- 0.9% into lungs

Cerebral cortex, basal ganglia and thalami (i.e., the grey matter) have high FDG activity because these tissues are very metabolically active and use glucose as their primary substrate.

Vocal cords at rest are mildly to not FDG-avid. But talking can cause the vocal cords to become FDG-avid.

Tonsils (especially palatine tonsils), lymphoid tissue at Waldeyer ring, and parotid and submandibular glands have some FDG activity, sometimes high if they are part of reactive inflammation. As with vocal cords, this FDG activity is symmetric.

Thyroid is typically not FDG-avid, but mild diffuse FDG activity is within normal.

Thymus is FDG-avid in children and adults up to ~30 years. Thymic FDG activity may be seen due to thymic rebound after chemotherapy.

Skeletal muscle at rest (and at basal levels of insulin) has low FDG activity. Increased muscular FDG activity may be seen at the shoulders and upper back due to patient's tension secondary to positioning. Increased FDG activity can also be seen in the diaphragmatic crura, intercostals muscles, psoas muscles, paravertebral muscles, forearms and muscles of mastication.

Brown fat (especially in the supraclavicular regions) can be FDG-avid if stimulated in adults, and is more often seen in children.

Left ventricular myocardium has variable (i.e., high to low and in-between) FDG activity. Myocardial cells use fatty acids as their primary metabolic substrate at rest, but glucose becomes the primary substrate if blood glucose levels are high (causing increased insulin levels) or oxygen demand is increased beyond supply (ischemia), prompting anaerobic metabolism. Intercollated patches of intense and fainter FDG activity is within normal as different foci of myocardium switch between fatty acids and glucose metabolism. Compared to the LV, the right ventricular myocardium has faint FDG activity.

Aortic wall FDG activity is minimal, but can be increased in older adults due to macrophages in atherosclerotic plaques.

Lungs have low and diffuse FDG activity (which is more visible on non-AC images versus attenuation corrected images).

Breast FDG activity is mild to moderate in young women and postmenopausal women on hormone replacement therapy. Dense breasts have greater FDG activity versus fatty breasts. FDG activity may be intense in lactating breast tissue.

Bowel FDG activity varies in intensity and location. Focally high FDG activity in the colonic mucosa can be within normal, though colonic FDG activity tends to be diffuse and highest in the ascending and cecal portions. Rest of GI tract:

Esophageal FDG activity tends to be mild and uniform, and stomach FDG activity can be much greater than liver activity especially if contracted or hiatal hernia. Small bowel activity is less than colon normally.

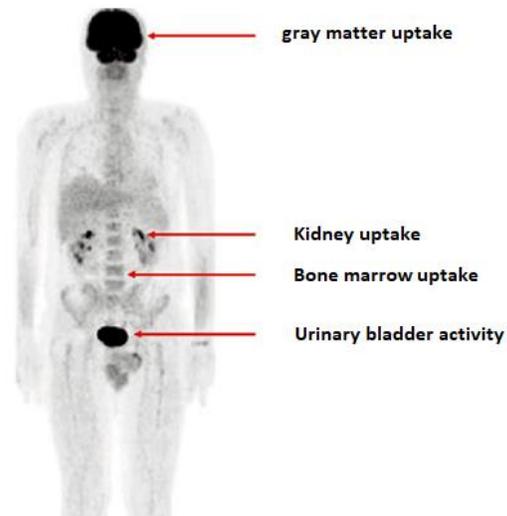
Liver FDG activity is heterogenous or "patchy." Benign lesions like focal nodular hyperplasia can be FDG-avid.

Urinary FDG activity is intense, so activity in the kidneys, ureters and bladder will be intense. This is because up to 40% of administered FDG is excreted by the kidneys within the first 2 hours. FDG accumulates in the renal calyces, pelvis and ureters. Ureteral activity may be discontinuous due to peristalsis.

Pelvic organ FDG activity is mild to minimal (but may be increased in the uterine during menstruation). FDG activity in the testes is mild. Faint FDG activity may be seen in the penis.

Bone marrow FDG activity intensity is similar to liver but more homogenous, which is mildly above blood pool FDG activity. FDG activity in the bone marrow may be increased in anemic patients or patients on medications like G-CSF. Splenic FDG activity is low but can be increased by stimulation, similar to bone marrow. Lymph node FDG activity is faint, except when extravasation occurs and infiltrated FDG concentrates in a downstream node.

