Normal and Variable Patterns in PET

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Introduction

The clinical applications and investigations of positron emission tomography (PET) have recently been increasing. The majority of the clinical PET studies and the use of ^{18}F-fluoro-2-deoxyglucose (FDG) are related to oncology, but the uptake of this radiopharmaceutical is not specific to malignant tissue. There are several physiologic uptakes and artifacts which make it difficult to evaluate or detect malignant tissue. It is important to be aware of normal variants and benign diseases that may mimic more serious pathology. Uptake of FDG in a number of sites may be variable and may normally be seen in the skeletal muscle after exercise or under tension, in the myocardium, in parts of the gastrointestinal tract, especially the stomach and cecum, and in the urinary tract. Some causes of increased physiologic uptake are avoidable, and measures can be taken to minimize accumulation [1].

In certain clinical situations, the lack of specificity of ^{18}F-FDG uptake has led to the applications of L-[methyl-C-11] methionine. Because of the short half-life of C-11, use of this radiopharmaceutical is limited to those PET scanners that are not far from a cyclotron. However, C-11 methionine has now become one of the most commonly used radiopharmaceuticals in clinical PET [2].

PET Imaging with 18F-FDG

A. Uptake mechanism

18F-FDG is an analog of glucose that is an energy substrate of metabolism [3]. Although tumors show increased glycolysis compared with normal tissues, the uptake of 18F-FDG is not specific to malignant tissue. 18F-FDG is transported into tumor cells by glucose transporter membrane proteins (Glut-1 to Glut-5). In particular, the expression of Glut-1 is increased in many tumors. After being transported into the cell, 18F-FDG is converted to 18F-FDG-6-phosphate by hexokinase.

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Fig. 8.1 Coronal 18F-FDG PET images of patient after meal. Note significantly decreased activities in liver, spleen, etc., which have normal FDG uptake. In contrast to liver, the muscle activities are increased

Following that, it does not enter further enzymatic metabolic process. Because of its negative charge, it remains trapped in tissue. Glucose-6-phosphatase mediated dephosphorylation of the 18F-FDG-6-phosphate. It occurs slowly in myocardium, brain. Many tumors have low concentrations of that enzyme, and hence the accumulation of 18F-FDG-6-phosphate is proportional to the rate of glycolysis. Conversely, tissues such as the liver, kidney, intestine, and resting skeletal muscle with high glucose-6-phosphatase activity may show lower activity.

Tumor uptake of 18F-FDG is poor in acute hyperglycemia as a result of competition between 18F-FDG and glucose. To optimize the accumulation in tumors, patients are usually fasted for 4–6 h prior to scanning. Hyperglycemia after meals reduce uptake in tumor and normal uptake in the liver, spleen, etc., and increased uptake in muscle (Fig. 8.1). Fortunately it appears that chronic hyperglycemia, as seen in diabetic patients, only minimally reduces tumor uptake, but that insulin-induced hypoglycemia may actually impair tumor identification by reducing tumor uptake and increasing background muscle activity.

It has also been noted that the hypoxia in tumors may increase the accumulation of 18F-FDG and also probably occurs through the activation of the anaerobic glycolytic pathway.

B. Normal physiologic distribution of ^{18}F-FDG

In the abdomen, low-grade accumulation of FDG is usually seen in the liver and the spleen. Small and large bowel activity may be variable, and unlike glucose, ^{18}F-FDG is excreted in the urine, leading to variable appearance in the urinary tract.

Skeletal muscle at rest usually shows low-grade uptake of ^{18}F-FDG but active skeletal muscle, after exercise, shows increased accumulation. Low-grade FDG uptake in muscles is part of the normal biodistribution pattern [4]. When this uptake is symmetric and corresponds to the location of a specific group of muscles, it is easily recognized.

Myocardial uptake of ^{18}F-FDG is also very variable [4,5]. Normal myocardial metabolism depends on free fatty acids and glucose. Optimal uptake of ^{18}F-FDG in myocardial metabolic studies can be encouraged by the administration of oral glucose to increase glucose metabolism with or without insulin to enhance the myocardial uptake of glucose, and hence ^{18}F-FDG. A hyperinsulinemic euglycemic clamping technique may further improve myocardial ^{18}F-FDG uptake but is technically more difficult. This allows maximal insulin administration without rendering patients hypoglycemic. An alternative method to encourage glucose metabolism in the myocardium is to reduce circulating free fatty acids pharmacologically. Improved cardiac uptake after administration of oral nicotinic acid derivatives has been reported. This will be a simple and safe intervention which may also be effective in diabetic patients.

