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Review Article

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Positron Emission Tomography: A paradigm in imaging sciences

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ABSTRACT

Positron emission tomography(PET) is a noninvasive, diagnostic nuclear imaging technique that produces three-dimensional images of functional processes of the body. PET uses unique isotopes especially of carbon, nitrogen, oxygen, fluorine, that are radioactive in nature, to study the various functional processes that are difficult to demonstrate by any other method. The amount of radioactive material required is very small and hence does not harm the system. The precise type of radioactive material and its delivery method depends on which organ or tissue is being studied by the PET scan. The radioactive material may be injected into a vein, inhaled or swallowed. More radioactive material accumulates in areas that have higher levels of chemical activity. This often corresponds to areas of disease and shows up as brighter spots on the PET scan. The most commonly used tracer is 18-fluorine coupled with glucose which is the main source of energy for living tissues. Active tissues within the body like tumors, inflammation can be visualized as it takes up more glucose than other tissues i.e. the concentrations of tracer imaged will indicate tissue metabolic activity by virtue of the regional glucose uptake.

Keywords: Cannihilation, coincidence, positron emission tomography (PET), radiopharmaceuticals, radiotracers.

INTRODUCTION

Conventional diagnostic imaging procedures study the anatomical or physiological features of the body or the alteration in the biochemistry of the injured tissue or cell via radiologic images. Apart from its ability to identify pathophysiology, which includes neurologic illnesses, such as dementias like Alzheimer's disease and movement disorders like Parkinson's disease, PET is also used to evaluate heart muscle function in patients with coronary artery disease and cardiomyopathy. PET is being used to study drug addiction, psychiatric illness and stroke. Because of the possibility to see and measure quantitatively physiological disorders in a nearly stage, before permanent morphological damage has occurred, which will only then be visible in x-ray or magnetic resonance computer tomography, PET is finally finding its way from a sophisticated research to routine clinical diagnosis [1].
The first medical application for the positron was reported by William H. Sweet at Massachusetts General Hospital (MGH) in 1951.This was a simple brain probe that utilized coincidence to localize brain tumors. Gordon L. Brownell along with William H. Sweet and the physics group at MGH developed and built the first brain probe using two opposing Sodium Iodide [NaI (Tl)] detectors. In the same year, Wrenn Good and Handler described and published studies of positron annihilation for localizing brain tumors in Science. In the early 1960's, Kuhl and Edwards were among the earliest pioneers to develop image reconstruction techniques for single photon tomography. However, the first PET scan of a human was reported in 1978 [2].

A combination of PET/CT scanner was introduced and marketed in the year 2000. Time magazine declared it as "invention of the year". PET/CT images provide valuable information that can be used for early diagnosis, more accurate tumor detection and precise localization, improved biopsy sampling and better assessment of patient responses to chemotherapy or radiation therapy. Hence it is also called as "SMART" Scanner [3].

Working principle

PET uses radiopharmaceuticals that contain positron- emitting radioisotopes. The emission occurs as positrons emerge from the decaying nuclei of radioactive isotopes specifically created in cyclotrons for use in radiopharmaceuticals. Positrons live short, violent lives. After a radiopharmaceutical is injected intravenously into a patient's bloodstream, it is distributed throughout the patient's body and accumulates in the organ or body system being examined where positrons (e+) or antimatter] are emitted and travel in the surrounding tissue dispersing kinetic energy until they encounter and collide with one of many nearby electrons (e-) or matter]. During the collision, the two particles combine and destroy each other in a process called as annihilation (**Figure 1**). The distance that a positron travels in the tissue before annihilation depends on the kinetic energy of the positron when it is emitted. The annihilation results in a burst of electromagnetic energy that is manifested in the discharge of two 511-keV gamma rays (according to Einstein's equation: E = mc2). The two gamma rays are discharged "coincidentally"180 degrees apart, and they travel outward in opposite directions from each other, forming a coincidence line. The coincidence line is an indicator that annihilation has occurred.

