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PET-CT: Emerging New Modality

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Abstract: Nuclear medicine is a specialty which uses radiopharmaceuticals to study function of different organs of the body. Some radioisotopes are very short lived and emit positrons. These are produced in a Cyclotron and imaged with a special camera combined with a CT scanner. The technique is then called PET or Positron Emission Tomography (PET-CT). This technique allows quantification of the various metabolic processes in the body. The PET isotopes of C^{11} , O^{15} , N^{13} , and F^{18} are used to label various compounds, drugs, receptor ligands, amino acids, peptides, proteins, and several other substances of interest in studying various aspects of body physiology and pathology. With PET-CT the physiological information from PET is fused with anatomical information of CT to get exact information of location of abnormal physiology. PET-CT finds application in Oncology for diagnosis, staging of tumors, detecting recurrence, measuring response to therapy and differentiating effects of radiation therapy, like edema and fibrosis from recurrent disease. In Neurology, PET is invaluable in differential diagnosis of dementias, helping to diagnose Alzheimer's disease versus fronto-temporal and other dementias, and patients with mild cognitive impairment, in movement disorders like Parkinson's disease and to localize seizure focus in refractory temporal lobe epilepsy before surgical ablation. In Cardiology, PET is the gold standard for determining myocardial viability in infarcted, dysfunctional myocardium. PET-CT is also useful in diagnosing cause in Pyrexia of Unknown Origin (PUO) where a focus of infection, inflammation or malignancy can be picked up in 40-50% of cases. PET-CT is a powerful new diagnostic modality whose time has come.

POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) is a unique imaging tool that can be used to visualize and measure many biologic processes in living subjects. Examples of biologic parameters successfully measured with PET include regional blood flow, rates of substrate use (e.g., glucose and oxygen) rates of protein synthesis, neurotransmitter synthesis, receptor binding and density, enzyme activity, and levels of gene expressions. PET imaging provides high resolution and high sensitivity and higher quality images than either planar nuclear imaging or SPECT. The PET/CT scanner, by combining two established modalities such as CT and PET, is an evolution in imaging technology. The two modalities are complementary, with CT images lacking the functional specificity of PET and PET images lacking the anatomic details seen on CT. Adequate anatomic alignment of both image sets permits convenient visualization of all information in one study.

Various positron emitters frequently used for positron emission tomography are C^{11} , N^{13} , O^{15} and F^{18} . Other less commonly used positron emitters include O^{14} , Cu^{64} , Cu^{62} , Rb^{82} , Ga^{68} and I^{124} . F^{18} , the most commonly used positron emitter, is substituted for hydrogen to produce radio labeled analogs.

Mechanism of ¹⁸F Labeled Fluorodeoxy Glucose (FDG)

Glucose is used by cells to produce adenosine triphosphate, the energy currency of the body, and the accumulation of FDG in cells is proportional to the metabolic rate for glucose. Because the energy demands of cells are altered in many disease states, FDG has been shown to be a sensitive marker for a range of clinically important conditions, including most cancers and their metastasis, neurodegenerative diseases, epilepsy and coronary artery disease.

Glucose is taken up by cells through glucose transporters (GLUT) expressed on cell surface. There are several types of GLUT. Once inside the cell, glucose is acted upon by Hexokinase and Glucose-6-phosphate is formed. This enters further metabolic cycle to generate ATP in the cell. ¹⁸F-FDG enters the cell just like glucose and is converted by hexokinase to ¹⁸F-FDG-6-phosphate. This cannot be further metabolized and remains trapped in the cell, allowing imaging of its distribution and concentration. In malignant cells, the earliest change is over expression of GLUT on cell surface and increased activity of intracellular hexokinase. Thus FDG PET scans detect early malignancy with high sensitivity.

Indications of PET Scan

- Oncology: in detection of early disease
Grading the degree of malignancy
 - Staging
 - Differentiating residual tumor or recurrence from necrosis and surgical scarring
 - Occult primary
 - Suspicious malignancy
- Neurology: in early diagnosis of neurodegenerative diseases such as:
 - Alzheimer's, Parkinson's and Huntington's diseases
 - Detection of Epileptic foci
 - Psychiatric disorders
 - Neurodevelopmental disorders
 - Cerebrovascular diseases
 - Movement disorders.
- Cardiology: Assessment of myocardial viability
 - Noninvasive detection of coronary artery disease
 - Estimation of severity of CAD
- Pyrexia of unknown origin (PUO)
 - Occult source of infection.

Normal PET Scans

Patient undergoing PET scans should fast for a minimum of 4 hours to ensure low serum glucose and insulin levels to achieve maximum FDG uptake in lesions rather than skeletal muscle. Patients are encouraged to take plenty of plain water to facilitate tracer clearance from the blood pool and urinary tract.

Normal physiological FDG uptake is seen in brain, brown fat, liver, gut, kidneys, sometimes ureters, and urinary bladder. Myocardial uptake is variable. Any uptake more than background and liver uptake is considered to be positive for active disease (Figs 27.1 and 27.2).

