PET-2

PET-CT – THE NEW CRYSTAL BALL OF MEDICINE! : IMPACT OF PET-CT IN NEW ERA OF MEDICINE

ABSTRACT

PET [acronym for Positron Emission Tomography] is a nuclear medicine imaging technology that allows three-dimensional, quantitative determination similar to tomographic imaging of positron emitting radionuclide tracer distribution within the human body; permitting measurement of physiological, biochemical and pharmacological functions at the molecular level.

PET scan has evolved through time, from just an attempt to obtain an image using positron emitters in the 1950s to a clinically useful tool in the present day. Even though the boom of biochemical and chemical studies during the Second World War provided a wide range of radionuclides; the discovery of F-18 flurodeoxyglucose (FDG) and the entry of commercial enterprises gave the final impetus for giving PET scan its present form.

The tracer nuclide accumulated in the glucose hungry cancer cells emit positrons which annihilates with an atomic electron producing two oppositely directed 511 keV photons; which is simultaneously detected by 2 small detectors of the PET scanner; giving as 'positive' scan The integration of functional imaging with CT anatomical imaging (PET-CT) has dramatically increased the clinical applicability of PET. The use of other tracer radionuclides specific for perfusion, lipid, DNA, aminoacid, hypoxia, Dopamine binding, apoptosis and angiogenesis are limited to research centers. Even though general interpretation of PET scan is qualitatively; quantitative measures of uptake assessment like Standardized Uptake Values (SUV) have been defined.

As PET scan can detect abnormalities in cellular activities generally before there is an anatomical change; it has been used for diagnosis, staging, treatment evaluation and assessment of recurrence of various cancers; as well as predicting the eventual response to chemotherapeutic agents to modify the non-effective regimen early. In radiation therapy planning; combined PET/CT scanners with the ability to coregister anatomic and functional images acquired in one session helps in target volume delineations that are more accurate, biological target volumes, exclusion of non malignant artifacts

The use of PET scan has been expanded to involve other areas of medicine also. PET is used in neurology in evaluation of early dementia; differentiating Alzheimer's disease (FTD) from Fronto-temporal dementia (FTD); evaluation of Parkinsonism, localization of epileptogenic focus in a patient planned for neurosurgical resection, in a complex partial seizure disorder which fails to respond to medical therapy. Cardiac PET scan is used to evaluate the myocardial viability prior a revascularization or transplantation procedure; calculate absolute or regional myocardial blood flow or blood flow reserve. PET scan is also used in genetherapy to determine if the gene transfer is a success.

PET scan may change the way we look at medicine, with better understanding of disease pathophysiology and behaviour, tumor tailored tracers, higher resolution and faster machines; 'biological target volumes' in radiation therapy planning resulting in better responses, PET result guided management guidelines, molecular imaging in other specialities of medicine and even in genetherapy. Even though the potential of this technology is just beginning to become obvious, this modality has already proven itself as a vital weapon in the clinicians' armamentarium by aiding in diagnosis, staging, treatment planning and evaluation of diseases like cancer.

PET-CT – THE CRYSTAL BALL OF MEDICINE: IMPACT OF PET-CT IN NEW ERA OF MEDICINE

Advancements in no other scientific field have touched medicine so much, when compared to the field of imaging. This field has proven indispensable to the medical fraternity, in such a way that, no medical speciality can exist independently without utilizing this technology. When it became possible for physicians to actually "see" inside their patients and cure them; diagnostic radiology and imaging received a medical speciality status. This era in imaging saw the beginning of a new chapter with the advent of PET scan. The inability of the imaging modalities like computed tomography (CT) and magnetic resonance imaging (MRI) to identify small masses and distinguish between scar tissue and tumor masses, gives PET an extra edge. PET is an imaging method that can be used to establish the metabolic or functional parameters of tissue and so it is hoped it may be able to better differentiate active tumors. The broad scope, versatility and sensitivity of PET makes it the most powerful molecular imaging technique currently available for clinical use.

PET is an acronym for Positron Emission Tomography. Positron emission tomography [also known as positron emission transverse tomography (PETT), or positron emission coincident imaging (PECI)], is a nuclear medicine imaging technology, that allows three-dimensional, quantitative determination similar to tomographic imaging of positron emitting radionuclide tracer distribution within the human body. It also permits measurement of physiological, biochemical and pharmacological functions at the molecular level, both in healthy and pathological states. Putting in another way, what PET scan performs is what is termed as "functional imaging".

PET IN EVOLUTION

PET has come a long way in past four decades; from just attempts to obtain an image using positron emitters to a clinically useful tool. Several early investigators demonstrated the advantage of positron imaging using coincidence-counting techniques.

