Pitfalls in PET/CT imaging

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Abstract. PET with 2-[fluorine 18] fluoro-2-deoxy-d-glucose (FDG), has been a clinical tool for the evaluation of various cancers providing valuable metabolic information clinically helpful in the diagnosis, initial staging, therapy monitoring and restaging. However, FDG is not specific for neoplastic processes. Unless anatomic correlation is available to delineate normal structures, pathologic sites of FDG accumulation can easily be confused with normal physiological uptake, leading to false-positive or false-negative findings. Co-registration of PET scans (functional and morphologic information) with computed tomographic (CT) scans (anatomic information) using a combined PET-CT scanner improves the overall sensitivity and specificity of information provided by PET or CT alone. In this paper, we discuss the probable causes of false negative images and pitfalls due to technical reasons, inflammatory processes or benign lesions as well as the utility of PET-CT in differentiating malignant from inflammatory and benign processes, since in some cases such differentiation cannot be made, with certainty, using FDG PET alone.

1. Introduction

Since the middle of 1995 Positron Emission Tomography (PET) with 2-[fluorine 18] fluoro-2-deoxy-d-glucose (FDG), has been a clinical tool for the evaluation of various cancers providing valuable metabolic information clinically helpful in the diagnosis, initial staging, therapy monitoring and restaging. FDG uptake and accumulation in neoplastic tissues is due to the fact that the vast majority of malignant cancer phenotypes exhibit an increased glycolytic rate (Warburg effect) [1]. This is because malignant cells have substantially enhanced glucose transporters on their surface (primarily GLUT-1), and express high levels of hexokinase and low levels of glucose-6 phosphatase, as a result of which FDG accumulates in these cells. Well recognized advantages of FDG-PET over anatomic based cross-sectional imaging modalities such as computed tomography (CT) and conventional (T1- and T2-weighted) magnetic resonance imaging is the high sensitivity due to its high lesion to background contrast and its ability to detect metabolic changes that may occur well before gross structural or contrast enhancement changes become visible [1-2].

FDG is not specific for neoplastic processes; it accumulates physiologically in various normal organs, including the brain, muscles, salivary glands, myocardium, gastrointestinal tract, urinary tract, brown adipose tissue, thyroid gland, and gonadal tissues. It is also taken up by different inflammatory as well as benign lesions. Unless anatomic correlation is available to delineate normal structures, pathologic sites of FDG accumulation can easily be confused with normal physiological uptake, leading to false-positive or false-negative findings. This is an important shortcoming in the determination of active disease sites, particularly for small lesions and lesions located near sites of physiological uptake. Coregistration of PET scans (functional and morphologic information) with
computed tomographic (CT) scans (anatomic information) using a combined PET-CT scanner improves the overall sensitivity and specificity of information provided by PET or CT alone [3, 4]. The unique advantage of PET-CT fusion imaging is the ability to correlate findings from two complementary imaging modalities in a comprehensive examination. Hence, PET-CT provides more precise anatomic definition for both the physiologic and pathologic uptake seen with FDG PET. Conversely, equivocal CT findings can be better evaluated with the help of the additional functional information provided by FDG PET.

In this paper, we discuss the probable causes of false negative images and pitfalls due to technical reasons, inflammatory processes or benign lesions as well as the utility of PET-CT in differentiating malignant from inflammatory and benign processes, since in some cases such differentiation cannot be made, with certainty, using FDG PET alone.

2. Discussion
2.1. Normal physiological FDG distribution
As a general rule, physiological FDG uptake follows the distribution pattern of glucose-metabolizing cells and organs. FDG shows avid physiological accumulation in the brain, because brain satisfies its high energy demand almost entirely with glucose, regardless of the substrate provided. This leads to a suboptimal contrast resolution for brain PET, which is inadequate for the detection of small lesions and low-grade tumors.

In the head-neck region, there are various structures showing normal increased FDG uptake. The salivary glands (parotids, submandibular and sublingual glands) may show moderate or intense activity. Lymphoid tissue in the Waldeyer ring (palatine and lingual tonsils) often shows increased activity, especially in kids, with peak at 6-7 years of age. Talking or crying during the uptake phase may induce FDG accumulation in the tongue, vocal cords and arytenoid muscles. Chewing gum or jaw movements may cause uptake within muscles of mastication. A symmetrical or almost symmetrical uptake pattern in head-neck structures is usually within normality [5].

