

FDG-PET AND PET/CT - Part I

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Positron emission tomography (PET) with ¹⁸F fluoro-deoxyglucose (FDG) is now an established functional imaging modality predominantly used in the work-up of several neoplastic diseases. It also has several neurological and cardiac applications in routine clinical practice. However, the radiopharmaceutical, ¹⁸F-FDG, most commonly used for clinical PET studies today is also taken up by inflammatory and infectious cells and it also has a potential role in inflammation imaging in the future. Since this technique provides a map of glucose metabolism in the body, it is extremely important to understand the bio-distribution of FDG in the human body and factors that alter it. Accordingly, the technique used and several patient factors have a significant impact on the quality of images obtained. Hence, it becomes critical to perform this highly sophisticated exam with adequate patient preparation, following an accepted technique and interpret the images with the knowledge of normal and physiologic bio-distribution of FDG in several body organs and tissues. With this objective, this two-series review article will review the current principles and practice of clinical FDG-PET. The first section of this article deals mostly with basic aspects of FDG-PET and PET/CT including properties of FDG, PET instrumentation and technique and normal variants.

Key words: FDG, PET, PET/CT

Introduction

Positron Emission Tomography (PET) is a nuclear medicine imaging technique that provides high-resolution tomographic images of the bio-distribution of a radiopharmaceutical *in vivo*. As such, it is a functional imaging modality as contrasted with an anatomic imaging modality such as CT scan. Similar to other nuclear medicine techniques (such as bone or myocardial perfusion imaging), compounds of interest are labeled with radioactive tracers and after intravenous injection are allowed to distribute according to the *in vivo* biologic behavior of the tagged compound. Unlike other nuclear medicine techniques, the radioactive moiety of the radiopharmaceutical consists of positron-emitters, usually very short-lived and produced in cyclotrons. Specialized external scintillation detectors are then used to detect the radiation emitted from the body and using complex mathematical algorithms, tomographic images of the radiopharmaceutical bio-distribution *in vivo* are reconstructed.

¹⁸F-labeled 2-deoxy-2-D-glucose (Fluorodeoxyglucose or FDG) is the most commonly used PET radiopharmaceutical, in which the hydroxyl group of glucose is replaced by a positron-emitting fluorine isotope. The concept and technique of FDG-PET imaging was initially developed in

the 1970s and was first applied to functional brain imaging. Stimulus for the initial studies came from the facts that metabolic activity was necessary for and accompanied neuronal function and that glucose was the sole substrate of energy metabolism for neural tissue. During this time, there was further innovation and refinement of PET instrumentation such that images of the body as well as the brain could be obtained. In the early 1980s, FDG-PET studies were also employed to assess cardiac metabolism. Otto Warburg in the 1920s had shown that tumors, in general, had much higher levels of glucose metabolism than the normal tissues from which they arose^[1,2] and by the mid to late 1980s, it had become clear that FDG-PET could have significant impact on the imaging evaluation of many neoplastic disorders. This was initially applied to brain tumors but with the development of scanners capable of imaging the whole body, there began a virtual explosion of studies investigating the potential role of FDG-PET in a variety of tumors. FDG-PET was found to have significant advantages over CT anatomic imaging and this has led to rapid and widespread clinical use. More recently, the development of scanners combining PET and CT, enabling the imaging of both structure and function in a single instrument at the same time, has allowed more accurate localization of focal areas of increased glucose metabolism, which has in turn increased the sensitivity and even more

importantly, the specificity of the technique. Today, PET and PET/CT imaging are no longer in the research realm and are routinely used for oncological, neurological and cardiac indications with numerous future applications on the horizon.

The first part of this two article series on FDG-PET and PET/CT will discuss basic aspects of FDG-PET and PET/CT including the radiopharmaceutical(s), instrumentation and protocol, followed by normal physiologic uptake and benign variants. The second part of the series will discuss the various clinical applications.

FDG

There are several radiopharmaceuticals employed in PET, but ^{18}F Fluorodeoxyglucose (FDG) remains by far the most commonly used PET radiopharmaceutical. FDG is a fluorinated radiopharmaceutical consisting of the radioisotope ^{18}F substituted into a glucose molecule at the 2 position, yielding 2- ^{18}F Fluoro-2-deoxy-D-glucose.

The radionuclide ^{18}F is a cyclotron-produced positron emitter with a half-life ($T_{1/2}$) of approximately 110 minutes. This facilitates transport of the radiopharmaceutical to PET centers without a cyclotron and also eases the time frame restrictions on study protocols. It has a relatively low average positron energy of 0.63 MeV and an average positron range in tissue of approximately 0.3 mm, which is the distance traveled by the positron before interacting with a tissue electron and producing the annihilation that produces the photons detected by the scanner. This provides the highest spatial resolution among all PET radionuclides.^[3]

FDG acts as a glucose analogue in the body and is transported from the plasma into the cells by glucose transporters (most important are GLUT 1 and GLUT 4). It then undergoes intracellular phosphorylation by the enzyme hexokinase and is converted to FDG-6-phosphate. Since this is not, however, a substrate for the enzymes phosphohexose isomerase or glucose-6-phosphate dehydrogenase, FDG-6-phosphate does not undergo further metabolism and remains metabolically trapped within the cell [Figure 1]. This trapping phenomenon is exploited for FDG-PET imaging such that following time for initial tracer uptake and transport into cells, there is adequate time at stable distribution to allow imaging. The increased glucose uptake in cancer cells is due to increased anaerobic glycolysis,^[1,2] a phenomenon known as the “Warburg Effect” and is postulated to be due to upregulation of glucose transporters and hexokinase levels and lower levels of the enzyme glucose-6-phosphatase in cancer cells, limiting further metabolism of the tracer.^[4-6] This makes image interpretation comparatively easy since all the activity visualized at imaging represents only FDG-6-phosphate

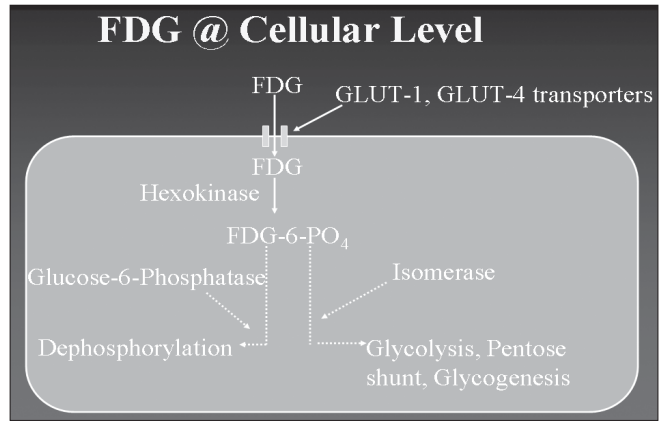


Figure 1: Schema for “metabolic trapping” of FDG in the cells.

and nothing else, as there are no additional daughter molecules.^[7]

FDG possesses many of the characteristics of an ideal tumor imaging radiopharmaceutical. In addition to ^{18}F being one of the most optimal positron emitters for imaging, FDG-PET is extremely sensitive and reasonably specific in clinical practice. It has a wide range of applications including tumor imaging, brain imaging, cardiac imaging as well as potentially, inflammation imaging. Despite its extensive utility in a wide range of clinical conditions, FDG retains reasonable specificity according to the nature of disease being assessed and the clinical setting. Although active inflammation and neoplasm may sometimes not be clearly distinguished by FDG-PET imaging, the situation is not sufficiently common to limit the value of FDG-PET imaging. Most frequently, the clinical scenario and the accompanying CT scan images (in PET/CT imaging or on review of a separately obtained CT) help to improve specificity.

