Review Article, Oncology

Pitfalls and Artifacts in PET/CT in Pediatric Malignancies

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INTRODUCTION:

Pediatric ^{18}F-FDG PET requires age-appropriate patient preparation, technically adequate acquisition, and appropriate image interpretation. Performing PET/CT in pediatric patients requires consideration of the developmental stage of each patient for accurate interpretation of the normal patterns of ^{18}F-FDG distribution, the ability to recognize common developmental, physiologic patternsand may require decisions about sedation and general anesthesia***(1).***A number of pitfalls are commonly encountered with ^{18}F FDG PET in children, including uptake in normal physiologic activity and benign lesions and, leading to possible misinterpretation and inaccurate disease staging.Also, different tumor entities or tumor subtypes with different tumor biology may be different in children in comparison to adults.***(2, 3).*****Patient Preparation:**The key to a successful PET scan begins with appropriate patient preparation, and pediatric imaging is no exception to this rule. When possible, information about the procedure should be given beforehand through information sheets givento the family with preparation instructions. Parents can be confused by the complexity of PET/CT, and ample time must be allotted to explain the study and allow the parents and patient an opportunity to ask questions ***(4).*** Patients are asked to fast for at least 4 hrs before injection to reduce the glucose level and to lower circulating insulin levels, thus optimizing the target-to-background ratio in patients with an oncology indication.The issue of cooperation in children presents many challenges to nuclear medicine technologists, and children undergoing a PET/CT scan are no exception. Therefore, it can be helpful to allow the child to bring a favorite toy or stuffed animal into the scanning room if possible or to allow a parent to remain in the room during the scan. With many nuclear medicine procedures, the use of a DVD player can be vital in obtaining patient cooperation throughout imaging.

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Pediatric sedation is a complex issue and requires case by case assessment. Often, the child's parents will be aware of previous cooperation difficulties and can assist with decision making. When sedation is required, it should be limited to the scanning phase of the study. Sedation protocols vary by institution, but guidelines should be available ***(5).***

PITFALLS and ARTIFACTS:

Are classified in PET/CT in pediatric malignancies into a number of categories as follow:

I. NORMAL DISTRIBUTION AND PHYSIOLOGICAL VARIANTS of ^{18}F-FDGUPTAKE: The normal distribution and physiologic variants of ^{18}F - FDG uptake in children differ from those in adults, and it is important that they be recognized so as to avoid misinterpretation ***(9, 20).***

a) Brain: The normal brain is characterized by a high level of ^{18}F-FDG uptake. In adults and older children, up to 6% of an administered dose of ^{18}F-FDG may be taken up in the brainas glucose provides approximately 95% of the energy used by the brain.[13, 11]Brain metabolism may account for as much as 20% of whole body metabolism in the fasting state ***(6).***

b) Head and Neck: Mild to moderate uptake is usually seen in the adenoids, in the tonsils, and at the baseof the tongue due to the physiologic activityof lymphatic tissue in the Waldeyer ring at 6–8 years of age, after which time it diminishes ***(7).***Usually, the symmetric pattern of physiologic tonsillar and adenoidal uptake is helpful in identifying this normal variant ***(8).***The soft palate can also show intense radiotracer uptake ***(9).***

Salivary glands uptake is variable but typically mild to moderate ***(7).*** Diffusely increased salivary gland uptake can also be seen after chemotherapy ***(10*)**. ^{18}F FDG uptake in the salivary glands can be asymmetric due to acute inflammation following recent surgery or radiation therapy. However, radiation therapy may eventually cause decreased uptake on the affected side ***(7).***