Essentially, muscular FDG uptake is low when the muscles are at rest; however intense muscular activity prior to the study or during the uptake phase may induce increased uptake. A pattern of diffuse muscular FDG uptake may be encountered as a result of hyperglycemia. Increased blood glucose has a deleterious effect on PET imaging for 2 reasons: (a) excessive “cold” glucose competes with “hot” FDG and may saturate glucose transporters of malignant cells, (b) hyperglycemia triggers high levels of insulin, which shunts FDG into skeletal muscles, hence compromising the quality and sensitivity of the scan. A heavy meal before the scan may induce the same response: increase insulin levels and FDG uptake in the skeletal muscles [6]. To prevent such an effect, specific attendance should be given in fasting instructions and a priori adequate glucose control in diabetics.

Brown fat FDG uptake is a frequent pitfall of PET-CT imaging. Brown fat is a thermogenic tissue, with activation and increased consumption of glucose and, consequently, FDG as a response to acute cold. In such cases, there is a symmetrical pattern in cervical, supraclavicular, axillary, paraspinal and perirenal regions, corresponding to areas of fat attenuation on CT [7].

Myocardial FDG activity is quite variable ranging from non-discernible to intense, throughout the left ventricle. Uptake depends on fasting state, substrate availability and insulin levels: in a fasted patient with low level of insulin, myocardium uses fatty acids, not glucose, as primary energy source. FDG shows normal homogeneous uptake in the liver. In the gastrointestinal tract, physiological uptake is highly variable in distribution and intensity. Usually, diffuse colonic uptake is normal, whereas focal uptake should be further investigated with colonoscopy to exclude malignancy [8]. Metformin medication is associated with a diffuse intense bowel uptake pattern.

FDG is excreted in the urine, without being reabsorbed in renal tubules. Thus, any part of the urinary tract may show increased FDG activity. Dilated ureters, bladder diverticulae, surgical urinary diversions (ileal conduits) or any other cause of retained activity may be confused with a lesion. Intense urinary bladder activity may obscure a true lesion in adjacent nodes or organs including uterus, ovaries and prostate. Good hydration and voiding before the scan can help minimize this effect [8].
Finally, FDG uptake in the genital tract should be interpreted in the context of menstrual status. In premenopausal women, normal focal FDG uptake is often identified in the ovaries during the midcycle periovulatory phase. Normal endometrial uptake may occur in the menstrual flow phase or less frequently the ovulating phase.

2.2. False negative findings

Despite the high sensitivity of FDG PET/CT, there are false negative results due to different causes like tumor biology, small tumor size under the system resolution, improper patient preparation or recent chemotherapy.

The vast majority of malignant tumors are FDG avid. Aggressive tumors tend to have higher levels of FDG uptake while less aggressive tumors tend to have lower levels of FDG uptake [9-10]. This dimension of diagnostic information provided by FDG-PET is very important because it can be used to improve determination of disease prognosis and treatment planning [11]. Variables that influence FDG uptake are tumor Ki67 index, grade of differentiation, low malignant tumor cell density within the tumor mass or presence of large mucinous components, type of glucose transporters on the cell membrane and, levels and activity of glucose-6-phosphatase enzyme in the cell. Neoplasms that are frequently not hypermetabolic and thus not FDG avid, leading to false-negative results, include certain renal cell cancers and lymphomas, hepatocellular carcinomas, cholangiocarcinomas, neuroendocrine tumors, colon mucinous adenoacarcinomas, prostate carcinomas, and carcinoid tumors.

Five functional mammalian facilitated hexose transporters (GLUTs) have been characterized by molecular cloning. By functional expression in heterologous systems, their specificity and affinity for different hexoses have been defined. There are three high-affinity transporters (GLUT-1, GLUT-3 and GLUT-4) and one low-affinity transporter (GLUT-2). GLUT-5 is primarily a fructose carrier. Because their Michaelis constants (Km) are below the normal blood glucose concentration, the high-affinity transporters function at rates close to maximal velocity. Thus, their level of cell surface expression greatly influences the rate of glucose uptake into the cells. In contrast, the rate of glucose uptake by GLUT-2 (Km = 17 mM) increases in parallel with the rise in blood glucose over the physiological concentration range. High-affinity transporters are found in almost every tissue, but their expression is higher in cells with high glycolytic activity. Glut-2, however, is found in tissues carrying large glucose fluxes, such as intestine, kidney, and liver. As an adaptive response to variations in metabolic conditions, the expression of these transporters is regulated by glucose and different hormones. Thus, because of their specific characteristics and regulated expression, the facilitated glucose transporters control fundamental aspects of glucose homeostasis [12].