The first, and perhaps most prominent, was the work of Brownell et al at Massachusetts General Hospitals; which was reported as early as 1953 where they used a rectilinear scanning technique.[1,2]

The driving force behind the use of positron emitters centered on the availability of the radionuclides C-11, N-13, O-15 and F-18. Of these various radionuclides, the most commonly used ones like C-11 and F-18 were discovered more than 60 years ago. The discovery of

carbon-11 preceded that of carbon-14 by several years, so that it became the first radioactive isotope of carbon to be used for chemical and biochemical tracer studies prior to and during World War II. The extraordinary experimental limitations as seen by the boom of biochemical and chemical studies during World War II; saw C-11 being replaced by C-14 and other short-lived positron emitters (F-18, N-13 and O-15) taking the centre stage. This interest was rekindled after 2 decades, when it was appreciated that their short half-lives and body-penetrating photons provided the potential to image biochemical transformations in the living human body.

First cyclotrons for production of positron emitters, emerged in hospitals in 1955, and in last ten years they are being commercially made for these purpose. But by 1960 they had developed a clinically usable positron camera. Even though their camera produced mainly planar images, they did give some tomographic information. In the late 1959, Kuhl and Edwards had successfully accomplished transaxial emission tomography and by the late 1960s, they had developed the Mark II scanner.

The Brookhaven National Laboratory group, in the early 1960s, produced a true transaxial positron tomograph utilizing a ring system of detectors that is highly reminiscent of modern tomographs; but due to inadequate reconstruction methods, the system gave poor results.

The successful synthesis and application of F-18 flurodeoxyglucose by Wolf et al in mid 1970s provided another impetus for the advancement of PET. Once the potential and broad utility of this tracer has been demonstrated; the medical community has been pushing this new technology for more clinical applications. The final push came from the entry of commercial enterprises into the field. The manufacturer of sophisticated equipment for routine use demands major involvement; if a modality is to gain widespread acceptance. This culminated in the finalization of PET as a widely used clinical tool.

Next few years showed the development of advanced reconstruction techniques that accompanied the development of X-ray computed tomography (CT), this give an accelerated thrust to the development of PET scan; resulting in the design and implementation of the more modern version of the PET scan by Phleps et al in mid-1970s. The first PET/CT prototype was introduced a little over 5 years ago. In the past 3 years, a number of commercial designs have become available featuring multidetector spiral CT scanners and high-performance PET devices.[3, 4]

WORKING AND DESCRIPTION

PRINCIPLE OF PET

Positron emission tomography (PET) exploits the annihilation of positrons and electrons to simultaneous back-to-back 511 keV photons, to achieve the nuclear-imaging analog of x-ray computed tomography (CT). The positron is the positively charged antiparticle of the electron. When the positron-emitting radionuclide decays, the positron emitted interacts with an atomic electron. The positron electron pair is then annihilated, and its mass is converted to energy. Two oppositely directed 511 keV photons are produced. When these are simultaneously detected by 2 small detectors, the location of the event is presumed to have occurred somewhere along a line between the 2 detectors. This radioisotope accumulation is evaluated by the scanner and the PET 'scan' is then defined as 'positive' or 'negative'. The intrinsic resolution of PET is limited by the positron range, which increases rapidly with positron energy, and the small noncollinearity of the annihilation photons.

MACHINE GEOMETRY AND DESIGN

The scanner geometry is designed to capture a large fraction of the photon pairs resulting from annihilations in the patient. A PET scanner is an array of detectors for 511 keV photons. There are about 12,000 such 4x8 mm detectors in a PET scanner. For adequate uniformity of response and geometrical efficiency, the cylinder inner diameter should atleast be 70cm, and its length atleast 15 cm. the intrinsic spatial resolution of PET is >1mm FWHM, depending upon the radioactive label. Current clinical scanners are designed to achieve spatial resolutions of 3 to 5 mm full width at half maximum (FWHM), which requires that the transverse dimensions of individual detectors be approximately that size.[5, 6]

PET TRACERS

A PET tracer is a biomolecule labeled with a positron-emitting nuclide that has suitable physiological and imaging characteristics. Tracers must be substrates for physiological processes. In 1924, Warburg showed that the metabolism of glucose is altered in tumor cells. [7]

The PET technique mainly utilized in cancer management is FDG-PET, which exploits the abnormal glucose metabolism of cancer cells as explained by Warburg. Thus useful tracers are often analogs of endogenous molecules, for example deoxyglucose (DG), which competes with glucose for transport and phosphorylation, and then is trapped as DG-6-P within cells, facilitating imaging. PET imaging requires a radiopharmaceutical, produced by a cyclotron. The most commonly used PET radiopharmaceutical in clinical oncology is 2-deoxy-2-[fluorine-18] fluoro-D-glucose (FDG), an analog of glucose with a hydroxyl group substituted by F-18]. The half life of Fluorine-18 is 110 minutes. In cancer, tumor cells generally use glucose more rapidly

than normal cells After a patient is injected with FDG, tumor cells have a greater accumulation of the non-degradable FDG tracer molecules. This radioisotope accumulation is evaluated with PET imaging and the PET 'scan' is then defined as 'positive' or 'negative'.