10. THIS IS AN EXAMPLE OF A NORMAL FDG SCAN.



11. INDICATIONS FOR CLINICAL STUDIES

Adapted from Procedure Guideline for Tumor Imaging with ^{18}F -FDG PET/CT 1.0 and reprinted from http://snmmi.files.cms-plus.com/docs/jnm30551_online.pdf, © SNMMI Inc.

- a) Differentiating benign from malignant lesions
- b) Searching for an unknown primary tumor when metastatic disease is discovered as the first manifestation of cancer or when the patient presents with a paraneoplastic syndrome
- c) Staging known malignancies
- d) Monitoring the effect of therapy on known malignancies
- e) Determining whether residual abnormalities detected on physical examination or on other imaging studies after treatment represent tumor or posttreatment fibrosis or necrosis
- f) Detecting tumor recurrence, especially in the presence of elevated levels of tumor markers
- g) Selecting the region of a tumor most likely to yield diagnostic information for biopsy
- h) Guiding radiation therapy planning
- i) Nononcologic applications, such as evaluation of infection and atherosclerosis

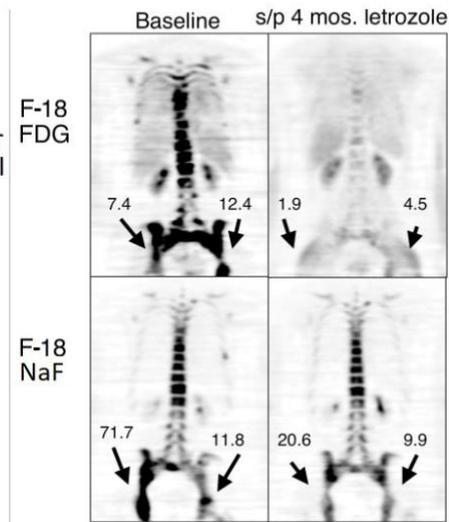
12. TYPICAL F-18 FDG PET SCANS IN VARIOUS DISEASES

Pre- and post- chemotherapy



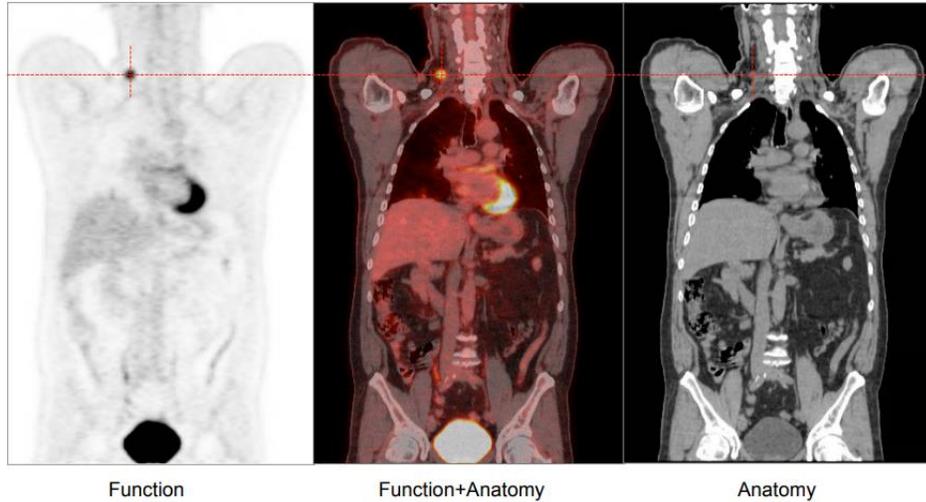
Quantitative Assessment of Response to Therapy

- Example: Change in SUV measures of FDG and fluoride incorporation for bony metastases from breast cancer before (left) and after hormonal therapy (right)
- Bone images look similar but have very different values
- CT helps with precise realignment of ROIs in serial studies



Imaging FDG uptake (PET) with anatomical localization (CT)