Instrumentation

Commonly used scintillators utilized as detectors in PET scanners include Sodium Iodide (NaI), Bismuth Germanium Oxide (BGO), Lutetium OxyorthoSilicate (LSO), Gadolinium OxyorthoSilicate (GSO) and the newer Lutetium-Yttrium OxyorthoSilicate (LYSO). These scintillators convert incident photons from the radioactive decay of the tracer within the patient to a light pulse. To improve spatial resolution, the scintillation crystals are constructed as block detectors with many small individual scintillation crystals tightly packed into blocks that are coupled to four or more small photomultiplier tubes, which convert the light pulse to an electric signal that then characterizes the radioactive decay event producing the photons. A typical PET scanner is a cylindrical assembly of numerous block detectors in a ring configuration.

Positron emitters undergo positron (β^+) decay, emitting a positron (β^+) and a neutrino (ν). The positron travels a very short distance in surrounding tissue (usually around 0.3 mm for ^{18}F) and then undergoes annihilation by combining

with an electron. In this process, a pair of 511KeV photons (from conversion of the mass of a positron and electron into energy) are released almost exactly 180° apart and are nearly simultaneously detected by the scintillation detectors in PET scanners [Figure 2] as coincidence events (or simply coincidences).

The PET raw data consists of a Line of Response (LOR) of the observed coincidences, which is essentially a line drawn between the detector pair in which the coincidence occurs. Millions of LORs are acquired/stored in sinogram form in a single image acquisition with multiple single image acquisitions (bed positions) being acquired for imaging a large area of the patient, the table moving between acquisitions. There are a number of factors that tend to degrade the image by introducing inaccuracies in precise positioning of the LORs. Interactions of the emitted photons with matter in the patient's body may attenuate the emitted photons by Compton scatter, the detectors may have variable detection efficiency and in addition to the true coincidences, random and scatter coincidences may also be detected. This necessitates the introduction of corrections during image reconstruction, the most important being attenuation correction (AC). Newer scanners have improved methods for accurately positioning the lines of response and for correcting for scatter, leading to better resolution. A typical contemporary scanner has a resolution approaching 4 - 5 mm. Accordingly, subcentimeter tumor nodules may be resolved depending on their location in the body and relative uptake compared with surrounding tissues.

The emission scan consists of images reconstructed from the raw data sinogram [Figure 3]. These non-attenuation corrected emission images are difficult to interpret due to under-representation of activity originating in deeper and central body areas (mediastinum, abdominal cavity) compared to the more superficial structures such as skin. This not only impairs visual interpretation of the images, but also renders quantitative analysis of the images impossible.

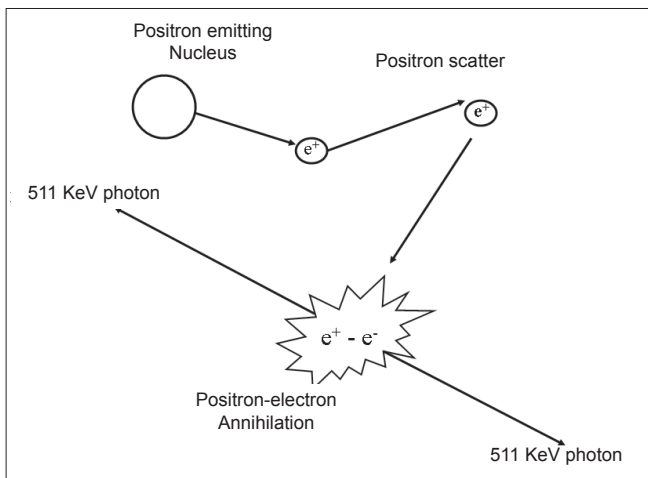


Figure 2: Schema for positron annihilation

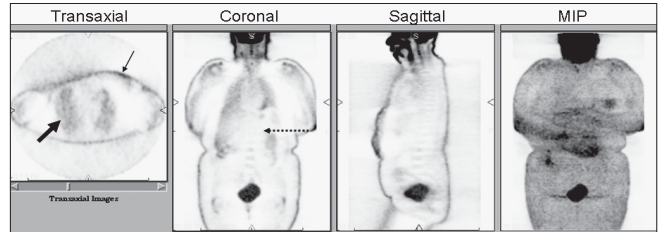


Figure 3: Non-attenuation corrected images in the transaxial, coronal and sagittal planes and a MIP image (from left to right). Note the increased skin and superficial activity (thin arrow), mild and diffuse lung activity (thick arrow) and lack of FDG activity within deeper regions of the body (dotted arrow).

To correct for attenuation, an attenuation map of the body (transmission image) is generated using either an external rod or point source of activity (such as gamma-emitting Cesium-137 or positron-emitting Germanium-68). In PET/CT scanners, the CT images acquired as a part of the protocol provide the attenuation map. Attenuation coefficients for various body parts/regions are calculated and applied to the emission images to generate AC images^[3,8] [Figure 4].

Protocol

FDG-PET is predominantly used for oncological purposes. There is no standardized protocol for oncological FDG-PET studies although most imaging centers follow at least the basic requirements.^[9] Adequate patient preparation is essential to obtain high quality images and improve the diagnostic yield. Patients should be fasting for at least 4h prior to the study (preferably overnight) to decrease endogenous insulin production with attendant alteration of FDG distribution to skeletal muscle. No glucose in any form should be ingested or given by IV or abdominal tube. They should avoid strenuous physical activity on the day prior to and the day of the study. The blood glucose level (BSL) is checked, usually with a hand-held fingerstick instrument on arrival at the imaging center and should be <200 mg/dL.