Short half-life radiotracers for PET imaging are produced using cyclotrons. The half-lives of other selected positron-emitting radioisotopes (Table 1 & 2) are much shorter than FDG-PET; hence their uses are currently confined to research centers with cyclotrons on site.

TABLE 1

HALF-LIVES OF SELECTED COMMONLY USED POSITRON-EMITTING ISOTOPES[8]

ISOTOPE	HALF LIFE	MAXIMUM β+ ENERGY (MeV)	EFFECTIVE β+ RANGE IN TISSUE (mm)
11C	20.3 min	0.97	2.06*
13N	10.0 min	1.19	3.0*
15O	124 sec	1.7	4.5*
18F	110 min	0.64	1.4*
62Zn/62Cu (generator)	9.19 hr/9.74 min	1.63	~4.3
64Cu	12.7 hr	0.58	~1.2
68Ge/68Ga (generator)	271 day/67.6 min	0.11	~0.2
82Sr/82Rb (generator)	25.6 day/75 sec	3.15	13.8
94mTc	52.5 min	2.47	~9.4
124I	4.18 day	0.29	~0.6

TABLE -2

RADIOPHARMACEUTICALS USED WITH POSITRON-EMISSION TOMOGRAPHY FOR CLINICAL AND RESEARCH STUDIES IN TUMOR PATIENTS[8]

RADIOPHARMACEUTICAL	Principal Use
$H_2{}^{15}O$ [^{15}O-Water]	Cerebral Perfusion
^{11}C -CO	Blood volume
^{11}CO	Perfusion

Rubidium 82	Perfusion
[^{11}C] methionine	Amino acid metabolism/ protein synthesis : brain cancer
[^{11}C] thymidine	DNA incorporation
[^{11}C] tryrosine	Amino acid metabolism/protein synthesis
[^{13}N] ammonia	Myocardial Perfusion
[^{13}N] glutamate	Amino acid metabolism
F-18 fluordeoxyglucose	Glucose transport, phosphorylation in cancer
[^{18}F] deoxyuridine	DNA incorporation
[^{18}F] tyrosine	Protein synthesis
[^{18}F] fluorouracil	Pharmacokinetics
[^{18}F] uridine	DNA incorporation
[^{11}C] choline and acetate	Lipid tracers: phospholipids synthesis: brain and prostate cancer
18F-fluoromisonidazole (FMISO) and 18F-fluoroerythronitroimidazole (FETNIM)	Hypoxia tracers
^{15}O-O_2	Cerebral oxygen utilization
^{18}F-DOPA	Dopamine synthesis, Parkinson's disease
^{18}F- fluoride	Bone turnover
^{18}F – misonidazole	Tissue hypoxia
^{11}C- raclopride	Dopamine D2 binding: psychiatric illnesses

PET imaging has better resolution than other nuclear medicine procedures, mainly explained by the unique decay mode of its radionuclide, which unlike single-photon emitters allows for coincidence-detection. PET scanning largely eliminates attenuation artifacts due to its soft tissues or other structures in the body by using transmission scans.

In essence, FDG-PET maps the distribution of glucose metabolism in the human body. Intense physiologic uptake is seen in the brain, an obligate user of glucose. Myocardial uptake is intense in the fed state and is variable in the fasting state depending on the extent of the transition from glucose to fatty acid metabolism, which typically occurs with fasting more than 12 hours duration.

