

Clinical Positron Emission Tomography Imaging—Current Applications

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Abstract

Positron emission tomography (PET) is an established imaging technique based on the use of short-lived radiotracers. The unique value of PET lies in the ability of various radiochemical compounds to serve as tracers for measuring specific metabolic processes in the body. This enables detection of the early biochemical anomalies that precede the structural changes seen on other imaging techniques. For decades, PET had remained essentially a research tool in academic institutions. However, in recent years, it has emerged as a vital clinical tool, particularly for cancer diagnosis and management. In this era of evidence-based medicine, the clinical applications of PET imaging have been subjected to intense evaluation, and its roles in oncology, neurology and cardiology have dominated nuclear medicine research and scientific publications in the past 5 to 8 years. This review article summarises the present status of the major clinical indications for PET scanning. The field is rapidly evolving and, with the recent advent of hybrid PET-CT scanners, new data continue to emerge, refining these clinical applications. Another important area of ongoing research is the development of new radio-labelled compounds for PET imaging.

Ann Acad Med Singapore 2003; 32:507-17

Key words: Cancer staging, Epilepsy, Fluoro-deoxy-glucose, Lung cancer, Myocardial viability, Radionuclide imaging

Introduction

Like other radionuclide techniques, positron emission tomography (PET) is based on the tracer principle – a small amount of labelled ligand is used to trace the metabolic pathway of an important chemical in the cell. PET complements anatomic imaging by its ability to map function or metabolism. In many cases of cellular or tissue pathology, biochemical abnormalities occur before any change in structure or anatomy is seen. Biochemical or metabolic imaging thus finds its greatest potential in detecting early or small changes in the body.

In PET, labelling is done with positron-emitting isotopes such as carbon-11, fluorine-18, nitrogen-13 and oxygen-15. This process is quite complex and generally requires a series of chemical synthetic reactions. The most common PET radiochemical tracer used in clinical practice is 2-[¹⁸F]-Fluoro-2-Deoxy-D-Glucose (FDG), in which the hydroxy group in the 2' position has been replaced by fluorine-18. FDG is a close analogue of glucose, the main substrate of carbohydrate and energy metabolism in cells. Many other PET tracers have been developed, and the main ones that have been used in clinical practice include amino acids (such as, methionine and tyrosine), nucleic acid bases (e.g., thymidine, uridine and guanosine), gene probes,

drugs, peptides (e.g., DOPA), tissue hypoxia agents (e.g., nitroimidazole derivatives), ammonium ions and even water molecules. Fluorine-18 in the simple chemical form of fluoride ions can be used as a bone scanning agent.

PET began as an experimental technique in the research laboratory about half a century ago. Since then, there have been numerous advances in PET radioisotope production, radiochemistry techniques and imaging technology. PET has retained its status as a powerful biomedical research tool, but at the same time, the many technical innovations have made these complex procedures more practical and cost-effective for daily use in clinical imaging. Within the last two decades, PET has moved on from the research laboratory to the busy hospital environment.¹

Clinical PET has become accepted as an important tool in the management of large numbers of patients. The number of PET scanners has increased exponentially over the last decade, in the US and Europe, as well as in Japan, South Korea, China, Taiwan, Hong Kong and Australia. Every year, there are hundreds of papers published in major journals, focusing on both PET technology and clinical studies. As a sign of the increasing importance of PET in clinical practice, the Medicare health insurance coverage in the US has approved reimbursement for certain PET

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scans. Due to the high start-up and running costs of PET imaging facilities, it was inevitable that the clinical applications for PET would be subjected to careful and objective scrutiny by health authorities and medical insurers. The clinical indications, that have been approved for reimbursement by US Medicare and other third party payers have therefore been critically reviewed and well supported by current evidence, include:

1. Diagnosis, staging and restaging of lung cancer, colorectal cancer, lymphoma, melanoma, head and neck cancer, and oesophageal cancer.
2. Evaluation of solitary pulmonary nodules.
3. Pre-surgical localisation of focal epilepsy.
4. Detection of myocardial viability prior to cardiac revascularisation.

In 2000, a group of German physicians met to discuss and evaluate the clinical use of FDG-PET. They reviewed more than 10,000 publications, of which 533 were selected for further review by an interdisciplinary panel of 58 experts from oncology, radiology and nuclear medicine.² Using evidence-based measures, they graded the indications for PET for various clinical situations, some of which will be elaborated below.

Special mention should be made of the following features of PET:

1. PET imaging makes use of radioactive tracers with very short half-lives (Table I). This requires close physical proximity of the radioisotope production and radiochemistry facilities. Highly skilled personnel are needed for these processes.
2. PET radiotracers are often biologically important compounds or their analogues (Table I). This confers

the technique with high sensitivity to metabolic and biochemical changes in disease states, often preceding structural changes seen on other imaging techniques.

3. In many applications, PET provides high sensitivity, high contrast images but low morphologic detail. This limitation can be circumvented by: viewing PET data in conjunction with computed tomography (CT) or magnetic resonance (MR) imaging; fusing (co-registering) the PET images with CT or MR imaging; dual-modality PET-CT imaging devices. Currently, many of the new scanners on the market are combined dual-modality PET-CT scanners.