FDG, unlike glucose, is not conserved by the kidneys and is excreted. Hydration (oral and/or intravenous) may be considered for an optimal scan and many centers including our own have rather rigorous hydration protocols and

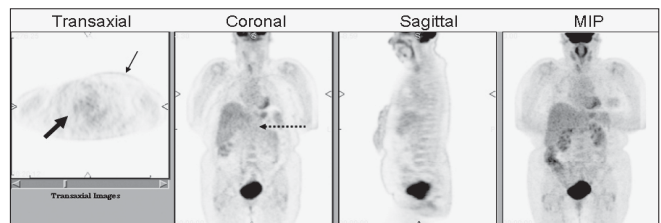


Figure 4: Attenuation corrected images in the transaxial, coronal, sagittal planes and a MIP image (from left to right). Note the mild skin and superficial activity (thin arrow), lack of lung activity (thick arrow) and physiologic FDG activity within deeper structures of the body (dotted arrow)

additionally give a short acting diuretic (furosemide) intravenously (IV). This minimizes the chance that renal pelvicalyceal and ureteral uptake might confuse the picture. Further, the hydration/diuresis frequently leads to less intense activity appearing in the bladder such that pelvic areas are more accurately assessed. On occasion, activity in the bladder may be even less intense than a bladder tumor, allowing the latter to be visualized [Figure 5].

The required dose of FDG is to some extent instrument specific: 0.05 mCi/Kg for a sodium iodide detector scanner such as Philips C-PET and 0.14 mCi/Kg for most other instruments, with a maximum dose of about 15 mCi for most new PET/CT machines. Dose may be varied with patient weight. FDG is injected IV, preferably into a freely-running saline IV line. Care is taken to avoid drawing back blood into the FDG syringe at the time of administration. The patient is advised to avoid any movement or talking for at least 30 min after FDG administration. If hydration is utilized, the patient should refrain from visiting the restroom until 20 - 30 min after FDG injection to avoid increased uptake in the muscles utilized for ambulation. Of course, a restroom should be conveniently available for the patient and to minimize exposure of other personnel in the area. The patient should empty the bladder immediately before imaging is to begin.

Imaging, usually from skull base to mid thigh, is obtained at minimal 60 min after FDG administration. On occasion, true whole-body imaging may be indicated, as in a patient with a melanoma of the lower extremity or of the scalp. For traditional PET studies (without CT attenuation correction), emission and transmission scans are obtained for each bed position in an alternating manner. For PET/CT studies, a rapid CT scan of the area to be imaged is acquired usually prior to the emission scan and used for both attenuation correction and anatomic localization. CT protocols vary from institution to institution. If a full CT scan with IV contrast is desired ("diagnostic"), standard CT protocols may be utilized. If the purpose of the CT is for attenuation correction and anatomic localization only, a lower beam current ("low dose") scan is obtained without IV contrast. This minimizes the radiation dose to the patient and, further,

intravenous contrast may produce attenuation artifacts on the reconstructed FDG-PET images. Some centers obtain a "diagnostic" CT scan with intravenous contrast (perhaps following the emission imaging) and separately interpret it as such. At our center, we perform a "low dose" CT scan without intravenous contrast. Most of our patients have had a diagnostic CT scan of the region of interest prior to performing PET studies for initial staging purposes. For other purposes, we rarely feel the necessity for contrast-enhanced CT since FDG itself acts as an excellent contrast agent for tissue characterization. We do administer oral contrast (low density or negative contrast to avoid attenuation artifacts from dense radio-opaque contrast). Although we interpret the CT findings to the best of our ability and report the additional CT findings as well, we primarily use the CT images for attenuation map and anatomic localization. Hence, we do not generate a separate CT report nor do we bill for it as a separate diagnostic CT study. Other centers may with justification bill the studies separately.

At our center, patient preparation and the imaging protocol are somewhat more involved than outlined above. In general and with the exception of oral hyperglycemic agents (some of which may induce hypoglycemia in a fasting patient), medications are allowed if they can be taken with water and not with food. Fasting must be absolute, the main purpose being to decrease endogenous insulin secretion at the time of the study. We request our patients not have anything with even potential glucose ingredient (like tea/coffee, mint, gum, soda, etc - even if some are "sugar free") on the morning of the scan. The BSL should be <200 mg/dL; if >200 mg/dL we consider insulin (if schedule allows and detailed below). We also routinely administer short-acting oral benzodiazepine (diazepam 5 mg) for selected patients (head and neck cancer patients, breast cancer patients, younger patients with lymphoma, young/anxious/nervous patients and patients who are cold and shivering) 20-25 minutes prior to FDG administration to prevent brown fat uptake. We find oral short acting benzodiazepine easy to manage but will not give it if the patient needs to drive or operate machinery after the scan. We also may consider additional oral diazepam (5 mg) for anxious, claustrophobic patients about 20 - 30 min prior to imaging, again not to patients who are driving alone or need to operate heavy machinery after the scan. This is likely an overly conservative measure but seems reasonable. Brown fat FDG uptake is discussed more completely below.

We hydrate all our patients with oral (16 - 18 oz water orally) and intravenous (250 cc of normal saline; 500 cc saline if patient cannot tolerate oral fluids) fluids. Unlike glucose, FDG is not reabsorbed at the renal tubule level and is excreted. We administer intravenous furosemide (10 mg) about 20 - 30 min after FDG to facilitate renal clearance and washout of collecting system activity in urine (unless

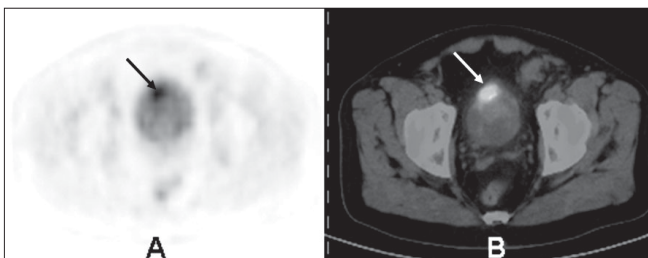


Figure 5 (A, B): Transaxial PET ("A") and Fused PET/CT ("B") images at the level of the urinary bladder showing intense FDG activity corresponding to a urinary bladder carcinoma (arrows) with less intense activity in the urinary bladder (due to good hydration and diuresis but without catheterization)

contraindicated). The excreted activity may lead to some confusion concerning focal activity in the renal collecting system or ureter. Intravenous hydration and furosemide are not administered to patients with renal failure and to patients with fall hazard precautions. Hydration must be judiciously given to patients with borderline cardiac function or known heart failure. Some additional comments on patient preparation are included in the section to follow on FDG distribution patterns and associated variations.

