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RESEARCH ARTICLE

A REVIEW AND UPDATE ON POSITRON EMISSION TOMOGRAPHY

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ABSTRACT

Since the inception of positron emission tomography many decades ago, this imaging modality has grown appreciably as one of the most valued imageology in both health and disease. Once upon a time PET had mere 20 detector elements, 2cm axial field of view and spatial resolution of approximately 25mm.Last couple of years witnessed its metamorphosis into 25000 detectors, 20cm field of view and 5mm spatial resolution. As a result, clinical applications of P*Et al*so grew tremendously. The current articles reviews the early days of PET, radioisotopes, radiopharmaceuticals used, principal basis of PET and clinical applications.

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INTRODUCTION

Positron emission tomography (PET) is a scientific tool used for probing biochemical processes. Owing to the researches in the field of instrumentation and synthetic chemistry, PET has grown by multiple leaps and is one of the most valued and accurate tool for clinical assessment of biochemical processes especially in oncology (Nutt, 2002). It is a non-invasive and quantitative method for measuring altered biochemical and metabolic levels. Moreover, its wide range of application, versatility and high sensitivity make it a powerful molecular imaging modality (Nutt, 2002; Mushtaq, 2012).

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Early days of PET

Last century witnessed the birth and growth of PET. The credit for initial steps ever travelled in this field goes to *Sir Brownell et al* in 1953 (Burket *et al.,* 2003; Wilson, 1998). They utilised the rectilinear scanning technique to develop a positron camera that can be used in clinical setups. It was capable of recording planar images. After few years in 1959, *Kuhl and Edwards* succeeded in developing transaxial emission tomography. In the following year, they utilised it to develop MarkII scanner (Burket, 2003). *Brookhaven National Laboratory group* in early 1960 developed a true transaxial positron tomography (Wilson, 1998; ClHo *et al.,* 2004). However due to inadequate reconstruction method, the resultant images obtained were not of adequate quality. With the introduction of computed tomography in 1980, PET was reborn (Burket, 2003; ClHo, 2004).