2-[¹⁸F]-Fluoro-2-Deoxy-D-Glucose

This is the most widely used radiotracer for clinical PET imaging. ¹⁸F-2-fluoro-deoxy-glucose (FDG) is an analogue of glucose. It is transported into cells by glucose transporters, mainly by GLUT1 and GLUT4. Like glucose within the cell, FDG is phosphorylated by hexokinase, being converted into FDG-6-phosphate. However, unlike its physiologic counterpart glucose-6-phosphate which proceeds through the glycolytic pathway, FDG-6-phosphate cannot be metabolised any further, but is trapped within the cell (Fig. 1).

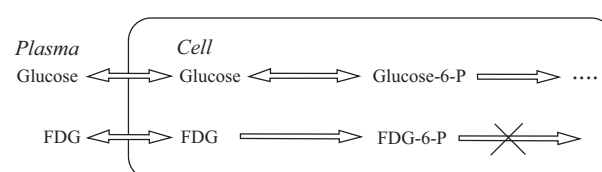


Fig. 1. Metabolism of FDG compared with physiologic glucose.

TABLE I: MEDICALLY IMPORTANT PET RADIONUCLIDES WITH SOME CLINICAL APPLICATIONS OF VARIOUS CHEMICAL LIGANDS

PET radionuclide	Physical half-life	Chemical form	Biological process	Clinical applications
Fluorine-18	110 min	¹⁸ F-FDG	Glucose metabolism	Tumour detection Myocardial viability Focal epilepsy Parkinson's disease
		¹⁸ F-DOPA	Receptor binding	
		¹⁸ F-fluorotyrosine	Protein metabolism	
		¹⁸ F-misonidazole	Tissue hypoxia	
Carbon-11	20 min	¹¹ C-methionine	Protein metabolism	Brain tumour imaging
		¹¹ C-palmitate	Fatty acid metabolism	Myocardial imaging
Nitrogen-13	10 min	¹³ N-ammonia	Blood flow	Cerebral perfusion Myocardial perfusion
Oxygen-15	2 min	¹⁵ O-water	Blood flow	Cerebral perfusion
Rubidium-82	76 sec	⁸² Rb	Blood flow	Myocardial perfusion
Yttrium-86	14.7 h	⁸⁶ Y-therapeutic	-	Pharmacokinetics and pharmaceuticals dosimetry studies

PET: positron emission tomography

Thus, the amount of FDG uptake within the cell reflects the rate of cellular uptake. The actual molecular picture is more complicated, as there is a very small element of FDG-6-phosphate breakdown and efflux out of the cell.

Tumour imaging with ^{18}F -FDG exploits the differences in physiology or metabolism between abnormal and normal tissue. It is well known that cancer tissues have substantially increased vascular supply, altered proportion of cell membrane receptors, increased glucose transport, glycolysis, glucose utilisation, DNA and protein syntheses. A recent study showed that in cells with the overexpression of the transcription factor oncoprotein c-Myc, genes encoding GLUT1, phosphofructokinase, enolase are activated. GLUT1 transcriptional rates are also elevated, increasing the expression of GLUT1 transporters.³

Due to its tracer properties, PET methodology can be employed to quantitate the glucose utilisation rate in mmol/min/g of tissue. In clinical practice, however, a semi-quantitative index is more commonly employed, to indicate the degree of metabolic activity in a pathological lesion or tissue. In addition to the qualitative assessment of FDG-PET images in oncology studies, the “standardised uptake values” (SUVs) of specific foci are measured, to help distinguish malignant from benign lesions. The SUV is the ratio of FDG uptake in the lesion to the average concentration of FDG in the body. A number of non-malignant processes are also known to demonstrate increased glucose uptake and FDG uptake, such as tuberculosis, sarcoidosis and other chronic granulomatous diseases.

This article reviews some of the well-established uses of clinical PET up to the present time. PET is often perceived as being expensive and superfluous, but the significant benefits gained in the management of many patients have proven PET to be a useful modality in routine clinical practice.

PET in Oncologic Practice

PET imaging complements anatomic imaging in several ways. Its functional character enables it to provide important information regarding:

- Diagnosis of malignancy
- Staging
- Determination of response and surveillance
- Prognosis
- Determination of site of activity
- Evaluation of residual mass for tumour activity

Lung Cancer

FDG-PET imaging for lung cancer is currently one of the most established of all clinical PET procedures. There is extensive published literature showing the value of PET in assessing solitary pulmonary nodules, staging of known

non-small cell lung cancer (NSCLC), evaluation of response to therapy and cancer re-staging

Lung Nodules

Asymptomatic pulmonary nodules are frequently detected on chest radiographs. If the radiographic pattern is indeterminate, the standard diagnostic algorithm is CT, followed if necessary by bronchoscopy and biopsy. Several studies⁴⁻⁸ have shown FDG-PET imaging to be very accurate in distinguishing malignant from benign nodules (average sensitivity and specificity is 94% and 81%, respectively, for the detection of malignancy). PET is useful when biopsy is not technically feasible, or non-diagnostic. If the PET scan is normal, most patients can be monitored with serial chest radiographs. False negative studies have been reported with bronchoalveolar carcinomas,⁹ slow-growing adenocarcinomas, bronchial carcinoids, and are also more likely with nodules that are <1 cm in diameter.

