Review Article, PET/CT.

Pitfalls in 18F-FDG PET/CT in Malignant Lymphoma.

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INTRODUCTION:

Positron emission tomography (PET) is a functional imaging modality using FDG which is the most commonly used radiotracer in oncology imaging. FDG is an analogue of glucose and its uptake is directly proportional to the glucose metabolism of tumor tissue. The widespread use of PET/CT takes advantage of the excellent anatomic resolution of CT scan and the biologic characterization provided by FDG-PET which together result in improvement in accuracy of detecting the extent of disease, response evaluation and prognostication.[18]F-FDG PET/CT in malignant lymphoma requires accurate patient preparation, technically adequate acquisition, and appropriate image interpretation [1]. However, there are some pitfalls that are commonly encountered with ^{18}F FDG PET, including uptake in normal physiologic activity and benign lesions and leading to possible misinterpretation and inaccurate disease staging [2].

Patient Preparation: Successful PET scan begins with appropriate patient preparation. Patients are asked to fast for at least 4 hrs before injection to reduce the glucose level and to lower circulating insulin levels and if he is diabetic he should control his disease before the study to optimize the target-to-background ratio oncology patient's [3]. Usually normal blood glucose levels (<7 mmol/L) can be reached by 4–6 hours' fasting prior to the PET examination. If blood glucose values are elevated (>7mmol/L), the PET-CT study should preferably be rescheduled, if clinically feasible.

Time interval applied between FDG administration and the start of the PET study ranges from 45 – 60 min. When PET studies are performed for response monitoring purposes, an appropriate interval between the end of the therapy cycle and the PET study needs to be considered as FDG uptake may vary strongly shortly after chemotherapy [4].

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The administered FDG dose needs to be known exactly. Discrepancies in assumed versus true net administered dose will result in incorrect SUV data. Decay correction should be applied between the FDG dose calibration time and the start time of the PET study.

For correct SUV assessments: (a) FDG dose calibration time or dose assay time, i.e. the time at which the amount of FDG (MBq) that is to be administered to a patient is specified; (b) injection or administration time and start of the PET-CT acquisition.

The difference between injection time and start of the PET-CT acquisition provides the uptake period, which should be as close as possible to 60 min. The time difference between dose calibration time and PET-CT acquisition time is needed to derive the decay-corrected FDG dose at the start of the PET/CT study [5].

Pitfalls PET/CT is classified into:

1) Normal distribution and physiological variants of ^{18}F-FDG uptake:

The normal distribution and physiologic variants of ^{18}F-FDG uptake is important to be recognized so as to avoid misinterpretation [6, 7].

1.1) Brain:

The normal brain is characterized by a high level of ^{18}F-FDG uptake. Up to 6% of an administered dose of ^{18}F-FDG may be taken up in the brain as glucose provides approximately 95% of the energy used by the brain [8]. Artifacts and pitfalls in brain imaging may result from medications altering cerebral metabolism, hyperglycemia, and patient motion during the data acquisition, misregistration between the emission and transmission scans. The most active area on a study may be hypo or hyper metabolic lesion which may influence the final interpretation [9].

1.2) Head and Neck:

Mild-to-moderate uptake is usually seen in the adenoids, in the tonsils, and at the base of the tongue due to the physiologic activity of lymphatic tissue in the Waldeyer's ring at 6–8 years of age, after which time it diminishes. Usually, the symmetric pattern of physiologic tonsillar and adenoidal uptake is helpful in identifying this normal variant .The soft palate can also show intense radiotracer uptake [8, 10]. Accurate alignment of CT and PET emission data is required for accurate diagnosis and properly corrected PET images.

In PET/CT examinations of extended co-axial imaging ranges, the time difference between acquiring the CT and the emission data of the head can be significant (up to 30 min) since the CT is acquired head first, whereas the multi-bed emission scan is acquired feet first in order to limit artifacts in the pelvic region. Given the rather lengthy delays in imaging the head and neck region, involuntary patient motion in that area is not uncommon. This relates to relaxation of the neck muscles, causing a misalignment of that anatomical region during the CT and PET scan [11].

Salivary glands uptake is variable but is typically mild to moderate. Diffusely increased salivary gland uptake can also be seen after chemotherapy. ^{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].

Otsuka, et al. conducted a study on 85 patients to evaluate the impact of FDG-PET/CT for diagnosis of salivary gland Lesions, with positive salivary gland lesions (29 malignant, 29 benign). SUVmax was measured for quantitative analysis of salivary lesions.

Diffuse large B-cell lymphoma showed

a higher uptake than follicular lymphoma. Mucoepidermoid carcinoma and adenoid cystic carcinoma showed lower uptake than other types of carcinoma [12].

Larynx and vocal cords usually show either no uptake or mild symmetric uptake, which may have an inverted U shape. Laryngeal uptake can range from mild to intense, reflecting recent talking or crying in young age patients. Therefore, it is important to instruct patients not to talk during the uptake phase, since excessive talking may cause prominent activity in the laryngeal structures. Asymmetric vocal cord uptake suggests the possibility of disease such as malignancy, post therapy change, or unilateral vocal cord paralysis [13].