Larynx and vocal cords usually show either no uptake or mild symmetric uptake, which may have an inverted U shape ***(9, 10).*** Laryngeal uptake can range from mild to intense, reflecting recent talking or crying. Therefore, it is important to instruct children not to talk during the uptake phase, since excessive talking may cause prominent activity in the laryngeal structures ***(10).*** Asymmetric vocal cord uptake

suggests the possibility of disease such as malignancy, post therapy change, or unilateral vocal cord paralysis ***(10).***Variable ^{18}F FDG uptake that corresponds to the genio-glossus-muscle in the floor of the mouth, which keeps the tongue forward when the patient is supine.placing the patient upright during the uptake phase, can minimize this uptake (11). Uptake in the tongue or muscles of mastication can be seen after vigorous or repetitive chewing, for example, in patients who chew gum during the uptake period. In infants, suckling can increase ^{18}F-FDG uptake in oral muscles. Muscle activity can also be identified at the convergence of the extra ocular muscles, as well as along the length of these muscles ***(10).***

c) Thyroid gland usually showed diffuse symmetric uptake ***(7, 10).*** However, such diffuse thyroiduptake may represent Graves' disease or thyroiditis. Focal thyroid uptake can be seen in benign thyroid nodules or malignancies, and further work-up is warranted in such cases ***(10)***.

d) Thymus: Diffuse and homogeneous uptake in the thymusis common in healthy children ***(12).*** The uptake is bilobed with an inverted V shape on coronal views ***(Fig 1) (10).*** Generally, physiologic uptake in the thymus disappears during adolescence in conjunction with involution of the thymus ***(11).*** Thymic hyperplasia (or "rebound") is seen following chemotherapy more often in children than in adults. Brink et al ***(11)*** reported increased FDG accumulation in the thymus in 75% of children with malignant disease who had undergone chemotherapy. Very intense uptake or heterogeneous uptake may raise suspicion for thymic or other anterior mediastinal disease. In general, it is accepted that the thymus can be seen at computed tomography (CT) in virtually every pediatric patient ***(Figure 1).***

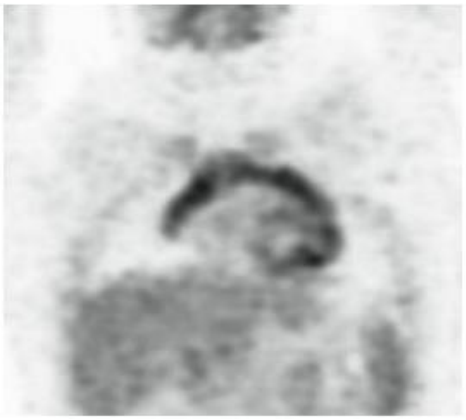

Figure 1. Coronal FDG PET scan shows diffuse and homogeneous uptake in the normal thymus. The uptake is bilobed with an inverted V shape (! 1).

e) Cardiac: Activity is variable, ranging from no discernible activity above background blood pool activity, to intense activity throughout the left ventricular myocardium ***(7, 11).***The degree of cardiac uptake depends on substrate availability. During the fasting state, ^{18}F FDG uptake is low because *(a)* the predominant myocardial substrates are fatty acids as a source of energy, and *(b)* the serum insulin level is low. In the postprandial state, when the serum glucose and insulin levels are high, myocardial uptake can be intense ***(7, 11).***

f) Gastrointestinal tract: ^{18F} FDG uptake in the normal GIT is highly variable and can range from mild to intense with a focal, diffuse, or segmental distribution. The origin of ^{18}F FDG uptake in the gastrointestinal tract is not fully understood and is likely multifactorial. It may be related to active smooth muscle, active mucosa, swallowed secretions, or microbial uptake ***(36).***

Esophageal activity can be noted as mild linear uptake anterior to the spine and is best seen in the sagittal plane ***(7, 11).***Most commonly this is seen in oncology patients, and esophageal uptake represents post- treatment mucositis related to either chemotherapy or radiation.