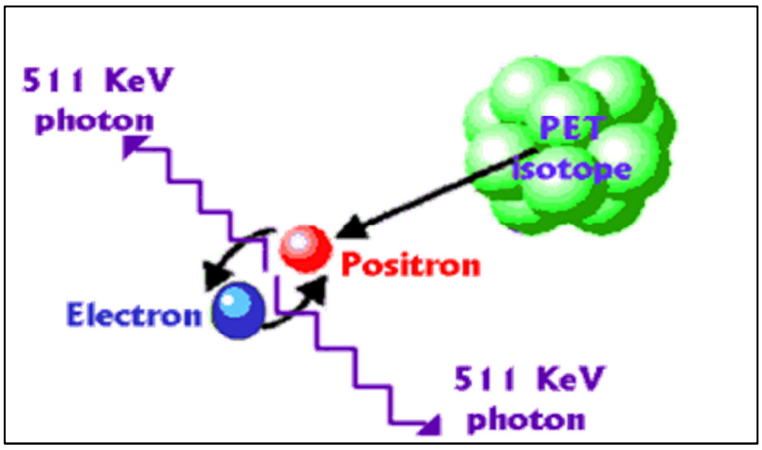


Figure 1: Collision between positron (e+) and electron (e-)

Two equal energy (511-keV) annihilation rays traveling in opposite directions, corresponding to equal-magnitude, opposite-sign (positive and negative) momentum are emitted. Only when signals from the two coincidence detectors simultaneously trigger the coincidence circuit the output, a "true coincidence event" is generated by this circuit. An event is counted only when each of the two 511-keV annihilation rays is detected simultaneously. A gamma ray is sensed by one of the scanner detectors, each of which is comprised of scintillation crystal and a photomultiplier tube or alternatively as a block detector that consists of rectangular bundle of crystals optically coupled to several photomultipliers. When the gamma ray interacts with the scintillation crystal, its energy is converted to a burst of light photons. The photons are detected and amplified by the photo-multiplier. The photomultiplier then generates an electronic signal and sends it to the electronics of the scanner. The scanner electronics record the electronic signals and determine which of the electronic signals are coincident. Coincidence is determined in this way. The electronics of the computer employs a timeframe or coincidence window. Based on that timeframe, if two coincident gamma rays are detected on opposite sides of the patient's body within nanoseconds of each other, the computer pairs and records them into coincident events, forming a coincidence line. A computer linked to the scanner reconstructs the coincident event information into images that portray the activity of the radiopharmaceutical in the patient's body. The image is reconstructed in this way. The PET scanner collects all coincident events and sorts them into a sonogram.

The sonogram is reconstructed with corrections by the computer to produce two-or three-dimensional images using algorithms. The image, which can be viewed in axial, sagittal, or coronal planes, depicts the localization and

concentration of the radiopharmaceutical within the organ or body system that was scanned. All commercially available PET scanners simultaneously acquire data for three-dimensional images, either by imaging the entire volume as a unit or by stacking adjacent two dimensional slices [4-7].

Procedure for PET scan [8]:

The PET scan procedure occurs in the following steps:

1. The radiopharmaceutical is synthesized from a cyclotron-produced, positron-emitting radioisotope onsite or it is transported from an off-site location to the imaging site.
2. The PET technologist administers the radiopharmaceutical to the patient vial V and allows time for its distribution throughout the body.
3. As the patient moves slowly through the scanner on a scanning bed, the radiopharmaceuticals emitting positrons (e+) collide with patient's electrons (e-).
4. As the collisions occur, annihilation and the discharge of gamma rays follow and detectors in the PET scanner detect gamma rays outside the patient's body. The scanner electronics determine which of the gamma rays are coincident and pairs them into coincident events.
5. A computer linked to the scanner constructs, from the coincident event information, images that portray the activity of the radiopharmaceutical in the patient's body.
6. A radiologist analyzes and interprets the images and sends the resulting information to the physician who ordered the PET study.

Patient preparation for PET scan

1. For a period of 6 hours prior to the PET-CT appointment, the patient may have nothing to eat or drink except plain water. This will insure that the scan is as accurate as possible.
2. Regularly scheduled medications may be taken as needed, if they can be tolerated on an empty stomach.
3. Patients, who have diabetes or have claustrophobia, should inform before coming in for the appointment. Special instructions will be provided for the scan.
4. Warm and comfortable clothing should be worn for the scan.
5. The patient waits for 40 to 60minutes with instructions to remain calm and quietly seated during this waiting period.
6. Patients should not exercise on the day prior to the PET-CT scan or on the day of the PET-CT scan.
7. Inject 18F-FDG (10 to 15 mCi or 370 to 555MBq in a shielded syringe) into the patient through the IV catheter. If the patient weighs over 250 lbs, the physician authorizes a dosage of 18F-FDG higher than the normal dosage.
8. Remove all metallic items such as belts, dentures, jewelry, bracelets, hearing aids etc. from the patient.
9. For melanoma patients, injection must not be administered to the affected extremity. Injection should be made away from the affected area [9].
10. For diabetic patients, if the glucose level in the bloodstream is higher, then the radiotracer will be taken up preferably by the bloodstream instead of the cancer cells. Also if insulin is high, it encourages normal tissues and organs to take up glucose and thereby will not effectively determine the cancer cells. So the appointment will be in the middle of the day after having a light breakfast at around 6 am and having prescribed medication after the early breakfast [10].
11. If you are pregnant or suspect that you may be pregnant, you should notify your health care provider due to the risk of injury to the fetus from a PET scan. If you are lactating, or breastfeeding, you should notify your health care provider due to the risk of contaminating breast milk with the radionuclide [11].