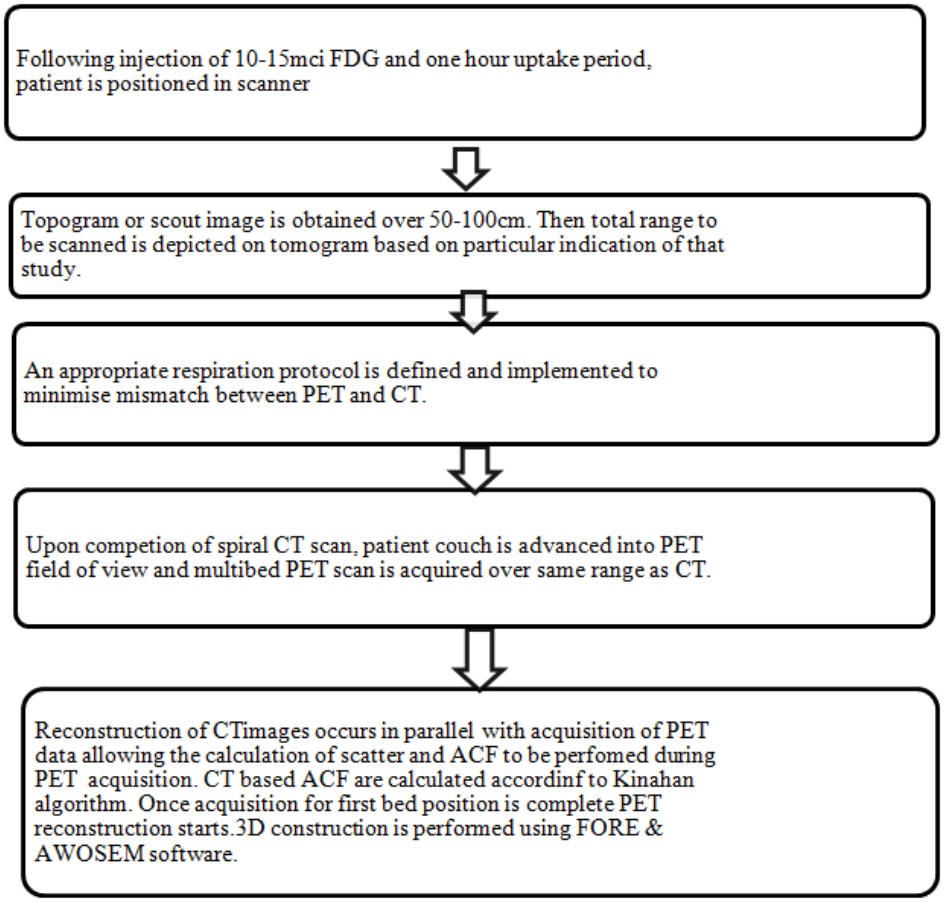

Fig.1. Figure shows a clinical protocol of PET scan examination

Table 1. Common indications of PET

Areas of use	Strong indications	Relative indications	Not recommended in current scenario
Brain and spinal cord tumour	a).To distinguish between residual/ recurrent disease from post-therapy scarring or radionecrosis b).To differentiate between benign and malignant tumor	a).Grading of primary brain tumour b).Evaluation of response to therapy c).Identifying the site of recurrent brain tumour	As primary imaging tool for suspected brain metastasis
Head and Neck cancer	a).restaging b).evaluation of suspected reoccurrence c).unknown primary tumour in patients with cervical nodal metastasis	a).staging b). Evaluation of response to therapy	Parotid tumours(unable to differentiate benign and malignant tumours)
Nasopharyngeal tumour	a).restaging b).localising or differentiating recurrence from therapy induced radiological changes	a).staging b). Evaluation of response to therapy	
Thyroid Carcinoma	Detection of residual/recurrent tumour(when serum thyroglobulin is elevated but radioiodine scan is negative)	Tumour recurrence In medullary carcinoma of thyroid	Routine assessment of thyroglobulin positive recurrence with radioiodine uptake
Parathyroid adenoma		Preoperative localisation	
Solitary pulmonary adenoma	Characterisation of newly discovered indeterminate lung nodule	Evaluation of response to therapy	
Non-small cell lung cancer	a).staging b).restaging c).assessment of recurrent disease		
Small cell lung cancer		staging	
Breast cancer		a).staging b).restaging c).evaluation of suspected recurrence d). Evaluation of response to therapy	
Oesophageal Carcinoma	a).staging b).restaging c).evaluation of suspected recurrence d).Distant lymph nodes and metastasis		
Gastric carcinoma	a).staging b).restaging		
Gastrointestinal stromal tumour		Evaluation of response to therapy	

…Continue

Hepatocellular carcinoma	staging	Evaluation of response to therapy	
Pancreatic Carcinoma		a).staging b).differentiating between benign and malignant	
Colorectal carcinoma	a).restaging b).evaluation of suspected reoccurrence		
Ovarian carcinoma		Evaluation of suspected reoccurrence	
Cervical tumour		a).staging b). restaging c).evaluation of response to therapy	
Testicular tumour		a).staging b). restaging c).evaluation of response to therapy	
Lymphoma	a).staging b). restaging c).evaluation of response to therapy d).evaluation of suspected tumour reoccurrence e).assessing bone marrow involvement		
Malignant	a).staging b). restaging c).follow-up		
Soft tissue		a).grading b).restaging	
Metastatic carcinoma of unknown primary cancer		Detection of occult disease	Widespread metastasis
Paraneoplastic syndrome		Unknown primary cancer	
Cardiology	Assessment of myocardial viability	a).Coronary artery disease b).Differentiating Ischemic cardiomyopathy from other types of dilated cardiomyopathy	
Neurology	Lateralisation of epileptogenic foci prior to surgery in patients with medically refractory epilepsy	a).dementia b).identification of early Alzheimer's disease c).Parkinson's disease	

Positron emitting radioisotopes

Though there are numerous radioisotopes which emit positron but some of them can be easily substituted and thus are more commonly employed in PET. These include ^{18}F, ^{11}C, ^{13}N, ^{15}O. (Nutt, 2002; Wilson, 1998) Subsitution of ^{11}C for ^{12}C does not significantly alter the reaction time or mechanism of action. Similarly ^{13}N, ^{15}O can also be easily substituted. ^{18}F can be substituted for hydroxyl group on a molecule or placed in a position where its presence does not significantly alter the biological behaviour of the molecule. Time is a critical parameter while using these short lived PET radioisotopes. For this reason, PET tracers must be synthesized and imaged within the timeframe corresponding to the half-lives of the particular radioisotopes used (Hohck *et al.,* 2002). For example, 10 minutes are required for ^{11}C isotope production whereas it takes 90 minutes for PET imaging. Thus entire study has to be completed within 2.5 hours otherwise it will result in unacceptable loss of specific activity (ClHo, 2004; Hohck *et al.,* 2002).