PET-CT IMAGING – PROCEDURE AND PREPARATIONS

Before a PET scan is done a fasting state of 4 hours or more is required, during which time the patient may drink only water or noncaloric beverages to ensure hydration and to promote diuresis. It is especially important that no sugar be ingested, because the glucose in foods (or in the case of inpatients, IVs) would compete with the uptake of the radioactive glucose. Blood glucose should be checked and preferably should be < 130 mg/dL. High glucose levels may decrease FDG uptake in tumors and impair image quality, thus consideration should be given to rescheduling scans when the patient's glucose is > 200 mg/dL. Patients' insulin level should be low, to avoid excessive uptake by striated muscle, heart, and liver. Diabetic patients will often be scheduled in the very early afternoon, peak control time after morning insulin. The patient should avoid extensive physical activity prior to FDG injection (preferably in the preceding day) and should remain relaxed and avoid talking, chewing, or hyperventilating during the uptake phase after FDG injection to minimize physiologic muscular uptake of FDG. This is particularly important in patients with head and neck cancer to minimize uptake in local muscles (laryngeal and masticatory muscles). Some authors recommend the use of benzodiazepines to obtain muscle relaxation. The patient should be well hydrated to dilute excreted tracer in the urinary system, which improves image quality, and minimizes bladder irradiation. The use of diuretic and/or bladder catheterization to reduce or eliminate urinary activity depends on the clinical context and local preferences.

After intravenous injection of 5 to 20 mCi of FDG, the patient is asked to rest quietly for at least 45 minutes before scanning and then voids immediately before image acquisition to minimize FDG activity in the bladder. In a typical procedure, the patient is scanned sequentially in overlapping bed positions for roughly 5 minutes/position, for an overall time of 30 to 60 minutes. It has been shown that, compared to non-malignant lesions, FDG uptake in cancer increases with time after injection. Sequential delayed imaging can be useful in lesion discrimination. Recently administered cancer chemotherapy may lead to possible altered tumor uptake of FDG, possible reactive changes (bone marrow, thymus, etc). Therefore it is desirable to allow several-weeks of interval. It is always preferable to schedule FDG-PET just before the next chemotherapy. Recently administered radiation therapy may lead to possible post radiation inflammatory change which may interfere with PET findings. It is desirable to allow at least 3 months interval between a PET scan and radiotherapy.[9]

DUAL MODALITY PET-CT

Accurate anatomic localization of functional abnormalities seen with PET is known to be problematic. Even though nonspecific tracers such as 18F-FDG visualize certain normal anatomic structures, the spatial resolution is generally inadequate for localization of pathology. Combining PET with a high-resolution anatomic imaging modality such as CT can resolve the localization issue, as long as the images from the two modalities are accurately coregistered. However, software-based registration techniques have difficulty accounting for differences in patient positioning and involuntary movement of internal organs, often necessitating labor-intensive nonlinear mapping that may not converge to a satisfactory result. Acquiring both CT and PET images in the same scanner obviates the need for software registration and routinely provides accurately aligned images of anatomy and function in a single scan. This recent advent of dual-modality PET-computed tomography (PET/CT) imaging systems has added unprecedented diagnostic capability by revealing the precise anatomical localization of metabolic information and metabolic characterization of normal and abnormal structures. The use of CT transmission scanning for attenuation correction has shortened the total acquisition time, which is an especially desirable attribute in pediatric imaging. There is an added benefit that they also provide an effective coregistered set of CT images for direct comparison, allowing superposition of anatomical and physiological images. The highly sensitive PET scan detects the metabolic signal of actively growing cancer cells in the body and the CT scan provides a detailed picture of the internal anatomy that reveals the location, size and shape of abnormal cancerous growth. So the combined “fused” images of PET and CT scans will provide complete information on cancer location and metabolism. Dual-section helical and multi-section helical CT were better than nonhelical and single-section helical CT.[10, 11]

INTERPRETATION OF PET

FDG-PET is generally interpreted in clinical practice qualitatively. However certain quantitative measures of uptake assessment have been introduced. Standardized uptake Value (SUV) is a measure of uptake normalized to the injected dose and the patient’s body weight. Although SUV is potentially useful in distinguishing malignant from benign lesions, especially in the lung, the variability and heterogeneity of uptake, and the interactions of scanner resolution with lesion size, are problems still yet to be solved. The role of SUV as a prognostic marker is also being evaluated. [12]

ROLE OF PET SCAN IN CLINICAL MEDICINE

PET scan has an extra edge over other imaging investigations in the fact that it can detect abnormalities in cellular activities generally before there is an anatomical change. So this

benefit can be translated in to identifying diseases earlier and more specifically than ultrasound, X-rays, CT or MRI.