1.3) Thyroid gland:

Usually shows diffuse symmetric uptake, however, such diffuse thyroid uptake 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 [8, 10].

1.4) Thymus:

Diffuse and homogeneous uptake in the thymus is common in healthy children. The uptake is bi-lobed with an inverted V shape on coronal views.

Generally, physiologic uptake in the thymus disappears during adolescence in conjunction with involution of the thymus. Thymic hyperplasia (or "rebound") is seen following chemotherapy more often in young adults. Very intense uptake or heterogeneous uptake may raise suspicion for thymic or other anterior mediastinal disease [14].

Benign thymic lesions are prone to misinterpretation on cross-sectional imaging, whether performed using CT, PET/CT, or MRI. Such misinterpretation may lead to unnecessary diagnostic intervention. Normal and hyperplastic thymic tissue may be avid on ^{18}F-FDG PET/CT. The frequent FDG avidity of thymic hyperplasia serves as a potential pitfall in the interpretation of FDG PET/CT examinations [15].

In patients with known malignancy, physiologic uptake of FDG by the hyperplastic thymus is more prevalent than previously thought, and it can be seen within the normal thymus as well. Therefore, it is important to correlate any FDG avidity of thymic tissue with morphologic and attenuation findings on CT [16]. Following chemotherapy, FDG uptake can be seen in the thymus of 75% of children and in 5% to 16% of adults and enlargement can persist for up to six months following completion of chemotherapy.

In general, physiologic uptake of FDG in the thymus disappears in adolescence in conjunction with involution of the thymus. Rebound thymic hyperplasia is seen in young patients treated for malignancy. Normal thymic activity will appear triangular or "V" shaped (bilobed) and will usually have low to moderate uptake. Lack of uptake in the pre-therapy scan should be an indicator for post treatment thymic hyperplasia. FDG accumulation in the thymus suggests pathology when it does not have a typical triangular shape or if the activity is very intense [17, 18].

Smith, et al. reported a superior mediastinal thymic extension associated with postchemotherapy thymic hyperplasia in 12% of 93 FDG PET/CT examinations. They did not find a superior thymic extension in any of subjects [19].

1.5) Cardiac:

Activity is variable, ranging from no discernible activity above background blood pool activity, to intense activity throughout the left ventricular myocardium. 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 [20].

1.6) Gastrointestinal tract:

^{18}F-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 [13, 21].

Esophageal activity can be noted as mild linear uptake anterior to the spine and is best seen in the sagittal plane. Most commonly this is seen in oncology patients, and esophageal uptake represents post-treatment mucositis related to either chemotherapy or radiation [13].

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.

Gastric uptake is usually mild, but more intense uptake may be associated with Helicobacter pylori infection.

Significant gastric uptake is noted following chemotherapy for lymphoma specially if containing Corticosteroids [20].

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. 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. Marked ^{18}F-FDG accumulation can be seen in young-aged patients with inflammatory bowel disease [20].

1.7) 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.

If there is significant retention in the renal collecting system, reconstruction artifacts may interfere with visualization of the upper abdomen.

Keeping the patient well hydrated and administering diuretics can minimize such activity and improve image quality.

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. Tracer accumulation in ureters usually can be identified by the distinctive contours of the ureters and by correlation with CT. 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 [22].

1.8) 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. 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 uptake, if present, is typically bilateral, whereas ovarian uptake is generally unilateral. The endometrium generally shows cyclically variable uptake, but marked uptake can be seen during menstruation. Therefore, it is necessary to know the pubertal status and menstrual phase to adequately interpret these findings in female patients [20, 22].

1.9) Skeletal system:

^{18}F-FDG skeletal uptake is a nonspecific finding that may represent pathology or normal physiology. In young adults, physiologic uptake of ^{18}F-FDG can be seen as sites of bone growth, such as the epiphyses of the long bones. Increased ^{18}F-FDG uptake also has been reported in growth arrest lines that can occur after resolution of skeletal growth arrest related to illness or prolonged immobilization [23].

Fractures: FDG is accumulated intracellularly at site of fracture. Complete evaluation of FDG uptake in bone requires careful analysis of the un-fused CT with bone window settings. Differentiating between fractures of malignant and benign causes can be challenging, and overlap between the FDG avidity of benign and malignant fractures is known to occur [23].

Osteomyelitis: FDG-avid lesions are included in the differential diagnosis of aggressive bone lesions. Three of the 10 cases of hematogenous osteomyelitis in the preceding study showed sufficiently high uptake to be mistaken for malignancy [24].

Numerous benign sources of FDG uptake in the musculoskeletal system can be mistaken for aggressive or malignant processes if the bone is not fully evaluated on the CT portion of the PET/CT examination. Common examples include fractures, degenerative disk disease, and osteophytes. Benign bone and soft-tissue lesions can simulate malignancy, particularly if they are highly avid and low-grade malignancies with low FDG uptake can be mistaken for benign lesions if the CT and radiographic characteristics of the lesions are not closely studied [25].