A positive scan usually indicates the need for biopsy. False-positive scans may be seen in patients with tuberculosis, coccidiomycosis, aspergillosis and cryptococcosis. Cross-correlation with radiographic or CT scan features and other clinical data may be helpful in these instances.

Lung Cancer Staging and Restaging

The treatment of patients with lung cancer is dependent on disease stage at the time of diagnosis. Surgical resection offers the only hope for long-term survival or cure, provided that the disease is limited to the lung and ipsilateral hilar or mediastinal nodes, and the patient has adequate pulmonary reserve. Accurate staging is vital in deciding between surgery and non-surgical treatment. PET has been shown to be more accurate than CT in staging the mediastinum, with overall sensitivity and specificity of approximately 90%.¹⁰⁻¹² In NSCLC, FDG-PET has been shown to be of particular value in preoperative staging. Conventional anatomic imaging classifies abnormal lymphadenopathy by the size criterion. As a result, FDG-PET has been able to provide higher sensitivity and specificity in nodal staging. It also more than occasionally picks up unexpected distant metastases. Change of clinical management has been documented in various published studies. Hicks et al¹³ reported that PET had a high impact in 35% of 153 patients and moderate impact in 25%. Many of the staging changes were to upstage the tumour stage, with a high proportion of patients having to change into non-surgical management.

FDG-PET also accurately screens the patient for distant metastases,¹⁴⁻¹⁸ identifying unsuspected disease resulting in “up-staging” of more than 10% of patients. In particular, adrenal metastases were accurately distinguished from benign lesions.

A “decision tree sensitivity analysis”, based on data available in 1996, showed that an average cost saving of US\$1154 per patient was achieved, when FDG-PET was included into the diagnostic algorithm for staging patients with lung cancer.¹⁹

The use of PET for detecting recurrent lung cancer has also been described. PET was shown to be very accurate in distinguishing recurrent disease from benign post-therapy changes when patients were scanned 12 to 124 months after therapy.^{20,21} In addition, FDG-PET is useful for differentiating recurrent tumour from post-radiation scar tissue. The use of FDG-PET for lung cancer staging is now in the guidelines issued by the British Thoracic Society and the Society of Cardiothoracic Surgeons of UK.

Lung Cancer Radiotherapy Planning

With the advent of three-dimensional conformal radiotherapy (3D-CRT) to increase dose delivery to tumour and minimise the dose to normal tissues, there is now considerable interest in the incorporation of the PET data into radiotherapy planning, to delineate the target volumes more accurately.²² FDG-PET has been shown to enhance the diagnostic accuracy of CT in target volume definition for radiotherapy of patients with NSCLC.²³ More research and validation of this data are needed to look at its impact on treatment outcome and patient survival.

Lymphoma

FDG-PET staging of both Hodgkin's disease and non-Hodgkin's lymphoma compares favourably with CT. The role of FDG-PET in the staging of lymphoma appears to complement CT and to provide important additional information beyond that of conventional anatomic imaging.²⁴ In several studies, FDG-PET shows increased number of sites compared to conventional staging.²⁵ A short compilation of these data by Delbeke and Martin²⁶ showed a 8% to 50% increase in the number of sites detected by FDG-PET compared to conventional staging, while a 1% to 17% increased number of sites detected by conventional staging compared to FDG-PET. Of note is that 7% to 16% of patients had their staging changed by FDG-PET. Additionally, lymphomatous involvement of the bone marrow may be detected by FDG-PET in a large number of patients, reducing the need for bone marrow biopsy. In fact, FDG-PET may detect bone marrow involvement even when posterior iliac crest biopsy is negative.²⁷

FDG-PET excels in the ability to monitor the response of lymphoma to chemotherapy. The biochemical response to chemotherapy or radiotherapy is often earlier than anatomic changes such as lesion size. The response of the lymphoma on the FDG-PET scan is often prognostic; in other words, the response has been shown to highly correlate with better

prognosis.²⁸ In addition, PET helps to differentiate between benign fibrotic tissue after therapy and residual tumour masses, a task that is often onerous and difficult with conventional anatomic imaging. A study by de Wit et al²⁹ showed that out of 32 patients with a residual mass after therapy, 17 showed no uptake and proved accurate in confirming no disease activity.

Head and Neck Cancer (Fig. 2)

Based on current evidence, FDG-PET has not been conclusively shown to be superior to conventional imaging for initial staging of head and neck cancers. This includes the detection of occult lymph node metastatic disease in the neck or metastases in the chest, although the German consensus group² felt otherwise and stated that PET contributed significantly to the staging of nodal disease with its greater sensitivity, and therefore graded this specific indication as “established clinical use” – its highest grade. Further confirmation of this application is anticipated, when the use of PET-CT becomes more widespread.