Gastric Curvilinear homogeneous uptake corresponding to the gastric wall is commonly identified. If the stomach is contracted, a round area of moderate activity may be seen ***(8).*** Gastric uptake is usually mild, but more intense uptake may be associatedwith *Helicobacter pylori* infection ***(30).***

Uptake in the **small bowel** is variable and is usually low grade when visible. Colonic activity is extremely variable and may be quite marked, affecting all or part of the colon. Uptake is typically more prominent in the cecum than in the rest of the colon, possibly due to a greater concentration of lymphoid tissue in the ileo cecal region ***(11, 13).*** Occasionally, intense uptake in the cecum may make differentiation of malignancy or inflammation from a normal variant quite challenging. CT part of the study can reduce diagnostic uncertainty by allowing direct anatomic correlation with normal bowel, leading to more confident image interpretation ***(13).*** Marked ^{18}F FDG accumulation can be seen in children with inflammatory bowel disease ***(14).***

g) Urinary tract: Unlike glucose, ^{18}F FDG is not reabsorbed by the renal tubules, resulting in significant urinary activity in any part of the urinary tract; the kidneys, renal collecting systems, ureters, and bladder (15). If there is significant retention in the renal collecting system, reconstruction artifacts may

interfere with visualization of the upper abdomen (13). Keeping the patient well hydrated and administering diuretics can minimize such activity and improve image quality **(Figure 2)**.

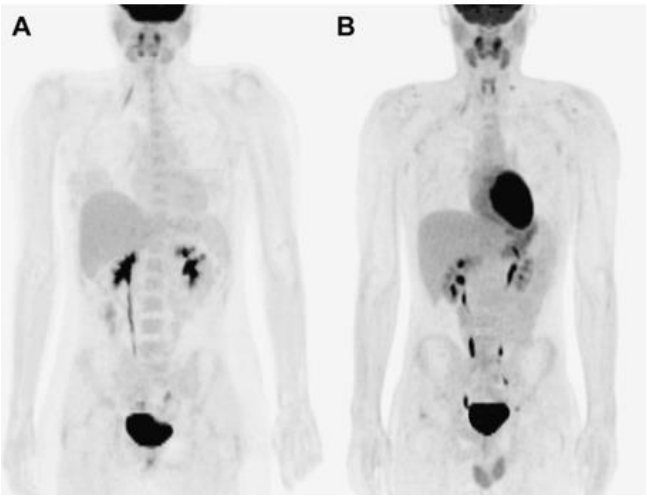

Figure 2. Normal uptake and accumulation of ^{18}F-FDG in the genitourinary tract. Physiologic ^{18}F-FDG uptake frequently is identified in the reproductive organs. (A) In a 15-year-old girl around the ovulation phase of her menstrual cycle (13).

Significant activity along the entire length of the ureter is not typically seen in patients with a normal urinary tract but can be identified in those with obstruction or dilatation ***(37).*** Tracer accumulation in ureters usually can be identified by the distinctive contours of the ureters and by correlation with CT. Bladder catheterization may be helpful inselected circumstances, such as in a sedated patient in whom tracer accumulation within the bladder may obscure ^{18}F-FDG uptake in nearby disease. Rarely, collecting system obstruction or hydro-nephrosis is identified on PET/CT. Persistent ^{18}F-FDG uptake in the renal cortex is abnormal and has a broad differential, including infection, leukemia, and lymphoma***(13).***

h) Reproductive organs: Uptake of ^{18}F-FDG in the reproductive organs varies with pubertal status and, in female patients, with the menstrual cycle.In males, testicular uptake normally demonstrates a symmetric and diffuse pattern, especially in per pubertal and post pubertal young men. The intensity is usually moderate and may decrease with age ***(16).***In pre-menarche female patients, ^{18}F-FDG uptake should not be seen in these organs. After menarche, ^{18}F-FDG uptake in the ovaries and fallopian tubes can be seen during follicular genesis and ovulation, at the mid-cycle. Fallopian tube uptakes, if present, istypically bilateral, whereas ovarian uptake is generally unilateral. The endometrium generally shows cyclically variable uptake, but marked uptake can be seen during menstruation ***(17).***Therefore, it is necessary to know the pubertal status and

menstrual phase to adequately interpret these findings in female patients.

