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Overview of clinical PET

M N MAISEY

Radiological Sciences, Guy's, King's and St Thomas' School of Medicine, Guy's Hospital, London SE1 9RT, UK

During the last decade, PET imaging has had a progressive impact on clinical medicine, dating approximately from the April 1991 issue of the *Journal of Nuclear Medicine* which proposed that "Clinical PET had arrived". Clinical PET services have grown rapidly and are now widely used throughout clinical medicine, in particular in oncology. This expansion continues and PET is now the fastest growth area in diagnostic imaging.

In the clinical PET centre at Guy's and St Thomas' Hospital, which opened in 1992, few patients were referred early on and, as in many other clinical centres, plans were based on the expectation that the work would be predominantly in cardiology and neuropsychiatry, with only a small amount of oncology. However, as in every other clinical centre worldwide, the massive growth in PET has been almost exclusively for cancer management. The use of FDG-PET (FDG, fluorodeoxyglucose) is now having such a major impact on the management of patients with cancer to the extent that it would now be reasonable to say that optimal oncological practice cannot be achieved without access to PET imaging.

In addition to the clinical evaluations that have been carried out during the last 10 years PET has been one of the first imaging modalities to be subjected to intense scrutiny from a health economics viewpoint in order to evaluate cost effectiveness, *i.e.* whether the benefits are sufficiently great to justify the costs. An increasing number of studies are being undertaken to demonstrate that FDG-PET has costs in relation to improved patient management and outcomes that make it worthwhile [1].

Although there is great potential for other PET tracers the vast majority of clinical PET is still based on the glucose analogue FDG; this is different from glucose but generally "reflects" tissue glycolysis, which is important because there is increased glycolysis in most cancer cells. FDG can be used as an effective imaging agent is because it is trapped and remains in the cell in proportion to the activity of local glycolytic pathways, is sufficiently stable and has a suitable half-life of approximately 2 h. The clinical data are now are sufficiently robust to justify new clinical diagnostic strategies, utilizing FDG-PET in a variety of clinical conditions [2].

Table 1. Applications of FDG-PET in oncology

- Confirmation of suspected malignancy
- Improved cancer staging
- Diagnosis of recurrent disease
- Localization of the site of disease
- Response to therapy

Oncology

Table 1 lists the generic classification of the applications which have resulted in new approaches to many clinical cancer problems. These will be briefly reviewed.

Confirmation of suspected malignancy

Because cancer has higher glycolytic rates than most normal tissues, FDG-PET can be used to differentiate benign from malignant tissue and to a limited extent define the grade of malignancy and hence the prognosis. Data are progressively being acquired to support this. Some of the roles for FDG-PET in establishing the presence and grade of malignancy are shown in Table 2.

Brain tumours were the first tumours to be studied by FDG-PET and it has been well established that it is possible to confirm malignancy and establish grade and prognosis. It may be most valuable for primary brain tumours when biopsy is difficult or carries too great a risk. This is often especially important in relation to cerebral masses in HIV/AIDS patients [3].

The clinical problem of differentiating benign from malignant tumours that has received the most attention has been the evaluation of the solitary equivocal lung nodule when biopsy fails or is impossible. In a recent meta-analysis of the literature on pulmonary masses, 1474 lesions were reviewed from 40 studies; 450 were nodules 2 cm or less, and PET showed a mean sensitivity of 94% for the identification of malignancy in these nodules with a mean specificity of 86% [4].

There have been two cost effectiveness studies

Table 2. Malignancy *versus* benign disease

- Brain tumours
- Lung nodules
- Breast masses
- Connective tissue masses

using decision analysis models, and these showed that a combination of CT and PET for the solitary pulmonary nodules was cost effective [5], as long as the pre-test probability for malignancy was between 0.19 and 0.79. Above 0.79 only CT was necessary and below 0.19 a ''watch and wait policy'' was the most cost effective. FDG-PET is now widely used for the evaluation and management of equivocal lung masses.