On the other hand, in the detection of residual or recurrent head and neck cancer, FDG-PET has been shown to be extremely useful. This is particularly important since the diagnostic and clinical management of the patient hinges on whether the residual or recurrent lesion is a malignant mass lesion or post-therapy fibrosis. In a report by Farber et al,³⁰ 28 patients with squamous cell carcinoma underwent radiation therapy with or without surgery and were followed up by biopsy or clinical follow-up for at least 6 months. There was clinical suspicion of recurrence for each patient, but no obvious mass was noted on physical examination or anatomic imaging. Thirteen patients had positive FDG-PET scans, of which 12 were confirmed to have active disease. Fifteen patients did not have positive FDG-PET scans, of which 13 patients were confirmed to be true-negatives while 2 were false negative. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy were reported to be 86%, 93%, 92%, 87% and 89 %, respectively.

In about 95% of all head and neck tumours, the primary lesion could be found by history, clinical examination, various types of endoscopy and anatomic imaging. In the remaining 5% of patients, the primary malignancy remains occult despite efforts to demonstrate it. In such patients, the role of FDG-PET has been examined, with favourable conclusions. In 2 studies that looked at the potential of FDG-PET in the localisation of occult primary tumours, FDG-PET detected the occult primary tumour in 9 out of 19 cases (47%) and 4 out of 16 cases (25%) respectively.^{31,32}

Oesophageal Carcinoma

Oesophageal carcinoma, like many epithelial cancers, displays a high glucose metabolism and hence a high FDG

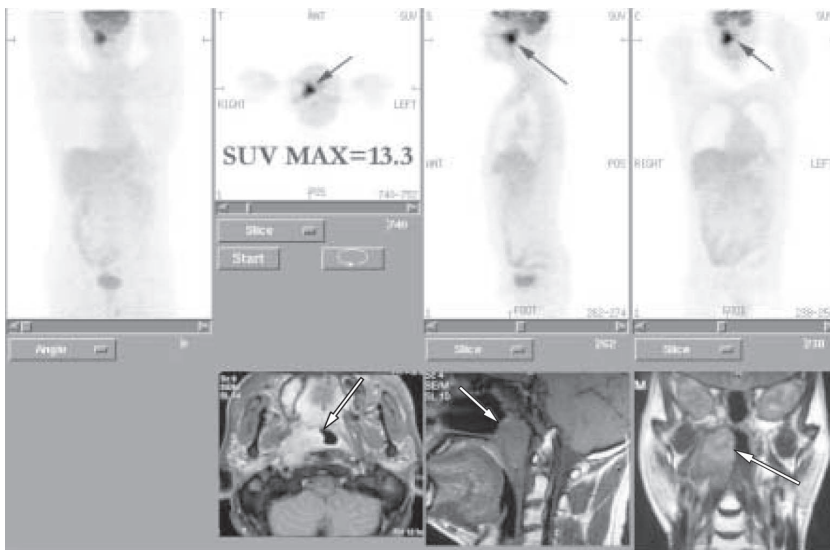


Fig. 2A. FDG-PET study was performed for metastatic survey in a patient with local recurrence of nasopharyngeal carcinoma 10 months after initial radiotherapy. Scan shows no obvious metastases. The recurrent tumour is seen in the right nasopharynx, a large metabolically active lesion (SUV = 13.3).

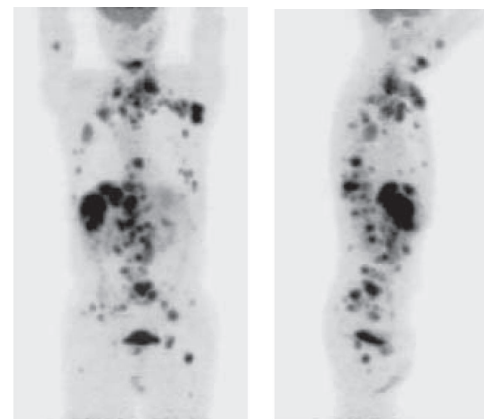


Fig. 2B. Another patient with widespread metastases from nasopharyngeal carcinoma, involving the skeleton, lymph nodes in the head and neck region, and liver.

Fig. 2. FDG-PET in nasopharyngeal carcinoma. (With permission from: Dr Kevin K M Tse, St Teresa's Hospital, Hong Kong.)