The brain typically shows high uptake of ^{18}F-FDG in the cortex, basal ganglia, and thalamus but a generalized reduction in cortical activity may be seen with sedative and general anesthetic drugs which may be required for uncooperative patients and children. This may limit the sensitivity for the detection of areas of hypometabolism. There is a general decline in metabolic activity in the frontal and somatosensory areas with normal aging [6].

C. Physiologic variants that may mimic pathology
   1. Skeletal muscle
      At rest, skeletal muscle does not show significant accumulation of ^{18}F-FDG, but after exercise or if contraction takes place during the uptake period after ^{18}F-FDG injection, there is an increased uptake in active skeletal muscle.
      This relates to increased aerobic glycolysis of active muscle tissue.

      Increased aerobic glycolysis of active skeletal muscle such as paraspinal, posterior cervical, or trapezius muscle may lead to increased accumulation of ^{18}F-FDG after exercise or as a result of tension, and is one of the most common causes of interpretative problems. Symmetric FDG uptake in the shoulder, neck, and thoracic spine region is possibly related to activated brown fatty tissue in underweight patients during increased sympathetic nerve activity as a result of cold stress [7]. Laryngeal muscle activity may be related to speech, and swallowing may cause hyoid and tongue base activities. Hyperventilation may create a diaphragmatic uptake. Exercise should be prohibited on the day of scanning to minimize muscle uptake, and benzodiazepines may be used to abolish the characteristic paraspinal and posterior cervical muscle uptakes often seen in tense patients. Even with these precautions, skeletal muscle activity may still be seen. Anxiety-related increased muscular tension may cause symmetric or asymmetric uptake in neck and paravertebral muscles.

      Problems may also result from involuntary muscle spasm such as that seen with torticollis, which can lead to asymmetric, unilateral uptake in the sternocleidomastoid muscle, and that may either mimic or obscure the pathology in the neck. Accurate interpretation of asymmetric muscle activity in the neck, shoulder, or arm is at times difficult [8]. Trauma and inflammation may also cause an enhanced skeletal muscle activity.
   2. Gastrointestinal system
      A number of regions in the gastrointestinal system may show uptake of ^{18}F-FDG. This may be partly because of smooth muscle activity, although it has been shown that gastrointestinal uptake of ^{18}F-FDG in rats may be reduced either by bowel lavage or by use of antimicrobials, suggesting an alternative mechanism such as smooth muscle peristalsis [9]. In humans, ^{18}F-FDG activity is most noticeable in the large bowel and to a lesser extent in the stomach and small intestine. Low-to-moderate stomach wall activity, particularly fundal activity, is commonly noted and may be mistaken for a tumor mass. Sagittal slices may be helpful in defining the oblique position of the stomach as it passes caudally. Marked activity may on occasion be seen in the cecum and sigmoid/rectum, leading to difficulties in interpretation when assessing local recurrence of large bowel tumors.

      Lymphoid tissues may also demonstrate the significant uptake of ^{18}F-FDG, and the normal appearance of the tonsils and adenoids (which may be particularly marked in children) would be recognized [5]. After radiotherapy or surgery, pharyngeal lymphoid activity may become asymmetric, making it more difficult to differentiate from physiologic activity. It is also possible that cecal activity, which is often seen as the normal variant, may be because of lymphoid tissue that is present in this region [1].

      Apart from excreted ^{18}F-FDG through the urinary system, which could be seen

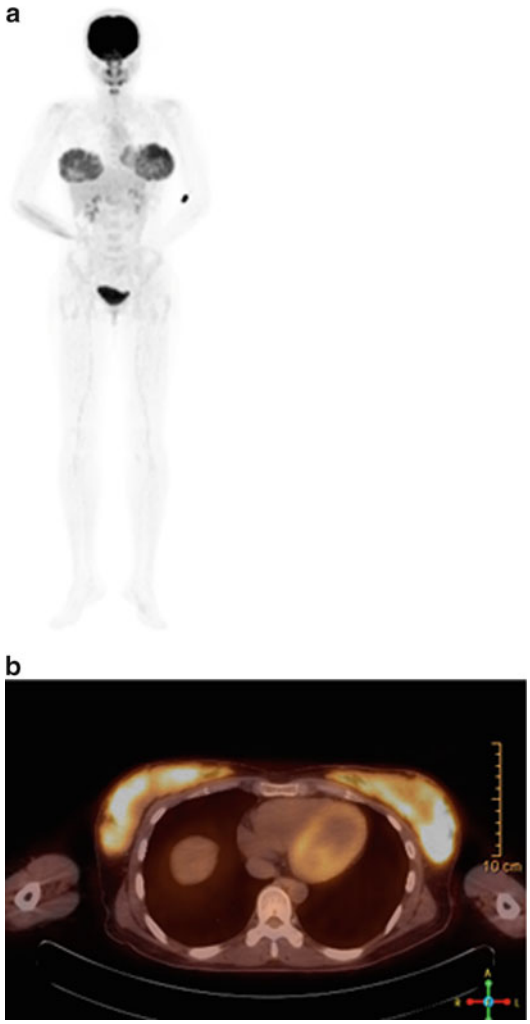

Fig. 8.2 Coronal ^{18}F-FDG PET image of nursing female. Note intense increased uptake of FDG in bilateral breast