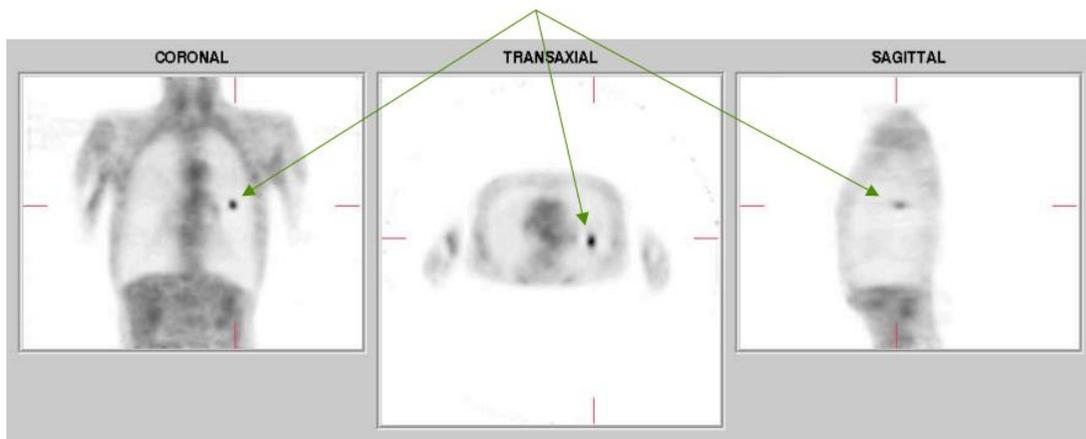
Thyroid cancer example



www.courses.washington.edu/bioen508/Lecture5-C-PETCT.pdf

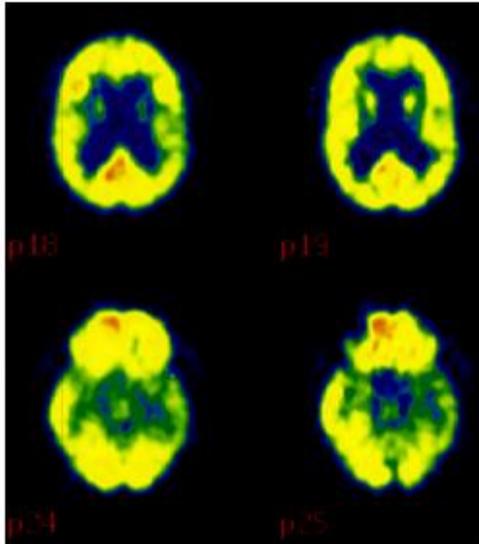
Typical PET Image

Elevated uptake of FDG (related to metabolism)



Lung cancer example

www.courses.washington.edu/bioen508/Lecture5-C-PETCT.pdf



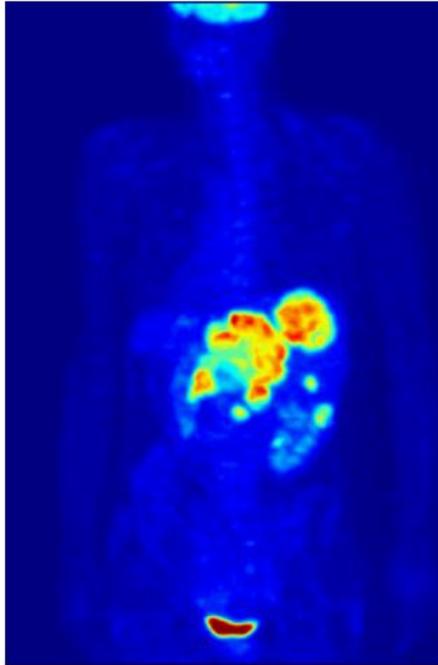
A PET scan of a patient with uncontrolled complex partial seizures. The temporal lobe on the left side of the brain metabolizes less sugar than the right, confirming for the surgeon the nonfunctioning area of the brain causing seizures.

www.mayfieldclinic.com/PE-PET.htm

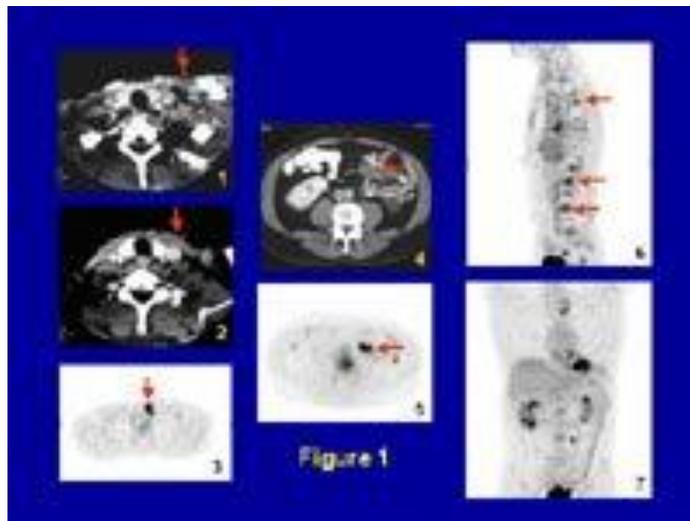
Cardiac PET Scan



www.myvmc.com/investigations/cardiac-pet-scan-positron-emission-tomography/



Graphic representation of a patient's PET scan shows abnormal activity in the abdominal region. Image courtesy of Wikipedia Commons.