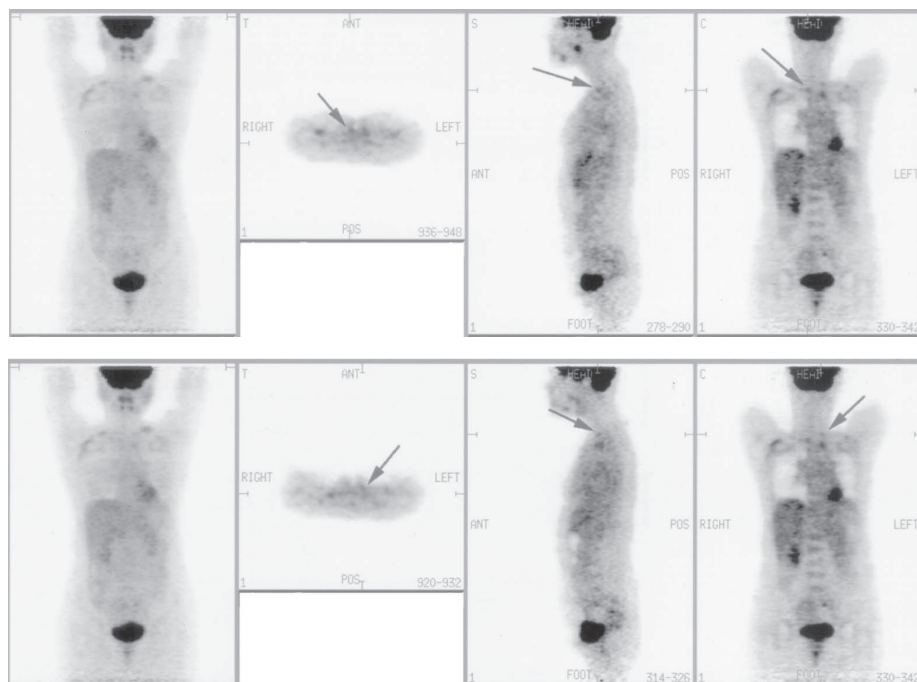


Fig. 3. Papillary carcinoma of thyroid.

Following thyroidectomy and radioiodine therapy, the patient had persistent mild elevation of her serum thyroglobulin but negative I-131 whole body scans. There were no palpable neck masses and CT scan of the neck was normal. FDG-PET shows several foci of abnormal FDG uptake at both supraclavicular regions, upper mediastinum and the right axilla, suggestive of lymph node involvement.

uptake. Although the sensitivity of FDG-PET in demonstrating the primary tumour is 95% to 100%,² FDG-PET is currently not recommended for T-staging or even N-staging for local nodes due to the limited spatial resolution and since conventional anatomic imaging already does well here. Results from several studies^{33,34} suggest that PET is not superior to CT for determining locoregional

involvement. However, the more recent advent of PET-CT fusion imaging would, quite likely, change the present conclusion on this matter.

However, based on several past studies, FDG-PET does have a recognised role in N-staging for distant nodes and M-staging, and outperformed CT staging in these 2 areas.³⁵ In about 17% to 20% of patients, FDG-PET findings

altered the management such that surgery was deemed contraindicated.³⁶

Pancreatic Cancer

One of the main issues in the management of suspected pancreatic cancer is the discrimination of pancreatic carcinoma from chronic pancreatitis, a relatively vexing clinical problem. This issue has been examined by at least 7 studies published to date. In general, the data appeared to support the use of FDG-PET to differentiate pancreatic carcinoma from chronic pancreatitis. Malignancy is characterised by high focal increased glucose uptake, while chronic pancreatitis normally exhibits a low glucose uptake. However, a few caveats need to be noted. False positives can occur and are due to the presence of superimposed acute pancreatitis, while the false negatives are found in those patients with small tumours (size <1 cm) and in patients with diabetes mellitus with a blood glucose of >130 mg/dL. An estimate of the accuracy of FDG-PET for differentiating between benign and malignant pancreatic masses was made by Diederichs³⁷ from 7 existing studies and the results were as follows: accuracy, 86%; sensitivity, 89%; specificity, 80%; positive predictive value, 89%; and negative predictive value, 79%. The value of PET for locoregional staging and its actual impact on clinical management have yet to be conclusively demonstrated, but PET seems to have a high sensitivity for detecting hepatic metastases (>1 cm) from pancreatic cancer.^{38,39}

Colorectal Cancer

The incidence of colorectal carcinoma has increased significantly and colorectal carcinoma has become the most common cancer in Singapore. For preoperative diagnosis and initial staging of colorectal carcinoma, there is no conclusive evidence at present to indicate a proven role for FDG-PET, beyond anatomic imaging. However, FDG-PET has an important role in the re-staging of patients with suspected recurrence of tumour, particularly for those planned for surgical resection. A sizable proportion of patients who have had definitive treatment for colorectal carcinoma will present with recurrence.

In such patients, some will have solitary hepatic metastases and others with more distant metastases. In these patients with suspected recurrence, FDG-PET is more sensitive than CT in detecting disease sites at all sites except for lung metastases where it is similar. For example, in a study of 61 patients, Delbeke et al⁴⁰ noted a sensitivity, specificity and accuracy of 79%, 58% and 76%, respectively, for CT and a corresponding results for FDG-PET are 93%, 89% and 92%, respectively. Imbriaco et al⁴¹ reported a positive predictive value of 96% to 98% and negative predictive value of 83% to 93% with FDG-PET compared to 75% to

88% and 67% to 71%, respectively, with CT for diagnosis of recurrent colorectal cancer.

Further inclusion of FDG-PET in the evaluation of patients with recurrent colorectal carcinoma was shown to be cost-effective in both a retrospective study and in a decision-tree sensitivity study.^{42,43} FDG-PET will guide clinical decision-making in many patients with recurrent colorectal carcinoma. Hence, it is recommended that FDG-PET be used for patients with evidence of recurrence for re-staging of the disease; in particular, to assess for those who have potentially resectable recurrence and avoiding unnecessary therapy in those with more extensive disease.