Our delay period for image acquisition after FDG administration is 90 min for all oncological studies. The logic underlying delayed imaging (more than the 60 min after FDG administration as is followed by most centers) is to help improve the sensitivity as well as the specificity of the study. It is now well-known that cancer cells as well as inflammatory cells show increased FDG activity and this is an important cause of false positives and decreased specificity of FDG-PET studies.^[10-19] However, it is postulated that cancer cells continue to exhibit increased FDG activity for longer periods of time as compared to inflammatory cells. In fact, some centers practice a technique called "Dual Time Point" imaging in which a second set of images of the desired region of body (like chest), is obtained after the initial set of skull-base to mid-thigh images.^[20] The second set of images is obtained at approximately 90-100 min after FDG administration and the intensity of the FDG uptake by the lesion of interest is compared at the two time points to aid in differentiating between inflammatory and neoplastic lesions.^[21-27] Some centers (our center included) simply perform a single set of delayed images at about 90 min after FDG administration. In addition to increasing FDG uptake in tumor, the longer delay also results in decreased activity in a number of normal organs and soft tissue sites. Both the increased uptake and decreased "background" render lesions more conspicuous and may improve both the sensitivity and specificity of the study. For neuro-oncology studies, the longer delay is also utilized though those studies are beyond the scope of this presentation.

Some additional miscellaneous factors also need to be considered while scheduling FDG-PET studies. Timing of the scan after a diagnostic/therapeutic intervention is important to avoid a false positive study due to the intervention itself. It is generally recommended to delay a PET scan by two to three weeks after surgical intervention (less if it is only a biopsy). Although response to chemotherapy can be sometimes visible on FDG-PET just a few days after completion of the chemotherapy cycle, generally, a two to three weeks interval is recommended after chemotherapy. This must be somewhat flexible to account for varying chemotherapy protocols but, in general, the scan should be performed as close to the next chemotherapy as possible. The appropriate delay for performing a PET scan after radiation therapy remains unresolved as there may be significant uptake within the radiation therapy port (particularly in the lung)

and full response with maximally diminished uptake may not be apparent until after several months. However, if surgical intervention (e.g. neck dissection in head and neck cancer) is required after radiation therapy, clinicians prefer to perform the surgery at six to eight weeks after radiation to minimize the difficulties in surgery arising from post-radiation fibrosis. Hence, although it may be optimal to perform a PET scan at three months or so after radiation therapy, for patients scheduled for possible surgery, post-radiation therapy, a PET scan can be performed at about six to eight weeks post-radiation therapy.^[28-33] Residual activity in the tumor at that early time point must be interpreted with caution since more delayed imaging after radiation may show further decrease in tumor activity with no additional intervention. Hence, though a complete response on FDG-PET at six to eight weeks is felt to be a reliable indicator of clinical response, a partial PET response is a less reliable predictor of the ultimate effect of radiation.

Some other important factors that require attention in female patients are pregnancy and breast-feeding. If possible, FDG-PET scans should not be performed on pregnant patients. At our centers, we have performed PET scans on pregnant patients on at least two occasions after thorough counseling and weighing the risks versus benefits of the study. In both cases, the FDG dose was minimized (and emission imaging times were increased) and attenuation correction was performed with the rod radiation source to minimize radiation dose. The pregnancy continued uneventfully in both patients and there are no documented adverse effects from PET scan to date even in this setting. As regards breast-feeding, there is minimal excretion of FDG in breast milk and hence, although most centers do not recommend any precaution or interruption in breast-feeding, there may be some exposure to the infant from being in close proximity to the mother's breast^[34] and in such cases (or when the mother is overly concerned/anxious), it may be advisable to interrupt breast-feeding for up to eight hours post-FDG administration (milk can be expressed and stored prior to the study for subsequent feeding in such cases).

Normal Distribution and Physiologic Variants

On an oncological FDG-PET scan from skull base to mid-thighs, the expected maximal FDG uptake is in the brain gray matter with lesser uptake in other parenchymal organs and soft tissue sites [Figure 6]. The visualized brain shows high uptake in gray matter structures (cerebral cortex, thalami, basal ganglia, cerebellum) and very low uptake in white matter. Myocardial uptake is highly variable ranging from very intense to nil. Salivary gland and tonsillar uptakes are commonly seen and are somewhat variable. The lungs typically show very low uptake with somewhat higher uptake in the mediastinum. The liver shows modest uptake (usually slightly higher than mediastinum) with somewhat less intense uptake seen in the spleen. Uptake in the gastrointestinal (GI) tract (esophagus, stomach,



Figure 6: MIP image showing usual physiologic distribution of FDG in the body with maximal grey matter uptake (thin arrow), intense myocardial uptake (thick arrow) and lesser activity in other parenchymal organs (dotted arrow) and soft tissues. Note the intense urinary bladder activity (dashed arrow) due to renal excretion of FDG

colon) is highly variable. Since FDG is excreted by the kidneys, there is frequently intense FDG activity in the renal collecting system and urinary bladder, with less activity in the renal cortex. Muscle shows low uptake at rest. Mild activity is seen in hematopoietic bone marrow but no bone uptake is present. There are several physiological/normal variations and benign pathological variants of FDG uptake in various body organs, tissues and regions that need to be recognized to avoid potential errors in interpretation and false positives.^[35-40]

Several structures in the neck show physiologic FDG activity [Figure 7]. Frequently, the tonsils may show moderate to intense FDG activity, usually symmetric. Asymmetric intense tonsillar FDG activity may be inflammatory, although in patients with an unknown primary malignancy, presenting with ipsilateral tumor-involved neck nodes,

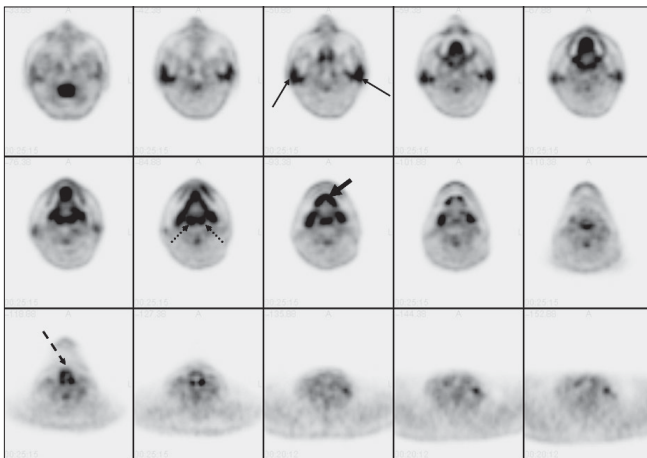


Figure 7: Transaxial images of the head and neck showing physiologic FDG activity in the parotids (thin arrows) oral cavity (thick arrow), tonsils (dotted arrows) and vocal cords (dashed arrow)

this may also represent the site of the occult primary. In addition, variable uptake is noted in the major and minor salivary glands. If the patient talks during the FDG uptake period, increased vocal cord muscle uptake is frequently noted, usually bilateral and symmetric. Lack of FDG activity on one side frequently occurs with ipsilateral vocal cord impairment with physiologic or even increased activity appearing on the opposite side.^[41-43] Increased FDG uptake is also frequently noted in neck muscles (sternocleidomastoid, longus capiti/coli, strap muscles of neck). In tense patients, increased uptake may be noted in the temporalis and masseter muscles. Frequently, an intense soft tissue focus of FDG uptake within the parotid gland is seen in patients with cancer elsewhere in the body (e.g., lung, colon, etc). This frequently represents Warthin's tumor, a benign entity.^[44] Another benign but important variant is brown fat uptake, frequently occurring in the neck (discussed in more detail below). An excellent review/atlas article by Graham *et al* discusses the normal and pathological uptake of FDG in the head and neck and is suggested for further reading.^[45]