Radiotracers used in PET scan

Radionuclides used in PET scanning are typically radioisotopes with short half lives such as carbon-11(~20 min), nitrogen-13(~10 min), oxygen-15(~2 min), fluorine-18(~110 min), rubidium-82(~1.27min). These radionuclides are incorporated either into compounds normally used by the body such as glucose (or glucose analogues), water, or ammonia, or into molecules that bind to receptors or other sites of drug action. Such labeled compounds are known as radiotracers. PET technology can be used to trace the biologic pathway of any compound in living humans (and many other species as well), provided it can be radiolabeled with a PET isotope. FDG is a glucose analogue extensively used in oncology for staging, restaging and recently for the evaluation of tumor response to treatment [12]. Cancer cells demonstrate up regulation of glucose metabolism that is uptake of glucose or glucose-analogues, as deoxy- glucose is increased. Labeling deoxy-glucose with the positron emitting radionuclide ^{18}F to form ^{18}F-FDG, renders the cells detectable using PET. ^{18}F-FDG is transported into the cells by the same carrier as glucose, but at a much higher rate. Then it is phosphorylated to FDG-6- phosphate (FDG-6-P) by the action of hexokinase or

glucokinase [13]. This substance does not enter the standard metabolic pathways because of the presence of fluorine at the C-2 position of the ring instead of the hydroxyl group in glucose and can leave the cell only slowly by the action of glucose-6-phosphatase. So it is trapped and accumulated in the neoplastic cells. This 'metabolic trapping' of FDG-6-P forms the basis of the analysis of PET data.

Types of radiotracers used-

1. Radiotracers for amino acid synthesis

Protein synthesis is a fundamental prerequisite for tumor growth. There is an up regulation of protein metabolism and cell-mediated transport of amino acids in tumors. Radiotracers that can measure the increase in protein synthesis will have increased sensitivity and specificity as compared to FDG. ^{11}C-labeled methionine has been the most widely studied. Unlike with FDG, the normal brain parenchyma exhibits overall reduced uptake of ^{11}C methionine. The pituitary gland shows increased uptake. It has thus proven superior to FDG in the evaluation of brain tumors as its reduced uptake in healthy brain tissue results in enhanced contrast between the brain tumor and the surrounding normal parenchyma [14]. A semi quantitative estimate of the level of radiopharmaceutical uptake in a particular tissue can be made by calculating the standardized uptake value (SUV). It can differentiate timorous from non tumorous lesions with a high degree of sensitivity and specificity [15].

2 Radiotracers for lipid synthesis

^{11}C-and ^{18}F-labeled choline have been used in brain tumors. The basis for this is the increased transport and phosphorylation of choline in tumor cells, where it gets incorporated into the phospholipids of the cell membrane. It has been found useful for the differentiation of low-grade from high-grade gliomas, but not for distinguishing low-grade gliomas from nonmalignant lesions [16]. In a comparative study of FDG, ^{11}C methionine, and ^{11}C choline in 95 gliomas, ^{11}C methionine was found to be the most superior among the three [17].

3. Radiotracers for hypoxia

Adequate tumor vascularization is an important precondition to tumor growth. Inadequate vascularization would culminate in tumor hypoxia and eventual necrosis. Hypoxic tissue is inherently more resistant to chemotherapy or radiotherapy and this is often responsible for failure of chemo-radiotherapy and an overall poor response. Several *in vivo* PET tracers have been developed to assess tumor hypoxia [18] like fluoromisonidazole (FMISO) and 64/60 Cu (II)-diacetyl bis (N-4-methyl thio semicarbazone) (64/60 Cu-ATSM), which have a propensity to accumulate in hypoxic rather than normoxic cells [19] the most extensively used radiotracer for hypoxia is FMISO. Inclusion of FMISO imaging data provides information that is complementary to FDG PET data by correlating metabolic activity to tumor hypoxia. In a comparative study on glioblastomas, the biological aggressiveness assessed by serial MRI was seen to be linked with the hypoxic tumor burden assessed on FMISO PET [20]. This aids the selection of alternative treatments and monitoring of their therapeutic efficacy.