i) Skeletal uptake: ^{18}F-FDG skeletal uptake is a nonspecific finding that may represent pathology or normal physiology. In children, physiologic uptake of ^{18}F-FDG can be seen as sites of bone growth, such as the physes of the long bones. Increased ^{18}F-FDG uptake also has been reported in growth arrest lines (Harris lines) that can occur after resolution of skeletal growth arrest related to illness or prolonged immobilization***(18).***

j) Muscle uptake: Generally, muscle uptake is low at rest. Physiologic muscle uptake is commonly encountered at ^{18}F FDG studies due to excessive muscle activity during the uptake phase or within a few days preceding the study; reflecting the involved muscles. ***(19).***High muscle uptake is most commonly seen in the head, neck, and thorax and less commonly in the lower extremities.The pattern is usually distinctive and symmetric in various muscle groups. However, asymmetric muscle uptake can occur. Marked uptake can be seen after excessive exercise or muscle tension. The chewing of gum after ^{18}F FDG injection can cause symmetric intense uptake in the masseter muscles. Uptake in these muscles may also be seen in babies who suck pacifiers during the uptake phase ***(20).*** Uptake in the diaphragm, the crura of the diaphragm, the intercostal muscles and accessory muscles of respiration can be detected in children who have been crying during the uptake phase or experiencing respiratory distress.Less commonly, widespread ^{18}F-FDG uptake in muscle reflects an inflammatory myositis. Compensatory muscle activity, such as increased muscle uptake in leg muscles after disuse or after amputation of the contralateral limb, can lead to increased muscle uptake of ^{18}F-FDG. In the same patients, use of a cane or crutches can increase ^{18}F-FDG uptake in arm and shoulder muscles. Insulin or recent food intake can cause diffuse skeletal muscle uptake, since insulin drives ^{18}F FDG into skeletal muscle. Muscle relaxants such as benzodiazepines may be used to minimize muscle uptake ***(21, 22).***To avoid marked muscle uptake, patients should rest comfortably during the uptake phase. Instructions may be given to children to avoid excessive exercise during the 48 hours prior to injection. Furthermore, technologists/ residents should discourage and report any excessive physical activity by the patient during the uptake phase ***(19).***^{8}F-FDG uptake in **BAT** is driven by sympathetic release of norepinephrine, resulting in activation of β3 receptors. Subsequent ^{18}F-FDG uptake through glucose transporter 1 (GLUT 1) and glucose transporter 4 (GLUT 4) ***(23, 24).*** BAT FDG

uptake in children is most commonly seen in the neck and supraclavicular-axillary, mediastinal, paravertebral-intercostal, mediastinal, per nephric-suprarenal and upper abdominal wall regions ***(Fig. 3),*** more in some regions than others. Whenever possible ^{18}F-FDG-PET images should be correlated with co-registered CT to improve anatomical localization and exclude underlying soft-tissue abnormality***(25).***Warming the patient prior to injection and during the uptake phase is a simple approach to reduce brown fat up- take ***(26).*** Brown fat ^{18}F FDG uptake can also be avoided by administering diazepam, fentanyl, or Propanolol prior to injection ***(27).***

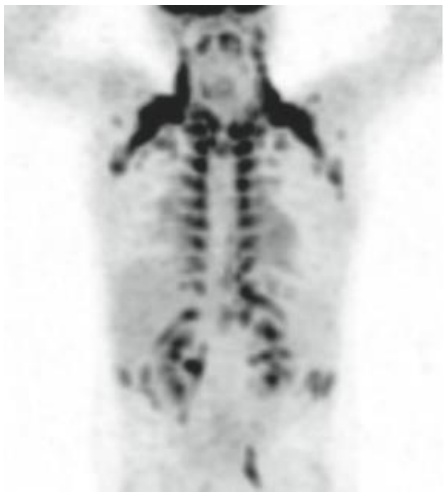

Figure 3. MIP FDG PET image shows the typical distribution of uptake in brown adipose tissue in pediatric patients in the neck, supraclavicular and axillary regions, mediastinum, paravertebral and perinephric areas, and anterior abdominal wall (27).

