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18FDG PET/CT: A Sensitive Tool That Needs Better Users' Understanding

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EDITORIAL

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Positron imaging tomography (PET) is the most powerful functional imaging having very high sensitivity and specificity depending upon the type of the radiolabelled probes used. Initially, it was considered as a research tool; however, over the last two decades it has become a clinical need. In early 2000, it was further strengthened by successful union with morphological computerised tomography (CT), which has resulted in improved diagnostic accuracy. Reasons for its popularity are the ability of PET to qualitatively study the perfusion, metabolism, and various receptors functions with absolute quantification as well. In PET imaging, we are detecting two photons of 511 keV moving at 180 degrees in opposite directions, produced as a result of annihilation of a positron with a free electron. Simultaneous detection of these photons by nuclear medicine detectors (scintillator or semiconductor materials) is the basis of the coincidence imaging (PET imaging). The number of true coincidence (photons of same annihilation events) ensures good count statistic, low noise, and good image resolution.

If we look over the evolution of imaging technology in medicine, in early 70s we used to have fuzzy and low resolution CT and PET images. However, over the last three decades there has been a tremendous development on technological frontiers resulting in today's high resolution CT and PET images, individually. In 2001, medical imaging was further strengthened by the arrival of first hybrid PET/CT scanner, which has revolutionised the oncology to a greater extent, and cardiology and neurology to a lesser extent.

The paraphernalia of a PET/CT facility include: (1) cyclotron which is used to produce short-lived positron emitting isotope like Carbon-11 having half-life of 20 minutes and Flourine-18 with half-life of 110 minutes; (2) radiochemistry unit which is used to label a chemical substrate or probe with the short-lived positron emitting isotope produced by the cyclotron; (3) an uptake room in which patient stays for 55-75 minutes in a calm and quiet manner after getting PET isotope injection; and (4) an imaging suite equipped with PET/CT scanner. Fluorodeoxyglucose (^{18}FDG) is the most commonly used radiolabelled probe because of the longer half-life of ^{18}F (110 minutes). Chemically, ^{18}FDG is similar to glucose except that at carbon-2 level, hydroxyl group is replaced with ^{18}F. ^{18}FDG competes with normal glucose and follows the same metabolic pathway except once it is phosphorylated inside the cell by hexokinase, it is not further metabolised and stays within the cell which enables *in vivo* imaging of ^{18}FDG avid tissue. Primary purpose of using ^{18}FDG (i.e. radiolabelled glucose) is that the most of malignant cells use glucose as the sentinel source of energy with overexpression of hexokinase and glucose transporters (GLUT). This process of aerobic glycolysis by tumor cell is called the Warburg effect.

Patient preparation is very important for PET/CT imaging as better ^{18}FDG uptake in tumor cell needs lower serum glucose and insulin levels at the time of its injection. Fasting for 4 - 6 hours for food is mandatory as hyperglycemia and hyperinsulinemia would result in enhanced localisation of ^{18}FDG in non-tumor sites like skeletal muscles. A fasting blood glucose (FBS) level less than 200 mg/dl is used as a cut-off by many laboratories; and procedure is rescheduled, if it is more than 200 mg. To achieve a FBS < 200 mg/dl is a real issue in diabetics with inadequate glycemic control. Good hydration is important as it ensures prompt wash-out of ^{18}FDG from kidneys because about 50 - 70% of the injected radioactivity is excreted through the kidneys within 1 hour after injection. Good hydration minimises radiation exposure to urinary bladder and improves image quality as well. The usual injected dose of ^{18}FDG is about 3 MBq/Kg (European recommendation focused towards low radiation exposure to patients) or 5 MBq/Kg (US practice). Once the ^{18}FDG is injected, patient stays in a calm and quiet manner in an uptake room to allow better uptake of radiolabelled glucose in glucose dependent tumor cells. After 55 to 75 minutes of uptake period, patient is asked to empty the urinary bladder and then the PET/CT imaging is started. First, a scout CT image is acquired for image planning, followed by a non-contrast enhanced CT (NCECT) examination from midbrain to midthigh in most of oncological cases as per

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recommendation of recent guidelines to minimise the radiation exposure and contrast associated morbidities, and also to avoid possible over-estimation of tumor FDG uptake by computer algorithm. After the NCEC, PET images are acquired which takes about 10 to 15 minutes depending upon length of patient and time per bed position required to cover the body. At the end of imaging, the computer reconstructs CT and PET images and during this process CT images are used for attenuation correction of the PET images, which is a mandatory step. CT images are also used for anatomical mapping of PET images which lacks anatomical information. Advantages of PET images include better lesion characterisation and detection; and with CT images, these have high diagnostic accuracy and clinical information.