The mediastinum usually shows relatively low, non-specific uptake. Various lymph node stations may show increased uptake in many inflammatory conditions, such as [Figure 8], histoplasmosis, tuberculosis, pneumoconiosis or reactive nodes, in addition to metastatic and neoplastic etiologies. Especially in sarcoidosis, where nodal uptake may be quite intense, the pattern of hilar and mediastinal nodal involvement, called the "lambda sign" or "Christmas tree pattern" may help to point to the correct diagnosis. Thyroid uptake is usually minimal and non-specific. However, increased thyroid activity can be seen with thyroiditis, either subacute or chronic [Figure 9] and thyroid dysfunction (Graves' disease, multinodular goiter, hyperfunctioning nodules). However, focal and intense uptake may represent differentiated thyroid cancer in 30-50% of cases. Parathyroid adenomas may also be detected on FDG-PET studies,

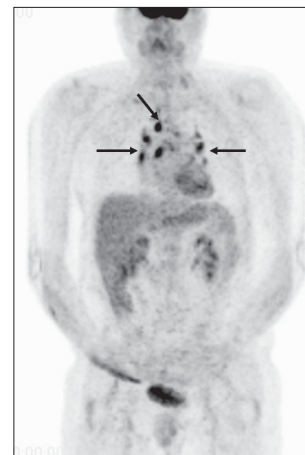


Figure 8: MIP image showing moderate to intense bilateral hilar and central mediastinal lymph nodes (arrows). This pattern (lambda) is typical for sarcoidosis (biopsy proven in this case), but may also be seen in other inflammatory/granulomatous diseases like histoplasmosis



Figure 9: MIP image showing intense bilateral intense thyroidal activity (arrows) in this patient with thyroiditis

usually with mild or moderate uptake. Thymic uptake may be seen in children up to puberty and usually correlates with other lymphoid tissue uptake. Increased thymic uptake due to “rebound” is frequently seen after chemotherapy.^[46] Breast uptake is variable with mild to moderate glandular uptake commonly seen in premenopausal women and with estrogen therapy. Relatively intense uptake is seen in lactating breasts, but the uptake is largely glandular with little activity in breast milk.^[34,47] Generally, low breast uptake is present in the postmenopausal state.

Myocardial FDG uptake is highly variable and can range from very intense to none, in the same patient on different scans. This is incompletely understood and is thought to be affected by several factors. It is not entirely minimized by fasting (although some groups recommend a low carbohydrate diet on the day prior to the study to minimize cardiac FDG uptake) and can occur without hyperinsulinemia. Glucose uptake in the myocardium is relatively insensitive to insulin levels. Myocardial FDG uptake may also be quite heterogeneous, even in normal subjects. Various cardiac pathologies (atrial fibrillation, dilated cardiomyopathy, infarct, hypertrophy) may alter the myocardial FDG uptake pattern.^[48]

GI tract uptake is also quite variable. Mild non-specific esophageal activity may be noted in some patients, although patients with esophagitis (from reflux or after radiation therapy) may show moderate to intense FDG activity along the esophagus, usually distally. Patients with hiatus hernia and Barrett’s esophagus also show increased uptake. Gastric uptake is also variable and sometimes can be quite intense (felt to be related to muscular activity in the stomach) or may be seen with Menetrier’s disease. The small bowel may occasionally show increased FDG activity, more commonly in the distal ileum/ileo-cecal region. Colonic FDG activity is extremely variable [Figure 10] and the most common pattern is increased FDG activity in the right colon (due

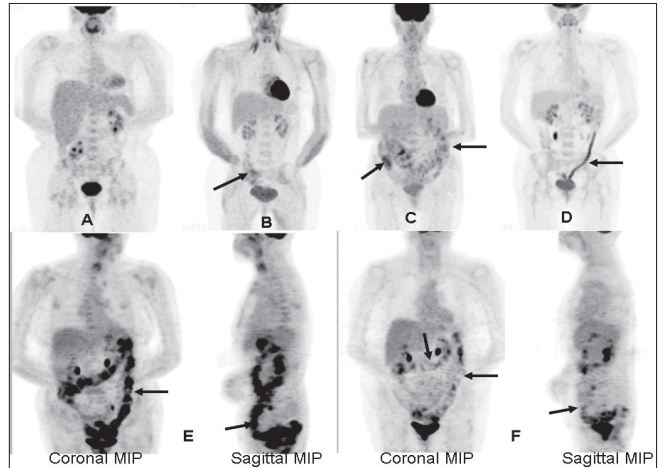


Figure 10 (A-F): Several MIP images showing variable colonic FDG uptake. In “A” there is no visible colonic FDG activity. In “B”, there is mild, diffuse right colonic (arrow) FDG activity (appears to be seen more commonly). In “C”, there is mild to moderate diffuse FDG uptake in most of the colon (arrow). In “D”, there is mostly descending colon uptake (arrow). Figures “E” and “F” show the same patient on different days (coronal and sagittal MIP images) showing intra-patient variability of colonic FDG activity (arrows)

to presence of lymphoid tissue) and rectosigmoid (“chain of beads” sign). Inflammatory conditions such as colitis, diverticulitis as well as adenomatous polyps and villous adenomas may all show intense FDG uptake. Focal colonic uptake may also be due to unsuspected colon cancer and must be taken seriously. In addition, increased FDG activity in the GI tract may also be seen associated with stomas (PEG tubes, colostomies, etc) and inflammation at the stoma penetration site in the abdominal wall or at an ostomy site, may result in quite intense activity. The variability of GI tract FDG activity is poorly understood; multiple protocols have been attempted to try and prevent increased GI tract uptake, usually with inconsistent or non-confirmed results.

Splenic uptake is usually low and less than hepatic uptake. However, increased splenic uptake may be seen in congestive splenomegaly and with cytokines (in addition to diffuse lymphomatous involvement). The adrenal glands usually do not show significant FDG activity. Diffuse mildly increased adrenal uptake may be seen in hyperplasia. Mild to moderately increased uptake is also noted in adrenal adenomas whereas focal and intense lesions are usually neoplastic.