Melanoma

For low to intermediate level melanomas, staging of lymph nodes is critical for determination of prognosis and therapy. In many centres, sentinel lymph node imaging and biopsy have become standard practices. If the sentinel node is free of tumour, the other nodes draining the area are likely to be non-involved as well, obviating the need to do more extensive surgical removal. In high-risk melanoma and recurrent melanoma, there may be an important role for FDG-PET – in metastatic screening, so as to determine prognosis and guide further therapy. Holder et al⁴⁴ reported the sensitivity and specificity of CT staging and FDG-PET staging in 103 patients. The results showed that the sensitivity and specificity for CT staging were 55% and 84%, respectively, while for FDG-PET, the rate were 94% and 83%, respectively. Schwimmer et al⁴⁵ reviewed the data from several studies on FDG-PET and found a pooled sensitivity of 92% and specificity of 90% for detection of melanoma lesions. However, PET was inferior to sentinel node biopsy for detecting microscopic nodal invasion.

Other Cancers

Other studies have looked at the use of PET in various other types of malignancy including soft tissue sarcomas, breast carcinomas, urogenital tumours such as renal carcinomas, prostate carcinomas, ovarian carcinomas, testicular carcinomas, hepatocellular carcinomas, astrocytomas, nasopharyngeal carcinomas, thyroid carcinomas and neuroendocrine tumours. Of interest to our local situation is a fairly recent study which showed promise for PET in detecting recurrent or persistent nasopharyngeal carcinoma with a sensitivity, specificity and accuracy of 100%, 96% and 97%, respectively, while CT was 72%, 88% and 83%, respectively.⁴⁶

Carcinoma With Unknown Primary

This is not an uncommon problem in oncologic practice, occurring in approximately 5% of all oncologic referrals. The patient usually presents with a site of metastasis,

commonly in the cervical lymph nodes, while conventional work-up does not reveal the presence of the primary malignancy. The goal of treatment is to search for the primary as much as possible, exclude potentially curable malignancies, and finally palliation and supportive treatment. In this scenario, FDG-PET had been used to detect the location of the primary tumour. So far, at least 8 such studies had been done. FDG-PET detected a primary tumour in 24% to 53% of patients. Kole et al⁴⁷ reported that FDG-PET was able to identify a primary tumour in 7 out of 29 patients who had an unsuccessful conventional diagnostic work-up, while Bohuslavizki et al⁴⁸ reported finding the primary tumour in 20 out of 53 patients who already had had extensive diagnostic work-up. A rough rule of thumb is that approximately 25% of such “unknown primaries” can be found with FDG-PET.

Cardiac PET

The main recognised cardiac application of PET is the assessment of myocardial viability using F-18-FDG. The term “viable” simply means “alive”, but in the context of coronary revascularisation for ischaemic heart disease, the goal of imaging is to identify viable myocardium that is severely hypoperfused, with impaired contractile function, but will show recovery of function after revascularisation. The goal of diagnostic imaging is to predict whether the patient’s cardiac function would improve after coronary blood flow is restored.

The underlying basis of this PET application is the way the human myocardium utilises fuel substrates for energy. Under normal resting conditions, the energy needs of the myocardium are met through fatty acid metabolism. When subjected to prolonged ischaemia the myocardium switches preferentially to glucose instead (a more oxygen-efficient fuel substrate). This adaptive response is also associated with reduced or absent contractile function, and is appropriately termed ‘hibernation’. An ischaemic but viable segment therefore shows preserved or increased FDG accumulation, whereas dead tissue and scar would be photopenic.

FDG imaging has been shown to be more reliable than Tl-201 redistribution imaging for detecting viable myocardium.⁴⁹ More recent data suggest that *combined* imaging of glucose metabolism (with ¹⁸F-FDG) and myocardial blood flow (with PET tracer ¹³N-ammonia, or SPECT tracers like ²⁰¹Tl, ^{99m}Tc sestamibi or tetrofosmim) provided better predictive information on functional recovery of cardiac function after revascularisation compared to FDG imaging alone. With two radiotracers, the aim is to identify areas of “flow-metabolism mismatch”, i.e., the presence of FDG uptake in an area corresponding to a defect on the perfusion scan. The pooled data from 20

studies show that this combined approach yields a sensitivity of 88% and specificity of 71%.⁵⁰

Traditionally, FDG imaging is done with dedicated PET scanners. More recently, cardiac FDG studies have been done also with modified gamma cameras capable of producing images from the 511keV photons of PET tracers. Combined with ²⁰¹Tl SPECT imaging of myocardial perfusion, it was possible to identify “flow-metabolism mismatch” with a gamma camera, with comparable diagnostic accuracy to dedicated PET systems.⁵¹ PET imaging of myocardial blood flow can be performed using ¹³N ammonia, ⁸²Rb or ¹⁵O-water. ¹³N ammonia is the most practical for clinical use. Its early accumulation in the myocardium is linearly proportional to perfusion. Imaging is performed at stress and rest. As the half-life of ¹³N is only 10 min, pharmacological stress is usually performed with intravenous adenosine.