1.10) Muscular system:

Physiologic muscle uptake is commonly encountered at ^{18}F-FDG studies due to excessive muscle activity during the uptake phase reflecting the involved muscles. 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.

The intercostal muscles and accessory muscles of respiration can be detected in patients who have been experiencing respiratory distress during the uptake phase.

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 [26].

BAT FDG uptake in patients is most commonly seen in the neck and supraclavicular-axillary, mediastinal, paravertebral-intercostal, mediastinal, per nephric-suprarenal and upper abdominal wall regions, 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 .Warming the patient prior to injection and during the uptake phase is a simple approach to reduce brown fat up- take [26, 27].

2) Technical artifacts:

2.1) Contrast-induced:

Modern PET/CT scanners incorporate the latest CT technology, thus technically allowing the execution of multiphase, high-quality CT imaging. Recently, there have been several reports of the possible superiority of contrast-enhanced PET (cePET)/contrast-enhanced CT (ceCT) over standard PET/CT in different clinical settings, including disease staging, restaging and treatment planning of different tumor types. However, the adoption of a low-dose, contrast-free CT protocol has been guided mostly by practical considerations, so as to reduce radiation burden, reduce patient discomfort, and minimize scanning time. In fact, the potential advantages of executing the CT part of a PET/CT scan with protocol encompassing contrast administration are related to the greater anatomical details given by ceCT, and its improved characterization of millimetric lesions and the delineation of known lesions with respect to surrounding tissues. For these reasons, a more comprehensive approach would help to identify patients that are more likely to benefit from cePET/CT imaging. This approach should account not only for tumor histopathology, but also for the site of known/suspected lesions and for the clinical question [28, 29, 30, and 31].

Oral contrast material may not significantly affect image quality and visual interpretation. Intravenous contrast material can 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 [32, 33].

2.2) Metallic objects:

Prostheses, pacemakers, or chemotherapy catheters can cause virtuously 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. 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.

Viewing the non-attenuation-corrected PET images can help distinguish this attenuation correction artifact from true hypermetabolism, since this virtuous high activity will not be present on the non-corrected images [32, 33].

2.3) Respiratory motion:

Respiratory motion 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 [34].

Respiratory gating software: CT has shortened the time for the transmission scan for attenuation correction of the PET data from minutes to seconds. CT, however, introduces a new problem of potential misregistration of the CT and PET data due to its fast scan speed resulting in each CT image being a snapshot or a single phase of the heart in respiratory motion. A series of continuous respiratory phases of snapshot CT images may not be suitable for attenuation correction of the PET data.

Average CT can improve registration of CT with PET and has been implemented on several vendors of PET/CT scanners.

Unfortunately, the average CT from vendors requires respiratory gating, typically used in four-dimensional CT (4D-CT) for radiation therapy treatment planning of the lung tumor, complicating the clinical solution, and making it impractical because most PET/CT scanners are either without respirator gating hardware or respiratory gating was deemed too complex to be applied in a clinical setting.

It will be beneficial to make the average CT available in cardiac PET without respiratory gating as it has been demonstrated in the original proposal of average CT [35].

The patient breathes the same way for average CT and PET. The radiation dose of average CT can be less than 1 mSv. We typically spend more time in expiration than in inspiration. The PET data will be weighted more toward the end-expiration and will have a better chance to match with CT at or near end-expiration, which can be implemented with proper patient coaching. The scan time with a 16-slice CT of 2-cm X-ray collimation can be as short as 3 seconds for coverage of 15 cm or one bed of PET scan field of view, which makes it relatively easy for the patient to hold breath at or near end-expiration in a fast CT scan of just a few seconds. Coordination between the patient and the technologist is important for the success of breath-hold at or near end expiration. Most vendors provide rigid-body-translation software for registration of the CT and PET images to ensure that PET activities do not overlap with the low density lung region to avoid under-correction of the PET activities due to photon attenuation [36].

Looking into the future, the most ideal solution to manage respiratory motion is to acquire data in list mode, use a data-driven self-gating technique to gate the PET activities into multiple bins over a respiratory cycle [37].

2.4) 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 patients (positioning the patient's arms above the head), to reduce truncation artifacts [40]. 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. This cannot be applied in head and neck region; instead it can be replaced for by separate PET position.

3) Benign causes of abnormal ^{18}F-FDG uptake:

3.1) Benign bone lesions:

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 CT findings from a PET/CT study can help in characterizing these lesions and will show an eccentric low-attenuation lesion with a thin sclerotic rim [40].

3.2) 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 patients with inflammatory bowel disease [38].

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].

4) Therapy-related pitfalls:

4.1) 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 tract infection as pneumonia with focal uptake that resolve after antibiotics.

Spleen is an integral part of the immune system and performs 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 [38].

4.2) 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 [40].

4.3) 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. 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 [35].

Treatment with granulocyte colony-stimulating factor (GSF), 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 three weeks after treatment. Diffusely increased ^{18}F-FDG uptake can be observed in the spleen during granulocyte GSF treatment, accompanying increased bone marrow uptake and reflecting granulocyte GSF– induced splenic extra medullary hematopoiesis [41].

4.4) 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 [42, 43].

4.5) 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 [13, 20].

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