Malignant cells have generally high-affinity transporters on the cell membrane. There are several tumors, however, like Hepatocellular Carcinoma (HCC) where GLUT 2 and GLUT5 transporters predominate. As a result, these tumors have low FDG uptake. Another cause of minimal or absent FDG uptake by HCC is the high level of glucose-6-phosphatase in liver tissue leads to the release of FDG-6-phosphate. Thus, 18F-FDG PET has an average false-negative rate of 40% to 50% for the detection of HCC [13], and data on the role of PET/CT in the detection of HCC metastasis are limited [14-15]. Nevertheless, it has been shown that the overall survival of patients with HCC but with negative or partially positive 18F-FDG findings is lower than that of patients with positive 18F-FDG findings.

In prostate cancer, the absence of FDG uptake is connected to a low Gleason score and to levels of Prostate Specific Antigen (PSA), and reflects less aggressive tumor behaviour [11]. Lymphomas are generally FDG avid tumors and consist the main indication for the prescription of an FDG PET/CT examination. There are, however, some indolent lymphomas, especially, the malt extranodal and the marginal zone splenic subtypes with low or even absent uptake. This is important to know as patients having such a histological lymphoma subtype can not be surveyed by FDG PET/CT. In aggressive lymphomas, however, FDG uptake may serve as a marker of disease aggressiveness. Maroun et al [16] have evaluated the association of the SUVmax of the ‘hottest focus’ with overall survival (OS) and failure-free survival (FFS) in patients with aggressive mantle lymphoma. They have shown that both
the OS and FFS for patients with SUVmax greater than 5 were significantly decreased (p < 0.01 and < 0.001, respectively) as compared with the patients with SUV ≤ 5.

18F-FDG PET might be of value for neuroendocrine tumors with a high proliferation index, whereas the diagnostic sensitivity seems to be low for tumors with a low proliferation index, slow growth rate, and low glucose consumption [17].

FDG PET is at least as sensitive as bone scintigraphy in detecting the majority of skeletal metastases. It has higher sensitivity than 99mTc MDP scintigraphy in lytic metastases - especially of lung cancer - but may be less sensitive in predominantly sclerotic lesions [18].

Small tumor size is another cause of a false negative result for two reasons: firstly, in the case of hypermetabolic but small lesions adjacent to normal structures with high FDG uptake (brain, heart, kidneys) and, secondly, because of the partial volume effect. Partial volume effect provokes false negative images of tumors that are smaller than two times the spatial resolution of the scanner, especially in a milieu of low FDG uptake (i.e. lung) [19].

Chemotherapeutic agents may reduce FDG uptake by altering the glucose metabolism of tumor cells. It has been shown that there is 40% decrease in tumor cell hexokinase activity in tumors resected from patients who had undergone recent chemotherapy [20]. For this reason, it is important not to perform a PET/CT in less than ten days after chemotherapy. Interim studies must be carried out near the next therapeutic schema, if possible just the day before.

2.3. False positive findings
Despite the high sensitivity of FDG PET in malignancies, one of the inherent pitfalls of metabolic imaging has been the relatively low specificity with false-positive results due to increased FDG uptake in normal organs, inflammatory conditions, and benign processes, findings that can complicate image assessment.

FDG is not a cancer specific radiopharmaceutical. It accumulates physiologically in various normal organs, including the brain, heart, gastrointestinal tract, urinary tract, brown fat, and gonadal tissues, as well as in benign conditions such as infectious and inflammatory lesions and several benign tumors. False-positive FDG uptake can occur with PET-CT due to granulomatous disease, abscess, postsurgical changes, post-radiotherapy, foreign body reaction, inflammation (e.g., in diverticulitis, gastritis, or arteriosclerosis) or technical artefacts.

2.4. Technical artefacts
The artefacts most commonly seen on PET/CT images are due to attenuation correction, respiratory motion, and truncation. These artefacts occur because the CT scan is used instead of a PET transmission scan for attenuation correction of the PET data.