PET identification of “flow-metabolism mismatch” is particularly useful in patients with severe left ventricular function and symptoms of congestive cardiac failure and poor surgical risk. There is a need to identify patients who are most likely to benefit, in whom left ventricular function will improve significantly after blood flow is restored. PET has been shown to be extremely reliable in predicting a low incidence of cardiac events, long-term improvement in global left ventricular ejection fraction (LVEF), improvement of cardiac failure symptoms, effort tolerance and long-term survival after coronary bypass surgery or angioplasty.⁵²

Neurological Applications

PET techniques have been employed extensively in neuropsychiatric research. A vast range of radioligands have been developed over the last 4 decades, to provide functional images of brain blood flow, glucose metabolism, amino acid metabolism, dopamine receptor activity and numerous other parameters of brain function. Table II shows a partial listing of neurologic PET applications.⁵³ The following discussion will be limited to the more established clinical applications.

Epilepsy

Surgical removal of a seizure focus is the most effective treatment for partial epilepsy that is refractory to medical therapy. PET is one of the most accurate methods available to localise the source of the seizure in the brain and determine if surgery will be beneficial. The focus of partial seizures would typically show increased metabolism during the seizure, but decreased metabolism in the interictal period. Performing ictal imaging with PET is logistically impractical because of the short half-life of the radiotracers. Fortunately, interictal imaging with FDG is helpful in detecting hypometabolism of glucose at the seizure focus.

TABLE II: A PARTIAL LISTING OF RADIOLIGANDS USED IN NEUROLOGIC PET IMAGING

Compound	Application
¹⁵ O-H ₂ O	Blood flow
¹⁸ F-fluorodeoxyglucose	Glucose metabolism
¹¹ C-methionine	Amino acid metabolism
¹¹ C-raclopride	Dopamine receptor activity
¹¹ C-methylspiperone	
¹⁸ F-fluorodopamine	
¹⁸ F-spiperone	
¹¹ C-carfentanil, ¹¹ C-etorphine	Opiate receptor activity
¹¹ C-flunitrazepam	Benzodiazepine receptor activity
¹¹ C-scopolamine	Muscarinic cholinergic receptors
¹⁸ F-fluoro-DOPA	Presynaptic dopaminergic system
¹⁸ F-fluoro-tyrosine	
¹¹ C-ephedrine	Adrenergic terminals

It has been shown that patients with a greater degree of hypometabolism tended to have a better post-surgical outcome.⁵⁴

Most surgical candidates are patients with complex partial seizures of temporal lobe origin. On interictal PET, there is ipsilateral hypometabolism at the seizure focus, but increased metabolism in the contralateral temporal lobe. This asymmetric activity can be assessed objectively by quantitative analysis of the FDG-PET images. A study using statistical parametric mapping (SPM) compared hemispherical asymmetry of temporal lobes in seizure patients with controls. The SPM programme identified the site of hypometabolism and predicted a favourable post-surgical outcome in 90% of patients.⁵⁵

Dementia

The diagnostic assessment of dementia includes a detailed clinical history, neurological examination, blood screening, and neuroimaging studies, such as CT or MR imaging. The initial diagnostic work-up is aimed at identifying treatable causes of disorientation and cognitive impairment. The availability of new drugs for Alzheimer's disease (AD) has led to greater interest in functional imaging to detect early disease, when intervention is most effective. Structural imaging studies are often normal or may show only non-specific cerebral atrophy. Functional imaging, particularly PET, is more sensitive in detecting early disease with >90% accuracy 2 to 3 years before clinical diagnosis is made.⁵⁶ Although a variety of neuroreceptor tracers have been employed in the research context, clinical imaging for AD relies on the identification of reduced glucose metabolism (with FDG) or perfusion (e.g. with ^{99m}Tc-HMPAO SPECT) bilaterally in the parietotemporal association cortex.⁵⁷ Silverman et al⁵⁸ did a cost-benefit analysis comparing the conventional approach to diagnosis of AD (based on clinical criteria and excluding non-AD

aetiologies) against PET-based diagnostic criteria, and found that the PET strategy produced lower false-negative and false-positive rates (3.1% versus 8.2% and 12.0% versus 23.0%, respectively, at a prevalence of 51.6% in the studied symptomatic population), without adding to the overall cost of evaluation and management.

Primary Brain Tumours

Cerebral uptake of FDG is consistently strong because the brain's sole energy source is glucose. Normal grey matter in the cortex, caudate nucleus, thalamus and cerebellum shows high FDG accumulation. Despite the high physiologic uptake in the brain, FDG-PET imaging has been shown to be useful in patients with primary brain tumours, particularly in grading of the tumour, distinguishing between post-therapy scarring and tumour recurrence and assessing prognosis⁵⁹ (Table III). Image fusion (co-registration) of PET data with corresponding CT or MR imaging slices is especially helpful in the brain to pinpoint the sites of pathology. The rigid anatomy of the skull allows the data from these different modalities to be aligned reasonably well (compared to abdominal or chest images which are more susceptible to anatomical shift).