PET IN ONCOLOGY

Recent studies using human tumor xenografts have shown that essential all human cancers accumulate FDG. So PET scans have been used for diagnosis, staging, treatment evaluation and assessment of recurrence of cancer For the following cancer management decisions, there is sufficient evidence to demonstrate the diagnostic value of FDG-PET: detection of distant metastases in primary or recurrent breast cancer; diagnosis of occult primary tumor in suspected head and neck cancer; diagnosis of solitary pulmonary nodules; restaging Non-Hodgkin's lymphoma to identify residual disease after induction therapy and detection of recurrence in epithelial thyroid cancer with elevated biomarkers not confirmed by ^{131}I scintigraphy. [13,14,15,16]

A few other tracers that have been used in oncology, such as ^{18}F-3'-deoxy-thymidine ([^{18}F] FLT) which measures cell proliferation. Even after its first human investigation in 1998, the question still remains whether metastases in various cancer types can be more accurately identified with ([^{18}F] FLT than with the classical universal PET tool, ([^{18}F] FDG Almost all lesions detected with FDG could be detected with ([^{18}F] FLT. It has also been suggested that ([^{18}F] FLT uptake is specific for malignant lesions since benign tumors do not exhibit uptake of ([^{18}F] FLT.[17]

Though PET has been tried in multiple cancers for various purposes [TABLE-3 & 4], other cancer management decisions require further diagnostic studies or a more focused and robust meta-analysis of existing diagnostic studies. Although the diagnostic evidence available for these cancers is sufficient, further evidence is required to demonstrate the clinical effectiveness of FDG-PET, in terms of patient management and improvement in patient outcomes.[18, 19]

TABLE 3

SUMMARY OF ONCOLOGIC CLINICAL STUDIES USING POSITRON-EMISSION TOMOGRAPHY[20]

STUDY	INVESTIGATOR	CONCLUSION
Lung	Kubota et al	FDG [^{11}C] methionine similar in detection of lung cancer
	Fujiwara et al	[^{11}C] methionine uptake does not correlate

		with histology
	Knopp et al	FDG uptake correlates with good therapy response
	Gupta et al	FDG highly accurate for differentiating benign from malignant solitary pulmonary nodules
	Knopp et al and Gupta et al	FDG superior to CT for restaging of treated lung cancers
Colon	Strauss et al	Accurate detection of recurrent colorectal cancer using FDG
	Haberkorn et al	Colon carcinoma following radiotherapy, PET detects treatment response
	Gupta et al	Detection of hepatic metastatic lesions
	Schlag et al	Recurrent pelvic tumor versus scar; PET superior to immunoscintigraphy
Breast	Wahl et al	Detection of primary and metastatic breast cancer using FDG
	Wahl et al	Accurate assessment of response to chemotherapy
	Mintun et al	Quantitation of estrogen receptors
	McGuire et al	[^{18}F] fluoroestradiol [estrogen labelled with fluorine 18] shows uptake in metastatic disease and effect of therapy
Soft tissue and Bone	Griffith et al	Correlation between tumor/ background, DUR, and tumor grade
	Adler et al	Accurate differentiation between benign and malignant tumor by PET with FDG
	Strauss et al	PET with FDG useful for imaging of melanomas before and after therapy
Brain tumors	DiChiro et al	PET with FDG useful for grading of gliomas
	DiChiro et al	PET with FDG highly accurate for differentiation of recurrent tumor from radiation necrosis

	Valk et al	Recurrent tumor versus necrosis differentiation after therapy using FDG
	Alavi et al	Accurate prediction of prognosis in gliomas using FDG
FDG = F-18 fluorodeoxyglucose PET= positron-emission tomography CT= Computed tomography DUR = differential uptake radio		

TABLE -4

REGIONWISE SENSITIVITY AND SPECIFICITY FOR PET SCAN IN CANCER

TUMOR REGION	STAGING *[SENSITIVITY /SPECIFICITY]	RESIDUAL OR POST THERAPY [SENSITIVITY /SPECIFICITY]	COMMENTS
BRAIN	intracranial cancers 89% recurrence sensitivity 79%/ specificity 77%		
HEAD AND NECK	67-91% / 82-100%	80-100% / 81-100%	Specificity increases prior 12 weeks of completion of therapy
NECK SECONDARIES	10-47%		
THYROID CANCER	69% /89%	73% /86%	FDG PET is not particularly sensitive. Useful only in elevated thyroglobulin and negative radioiodine imaging

LUNG	83%/91%	98% /92% and 94%/90% in evaluating response to therapy	
PLEURAL MESOTHELIOMA	91%/100%		
ADRENAL METS FROM LUNG CANCER	100%/ 94%		
BREAST CANCER	91 % /88% [91% /93% for diagnosis]	80% / 85% for recurrence and 81% /96% for monitoring response	"Flare" response in responders to tamoxifen therapy. Eve though sensitive to distant mets, clearly cannot detect all tumor infiltrated nodes.
STOMACH CARCINOMA	73% / 90% and 96% sensitivity for diagnosis		
ESOPHAGUS		For both distal and regional recurrence 94% / 82%	
COLORECTAL CANCERS	100% sensitivity for primary intraluminal carcinomas, but only 29% for lymphatic mets ; and 96%/99% for liver mets		Colorectal Liver mets <1.5 cm – 14% 1.5-3 cm -84% >3cm – 100%
HEPATOCELLULAR CARCINOMA	Sensitivity 50-57%		Not FDG avid