II – TECHNICAL ARTIFACTS:

a) Metallic objects: Prostheses, pacemakers, or chemotherapy catheters can cause art factually increased activity and lead to false-positive results. The high CT attenuation values (in Hounsfield units) cause falsely high PET attenuation coefficients, leading to overestimation of the PET activity corresponding to the metallic objects on the attenuation-corrected images***(32).*** Similarly, highly concentrated intravenous and oral contrast material can lead to overcorrection of activity and false-positive results at PET if enhanced CT data are used for attenuation correction. Overly concentrated *intravenous contrast* material is typically seen in the region just proximal to the intravenous catheter (eg, upper arm and axilla after antecubital injection). Overly concentrated *oral contrast* material usually represents retained barium in the colon after a recent fluoroscopic or CT examination. Viewing the non-attenuation- corrected PET images can help distinguish this attenuation correction artifact from true hyper metabolism, since this art factually high activity will not be

present on the non-corrected images (30, 60). Oral contrast material may not significantly affect image quality and visual interpretation. Intravenous contrast material can also result in the overestimation of PET attenuation factors and an increase in SUV in regions of highly concentrated contrast material. However, this increase may be clinically insignificant, and PET/CT with intravenous contrast-enhanced CT can be used in combination with PET to evaluate patients with cancer ***(34, 35) Figure4.***

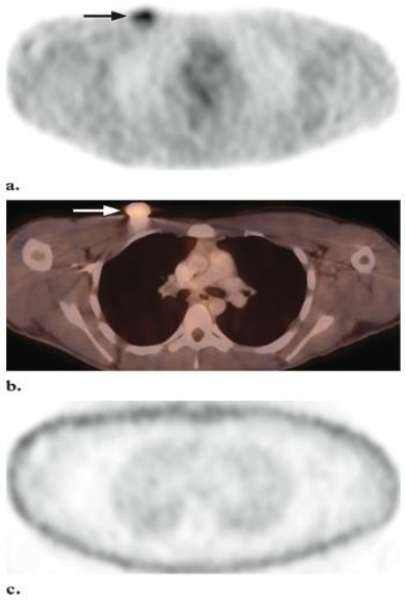

Figure 4. Attenuation correction artifact. **(a)**Transverse attenuation-corrected FDG PET scan shows a focus of increased uptake in the upper right chest wall (arrow). **(b)** Transverse fused PET/CT image also shows the focus of increased uptake (arrow), a finding that represents a catheter. **(c)**Transverse non-attenuation-corrected FDG PET scan shows no increased uptake. The high attenuation of a catheter leads to overcorrection of the activity on attenuation-corrected images. This artifact is not present on non-attenuation- corrected images. (35)

a) Respiratory motion: In children can cause misregistration of PET and CT scans, leading to attenuation correction artifact. The liver dome and spleen may be seen above the diaphragm at CT, there may be crescentic areas of photopenia above the diaphragm ("banana sign"), or focal uptake in the dome of the liver may be falsely localized to the lung base on the attenuation-corrected images, thereby mimicking a lung nodule. These artifacts are due to the difference in diaphragm position at CT and PET. PET is performed over several minutes during tidal breathing, with the final PET scan depicting the average position of the diaphragm during respiration. In contrast, CT is performed during a specific stage of the breathing cycle—usually full inspiration, when the diaphragm is at its lowest point. A way to reduce breathing artifacts recommends acquiring the CT scan during shallow breathing. However, this technique results in varying amounts of breathing artifacts. The shallow-breathing method does not

accurately match the average PET image and degrades the CT image quality (32).Any change in patient position between PET and CT can lead to misregistration on the fusion images and attenuation artifact on the attenuation-corrected images. Patient sedation is cardinal for this reason.

Involuntary patient movement may also be due to relaxation of muscles during the combined examination, which takes about 20- 35 min for a whole- body (WB) acquisition. The likelihood of muscle relaxation increases with the scanning time; therefore, body regions such as head and neck, with the largest time differences between the CT and PET portions, are prone to misregistration. Accurate fusion is of critical importance in evaluating head and neck cancer cases where differentiation between FDG avid lesion from normal physiologic FDG avid muscle and lymphoid tissues can be challenging. Image fusion artifacts may be reduced in unrestrained subjects by the use of rigid head and neck positioning aids, such as foam molds, or vacuum bean bags (32).