Some work has been undertaken to assess the value of FDG-PET in breast lumps, and although there is undoubtedly a high degree of accuracy there is as yet no clear role compared with other modalities [6]. It is worth using FDG-PET to investigate soft tissue masses suspected of being malignant sarcomas and greater accuracy is gained by delayed imaging [7].

Staging

FDG-PET has found a role in the staging of a number of malignant tumours; the most studied are shown in Table 3.

For staging of lung carcinoma (NSCLC), the problem with CT and MR is that it is based on size rather than functional criteria, which results in a relatively poor accuracy in all the reviewed literature. FDG-PET has clearly been shown to improve the management of non-small cell lung cancer [8]. In an unpublished literature review of 1144 cases the mean nodal staging sensitivity using FDG-PET was 96% and the specificity was 80%, with management changes resulting in 20–30% of cases. Between 11% and 16% of distant metastases were detected, which is considerably better than CT alone (Baum, personal communication).

There are now published studies which show that it is also cost effective for NSCLC staging [9]. For patients with enlarged lymph nodes on CT scans incremental cost effectiveness was shown in one decision analysis model to be 11000 Euros per life year saved, and if the nodes were normal size it was only 143 Euros. If these patients do not have a biopsy of positive nodes, to exclude those who might be inappropriately turned down for surgery, then it is probably not cost effective; therefore it is still important, where there is doubt, to biopsy positive nodes. The British Thoracic Society and Society of Cardiothoracic Surgery Working Party on Positron Emission Tomography has confirmed in their guidelines ''It is advocated as a routine test in those centres where PET is available''.

There is now good evidence that FDG-PET is the most accurate staging procedure for Hodgkin's and non-Hodgkin's lymphoma and is helpful in assessing marrow involvement, thereby increasing the effectiveness of marrow biopsy in non-Hodgkin's lymphoma [10]. It is likely, but remains to be proven, that this improvement in staging translates to improved outcomes for the patients. FDG-PET staging of lymphoma has also been shown to save money and is likely therefore to be cost effective [11].

In a prospective study of the cost effectiveness of FDG-PET, cost per correct stage was assessed and showed that when using conventional staging with CT the stage was correct in 81% of cases and was 100% correct with FDG in this particular group. The incremental cost effectiveness ratio, *i.e.* the cost per correct stage, in this particular study was 3000 Euros, which is a very acceptable amount in health economic terms.

Initially it was proposed that FDG-PET might be useful for the local nodal staging in malignant melanoma to avoid unnecessary elective lymph node dissection; however, it has now been shown that sentinel node biopsy is superior [12]. However, in situations when the sentinel node is positive and therefore the likelihood of distant metastases is high, FDG-PET is a worthwhile addition to the routine staging procedures [13].

There have been several studies of the use of FDG-PET for oesophageal cancer staging [14], as in this condition it is well known that routine methods understage, resulting in unnecessary surgery and frequent early relapse. FDG-PET as an adjunct to CT scanning significantly improves the staging mainly by upstaging and changes management significantly in up to 30% of patients.

Diagnosis of recurrent disease

FDG-PET can contribute to the management of a variety of cancers by confirming treatable recurrent disease. The reasons for this are the high sensitivity of FDG-PET and the fact that after surgery or radiation therapy the normal anatomy may be distorted such that standard anatomical imaging methods may be extremely difficult to interpret added to which it may not be possible to distinguish scars from tumour. Table 4 shows the

Table 3. Staging

- NSC lung cancer
- Oesophageal cancer
- Malignant melanoma
- Lymphoma

Table 4. Recurrent disease

- Colorectal cancer
- Melanoma
- Breast cancer
- Head and neck

tumours for which FDG-PET is particularly valuable in assessing recurrences.