Images 1 and 2 are the images from the CT scan of the patient. These do not demonstrate any abnormality in the region of the swelling in the neck. Image 3 is the PET scan of the neck region, which shows foci of intense activity in the lower neck in the region of the swelling. Image 4 is the image from the CT scan showing a mass in the abdomen and this area shows intense activity on the PET scan as seen on image 5. Image 6 shows multiple lesions in the spine and image 7 is the whole body projection image. In this patient with known lymphoma in the abdomen, the PET scan identified more lesions in the neck and in the bones.

13. PATIENT PREPARATION FOR FDG PET SCAN

- a) The rationale for performing the procedure and the details of the procedure itself should be explained to the patient in advance.
- b) Patients should be instructed to fast and not consume beverages, except for water, for at least 4–6 h before the administration of F-18 FDG to decrease physiologic glucose levels and to reduce serum insulin levels to near basal levels. Oral hydration with water is encouraged. Intravenous fluids containing dextrose or parenteral feedings also should be withheld for 4–6 h.
- c) The blood glucose level should be checked before F-18 FDG administration. Tumor uptake of F-18 FDG is reduced in hyperglycemic states. Most institutions reschedule the patient if the blood glucose level is greater than 150–200 mg/dL. Reducing the serum glucose level by administering insulin can be considered, but the administration of F-18 FDG should be delayed after insulin administration (with the duration of the delay being dependent on the type and route of administration of insulin).
- d) For brain imaging, the patient should be in a quiet and dimly lit room for F-18 FDG administration and the subsequent uptake phase.
- e) For body imaging, the patient should remain seated or recumbent for F-18 FDG administration and the subsequent uptake phase to avoid muscular uptake.

14. TYPICAL ADMINISTERED DOSE FOR ADULTS

- a) The usual administered activity for adult patients is 5-15 mCi, injected intravenously.

15. DRUG ADMINISTRATION PROCEDURE

- a) The injection is performed intravenously over a period of a few seconds. A small volume of blood is drawn back into the syringe and then re-injected to insure complete delivery of the bone agent.
- b) Hemostasis is accomplished using a gauze pad and pressure. The gauze pad at the injection site is covered with a Band-Aid or tape.

16. IMAGING PROTOCOLS

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Field of view, positioning, and pre-acquisition preparation

- a) Skull base-to-proximal thigh imaging generally is recommended to survey the body in the search for areas of abnormal F-18 FDG accumulation for most tumor types. Such PET/CT scans typically are acquired from the external auditory meatus to the midthigh region. For tumors with a high likelihood of scalp, skull, or brain involvement or lower-extremity involvement, whole-body tumor imaging is performed.
- b) Limited-area tumor imaging can be considered when critical abnormalities are likely to be localized in a known region of the body (e.g., solitary pulmonary nodule, probable lung cancer, evaluation of hilar lymph node involvement, diagnosis of head and neck cancer, and monitoring of therapy of locally advanced breast cancer). However, performing whole-body tumor imaging offers the advantage of staging the entire body.
- c) For optimal imaging of the body, the arms should be elevated over the head if that position can be tolerated by the patient. Arms along the side may produce beam-hardening artifacts over the torso. However, for optimal imaging of the head and neck, the arms should be positioned along the side.
- d) The patient should void the bladder before the acquisition of the images to limit the radiation dose to the renal collecting system and bladder.
- e) Metallic objects should be removed from the patient whenever possible.

Protocol for PET emission imaging

- a) The radiopharmaceutical should be injected at a site contralateral to the site of concern. Emission images should be obtained at least 45 min after the injection. The optimal F-18 FDG distribution phase is controversial. Many facilities start the acquisition of the images at 60 or 90 min after F-18 FDG administration. Some facilities obtain a second set of images to assess the change in uptake over time. The F-18 FDG uptake time should be constant whenever possible and certainly when 2 studies are compared by use of semiquantitative parameters, especially the SUV.
- b) The emission image acquisition time varies from 2 to 5 min or longer per bed position for body imaging and is based on the administered activity, patient body weight, and sensitivity of the PET scanner (as determined largely by detector composition and acquisition method). Typically, for imaging skull to midthigh, the total acquisition

- time ranges from 15 to 45 min. The imaging time typically is prolonged for the acquisition of brain images or for images of a limited region of interest.
- c) Semiquantitative estimation of tumor glucose metabolism by use of the SUV is based on relative lesion radioactivity measured on images corrected for attenuation and normalized for the injected dose and body weight, lean body mass, or body surface area. This measurement is obtained on a static emission image typically acquired more than 45 min after injection. The accuracy of SUV measurements depends on the accuracy of the calibration of the PET scanner, among other factors. The reproducibility of SUV measurements depends on the reproducibility of clinical protocols, for example, dose infiltration, time of imaging after F-18 FDG administration, type of reconstruction algorithms, type of attenuation maps, size of the region of interest, changes in uptake by organs other than the tumor, and methods of analysis (e.g., maximum and mean).
 - d) Semiquantitative estimation of tumor metabolism can be based on the ratio of F-18 FDG uptake in a lesion to F-18 FDG uptake in internal reference regions, such as the blood pool, mediastinum, liver, and cerebellum.