Since FDG is excreted by the kidneys, there may be intense FDG activity in the renal collecting system and urinary bladder; hence, the rationale for use of hydration and diuresis outlined above. The renal excretion of FDG does hamper evaluation of renal and urinary bladder neoplasms with FDG-PET and some centers practice bladder catheterization during the evaluation of urinary bladder/pelvic neoplasms. We have never utilized this technique and feel it unnecessary. Intense urinary bladder

FDG activity in a small, contracted bladder may cause apparent decreased activity around the urinary bladder due to image reconstruction artifact [Figure 11].

The testes show variable uptake but are commonly moderately intense but usually symmetric. The ovaries are usually not visible on FDG-PET studies but corpus luteum cysts and sometimes ovulating ovaries may show increased FDG uptake, usually moderate. The uterus generally shows very low FDG uptake, but some active fibroids may show intense uptake. Variably increased FDG activity in the uterine cavity/lining is noted during menstruation [Figure 12].

Hematopoietic bone marrow usually shows only mild uptake with no uptake in fatty marrow. Increased uptake

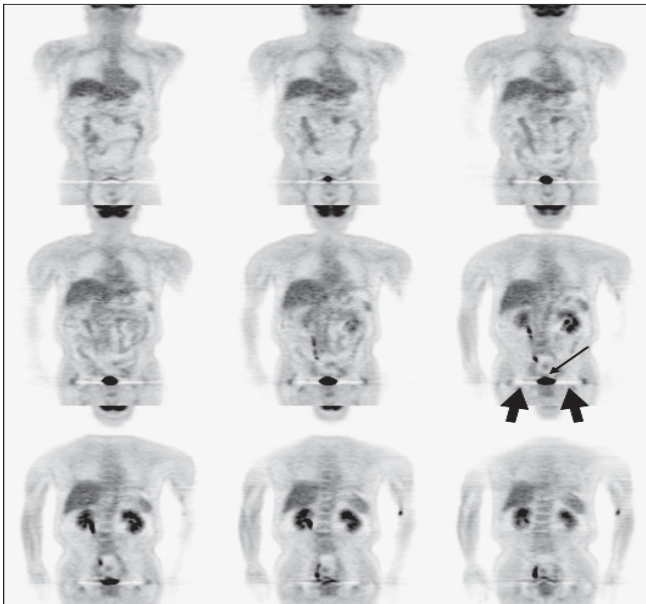


Figure 11: Coronal images showing the “hot” bladder artifact in the form of a “cold” artifactual band (thick arrows) adjacent the urinary bladder (thin arrow)

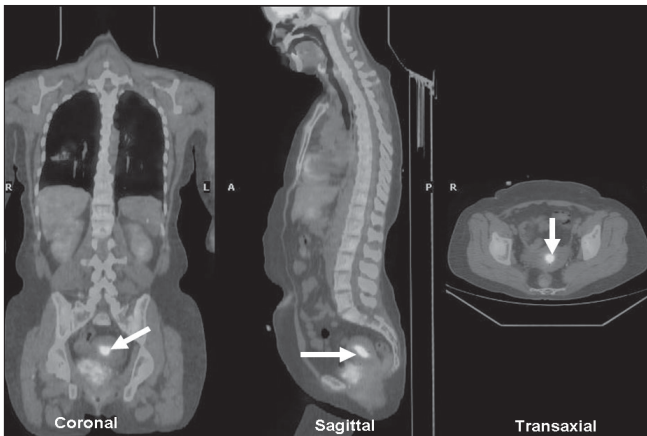


Figure 12: Fused PET/CT images in coronal, sagittal and transaxial planes (from left to right) showing intense FDG activity in the center of the uterus (arrow) in a menstruating patient

may be seen with hyperplasia and hematopoietic stimulation resulting from anemia, chemotherapy recovery, cytokines, myelo- and lymphoproliferative disorders. Decreased bone marrow activity is seen in radiation therapy ports and infarcts. Focal increased uptake in bone may be seen in benign conditions like trauma, arthropathy/enthesiopathy, Paget’s disease and sternocostoclavicular hyperostosis - with an appearance similar to that on radionuclide bone imaging.

Vascular uptake is usually low to negligible. However, increased vascular uptake may be seen with arteriosclerotic lesions (usually with active inflammation), large vessel vasculitis, chronic thrombosis, thrombophlebitis, bypass grafts (which may persist indefinitely) and venous access devices. Frequently, an intense focus at the catheter tip of a venous access device (like central line) is seen when it is utilized for FDG administration. It is important to recognize this as a normal variant not to be confused with pathologic focal mediastinal uptake.

Muscle uptake is generally low at rest. Increased muscle uptake may be seen with exercise, muscle tension, talking, chewing, gnashing of teeth, dyspnea, tachypnea, coughing, shivering, “imbalance” (e.g. with hemiparesis, amputation) or due to muscle utilization during uptake period (e.g. pushing against uncomfortable pillows, in head and neck cancer patients post-radical surgery due to altered muscle utilization).^[49] Marked, generalized, intense muscle uptake may result in a false negative study due to lack of sufficient FDG availability to localize in pathological lesions [Figure 13]. To prevent/minimize muscle uptake, we ensure that all our patients are fasting overnight (to minimize endogenous insulin secretion) and avoid rigorous physical activity and

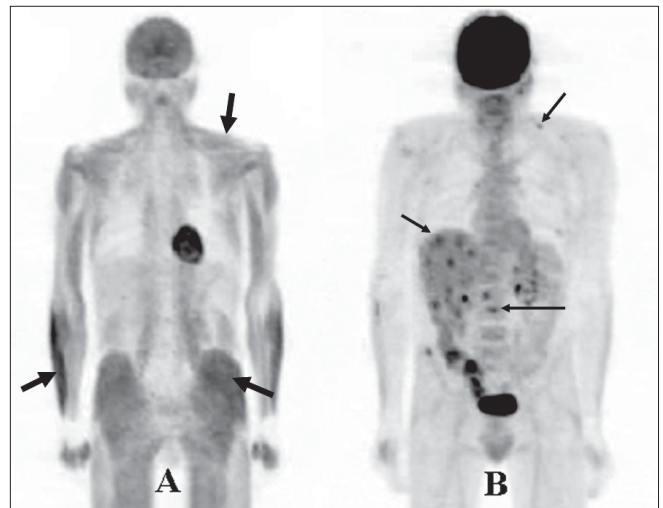


Figure 13 (A, B): MIP images of the same patient with lymphoma, on 2 different days. Intense physical activity on the day prior to scan “A” caused a false negative study with significant muscle uptake (thick arrows). A repeat study “B” after adequate patient preparation (without rigorous physical activity prior to the study) showed the lymphoma lesions (thin arrows) in this patient

exercise on the day prior to the scan. Patients should rest comfortably with as little movement as possible during the uptake period and should be warm and cozy (with warm blankets if required).