Colorectal cancer is particularly important because resection of limited recurrence by metastatectomy is a well established surgical option which significantly improves prognosis, but there is also a high relapse rate owing to undiagnosed metastases. The high sensitivity of FDG-PET for detecting colorectal malignancy together with the whole body capability make it an ideal modality for accurately restaging these patients. It has been shown that up to 30% of patients referred for elective metastatectomy have further lesions either in the liver or elsewhere shown on FDG-PET scans, which either makes surgery contra-indicated or significantly alters the surgical procedure, *e.g.* excising more than a single lesion or even removing metastases from two different sites such as lung and liver [15].

Park [16] and colleagues looked at the cost effectiveness of CT only compared with CT plus PET as a way of evaluating patients with suspected recurrences, who were potential candidates for metastatectomy. They showed that by adding PET the incremental cost effectiveness ratio was $16000 per life year saved. Again, in health economics terms this is good value.

In breast cancer, while it may be helpful in many clinically equivocal situations [17] one particularly difficult area where its value has been established is in suspected brachial plexopathy when morphological imaging can fail to distinguish between malignant infiltration and past radiation plexopathy [18].

Primary brain tumours were the first to be investigated with FDG-PET [19]; whilst it is rarely used routinely now, it can be exceptionally valuable for diagnosing recurrence. The two main reasons why it is helpful are that (1) it may be difficult to distinguish radiation necrosis from recurrence using CT/MRI and (2) low grade tumours may transform to high grade and FDG uptake correlates well with tumour grade.

It was thought that FDG-PET would be valuable for staging squamous cell cancers of the head and neck; however, it turns out that it is probably no better than conventional procedures. What has been shown, however, is that in the diagnosis of recurrent disease it is far superior to conventional imaging methods. In addition, some early studies suggest that it may be worthwhile as a surveillance procedure for high risk patients [20].

FDG-PET may be useful for suspected recurrent malignant melanoma because of the very high FDG uptake of these tumours. Metastases may appear in unpredictable sites so whole body imaging is effective, as it can identify tracer in any soft tissue or skeletal site anywhere in the body [21]. Recently a meta-analysis of sensitivity and specificity of malignant melanoma was published. The sensitivity for detecting malignant melanoma lesions was 92%; with FDG specificity was 90% and the sensitivity of local regional nodes came out at only 55%, although the specificity was quite high. The management changed for 22% of patients with malignant melanoma. It is not therefore appropriate in the initial staging, and sentinel node biopsy is the appropriate means of staging the local lymph nodes [22].

The site of tumour

It may be difficult to identify the site of a primary malignant tumour even when there is a very high probability of disease being present. Table 5 shows when FDG-PET can be most useful for this purpose.

FDG-PET has been found to be useful for identifying the site of squamous cell, head and neck carcinoma when a patient presents with nodes and the primary site is unknown (CUP syndrome) [23], for identifying the site of tumour in patients who are suspected of having para neo-plastic tumours [29], and for patients with raised markers, including colorectal cancer with carcinoembryonic antigen (CEA) marker α-Feto proteins (α-FP) for patients with teratoma. Serum thyroglobulin and calcitonin patients with differentiated follicular and medullary thyroid carcinoma are further examples for which FDG-PET scans have been demonstrated to be of clinical benefit for tumour localization [24].

FDG-PET may also have a role in defining the limits of a tumour for radiotherapy or surgical excision when defining the line of demarcation between tumour and inflammatory response is not possible using anatomical imaging. A head and neck tumour is probably the best example. When a biopsy is required at a particular part of a tumour with, for example, the site of highest grade disease, FDG-PET may be used to direct the biopsy; mesothelioma and sarcoma are two good examples as there may be very considerable inhomogeneity in disease activity throughout the tissue.