Attenuation correction refers to manipulation of the PET data to produce an image that takes into account the greater attenuation of photons that arise from deeper structures in the body or pass through highly attenuating structures such as bone on their route to the detector. It is generally achieved by applying an attenuation map to the PET data, derived from the CT image (after correction for the different photon energies used in both modalities). Attenuation correction artefacts can occur where there are highly attenuating objects in the path of the CT beam, such as dental fillings, hip prostheses, metallic stents, chemotherapy ports and high-density drainage tubes, and contrast-enhanced vessels. The CT-derived attenuation map corrects (or overcorrects) photopenic areas adjacent to high-attenuation structures at CT and makes them appear hypermetabolic on the attenuation-corrected PET images. Non-attenuated PET images, which do not manifest this error, can be used in these cases to aid the interpretation of these artefacts [21].

Respiratory motion during scanning causes the most prevalent artefact in PET-CT imaging. Because of the long acquisition time of a PET scan, it is acquired while the patient is freely breathing. The final image is hence an average of many breathing cycles. On the other hand, a CT scan is usually acquired during a specific stage of the breathing cycle. This difference in respiratory motion between PET scans and CT scans can cause misregistration on PET-CT images. This affects structures close to
the diaphragm (i.e. lung nodules). In clinical practice, it most often causes difficulties in differentiating activity in the liver and adjacent structure [22].

Truncation artefacts are frequently seen in large patients or patients scanned with arms down, such as in the case of melanoma and head and neck indications. When a patient extends beyond the CT field of view, the extended part of the anatomy is truncated and consequently is not represented in the reconstructed CT image. This, in turn, results in no attenuation correction values for the corresponding region in the PET emission data, hence introducing a bias on the PET attenuation-corrected images that underestimates the standardized uptake values in these regions. Truncation also produces streaking artefacts at the edge of the CT image, resulting in an overestimation of the attenuation coefficients used to correct the PET data. This increase in attenuation coefficients creates a rim of high activity at the truncation edge, potentially resulting in misinterpretation of the PET scan [22-23].

2.5. Infection-Inflammation

Monocytes, macrophages and lymphocytes have Glut3 transporters in intracellular vesicles, in normal state. During their activation, these transporters are translocated fused to the cell membrane. As a result, high FDG uptake is observed in a number of infectious and inflammatory conditions as infected or inflamed sites [24].

Active granulomatous processes (tuberculosis, sarcoidosis), active fibrotic lesions and other infectious conditions (abscesses, pneumonia, sinusitis, gastritis, esophagitis, diverticulitis, appendicitis) are common causes of false positive images. Inflammatory changes from recent surgery may be FDG avid for a time longer than eight weeks while post radiation inflammation may last more than six months [25].

Degenerative or inflammatory joint disease can also give rise to elevated FDG uptake. Osteophytes can demonstrate FDG uptake, which depends on the degree of metabolic activity. Although osteophytes can occur at any level of the vertebral column, those that are located anteriorly may be confused with the paravertebral lymph nodes unless the CT images are evaluated on bone window settings.

Healing bone is associated with elevated FDG uptake. Although the uptake in healing fractures is typically modest, it can be indistinguishable from small metastases. The origin of such uptake is unclear. Hematoma formation and the granulomatous tissue associated with resorption of the hematoma could account for the early phase of FDG uptake but the uptake observed weeks into the healing phase suggest that the procallus itself is associated with elevated glycolytic metabolism [26].

2.6. Benign tumors

Several benign tumors may also demonstrate moderate or even high FDG uptake. Such tumors are follicular thyroid adenomas, adrenal adenomas, uterine fibromas, Schwannomas, adenomatous polyps etc [27]. In such cases, the distinction between benign and malignant lesion may be impossible if CT image is not typical.

3. Conclusions

PET-CT using FDG is a very useful modality for cancer imaging. Combined PET-CT imaging permits easier recognition of normal variants and better localization and characterization of miscellaneous findings. Although the addition of anatomic CT information does aid in the interpretation of PET, artefacts can be introduced as a result of the dual-modality nature of the examination. To optimise interpretation, PET-CT images should be acquired after proper patient preparation and right quality control system, reviewed with the help of non-attenuation-corrected images, using all other available imaging and knowledge of the patient’s history and system technical parameters.

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