Radionuclides

The first radionuclide known to mankind was ^{11}C which was used for chemical and biochemical tracer studies prior and during World War II (Mushtaq, 2012; Burket, 2003). Since it had a shorter half-life of approximately 20.4 minutes, it was substituted by ^{14}C which had a longer half-life of 5730 years. This led to interest in discovering other nuclides at the global level. Two decades later, three other positron emitting nuclides were discovered. These were ^{18}F, ^{13}N, ^{15}O.Results of studies revealed that their body penetrating photons and shorter half-live can be put to use in imaging biochemical transformation in living human body (Wilson, 1998; Hohck *et al.,* 2002).

Precursor production

In PET, the radiotracer's synthesis starts with small precursor molecules originating from cyclotron target. These precursors are then subjected to electronic and thermal reactions in harsh environment of cyclotron target (ClHo, 2004; Hohck *et al.,* 2002). Undoubtedly within this environment there is sufficient energy available to overcome almost all activation barriers. Final chemical form is often determined by thermodynamics of the constituents. Thus at the end of irradiation, very stable and un-reacting molecules are left (Phelps and Cherry, 1998).

- C^{11}: most stable molecule in oxidising environment is CO_2 while in reducing environment is CH_4
- N^{13}: N_2 in gas phase and NO_3^- in aqueous phase
- O^{15}: O_2 in gas phase which can be transformed into more useful chemical forms. Water in aqueous phase which can be directly used as a precursor
- F^{18}: F^- ion or fluorine gas deprnding on the environment.

All of these radioisotopes can be produced through a wide array of nuclear reactions where bombarding particle can be proton, deuteron, helium-3 or helium-4. Usually due to non-availability of others, proton accelerators are the most commonly used (Phelps and Cherry, 1998; Humm *et al.,* 2003).

Radiotracers and their target

Although every molecule is prone to be damaged by ionising radiation damage to DNA is most effective in causing cell death. The factors that govern the cell death are linear energy transfer, cell cycle position, pressure of oxygen within tumour and expression of number of oncogenes and growth factors (Phelps, 1998). PET can be used for evaluation of functional physiology. It can assess the physiology, metabolism, proliferation of cancerous cells and can evaluate the parameters that determine the outcome of radiotherapy treatment. FDG is clinically less useful as a predictor for therapeutic outcome in slowly proliferating tumours like prostrate tumour. It can be due to low FDG uptake which further makes the differentiation between responders and non-responders difficult.[9]Tumour proliferation can be better visualised using radiotracer nucleosides and amino acids. But these have disadvantage of being rapidly metabolised. Rapid metabolisation requires sophisticated kinetic modelling. Time is another limiting factor while using C^{11} has a shorter half-life. In order to overcome these limitations, halogenated analogues with sufficient half-life were developed and tested in vivo. These allow imaging after most labelled metabolites are washed out. To name a few are [^{76} Br] deoxyuridine and[^{131,} ^{124}I]deoxyuridine. Both these radiotracers are incorporated into DNA. Rapid dehalogenation limits their clinical application due to high background activity and low tumour uptake (Gambhir *et al.,* 2001).

Basic mechanism of PET

Pharmaceutical or substrate interacts with the body through metabolic process; radionuclide allows the interaction to be followed mapped and measured. The steps involved in PET procedure are as under:

- Selection and production of suitable molecular probe. (It is a pharmaceutical labelled with positron emitting radionuclide)
- Administration of probe to patient
- Imaging and distribution of probe in the patient

Positron emitters are neutron deficient isotope that becomes stable through nuclear transmutation of proton into neutron. It involves emission of positron and electron neutrino as depicted by the following equation: (ClHo, 2004)

$$\text{Positron} \longrightarrow n + e^{+} + \nu_e$$

After emission, positron loses energy through interaction with surrounding tissue until it annihilates with electron. The range positron travels depends on the energy with which it is emitted, that is dependent on particular isotope. Two annihilation gamma rays are emitted in opposite direction and are detected in coincidence. Positron emitters like ^{18}F are used to label substrate like deoxyglucose to create radiopharmaceuticals. These radiopharmaceuticals are injected into patient who is then positioned in PET scanner. Gamma ray pairs from positron are captured in coincidence by opposing detectors. The pairs of coincident photon or events are stored in matrices or sonograms. These are then subjected to image reconstruction algorithm to recover underlying radioactivity distribution (Hohck, 2002; Humm *et al.,* 2003; Gambhir *et al.,* 2001).