CHOLANGIOCARCINOMAS	100% sensitive		
LIVER METS			Sensitivity Vary with disease
PANCREATIC CANCER	85%/84%		Liver mets - sensitivity >1 cm – 97% <1 cm – 43% Specificity -95%
RENAL CELL CARCINOMA	94%/94%		For regional nodes and distant mets 76%/100%.
URINARY BLADDER CANCER	For lymph node staging 76%/87%.		
OVARIAN CANCER	93%/82% for primary ovarian cancers and 83%/80% for all lesions	recurrent epithelial ovarian cancer, 45%/100%.	Low sensitivity and specificity
CERVICAL AND UTERINE CANCERS	Stage IB and II cervical cancer - 91%/100%. 83%/92% for pelvic disease, and a specificity of 92% for nodal involvement.	Uterine cancer recurrence 96% / 78%	not been studied thoroughly with FDGPET, partly because the presence of radioactivity in the bladder in non-attenuation-corrected scans produces confusing artifacts.
TESTICULAR CARCINOMA	87% /94% for germ cell tumor metastasis		Insensitive to teratomas
PROSTATE	64% /100%. For bone		Generally not FDG-

CANCER	mets only 18% lesions seen with FDG-PET		avid
SOFT TISSUE SARCOMA	73.7%/94.3%	For pulmonary mets 86.7%/100%	The intensity of FDG uptake by the tumor was correlated with the grade of malignancy, with higher-grade tumors demonstrating more intense uptake in areas of viable tumor than lowgrade or benign tumors
PRIMARY OSSEOUS METASTASIS	90%		
PLASMA CELL DISORDERS	83.8-91.9% / 83.3-100%		
HODGKIN'S AND NON-HODGKIN'S LYMPHOMA	90%/93%,	87%/93% for recurrence and 90%/93% for monitoring response to therapy	In untreated non-Hodgkin's lymphomas, high FDG uptake is associated with a high histologic grade of malignancy and a high proliferation rate
MELANOMA	83%/91%		the sensitivity and specificity

			increase significantly with stage. FDG-PET cannot be relied upon, as for breast cancer, to identify small local nodal metastases

PET IN RADIATION THERAPY TREATMENT PLANNING

In radiation therapy planning, the metabolic information from FDG-PET in patients with FDG-avid tumor provides incremental value to anatomic parameters obtained from conventional morphologic imaging. Target volume to be treated can be more accurately defined based on metabolic activity from FDG-PET. Planned treatment volume can be increased by the detection of increased FDG uptake in normal-sized lymph nodes (suggestive of nodal metastases). Planned treatment volume can be decreased in areas not deemed involved by FDG-PET, such as atelectasis or other benign anatomic distortion. Information from PET is complementary to CT and does not replace morphologic imaging. Imaging technology is always evolving and integrated PET/CT scanners have been developed and are being used for radiation oncology applications in some countries. It is generally accepted that PET/CT will be comparable or possibly superior to PET alone. As we move toward the era of IGRT, the use of multi-modality imaging fusion, and the introduction of more sensitive and specific PET-CT tracers may further assist target definition. Furthermore, the potential to predict early outcome or even detect early recurrence of tumor, may allow for the tailoring of intervention in cancer patients. The convergence of a biological target volume, and perhaps multi-tracer tumor, molecular, and genetic profile tumors will probably be vital in cancer treatment selection. Combined PET/CT scanners with the ability to coregister anatomic and functional images acquired in one session will likely play an important role in radiation therapy planning. Practical challenges include expertise in the interpretation of PET images, optimal technique in image coregistration, compatibility of PET images with treatment planning system software, motion correction, and, most important, the validation that more therapy to a more precisely planned target volume would lead to improved patient outcome[21-26]