4. Radiotracers for Deoxyribonucleic acid synthesis

DNA synthesis is an important prerequisite for cellular proliferation. The most widely used radiotracer for assessing DNA synthesis is 3-deoxy-3-[18F] flurothymidine (FLT). This compound gets phosphorylated by thymidine kinase, which shows markedly increased activity in proliferating tumors, and thereafter gets trapped within the cell. The imaging of cellular proliferation has a potential advantage over glucose imaging because FLT is specific to tumors, while high levels of energy metabolism are also seen with other processes including inflammation [21]. Thus, unlike FDG it does not show uptake into inflammatory cells and has been widely used to distinguish benign from malignant pulmonary lesions. Although this differentiation may not always be feasible, the possibility of using FLT for monitoring treatment with cytostatic anticancer drugs needs to be explored [22]. Like ^{11}C methionine, the background uptake in normal brain parenchyma is low, thus enhancing tumor detection.

Applications of PET

The various applications of PET are highlighted in **Table 1** below.

Table 1: Applications of PET

Area of application	Uses
Oncology [23]	➢ PET is a useful technique in staging and re-staging malignant tumors ➢ Can be helpful to increase accuracy in differentiating malignant from benign tumors, as in solitary pulmonary nodules. ➢ Helps to locate the best site for biopsy of a suspected tumor. ➢ Helps to define the tumour target in radiotherapy ➢ Is useful in monitoring the effects of therapy(either radiation or chemotherapy or both) ➢ Is able to detect the sites of recurrent disease and differentiate it from radiation tissue necrosis
Cardiology [24]	➢ PET can be used to assess the extent of cardiovascular disease, especially coronary artery disease (CAD), and is particularly centered on the detection of viable myocardium. ➢ PET helps in identifying patients who are likely to benefit from heart bypass surgery
Neurology [25]	➢ PET is useful in diagnosis, planning treatment and predicting outcomes in various neurological diseases.

Applications of PET in pharmaceutical sciences

1. Determination of physiological functions of the body:

PET was undertaken to study Dopamine D_2 and Serotonin 5-HT_2 Receptor Occupancy in patients with schizophrenia treated with therapeutic doses of Ziprasidone [26]. Ziprasidone is an atypical antipsychotic drug that shows a higher affinity for serotonin 5-HT_2 receptors compared with dopamine D_2 receptors in vitro. The affinity of Ziprasidone for these receptors *in vivo* in patients was examined. The authors conducted a PET study to evaluate D_2 occupancy (using ^{11}C raclopride) and 5-HT_2 occupancy (using ^{18}F setoperone) in brain regions of interest in 16 patients with schizophrenia or schizoaffective disorder randomly assigned to receive 40, 80, 120, or 160 mg/day of ziprasidone, which reflected the recommended dose range. PET scanning was done after 3weeks of administration and at trough plasma levels, i.e., 12–16 hours after the last dose. The mean 5-HT_2 receptor occupancy was significantly higher than the mean D_2 receptor occupancy (mean = 76%, SD = 15% and mean = 56%, SD = 18% respectively). The estimated plasma Ziprasidone concentration associated with 50% maximal $5HT_2$ receptor occupancy was almost four times lower than that for D_2 receptor occupancy.

2. PET micro dosing to study pharmacodynamic responses and pathophysiology of neurological diseases:

PET micro dosing can also be used to measure a drug's effect on important pharmacodynamic responses in the brain. For example, the binding of ^{11}C Raclopride to the dopamine D_2 receptor has been shown to be sensitive to the release of endogenous dopamine in the brains of monkeys or humans after dosing with amphetamine or nicotine. These PET imaging tools can thus provide proof of mechanism by the assessment of a PD response in the primate brain [27].