Imaging technology

The past couple of years have witnessed significant advances in the PET scanning.The incorporation of fast scintillators and incorporation of CT has boosted its growth potential (Humm *et al.,* 2003). PET BLOCK DETECTORS were developed by Casey and Nutt in mid-1980.They developed innovative models by multiplexing first 32 and 64 detectors to only 4 phototubes. This resulted in reduced complexity and cost (Humm *et al.,* 2003; Muehllehner *et al.,* 2001). SCINTILLATORS were introduced in early 1970. These were based on different geometric configuration of thallium activated sodium iodide crystals (NaI (T1)). But low density of NaI is a demerit unless thicker crystals are used to compensate for the reduced stopping power. Later in 1970, Bismuth GermanateB (Go) replaced NaI (T1) as it was more dense and had greater stopping power. The light output of BGo is only about 15% of NaI and decay time is about 30% longer. BGo block detectors ruled the world of PET scintillators till late 1980 when newer ones were introduced. Introduction of newer, faster scintillators like Gadolinium Oxyorthosilicate (GSo) and lutetium oxyorthosilicate (LSo) both doped to Cesium further improved the clinical performance of PET scanners.[12,13] Both GSo and LSo have much shorter decay time thereby reducing system decay time and improving count rate performance.[14] Recent developments in detection technology and image reconstruction have led to reduced scan times to as less as ten minutes. Combination OF PET and CT revolutionised the field of imaging.[15] Accurate anatomical localisation is a limiting factor for PET.In oncology while a positive PET may be the first step in identifying or staging tumour, detailed information like localisation to lymph nodes, bone or soft tissue can serve as a useful guide in selecting appropriate treatment or assess response to therapy. PET scan yields low resolution images but with combination of CT in PET scanner, the resultant images have higher resolution with improved registration of anatomical details.

Though CT and PET scans of same patient acquired on different scanners can be aligned using software, but it will be labour intensive and more importantly fail to converge to satisfactory resolution. Thus a successful alternative solution would be combining imaging technology of CT and PET in one scanner (Melcher, 1992; Trantola *et al.,* 2003). The added benefits are both anatomy and physiology accurately acquired and registered in a single scan examination. The acquisition of accurately co-registered anatomical and functional image is strongest advantage of combined PET/CT scanner. Moreover, CT can be used for attenuation correction which not only reduces whole body scan time by 40% but also provides

noiseless ACF compared to those from standard PET (Bendriem *et al.,* 1998; Schoder *et al.,* 2003). Iodinated contrast is used in CT to enhance attenuation in vasculature (administered through Intravascular route) and GIT (administered through oral route). Contrast enhanced pixels that are incorrectly scaled to 511 Kev can potentially generate focal artifacts in PET image. The solution to this lies in performing two CT scans: one with appropriate contrast administration and a low dose non-contrast CT for anatomival correction and cor-egistration. (Beyer *et al.,* 2000; *Carney et al*., 2001) modified the original algorithm of Kinahan *et al.*[20] to separate contrast enhanced CT pixels from those of bone. This modified algorithm can to a considerable extent reduce artefacts due to catheters and metallic objects in the patients. (Carney *et al.,* 2000; Kinahan *et al.,* 1998) Figure 1 shows a clinical protocol of Pet scan examination.