The histopathologic grading of glial cell tumours is closely related to prognosis and survival. In general, high-grade brain tumours are hypermetabolic on FDG-PET scanning, whereas low-grade tumours are hypometabolic.⁶⁰ Numerous other studies have thus shown that PET results accurately predicted survival of patients with gliomas more accurately than CT or MR imaging.⁶¹ FDG-PET images do not always correlate with CT scans. Although most hypermetabolic lesions show enhancement on CT, only 50% of the low-grade tumours show enhancement,⁶¹ a feature usually attributed to high degree of malignancy.

Another useful clinical application of FDG-PET is in the differential diagnosis between tumour recurrence and post-interventional changes. Radiation necrosis can develop years after RT and present with symptoms similar to tumour recurrence, as well as CT or MR imaging features indistinguishable from recurrent tumour. For tumours that usually show high FDG uptake, e.g., high-grade gliomas,

TABLE III: INDICATIONS FOR ¹⁸F-FDG PET IN PATIENTS WITH BRAIN TUMOURS⁵⁹

1. Tumour grading
2. Diagnosis of grade change (dedifferentiation from low to high grade)
3. Determination of regional differences in FDG uptake before biopsy
4. Assessment of prognosis
5. Therapy monitoring
6. Distinguishing tumour recurrence from radiation necrosis

a tumour recurrence would show up as a hypermetabolic lesion (often at the rim of the resection margin), whereas areas of radiation necrosis would appear hypometabolic.⁶²

There is another useful PET technique for imaging of brain tumours, employing a tracer that, unlike FDG, has inherently low brain background activity. Amino acid analogues (such as ¹¹C-methionine) are actively taken up by most tumours, but do not actively localise in normal brain tissue. ¹¹C-methionine imaging detects the increased protein metabolism in tumours, and its uptake is thought to be an indicator of the tumour proliferation rate. The low uptake in normal brain facilitates detection of small tumours (primary or recurrent), and delineates the extent of the tumour more reliably than FDG.⁶³ Some authors have suggested that, due to metabolic heterogeneity of gliomas, imaging with both FDG and ¹¹C-methionine provides complementary information in guiding stereotactic biopsy⁶⁴ and preoperative assessment⁶⁵ of gliomas. The main drawback of ¹¹C-methionine is the short physical half-life of ¹¹C (20 min), limiting the availability of all ¹¹C labelled compounds to scanning facilities with on-site cyclotrons. The radiochemistry for ¹¹C-methionine production is also more complex.

Infection

Another emerging clinical role for PET is the localisation of infection and inflammation. As with the established nuclear techniques, such as ⁶⁷Gallium citrate, ¹¹¹Indium or ^{99m}Tc-labelled leukocytes, the focal uptake of FDG is based on various physiologic and metabolic changes associated with inflammation, and is superior to anatomical imaging techniques in determining the location and degree of disease activity. FDG has been found to accumulate at sites of infection, in inflammatory cells like neutrophils and activated macrophages. These inflammatory cells also have increased expression of glucose transporters. In addition, multiple cytokines and growth factors have been shown to increase the affinity of glucose transporters in inflammatory cells to deoxyglucose.⁶⁶ In general, the level of FDG uptake in inflammation is lower compared to malignant tissues.

A variety of infections have been shown to accumulate FDG (abscesses in the brain, lung, and abdomen, tuberculosis, lobar pneumonia, bone and joint infection). Inflammatory processes have also been visualised with FDG, e.g., sinusitis, sarcoidosis, thyroiditis, myositis and gastritis. Currently, the most promising clinical applications appear to be the diagnosis of chronic osteomyelitis and infected orthopaedic prostheses, for which standard techniques like bone scanning, leukocyte or gallium scanning have difficulty.

Beyond FDG

Although FDG is the compound behind the recent rapid development of clinical PET, there are many other interesting radiotracers that will find a place into routine clinical imaging. The main driving factors would be the unfolding of strong evidence of clinical usefulness and the ability to synthesize the compound conveniently. In oncology, the study of glucose metabolism with FDG provides information on just one of the many biologic characteristics of tumours. Treatment decisions are increasingly based on other aspects of tumour biology. PET techniques can provide quantitative estimates of regional biochemistry and overcome the difficulties with serial biopsy and problem of sampling error. In fact, PET scanning has been dubbed as “metabolic biopsy”. There is already a fair amount of data on the use of PET to study cellular proliferation (¹⁸F fluorothymidine, ¹¹C thymidine), tumour hypoxia (¹⁸F fluoromisonidazole, ¹⁸F fluoroazamycin arabinoside), and amino acid metabolism (¹¹C methionine, ¹¹C tyrosine). In neurology, the radiochemist’s “menu” of available compounds is even wider, but the most promising agent is probably ¹⁸F fluorodopamine, for diagnosis of Parkinson’s disease. Clinical PET is still rapidly evolving, and we expect to see further developments in radiochemistry, new innovations in imaging devices, more data on new clinical applications, and further refinement of existing applications.

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