C) **Truncation artifacts:** The CT scanner may have a relatively smaller- diameter field of view (50 cm) compared with the PET scanner (70 cm). This difference can lead to truncation artifacts when the patient's body extends beyond the CT field of view, causing under- estimation of the SUV of the peripheral portions of the attenuated-corrected images. In addition, truncation can cause streak artifact at the edges of the CT scans and overestimation on the attenuation-corrected images, producing high activity at the edges. Therefore, it is important for technologists to ensure that the patient is at the center of the field of view and that the patient's entire body is included, especially in morbidly obese children (positioning the child's arms above the head may be helpful), to reduce truncation artifacts (32). If it is technically impossible to include the entire body in the field of view, the patient should be positioned in such a way that any body parts of specific clinical concern are completely included:

III- BENIGN CAUSES OF ABNORMAL ^{18}F FDG UPTAKE:

a) Benign bone lesions: fibro-osseous defects are of particular importance in children. Non-ossifying fibromas and fibrous cortical defects are typically located in the metaphysis or diametaphyseal junction of the distal femur or proximal tibia. Such lesions manifest with variably, often intensely, increased ^{18}F FDG uptake and may mimic malignant bone disease. Correlation with the CT findings from a PET/CT study can help in characterizing these lesions and obviating further diagnostic procedures. CT will show an eccentric low-attenuation lesion with a thin sclerotic rim. It can also help determine whether a pathologic

fracture has occurred (30). Acute or healing fractures may also show increased ^{18}F FDG activity. Osteoid osteoma, chondroblastoma, Langerhans cell histiocytosis and fibrous dysplasia are other examples of pediatric bone lesions that can exhibit high FDG uptake (35, 36).

b) Infection and Inflammation: Focal increased ^{18}F FDG accumulation is seen with various infectious or inflammatory processes, including abscesses, pneumonia, sinusitis, osteomyelitis, prosthetic joint infection, tuberculosis, infectious mononucleosis, and fungal or granulomatous disease such as aspergillosis, cryptococcosis, histoplasmosis, tuberculosis, Wegener granulomatosis, histiocytosis, and sarcoidosis. ^{18}F FDG uptake has been reported in children with inflammatory bowel disease (25, 31). Pneumonia may manifest with marked focal increased uptake in the lung, usually resolving after antibiotic therapy (37). Foci of ^{18}F FDG accumulation in the gluteal muscles of the buttocks strongly suggest injection site granulomas especially after repeated injections of drugs into the subcutaneous fat (38). Figure 5.Active vascular inflammation may demonstrate ^{18}F FDG uptake. ^{18}F FDG PET/ CT images can help detect Takayasu arteritis and reflect the distribution of inflammatory activity in the vascular wall (39).

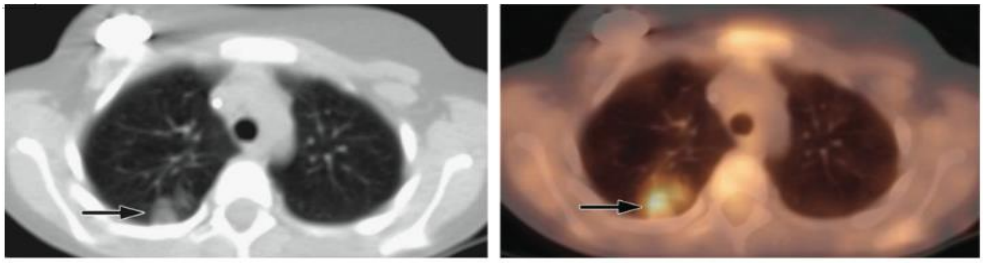

Figure 5, Pneumonia in an 8 year old boy with history of neuroblastoma, fever and cough. (a) Transverse CT scan (lung window) shows an area of infection in the right lung (arrow). **(b)** Transverse fused ^{18}F FDG PET/CT image shows markedly increased uptake in the right lung (arrow), a finding that corresponds to the area of infection. At follow-up imaging performed after a course of antibiotic therapy, the infection had resolved. (39).