anywhere within the urinary tract, prior knowledge of any urinary diversion procedure may be helpful to avoid errors in interpretation. An ileal conduit or other urinary intestinal diversions may produce unusual images unless the alteration in anatomy is appreciated.

3. Urinary tract
   Unlike glucose, FDG is not totally reabsorbed in the renal tubules [1]. Significant and variable urinary activity is seen in all patients. Renal collecting system activity is easily recognized but may limit the use of FDG in the investigation of tumors in the urinary tract. If there is significant hold up in the renal collecting system of an obstructed kidney, reconstruction artifacts may interfere with visualization of the upper abdomen. Imaging may be improved in a nonobstructed but dilated system by keeping the patients well-hydrated, and by administrating diuretics.
4. Reticuloendothelial system
   Hepatic and splenic activities on attenuation-corrected images are slightly nonuniform, and thus small metastatic lesions are very difficult to be identified.
   Hepatic activity on uncorrected images is similar to lung uptakes with slightly increased activity in the periphery. There is no gallbladder activity.
   Bone marrow and thymus harbor many white cells which are known to take up ^{18}F-FDG. When these cells are activated by the growth factors or cytokine therapy, the activities in the bone marrow and spleen are markedly increased. Increased marrow activity is also seen in patients with acute infection resulting from increased production of white cells [10].
5. Miscellaneous variants
   On occasion, skin contamination from urinary activity may be limited at the superficial areas which are usually easily recognized as such. Breast uptake may be variable, and focal increased uptake may be seen at the nipple. Asymmetric uptake may be noted in a woman who fed her baby on one side. Thymic activity may be seen in children or late teens with an inverted V shape [1].
6. Other variants
   Intense breast tissue uptake of ^{18}F-FDG is noted in breast-feeding women (Fig. 8.2). Glandular breast tissue often demonstrates moderate uptake of ^{18}F-FDG in premenopausal women. After menopause there is little breast activity, but women on estrogen for hormone replacement therapy (HRT) may also show an enhanced uptake. The symmetric nature would suggest taking HRT but there is the potential for lesions to be obscured by this physiologic activity.

D. Artifacts

If attenuation correction is not performed on whole-body PET imaging, it may lead to higher apparent activity in superficial structures such as the skin, which may obscure lesions (e.g., cutaneous melanoma metastases). A common artifact resulting from this phenomenon is caused by the axillary skin fold, where a double layer of skin may mimic focal lymphadenopathy on coronal sections. The linear distribution of activity on axial or sagittal planes would help to prevent a misinterpretation.

Artifacts caused by prostheses are usually readily recognizable. Photon-deficient areas may result from metallic hip prostheses, breast prostheses, implants, medallions, and coins and keys in pockets, etc. Ring artifacts may occur if there is a misregistration between transmission and emission data (e.g., due to slight patient movement), and are especially apparent at borders where there are sudden large changes in activity (e.g., at a metal prosthesis).

Patient movement may compromise image quality. In brain imaging, splitting the study into a number of time frames may be helpful so that if movement occurs in one frame, it can be discarded before summation of the data. Whole-body imaging can lead to unusual appearances if the patient moves between bed scan positions with, for example, the upper part of an arm being visible in the higher scanning positions, but being absent or "amputated" lower down when moved out of the field of view scanning positions.

Problem with injections may interfere with image interpretation. A partly infiltrated injection not only may cause reconstruction artifacts across the trunk, but may result in a low-count study and inaccuracies in standardized uptake value (SUV) measurement. Local axillary lymph node uptake may occur following subcutaneous extravasation, and thus radiopharmaceuticals should be administered on the opposite side to the known or questioned pathologic lesion, if possible. Although rare, an inadvertent intra-arterial injection may be easily recognized.

PET Imaging With C-11 Methionine

A. Uptake mechanism

C-11 L- methionine represents the amino acid with which there is a sufficient clinical experience in PET imaging. Increased transport and utilization of amino acids are common in cancers. The use of L-methionine in cancer imaging is based on this observation and the increased activity of the transmethylation in some cancers. There is normally substantial uptake of C-11 methionine in the pancreas, salivary glands, liver, and kidneys. As a natural amino acid, there is some metabolism of L-methionine in the bloodstream. This tracer is mostly used in imaging of brain tumors, head and neck cancers, lymphoma, and lung cancers as well as several other clinical settings. Early clinical studies demonstrated the stereospecificity of tumor uptake. L-methionine uptake is much greater in brain tumors than the uptake of D-methionine when an intact brain–blood barrier was present [2].