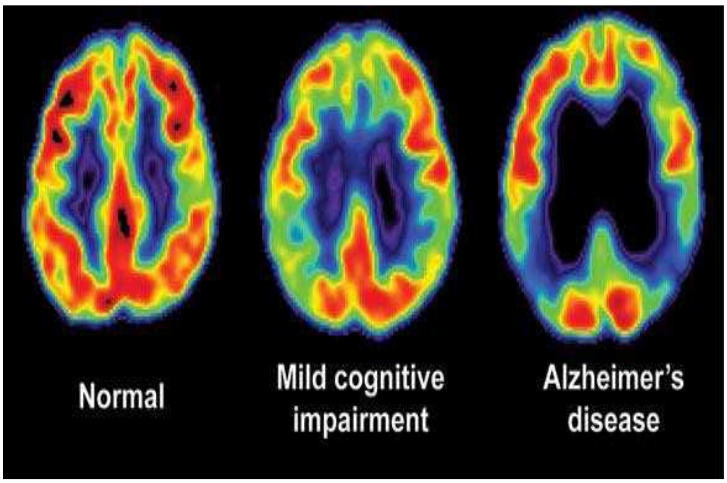
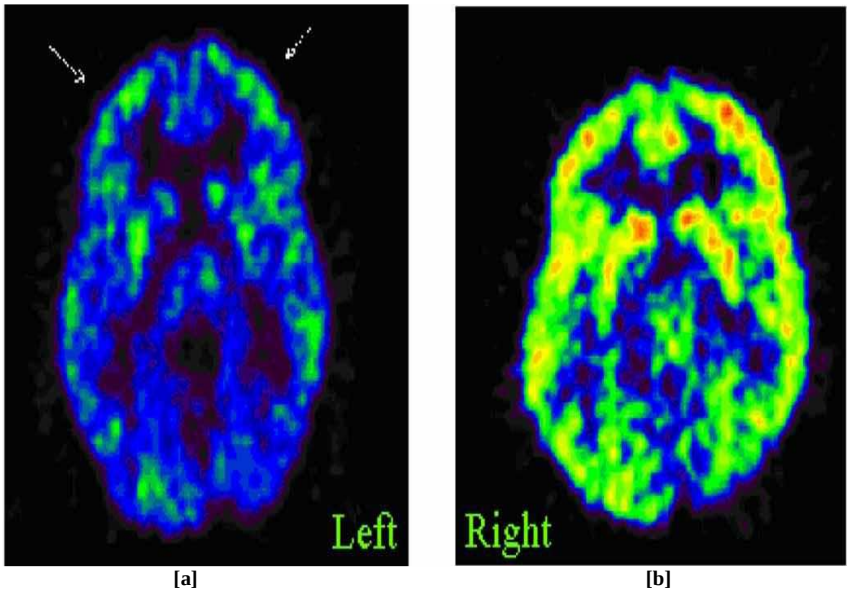


Figure 2: PET scan image showing occurrence of Alzheimer's disease

In recent years, there has been an increasing interest in the development of PET radiotracers as biomarkers for disease pathology in various neurological diseases. Particular progress has been made in the development of amyloidplaque binding PET tracers for Alzheimer's disease. Such approaches offer a plethora of opportunities for further understanding of the pathophysiology, early diagnosis of Alzheimer's disease as well as stratification of

patients. Importantly, the technology is non-invasive and allows for longitudinal studies to follow disease progression and monitor treatment responses in patients [28]. **Figure 2** and **Figure 3** depict PET scan images for Alzheimer's disease and depression respectively.



[a] **[b]**

Figure 3: PET-FDG scans demonstrating a comparison between a control patient with no depression [a] and a clinically depressed patient [b]. The blue color represents less activity (glucose metabolism) while the green represents more activity (glucose metabolism).

Drawbacks of PET

1. Allergic reactions to radiopharmaceuticals may occur but are extremely rare and are usually mild. Nevertheless, you should inform the nuclear medicine personnel of any allergies you may have or other problems that may have occurred during a previous nuclear medicine exam.
2. Injection of the radiotracer may cause slight pain and redness which should rapidly resolve.
3. Women should always inform their physician or radiology technologist if there is any possibility that they are pregnant or if they are breast feeding.
4. It is time consuming. It can take hours to days for the radiotracer to accumulate in the part of the body understudy and imaging may take up to several hours to perform.
5. Test results of diabetic patients or patients who have eaten within a few hours prior to the examination can be adversely affected because of altered blood sugar or blood insulin levels.
6. Because the radioactive substance decays quickly and is effective for only a short period of time, it is important for the patient to be on time for the appointment and to receive the radioactive material at the scheduled time. Thus, late arrival for an appointment may require rescheduling the procedure for another day.
7. The technique is comparatively expensive since cyclotron needs to be present at the site for the manufacture of radiotracer which has a short decay time.

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