IV- THERAPY RELATED PITFALLS:

a) Infection: One of the well-known side effects of chemotherapy is bone marrow

suppression, which leads to neutropenia, anemia, and thrombocytopenia. Affected patients are at increased risk for infections such as upper respiratory infection, pneumonia, enter colitis, and cholecystitis. Anti-inflammatory cells such as activated macrophages or granulation tissue that are present in areas of inflammation have been shown to actively take up FDG.

Spleen: Is an integral part of the immune system and per forms multiple tasks, including clearance of encapsulated bacteria, phagocytosis, and production of inflammatory substances and immunoglobulin antibodies. Presumably, diffusely increased splenic activity reflects increased glucose usage by this organ in the setting of extra splenic infection. It is important to recognize that increased splenic activity can also occur in patients with extra splenic infection; therefore, splenic uptake should not automatically be interpreted as either splenic infection or tumor (31).

b) Drug Toxicity: Drug toxicity of the lung is not uncommon during or after chemotherapy. Bleomycin is one of the most commonly used drugs for the treatment of Hodgkin disease, with up to 5% of patients to whom it is administered developing pulmonary drug toxicity. Diffuse increased FDG accumulation in the lungs has been reported with this condition.

c) Granulocyte Colony- Stimulating Factor Therapy: G-CSF is a glycoprotein hormone that primarily regulates proliferation and differentiation of granulocyte precursors. G-CSF has been used increasingly to correct chemotherapy-induced neutropenia and has reduced infections. Increased FDG uptake is often observed in bone marrow and spleen during and after G-CSF therapy.

Bone marrow: Bone marrow activity that is more intense than liver activity is considered abnormal. Normal accumulation is generally homogeneous, with more extensive distribution in children than in adults (28). Increased bone marrow activity can be seen following chemotherapy, usually resolving within 1 month. Increased uptake can also be seen with hyperplasia and hematopoietic stimulation from anemia. Treatment with hematopoietic cytokines such as granulocyte colony-stimulating factor (CSF), hematopoietic growth factor, or erythropoietin can also produce diffuse skeletal ^{18}F FDG accumulation. Increased activity can persist for up to 3 weeks after the discontinuation of granulocyte CSF treatment; therefore, it is advisable to postpone ^{18}F FDG PET until approximately one week after treatment (29). Diffusely increased 18F FDG uptake can be observed in the spleen during granulocyte CSF treatment, accompanying increased bone marrow uptake and reflecting

granulocyte CSF– induced splenic extra medullary hematopoiesis.

d) Radiation Therapy: The accumulation of FDG in tumor cells may be enhanced following radiation therapy, since radiation therapy may cause inflammation in normal structures such as the lungs and mucous membranes, thereby inducing pneumonia, pharyngitis, and esophagitis. Reduced bone marrow ^{18}F FDG uptake can be noted several months after external beam radiation therapy. This phenomenon has been attributed to the replacement of bone marrow by fatty tissue. Typically, no ^{18}F FDG uptake is identified in normal bone (30).

e) **Post-operative Changes:** Healing involves an inflammatory reaction even in the absence of infection. Leukocytic infiltration is present in the granulation tissue associated with wound repair and the resorption of necrotic debris and hematoma. Recent surgery can result in spurious increased FDG uptake in areas of resolving inflammation. Focal FDG uptake associated with ostomies or various indwelling stents (e.g., tracheostomy gastrostomy) is not uncommon. Persistent FDG uptake in uninfected surgical incisions has been observed. In patients with tumors, it is generally suggested that at least several weeks be allowed to elapse between surgery and FDG PET to minimize the likelihood of false-positive results secondary to postoperative changes (40).

f) Fractures: Fractures are often seen in patients with malignant disease due to metastasis or radiation therapy and are frequently associated with increased FDG uptake.

g) **Injection Leakage**: Leakage at the injection site or residual radiotracer in the indwelling catheter used for injection causes accumulation of FDG. Abnormal FDG accumulation in lymph nodes can be as a consequence of delivery of the radiotracer by means of lymphatic drainage, when the radiotracer extravacates into tissue drained by a regional lymph node group.

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