Clinical applications of PET tracers

Any day the main purpose of medical practice is to improve the outcome of ailing patient. This can be very well accomplished using PET radiotracers as they can be used for preliminary diagnosis, evaluation of therapy or to assess the aggressiveness of disease (Bomanji *et al.,* 2001). The estimation of glucose metabolism rate is one of the prime measures of normal physiological function in human body. [25]It can be achieved using Fluoro-deoxy-glucose (FDG).PET can detect viable myocardium that may respond to reperfusion. It can serve as a useful clinical tool in epilepsy (Lee *et al.,* 2003; Chung *et al.,* 2002). Staging of the disease in oncology is an important parameter to assess the prognosis of cancer. As it is known that prognosis of a localised malignant disease is far better than a case of metastatic spread, staging is essential to select adequate therapy. It is prudent to scan whole body so as to exclude metastasis. FDG-PET deserves special acclaim as it reliably meets the requirement of whole body staging to high diagnostic accuracy. The mechanism of PET oncology scan lies on the fact that anaerobic glycosis occurs in malignant transformation of cells and serves as an early indicator (Hohck *et al.,* 2002). Whole body imaging with PET-FDG enables evaluation of glucose metabolism through body in single scan. It improves the detection and staging of cancer, selection of therapy and assessment of response of therapy (Hohck *et al.,* 2002; Hustinx *et al.,* 2002). It has been successfully used to diagnose, stage and restage a wide variety of cancers (Hustinx *et al.,* 2002). According to a research finding, PET has 79%sensitivity and 91% specificity in lung carcinoma. Results of study revealed that FDG-PET has ability to stage lymphoma and shows similar sensitivity to computed tomography but much better specificity.96% vs 41% for Hodgkin lymphoma and 100%vs 67% for Non-Hodgkin lymphoma. Similar results were found with other types of cancer (Kahn *et al.,* 1994; Bury *et al.,* 1996; Verbroom *et al.,* 2003).

18 f-3'-Fluoro-3'-deoxy-thymidine ([^{18} F] FLT) is a radiotracer that can measure cell proliferation. A study was conducted by Shields etal in 1998 to determine whether metastasis in various cancer types can be identified more accurately using [^{18}F]FLT than with classical universal PET tool. It was found that almost all lesions detected with FDG could be detected with [^{18}F]FLT. Authors suggested that uptake is specific for malignant tumours since benign tumours do not exhibit its uptake (ClHo, 2002). PET has been extremely valuable in understanding the physiology of heart in health and disease. Quantification of cardiac perfusion is the most widely used PET procedure. It is used to evaluate the presence of coronary artery disease and to assess the efficacy of selected therapy. Metabolic imaging can be done using FDG which can be helpful in differentiating ischaemic tissues from completely infarcted and non-viable tissues (Hohck *et al.,* 2002; Hustinx *et al.,* 2002; Bomanji *et al.,* 2001). Results of a recent research have identified receptor specific radiotracer that can be used to evaluate the role of sympathetic, parasympathetic and muscarinic receptors and their association to health and disease (Bomanji *et al.,* 2001). ^{13}N ammonia and ^{15}O can be used as a blood flow tracer while myocardial oxygen consumption can be measured using ^{11}C labelled acetate. ^{11}C labelled palmitate can be used to measure fatty acid metabolism (Bomanji *et al.,* 2001). Pet scan has also been used in TMD'S . In a study conducted by J. Lee *et al*. in 2013 18F PET/CT showed high TMJ uptake ratios in TMD with osteoarthritis and demonstrated higher sensitivity and accuracy than those of a conventional bone scan for detecting TMD with osteoarthritis (Lee *et al.,* 2003).

Gene therapy

The rationale behind gene therapy is to use a gene to produce missing or therapeutic protein to treat a disease or disorder. The difficult aspect in gene therapy is to determine whether gene transfer is successful or not. There are ways to ensure its success: First method incorporates conventional procedure of biopsy of tissue for that gene that has been transferred. Second and better method is PET scanning of that tissue. PET scan can be used to image the transgene or expression of gene in other endogenous molecule (Delbecke *et al.,* 2001). For imaging transgene expression, reporter gene and probe are required. An ideal reporter gene produces reporter probe only in those tissues where transgene is expressed. Thus estimation of levels of reporter probe can be correlated with the expression of transgene. For the ease of studying, we have classified the indications of PET as strong, relative and not recommended. These are tabulated in table 1.

Conclusion

With the expansion of diagnostic imaging, it has been customary for dental practitioners should be well versed with the various indications for PET/CT imaging techniques in oral/dental pathologies. PET/CT imaging increases the accuracy of diagnosis by combining anatomic information with functional imaging. Although not specific, exquisite sensitivity makes it useful screening procedure for many pathologic conditions.

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