EXPANDING APPLICATIONS FOR PET SCANNING

MONITORING THERAPEUTIC RESPONSE AND DEVELOPMENT OF NOVEL ANTI CANCER DRUGS

Functional and metabolic information from FDG-PET can provide valuable prognostic information also. FDG-PET shows promise identifying responders from non-responders early in the course of chemotherapy based on significant decline in (or the lack of) FDG uptake in known tumors. This potential to predict eventual response to chemotherapeutic agents is important in treatment planning so that the ineffective therapy can be discontinued or modified to provide the patient a better option of chemotherapeutic agents as early as possible. This use is presently used in breast cancer alone, but trails are in progress regarding the same in other tumors.[27, 28] The ability of PET scan to assess drug responses as well as to evaluate the drug distribution within the body makes this technology very useful in the development of novel anticancer drugs.[29]

PET IN NEUROLOGY

Alzheimer's disease (AD) is an age-related and irreversible brain disorder that occurs gradually and results in memory loss, behavior and personality changes, and a decline in thinking abilities. There are no established biological or neuroimaging markers for the diagnosis of AD. Glucose metabolism in affected areas decreases as the disease progresses providing the basis for the use of FDG-PET. Functional neuroimaging, such as FDG-PET, has been proposed for the evaluation of elderly patients who may have early dementia and for whom the differential diagnosis includes one or more kinds of neurodegenerative diseases. FDG-PET may be able to diagnose AD by identifying anatomical patterns of brain hypometabolism, which typically occur bilaterally in the temporal and parietal lobes. FDG-PET scans typical of AD may be differentiated by visual inspection from scans suggestive of vascular dementia (asymmetric and focal abnormalities) and scans indicative of Fronto-temporal dementia [FTD] which shows marked hypometabolism of frontal or temporal lobes with sparing of parietal lobes An accurate distinction, for instance between AD and FTD may prove helpful in patient management given the variation in the course of these two diseases. But still not FDA approved, and still remains an off-label use.

PET scan is also used in evaluation of Parkinsonism using 18F- DOPA tracer which involves in dopamine synthesis pathway. Another use of PET scan in neurology is to localize an epileptogenic focus; in a patient candidate for neurosurgical resection, in a complex partial seizure disorder which fails to respond to medical therapy.[30]

PET IN CARDIOLOGY

PET scan is used to evaluate the myocardial viability to determine the potential benefit from a revascularization procedure; in diagnosis and management of patients with known or suspected coronary artery disease (CAD) using the FDA-approved radiopharmaceutical Rubidium 82 (Rb 82) for noninvasive imaging of the heart. It is also used to calculate of absolute regional myocardial blood flow or blood flow reserve, evaluation of myocardial viability before transplantation. Metabolic imaging with FDG will distinguish ischemic tissue from completely infracted and non-viable tissue. Recently, receptor-specific radiotracers were used to evaluate the role of sympathetic, parasympathetic and muscarinic receptors, as well as how these differ in health and disease. 3D cardiac PET is preferred now days for flow quantification. This technology combines the strengths of cardiac CT for evaluation of anatomy with cardiac PET for quantification of the hemodynamic impact on the myocardium.[31, 32]

The various tracers used are N-13 and 0-15 water as a blood flow tracers, C-11 labelled acetate for myocardial oxygen consumption and C-11 –labelled palmitate for fatty acid metabolism measurement. As compared to conventional method of angiography, PET/CT had shown exceptional accuracy especially in overweight and obese patients, suggesting that PET/CT scan could prove to be an alternative for conventional procedures in the future. In patients with structural heart diseases, PET/ CT has the potential to provide supplementary scar characterization by displaying additional metabolic and morphologic tissue-specific information. Three-dimensional scar maps can be created from the imaging datasets, which are uploaded into clinical mapping systems, and can facilitate substrate-guided ablation procedures. This has the potential to shorten procedure times, decrease complications, and improve the procedural success.[33]

PET IN GENE THERAPY

The idea behind gene therapy is to use a gene to produce a missing or therapeutic protein to treat a disease or disorder. It is often difficult to determine if gene transfer is a success in patients with the present technique of biopsy of the tissue for the gene that has been transferred. PET scan can be used as an alternative tool by using it to image either the transferred gene (transgene) or the expression of the gene in other endogenous molecule. The

assessment of gene expression (gene imaging) by PET is still in an infantile stage with present application only in animal studies.

LIMITATIONS OF PET

FDG-PET has been shown to be highly effective in cancer. Most cancers take up FDG avidly, its biological and physical half-lives are appropriate for clinical use, it is inexpensive to manufacture reliably, and is chemically stable, facilitating distribution. Depending on the cancer, the indications for oncological FDG-PET include diagnosis, staging, assessment of therapeutic response, restaging, and evaluation for possible recurrence. However, FDG-PET has the following limitations: Sensitivity: FDG-PET is highly sensitive in many common cancers. However, it is less sensitive in lesions such as bronchioalveolar and hepatocellular carcinomas and relatively insensitive in prostate cancer, papillary, follicular and medullary thyroid carcinomas, carcinoid, pheochromocytoma, teratoma, and generally in highly differentiated cancers. Specificity: There are many tissues that demonstrate significant physiological FDG uptake. FDG is excreted in the urinary system. Uptake is highly variable in the salivary glands, tonsils, oropharynx, nasopharynx, larynx, and muscles in the head and neck. Some benign tumors, such as functioning pituitary adenomas, demonstrate intense uptake, surgical changes, radiation therapy, and degenerative lesions can also produce false-positive scans.