In clinical practice, 90% of the PET/CT burden is related to oncology and 5% each for brain and cardiac imaging. Recently, ^{18}FDG PET/CT has also been used for evaluation of pyrexia of unknown origin (PUO). ^{18}FDG-based PET/CT provides a wide spectrum of indication in clinical oncology. It may be used for the differentiation between benign and malignant tumors (although not very popular) like evaluation of solitary pulmonary nodule. ^{18}FDG-based PET/CT is an important step in managing paradigm of various malignancies (more than 17 cancers as per National Comprehensive Cancer Network guidelines, NCCN). It has an established role in staging, restaging of non-small-cell lung cancer, lymphoma, head and neck, esophagus, colorectal and female genital cancers. Use of PET/CT in the diagnostic workup results in upstaging in about 20 - 40% cases (avoid under-treatment) and downstaging in 10% cases (avoid over-treatment, its cost and morbidity as well). ^{18}FDG-based PET/CT has also an established role in monitoring therapy response and can stratify the patients as responder and non-responder in the early phase of treatment. Therefore, treating oncologist can always change the therapy regime as per available information by a PET/CT exam. It also has a very strong prognostication value as a negative ^{18}FDG PET/CT study has a significantly high negative predictive value (NPV) for overall and disease-free survivals. However, positive predictive value (PPV) is relatively low because of false-positive results caused by ^{18}FDG uptake by non-malignant foci, like infection or inflammatory lesions. In recent days, the ^{18}FDG-based PET/CT has also entered into the radiation oncology suite due to promising results of radiation therapy planning using metabolic tumor volume (MTV) derived from ^{18}FDG PET images. In theranostics, the positron emitting isotope labelled peptide and monoclonal antibodies imaging with PET/CT have been used to select cases of metastatic neuroendocrine tumors which can be treated using same probe labelled with particle emitters (Alpha emitter as Radium-223 or Lutitium-177 as beta emitter).

A normal ^{18}FDG PET/CT shows uniform distribution of mild intensity of labelled glucose over mediastinum and liver with variable ^{18}FDG uptake over the myocardium, depending upon the preparation of the patient. Presence of tracer in kidneys and urinary bladder is a common finding; and hydration before and after the injection of the ^{18}FDG is recommended to have quick washout from the kidneys. Uptake of the ^{18}FDG in the bowel is not uncommon and more commonly seen in diabetic patients who have been on metformin for some unknown reasons. Abnormal focal ^{18}FDG deposit is considered when it is higher than the background activity (mediastinal or liver uptake); and reviewing with CT images of same level provides correct localisation and diagnostic input based on morphological abnormality (if present). While interpreting ^{18}FDG PET/CT images, the reader must be aware of the false-negative findings which are not unusual, indeed. Some well differentiated cancers like thyroid, prostate, renal, and NET are not ^{18}FDG avid. Lesions smaller than 8 mm are beyond the resolution of the current scanners and most importantly inadequate patient preparation must also be considered as an important cause of false-negative results. False-positive findings are seen with areas of physiological uptake like intraocular muscles, laryngeal activity, cardiac uptake, or some infective or inflammatory conditions which are not uncommon in patients with cancers. It is also not uncommon for the ^{18}FDG to be taken up by benign tumors like hepatic adenomas or ovarian follicles.

In addition to the qualitative analyses mentioned above, semi-quantitative parameters have also been introduced and considered as one of the major strengths of PET imaging. The most commonly used semiquantitative parameter in clinical practice is standardised uptake value (SUV). SUV is the ratio of the ^{18}FDG, in the region of interest, divided by the injected ^{18}FDG, divided by patient's weight. If it is assumed that the distribution of ^{18}FDG is uniform in the body and mass is equivalent to weight (gm = ml), then SUV is considered equal to 1. Various types of SUVs are being used like SUVmax, SUVmean and SUVpeak (depending upon ROI drawn). SUVmax is the most commonly used parameter worldwide due to its simplicity albeit lacks reproducibility. These SUVs are commonly used for response evaluation in patients receiving chemotherapy or radiation therapy. Based on differential SUV values between baseline and follow-up scans, various response evaluation criteria have been formulated. However, when comparing the SUV values of 2 PET/CT of a patient, reader must consider the confounding factors which could result in different values despite no significant change in tumor biology. These confounding factors include calibration of dose calibrator and PET/CT scanner, fasting blood glucose level, uptake time

between two studies, partial volume effect for small lesions, use of oral or intravenous contrast, size of the ROI, and reconstruction algorithm used for two studies. To make PET/CT more meaningful, standardisation of imaging protocols among imaging facilities worldwide is very important.

^{18}FDG-based PET/CT is the most commonly used hybrid imaging modality in oncology. It plays an important role in staging, restaging, response evaluation, and prognostication of various cancers. Judicious and rationale use of this tool with high diagnostic accuracy, ensures optimal selection of therapy and tailoring the therapy in non-responders in the early phase of treatment. SUV (SUVmax most commonly used) is a good semiquantitative metric which is extensively being used for response evaluation. However, one must not forget the impact of confounding factors upon these calculated values. To make PET/CT more meaningful, standardisation of imaging protocol among imaging facilities worldwide is very important.