Response to therapy

FDG-PET is increasingly being used to measure and predict the response to therapy (radiation or chemotherapy) and this may eventually be

Table 5. Site of tumour

- SCC in cervical lymph nodes
- Elevated markers (CEA, αFP, Tg and Calcitonin)
- Para-neoplastic syndromes
- Unresolved pneumonia

the most important role for PET in the future, possibly with other tracers, and this is discussed in more depth later. FDG-PET can distinguish residual active from inactive masses in lymphoma and teratoma and a recent study demonstrated high positive predictive accuracy for predicting relapse of lymphoma (100% FDG) *versus* (41%) for CT. Increasingly FDG-PET is being used to measure response to therapy in breast cancer, ovarian cancer and for neoadjuvant chemoradiation when it is used for downstaging prior to surgical excision (*e.g.* rectal, oesophageal and lung cancers) but prospective studies are needed to determine the best way to use this information.

It is now essential to have access to clinical PET to manage patients with cancer optimally. It is worth remembering what was said in the 1920s by Ewing, when he was the pathologist at the Sloane Kettering Memorial Hospital, New York: ''It's dangerous to rely too much on histology (anatomy) for the assessment of malignancy''.

Neuropsychiatry

Although clinical PET has become dominated by oncological applications which are also increasing, there remains a small but important role in neuropsychiatry. The first is as an adjunct to the routine work up of patients having elective surgery for the control of partial epilepsy [25]. Often there is no problem in identifying the culprit focus, usually in the temporal lobe with the MRI showing mesial temporal sclerosis that can be lateralized with EEG recordings. When, however, it is not clearcut or the evidence is conflicting then an interictal FDG-PET brain scan may be crucial in demonstrating the lateralization of the hypometabolic changes. Alternatively, it may be helpful if the focus is suspected to be either multifocal or outside the temporal lobes, often in conjunction with ictal single photon emission computed tomography (SPECT) studies which are not possible with PET.

Changes in the FDG-PET brain scan have been shown to be the earliest objective finding for the diagnosis of dementia and the differential diagnosis of the type of dementia. As treatments for Alzheimer's disease become available this role is likely to increase significantly.

Cardiology

PET using NH_3 for myocardial perfusion with adenosine for coronary vasodilatation is the most accurate method of diagnosing the functional effects of coronary artery disease (CAD). However, because of the cost and its limited availability it is not cost effective to use PET for the routine diagnosis of CAD [26], although it remains valuable in particularly difficult cases.

It is certainly possible to diagnose myocardial ischaemia with a high sensitivity and specificity but it is not generally appropriate.

Where FDG-PET with or without NH_3 perfusion studies is valuable, however, is for the diagnosis of hibernating myocardium and the selection of patients for revascularization therapy. This is of particular importance in patients with poor prognosis and at high operative risk for revascularization surgery when the balance between risk and potential benefit is often finely balanced. FDG/NH_3 PET is regarded as the gold standard for hibernating myocardium and the prediction of recovery of function with the consequent improvement in quality of life [27]. The diagnosis of hibernation is also important as it is a good predictor of future cardiac events.

A study was undertaken by Garber and his colleagues who studied PET and other methods for the diagnosis of coronary artery disease using decision analysis modelling. They compared PET and SPECT for the diagnosis of CAD and it showed that it would be necessary to spend $640000/LYS extra to use PET instead of SPECT in a routine context, which would not be appropriate simply for the diagnosis of coronary artery disease. Where PET is appropriate is in patients with known CAD who are being considered for medical treatment or cardiac transplants. Trying to distinguish patients who would benefit from further surgery from those who need to be treated medically or placed on a transplant list is highly cost effective because this avoids unnecessary surgery with associated mortality as well as the high costs involved [28].

What are the future directions of clinical PET? It does appear as though further work with software image registration and integrated PET/CT systems is going to be an important part of the extension of this imaging modality. Huge opportunities will be presented by new ligands and the new concepts of molecular imaging in many diseases and for monitoring gene therapies. In cancer, rather than current staging methods based on disease spread it is likely that the biological characterization of the tumour will become much more important in selecting patients for particular therapies, and PET will have a key role.

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