17. INTERPRETATION CRITERIA

- a) Normal physiologic uptake of F-18 FDG can be seen to some extent in every viable tissue, including the brain, myocardium (where the uptake is significant in some patients despite prolonged fasting), breast, liver, spleen, stomach, intestines, kidneys and urine, muscle, lymphoid tissue (e.g., tonsils), bone marrow, salivary glands, thymus, uterus, ovaries, testes, and brown adipose tissue (see Section K).
- b) For whole-body surveys, studies have shown that F-18 FDG PET of the brain is relatively insensitive for the detection of cerebral metastases, because of high physiologic F-18 FDG uptake in the gray matter.
- c) Increased uptake of F-18 FDG can be seen in neoplasms, granulation tissue (e.g., healing wounds), infections, and other inflammatory processes.
- d) Although the pattern of F-18 FDG uptake and specific CT findings as well as the correlation with history, physical examination, and other imaging modalities usually are the most helpful features in differentiating benign from malignant lesions, semiquantitative estimates (e.g., SUV) also may be of value, especially for evaluating changes over time or with therapy. i.

18. ADVERSE REACTIONS FOLLOWING IV INJECTION OF F-18 FDG

Adverse drug reactions that required medical intervention have not been reported. There have been a few cases of transient hypotension and of hypo- or hyperglycemia. Overall,

adverse reactions are very rare.

19. INTERNAL RADIATION DOSIMETRY

Table 4. Estimated Absorbed Radiation Doses (rem/mCi) After Intravenous Administration of Fludeoxyglucose F 18

Organ	Newborn ¹ (3.4 kg)	1-year old ¹ (9.8 kg)	5-year old ¹ (19 kg)	10-year old ¹ (32 kg)	15-year old ¹ (57 kg)	Adult ¹ (70 kg)
Bladder wall ²	4.3	1.7	0.93	0.60	0.40	0.32
Heart wall	2.4	1.2	0.70	0.44	0.29	0.22
Pancreas	2.2	0.68	0.33	0.25	0.13	0.096
Spleen	2.2	0.84	0.46	0.29	0.19	0.14
Lungs	0.96	0.38	0.20	0.13	0.092	0.064
Kidneys	0.81	0.34	0.19	0.13	0.089	0.074
Ovaries	0.80	0.80	0.19	0.11	0.058	0.053
Uterus	0.79	0.35	0.19	0.12	0.076	0.062
LLI wall	0.69	0.28	0.15	0.097	0.060	0.051
Liver	0.69	0.31	0.17	0.11	0.076	0.058
Gallbladder wall	0.69	0.26	0.14	0.093	0.059	0.049
Sm Intestine	0.68	0.29	0.15	0.096	0.060	0.047
ULI wall	0.67	0.27	0.15	0.090	0.057	0.046
Stomach wall	0.65	0.27	0.14	0.089	0.057	0.047
Adrenals	0.65	0.28	0.15	0.095	0.061	0.048
Testes	0.64	0.27	0.14	0.085	0.052	0.041
Red marrow	0.62	0.26	0.14	0.089	0.057	0.047
Thymus	0.61	0.26	0.14	0.086	0.056	0.044
Thyroid	0.61	0.26	0.13	0.080	0.049	0.039
Muscle	0.58	0.25	0.13	0.078	0.049	0.039
Bone Surfaces	0.57	0.24	0.12	0.079	0.052	0.041
Breast	0.54	0.22	0.11	0.068	0.043	0.034
Skin	0.49	0.20	0.10	0.060	0.037	0.030
Brain	0.29	0.13	0.13	0.078	0.072	0.070
Other tissues	0.59	0.25	0.25	0.083	0.052	0.042

¹MIRDOSE 2 software was used to calculate the radiation absorbed dose. Assumptions on the biodistribution based on data from Gallager et al. (*J. Nucl. Med.* 18: 990-996) and Jones et al., (*J. Nucl. Med.*, 23: 613-617).