PET imaging shows limited credibility in the detection of small foci of tumors within radiation-damaged or necrosed tissue due to the partial volume effect. This decreased sensitivity in detecting small foci has been described inpatients treated with intracranial neoplasm. However, the new generation PET scanners with improved resolution might overcome this problem.

Amidst of all the heightened anxiety in the medical community, an important limitation that this technology possesses is its high cost, especially in Indian patients. A PET scan adds to the cost of patient evaluation. The expense of PET must be weighed against the cost of an operative procedure which was inappropriately performed considering a wrong diagnosis using other available tests; and the growth proving benign in the histopathology. Also PET scan ahs to be weighted against the mortality and morbidity with an invasive procedure like surgery. Due to this important and ever increasing role in medicine including oncology, it might be hoped that the cost of PET may decrease in the future with the more widespread usage of this technology.

FUTURE PERSPECTIVES: WHAT NEXT?

The medical and scientific community has just begun to realize the potential of this new innovation. Research in positron emission tomography (PET) over the last 20 years has focused on novel methods of detection, image reconstruction and applications to neurological diseases and cancer. Many of the diagnostic trials are of poorly structured; so that more robust diagnostic trials have to be designed and conducted. When diagnostic accuracy has been proven, it is necessary to demonstrate the clinical utility of FDG-PET in well designed studies that document its impact on patient management and outcome.

Current evidence is insufficient to determine whether the routine use of FDG-PET should be permitted, and new studies have to be put forth in that direction. The question also still remains whether PET scan is an addition or a replacement to the current diagnostic imaging tests? Also how a PET scan result can alter the course of management. A PET scan based staging system can be expected to guide the management decisions of the future.

PET offers the opportunity to evaluate other biochemical characteristics of tumors with other positron-emitting radiopharmaceuticals. PET can be used to evaluate fundamental tumor processes such as perfusion, oxygen metabolism, protein synthesis, and DNA replication rates. Also these scans should be correlated with the biological behaviour of tumors to predict their behaviour and to correlate with treatment response.

Further trials are on the way which may prove PET findings as an independent predictor of survival and prognosis.

The number and variety of biochemical processes that can be monitored by PET are so large that only some of them have been used in clinical application. The ability to design a molecule to assess a particular interaction in question, and which are amenable to common synthetic routes for PET radiotracers is a more difficult and rewarding challenge. As mentioned earlier, the role of PET in gene imaging is an arena which will be explored in the coming years.

The present PET/CT imaging device can upgraded for shorter imaging time and for better resolution. With developments in technology, an integrated scanning machine with better image quality as well as provisions for structural as well as functional imaging may change the way medical community practices clinical medicine.

In radiation treatment planning, the usage of different tracers depending on the tumor characteristics may pave the way for “Biological target volumes” where dose distribution and delivery are guided by the biological and functional characteristics of the malignancy. The radiation doses in different parts of the same tumor can be escalated or modulated depending upon the property of the tumor tissue. This will help the radiation oncologist to practice the next generation of intensity modulation. This may culminate in better treatment responses and

reduction in post radiation recurrences. Also dedicated combined PET-CT simulators and four-dimensional (4D) PET/CT scans could come up more in numbers.

If adequate tracers which are designed to search for expression of certain tumor receptors [for e.g.: EGFR-TK] and image in PET scan are used, this will help identify the tumor tissue overexpressing these receptors. This will help the oncologist optimize and tailor the chemotherapeutic agents depending upon the tumor behaviour and characteristics. This constitutes what is called 'molecular imaging'.

With tremendous advancements in instrumentation and synthetic chemistry, the clinical application of PET has mushroomed in the last decade; but still this technology is its infantile stage. The potential for oncological applications of PET imaging is just beginning to become obvious. In the future, PET imaging will perform the dual functions of both as an imaging modality as well as significantly enhancing our knowledge of tumor characteristics and behaviour; to prove itself to be vital weapon in the clinicians' armamentarium by aiding in diagnosis, staging, treatment planning and evaluation of diseases like cancer.[34]

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