Acute insulin effect (postprandial as well as iatrogenic) also causes increased skeletal muscle uptake. Insulin shifts glucose (and FDG) uptake to skeletal muscle and to a lesser extent fat and may thus decrease tumor FDG uptake [Figure 14]. Myocardium is not significantly affected by plasma insulin levels. These effects of insulin are seen both with injected insulin and increased endogenous insulin levels. Hence, if the patient's fasting BSL on the day of the scan is greater than 200 mg/dL, most centers reschedule the patient for another day recommending better diabetic control before the rescheduled scan rather than using insulin to reduce the BSL. However, at our center, we frequently use small amounts of short acting human insulin intravenously.^[50] The injected dose depends on the actual BSL, type and severity of diabetes, whether on insulin (including dose), the possibility of insulin resistance and the use of oral hyperglycemic agents (OHA). It is however, usually less than 10 units. We then monitor the BSL every 15-30 min to ensure appropriate drop in BSL. FDG injection must be delayed until 90 min after insulin by which time plasma levels have markedly decreased and the BSL is sufficiently low in most cases (< 200 mg/dL) to proceed with the usual protocol. Since we scan a large number of diabetic patients with poor control and some of our patients drive four to five hours to reach our imaging center for their PET scan (and frequently have to make travel arrangements for the same), we try to schedule such patients on "Diabetic Days" when we have two technologists at the center and allow for longer time interval in the schedule for the insulin protocol.

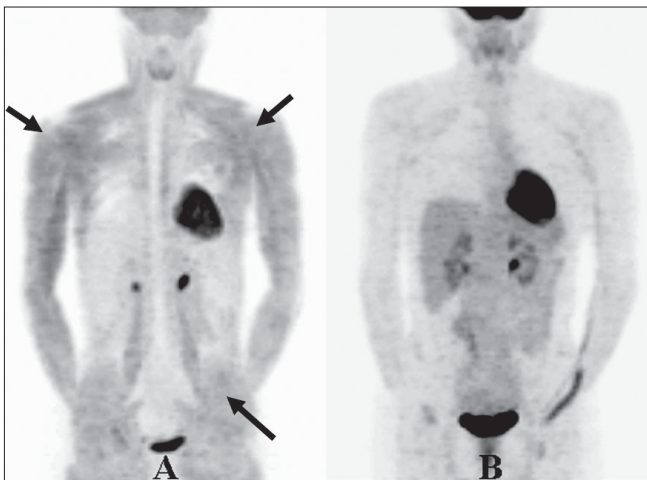


Figure 14: MIP images of the same patient with and without adequate fasting. Coronal image (A) shows increased muscle uptake (arrows) when the patient was fasting for only 45 minutes prior to the study (BSL was 85 mg/dL). The same patient with a repeat study after overnight fasting (B), shows normal biodistribution of FDG (BSL was 70 mg/dL)

Although this makes the study significantly longer, it is more efficient than rescheduling, for most of these patients. However, if BSL is greater than 300 mg/dL, we usually reschedule the patient, since if the dose of insulin is too high, 90 min may not be an adequate time interval for it to clear from plasma despite using short acting insulin with IV administration.

Increased brown fat uptake is an important benign variant^[51,52] [Figure 15]. Brown fat represents a rapidly mobilizable energy source and is important in thermoregulation. It contains high concentrations of adrenergic receptors (stimulatory) and benzodiazepine receptors (inhibitory). It becomes metabolically active via adrenergic stimulation (anxiety, shivering due to cold). Since the typical locations for brown fat include neck, supraclavicular regions, anterior mediastinum, para-spinal regions and supra-renal space, intense brown fat activity may hinder interpretation of many nodal areas in patients with lymphoma, head and neck cancer and breast cancer. However, brown fat uptake can be blocked by benzodiazepines^[53] like diazepam and alprazolam [Figure 16] and by keeping the patient warm during the uptake period.^[54] Hence we consider "routine" benzodiazepine use in patient groups frequently anxious (breast cancer patients, young patients with lymphoma/Hodgkin's disease and others as felt necessary). We ensure that the patients are accompanied by someone and are not driving or operating machinery after the study. However, the effect of benzodiazepines can likely be over-ridden by nicotine and adrenergic agonist drugs (pseudoephedrine) and hence we recommend abstinence from smoking (or nicotine patches) and anticongestant use on the day of the scan for all our patients. Other pharmacologic agents that decrease brown fat FDG uptake include opiates and beta-blockers, both used in some centers.

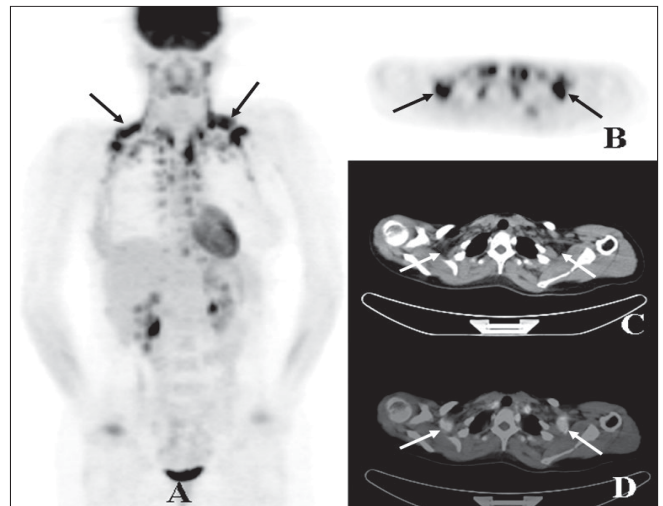


Figure 15 (A-D): Brown fat uptake. MIP (A), transaxial PET (B), CT (C) and fused PET/CT (D) images, showing intense bilateral supraclavicular uptake localizing to fat (arrows)

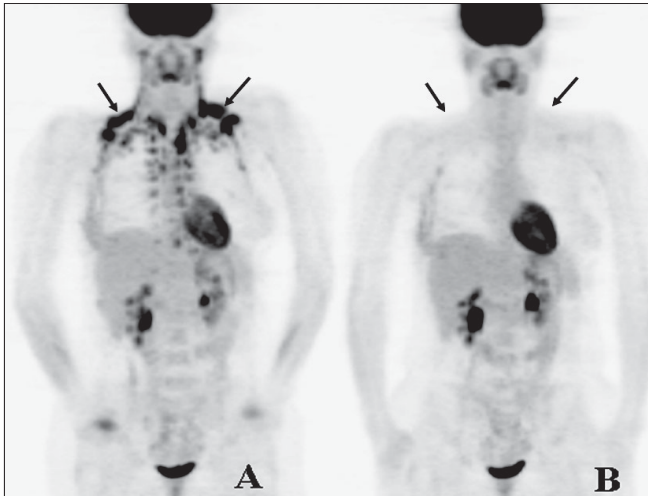


Figure 16 (A, B): Pharmacologic suppression of brown fat uptake. MIP image (A) shows intense bilateral supraclavicular brown fat uptake (arrows). MIP image (B) of the same patient after pre-treatment with oral diazepam prior to FDG administration shows complete suppression of brown fat uptake (arrows) with no change in FDG biodistribution elsewhere

Other miscellaneous benign conditions causing increased FDG uptake include many active inflammatory/infectious diseases such as active sarcoidosis, active tuberculosis and other granulomatous diseases, talc pleurodesis, Castleman's disease, pancreatitis, fibrosing mediastinitis/retroperitoneal fibrosis, rheumatoid disease, Wegener's granulomatosis. Inflammation from acute radiation effect, wound healing and decubitus ulcers also cause increased FDG uptake. The list is extensive and is not limited to these entities.