Clinical Applications of PET in Oncology

PET has been found to assist in diagnosing, staging, monitoring response and assessing recurrence in patients with tumors. The exact role of PET depends on the tumor type, the clinical situation and sensitivity and specificity of FDG imaging. FDG PET may be used as a noninvasive and appropriate diagnostic tool for the evaluation of solitary pulmonary nodule to differentiate

benign from malignant lesions. PET/CT is more sensitive than other conventional imaging like CT or MRI in identifying involved but normal sized lymph nodes; changes stage and therefore management in up to 50% of patients with cancer. PET/CT can give accurate anatomical localization for radiotherapy planning in cases of lung cancers. PET may help in diagnosing unknown primary malignancy.

Whole body PET scan is a sensitive modality in identifying distant metastasis and it saves the need for performing a battery of test. It is cost effective and gives less radiation as compared to a series of CT scans.

In patients of Lymphoma PET/CT provides sensitivities and specificities of 90% and 100% respectively. It is proved to be superior to conventional imaging techniques for detecting extranodal disease involvement. PET has a role in the initial staging, restaging, to look for response to therapy and recurrence.

False-positive scans can be caused by inflammatory or infectious lesions and can be mistaken as malignant lesions. Delayed imaging can be helpful in such cases as malignant lesions will retain FDG uptake till delayed images. Standard uptake values (SUV) may be helpful.

Some tumors like bronchoalveolar carcinoma, MALT, renal cell carcinoma prostatic cancer and any mucinous carcinoma carcinoids or slow growing tumors are less FDG avid hence, may show false negative results. Metastasis from RCC, Ca Prostate can be picked up by PET scan. In case of Hepatocellular carcinoma up to 50% tumors show more FDG uptake than normal liver uptake.

PET Imaging of the Brain

Neurodegenerative diseases in which bio-chemical changes precede anatomic changes, PET helps in early diagnosis thus helping in implementing therapy earlier. The diagnosis of Alzheimer's disease was shown to have 93% accuracy 3 years before the clinical diagnosis of probable Alzheimer's disease could be established. PET images show hypometabolism in bilateral parietotemporal cortices in AD. Small radiolabeled molecules for use as biological markers of β -amyloid deposits in AD are being developed.

Combination of Ictal SPECT and Interictal PET along with MRI coregistration is the most sensitive technique to localize epileptic foci in cases of Temporal lobe epilepsy. PET is helpful in establishing prognosis and grading of brain tumors and helps in differentiating recurrence versus radiation necrosis. ^{15}O labeled water or carbon dioxide is used in evaluation of cerebral perfusion in cases of cerebrovascular diseases.

The ability to evaluate receptor changes in neurodegenerative diseases can help in designing new drugs and also serves as a method to adjust the dose of drugs according to patients needs. For example, in cases of Parkinson's disease, it is now possible to examine all aspects of Dopamine neurotransmission with the help of ^{18}F - Levodopa. Such measurements can help in differentiating various movement disorders. Application of PET in drug development and testing can significantly reduce both molecule-to-drug time and costs.

PET in Cardiac Diseases

A number of tracers have been used for the measurement of myocardial blood flow using PET, in particular ^{15}O -labeled water, ^{13}N - labeled ammonia, $^{82}\text{rubidium}$ and ^{11}C . Their use has been restricted in India because of short half life and cost and need of cyclotron near the PET setup ^{11}C labeled free fatty acids can be used to image myocardial metabolism. The utilization of exogenous glucose by the myocardium can be assessed using PET with ^{18}F -labeled FDG.

The identification of viable myocardium has become an area of interest for several reasons. Based on Perfusion-Metabolism mismatch assessment of myocardial viability can be done and decision of revascularization and prognosis after revascularization can be made. FDG PET

remains the **gold standard** for the assessment of myocardial viability through assessment of regional myocardial metabolism.

PET in PUO

An exciting new approach to the imaging of undiagnosed fever is FDG-PET. This arises from the fact that FDG is taken up in increased amounts by activated inflammatory cells. FDG appears as a promising agent for localizing inflammation like in synovitis, temporal arteritis, infected joint prosthesis and inflammatory bowel diseases, though not many comparisons have been made with leukocyte scan or other techniques. FDG accumulates in granulomatous lesions like tuberculosis and sarcoidosis. PET is found to be helpful in localizing the lesion in 20 to 30% cases of PUO.

Future Advances in PET

In the era of fusion imaging, combined PET/CT has become a useful tool to deliver information about anatomy and metabolism in a single study, there have been attempts made to develop a combined PET/MRI system. Research is going on to improve on spatial resolution to improve image quality further. Cardiac and Respiratory gating is used to avoid artifacts. Various new labeling agents are being developed to concentrate on molecular levels of diseases. β -amyloid imaging in Alzheimer's disease is an example of the progress in the research.

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