B. Physiologic distribution of C-11 methionine

By far the greatest experience with C-11 methionine lies in brain tumor imaging. Uptake of ^{18}F-FDG into brain tumors is closely related to grade of malignancy. As there is high uptake of ^{18}F-FDG into the normal brain cortex and basal ganglia, it may be difficult to identify low- or intermediate-grade tumor with similar or less activity. The relatively high uptake of ^{18}F-FDG in normal structure may, however, allow better anatomic localization of those tumors that are visible or similarly may give a number of anatomic landmarks to aid image registration with magnetic resonance imaging (MRI) or computed tomography (CT). In contrast to ^{18}F-FDG, C-11 methionine typically shows low-grade uptake in the normal cortex and is better suited for detection of low- and intermediate-grade tumors. However, while tumor margins and extent may be more easily identified with C-11 methionine, the correlation between tumor grade and uptake appears less strong than that with ^{18}F-FDG.

One of the most difficult problems in the management of primary brain tumors is the assessment of tumor recurrence versus posttreatment scar and gliosis, which often remain problematic with anatomic imaging such as MRI and CT, and where functional imaging with PET has a role. Soon after radiation therapy, accumulation of ^{18}F-FDG may occur in macrophages surrounding necrotic areas in addition to any viable tumor cells. By contrast, methionine has low uptake by macrophages and other cellular components but accumulates in viable cancer cells. Uptake of C-11 methionine therefore correlates better with tumor extent when compared with surgical and biopsy findings. Unlike ^{18}F-FDG, there is no significantly increased uptake of C-11 methionine in stressed muscles.

Tumor imaging in the pelvis may be problematic because normal excreted activity in the urine may interfere with tumor identification. Because there is very little urinary C-11 methionine activity in the majority of patients, the use of this tracer has been evaluated in a number of urinary and gynecologic cancers. Besides the response of invasive bladder tumor to chemotherapy, ovarian and uterine cancers have been assessed with this radiopharmaceutical.

C. Physiologic variants

As with all imaging techniques, a thorough knowledge of normal distribution and anatomic, physiologic, and pathologic variants is required to avoid misinterpretation. As the clinical use of C-11 methionine PET develops, more and more potential pitfalls will be recognized. Here we summarize the status from our own and others' experience.

There are a number of structures in the head during brain tumor imaging that normally show accumulation of C-11 methionine. The lacrimal glands may show moderately intense uptake but may be easily recognized by virtue of the symmetric distribution and the anterior position below the frontal lobes. Normal bone marrow uptake within the sphenoid and clivus may cause confusion at the skull base, however. Pathologic variants that we have experienced include uptakes within a recent biopsy tract, into an incidental benign meningioma, and also within the pons to the surrounding area following radiotherapy.

In the neck, bone and bone marrow activity, which may appear quite focal at the medial tips of the clavicles, may cause false positive interpretations when investigating hyperparathyroidism or focal metastatic lymph node. The majority of patients show no thyroid C-11 methionine activity; however, a small percent show a low-grade activity that is lower than the activity seen in abnormal parathyroid glands. This may actually be helpful in identifying anatomic landmarks for the surgeon. Unfortunately, as with other nuclear medicine procedures for investigating hyperparathyroidism, the uptake within the thyroid may on occasion interfere with diagnosis. We have noted diffusely increased uptake in patients with coincidental Hashimoto's thyroiditis and thyrotoxicosis resulting from Grave's disease. Uptake may also be seen in benign thyroid nodules and thus correlative imaging may be required with this technique in specific cases.

High salivary gland activity is demonstrated by C-11 methionine PET. This is unlikely to cause confusion but asymmetric activity following unilateral radiotherapy or extensive surgery for head and neck cancers may be problematic.

In the abdomen, physiologic accumulation within the bowel may cause difficulties and limit the use of this tracer in the investigation of bowel cancer and pelvic tumors. High pancreatic uptake in the upper mid-abdomen is normally identified although this may obscure the uptake within pancreatic tumors. We have found that anatomic information obtained from a C-11 methionine scan complements an 18F-FDG scan where no significant pancreatic accumulation normally occurs.

Presence of urinary C-11 methonine activity is variable but occurs in the minority of patients. It may nevertheless lead to interpretative problems in the pelvis. In our experience, there is low-grade renal cortical activity which would not be expected to interfere with renal tumor evaluation.

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