Technical Artifacts:

Several technical artifacts can affect FDG-PET studies. These may be due to patient related factors or instrumentation. The most common artifacts are due to patient motion, especially in PET/CT studies. Although the patient remains on the same gantry during the PET and CT acquisitions for a PET/CT study, the PET and CT acquisitions are sequential, not simultaneous. Hence very small movement (especially in the head and neck region) may occur between emission and transmission scans [Figure 17]. Another common artifact is due to respiratory motion. Since the CT acquisition is quite rapid (in a few seconds), it is usually acquired during mid-tidal breath holding or shallow respiration. However, the PET acquisition for the same region requires several minutes and results in volume averaging. Hence, frequently, there is mis-registration in the lungs (most pronounced in the lung bases and the hepatic dome) between the PET and CT images [Figure 18]. Other motion artifacts can result from arm motion, coughing, shifting and the like during image acquisition.

Artifacts at injection sites are also relatively common. They usually are a result of infiltration of a portion of the injected



Figure 17: MIP image showing motion artifact (arrows) in the head and neck region (arrow) due to patient head motion between the PET and CT images. Similar artifact can also occur due to head motion between the emission and transmission scans or during the emission scan

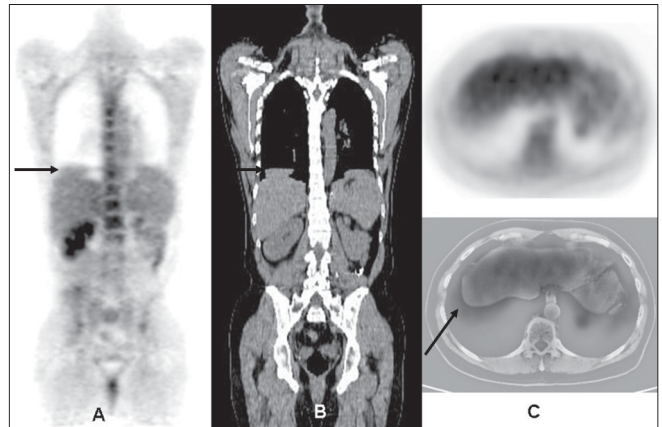


Figure 18 (A-C): Coronal PET (A), CT (B) images and transaxial PET (upper C) and fused PET/CT image (lower C) at the hepatic dome showing misregistration (arrows) due to the inherent respiratory motion artifact in PET/CT studies

dose and are easy to discern. Not infrequently, this causes increased uptake in the lymph nodes draining that site (e.g. right axillary nodes with right wrist or antecubital injection with infiltration). Hence, in patients with breast cancer, usually the opposite extremity (left extremity in case of right breast cancer) or even the foot is utilized for FDG administration. This is one of the reasons we prefer to inject using a known freely flowing IV.

In addition, incidental "hot" spots may be seen with surface contamination of patient clothing or skin or IV or other tubing, IV leaks and urine "drips", usually in the perineal area. As mentioned earlier, intense radioactive urine in the urinary bladder also may cause a "cold" artifactual defect around it.

Dense structures (dental work, pacemaker hardware, dense barium contrast and pooled intravenous contrast

for CT scans) may also cause artifactual areas of increased FDG activity. Metal objects like prostheses and metal rods generally appear as “cold” areas. An atlas article of iatrogenic artifacts on whole body FDG-PET imaging by Bhargava *et al*^[55] is suggested for further reading.

“Quantitation” of FDG Concentration - the Concept of SUV

As implied earlier, one of the potential strengths of PET, is that absolute metabolic rates for various PET tracers can be derived from PET imaging. This remains largely a research endeavor, not often used clinically. Nonetheless, semi-quantitative measures of local FDG uptake have been developed and are utilized in differentiating benign from malignant lesions (malignant lesions in general having greater uptake) for determination of prognosis (more intensely labeled tumors generally behaving more aggressively) and for assessing response to therapy on successive FDG-PET scans, in a manner, more objective than visual assessment alone. SUV or Standardized Uptake Value is the most commonly used semi-quantitative parameter utilized for analyzing FDG-PET images in routine clinical practice. It is also referred to as Standardized Uptake Ratio (SUR) and it gives a measure of activity in a defined region of interest (ROI) normalized to the patient's body weight and administered dose. Being a ratio, it is unit less and is calculated by the formula: $SUV = (\text{measured activity in ROI}) / (\text{injected dose per body weight})$. Although some physicians prefer to utilize SUV extensively in their interpretations, it is affected by several factors having little to do with specifics of tumor FDG uptake, such as patient body mass and body composition, dose extravasation, attenuation parameters (CT attenuation correction *v/s* transmission attenuation correction), reconstruction parameters, partial volume effects, BSL, time of SUV measurement and others.^[56,57] Hence caution is recommended when comparing SUV in two studies even for the same patient in the same imaging center. Moreover, the initial view that SUV of malignant lesions is higher than non-malignant lesions with a cut-off value of 2.5 has largely been proven to be an oversimplification. Although active malignant lesions tend to be significantly more intense than benign lesions, there is a significant overlap and certain low grade and well-differentiated neoplasms (e.g. well differentiated adenocarcinoma in lungs) may show only mild FDG uptake ($SUV < 2$) and certain inflammatory lesions (e.g. sarcoidosis) may show quite intense FDG activity ($SUV > 5$). Due to its several limitations, it is sometimes referred to as “silly useless value”.^[58] Hence for most routine clinical purposes, visual analysis of PET images is sufficient for clinical interpretation and routine use of SUV is not practiced by many centers (including ours). SUV does provide an objective parameter for image analysis and is routinely used for research purposes. SUV is also believed to carry prognostic information in many tumors, especially lymphoma.^[59] It should be pointed out that visual

assessment of relative uptake in a tumor focus may be as effective as actual calculation of SUV.^[60]

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