Positron emission tomography scanning is coming to a hospital near you soon!

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Clin Med 2008;8:134–9

ABSTRACT – Positron emission tomography (PET) is still generally not available in the UK; however, there are plans to introduce a national service in England from April 2008. Plans are also at an advanced stage in Scotland and Wales. The main uses of PET are in preoperative staging of lung cancer, detection of recurrent colorectal cancer, and management of patients with lymphoma. Although these provide the bulk of the referral base, PET is also of use in specific situations in patients with less common cancers, such as head and neck cancer, gynaecological cancer, and melanoma. In its more common uses, PET has been shown to be cost effective. Positron emission tomography will play an increasing role in the evaluation of response to treatment to enable early separation of patients who are responding well to chemotherapy from those who are not responding and need to be transferred to another therapy.

KEY WORDS: colorectal cancer, 18-fluorodeoxyglucose, lung cancer, lymphoma, positron emission tomography

Position emission tomography (PET) has been in clinical use for more than 10 years; however, the provision of PET in the UK is limited and there are few units outside London. The Department of Health has recently issued a document recommending the expected need in England at 40,000 scans per year.[1] This is twice the current provision. Tenders are being assessed, with the aim that roll out should start in April 2008. (Northern Ireland has a well-established service, and Scotland and Wales are establishing their own services.)

This paper describes the established uses of PET, so that potential users who currently do not have access to PET are aware of its role.

Table 1. Radionuclides commonly used in clinical practice.

Radionuclide	Half-life	Parameter
11-carbon	20 minutes	Amino acid metabolism
13-nitrogen	10 minutes	Myocardial blood flow
15-oxygen	2 minutes	Blood flow
18-fluorine	110 minutes	Glucose metabolism

What is PET?

Positrons are positively charged electrons that are produced by the decay of certain radionuclides. They are a form of antimatter, and they travel only a few millimetres before colliding with a negatively charged electron, at which point the two particles annihilate each other. Two equal energy photons that can be detected by a PET camera are produced. The radionuclides that are used in clinical PET are listed in Table 1.

Table 1 also shows the half-lives, which are relatively short. The radionuclides are produced by cyclotrons, which must therefore be located within a distance equivalent to the travelling time of about one half-life from the camera. For 18-fluorine tracers such as 18-fluorodeoxyglucose (18-FDG), which currently is used in more than 95% of clinical studies, the cyclotron could be about two hours away, but for 15-oxygen, it needs to be adjacent to the camera. This has a significant impact on service provision. A cyclotron unit can produce enough 18-FDG to supply several centres, as long as they are within the appropriate distance. The current plan envisages a number of cyclotrons and radiochemistry units placed so that they can supply several units with 18-fluorine tracers (mainly 18-FDG).

The images are acquired with a PET camera. Older cameras (of which a few remain) are PET only. The current standard of camera is a combined PET–computed tomography (CT) camera. The addition of the CT camera enables the image obtained with PET to be corrected for attenuation much more quickly than the method used for PET cameras alone, so the throughput is increased considerably. The other advantage is that CT enables registration of the two images, so it is possible to localise PET abnormalities with CT.

As Table 1 shows, numerous tracers are available for PET of parameters such as blood flow, amino acid synthesis, and cell membrane receptor status. In clinical use, however, most PET scanning is used in oncology, and the service to be rolled out in the UK envisages using 18-FDG only.

Table 2. Generic uses of positron emission tomography.

Generic category	Clinical role	Examples
Diagnosis	Differentiating benign and malignant lesions	Solitary pulmonary nodules
Staging	Lung cancer Colorectal cancer	Presurgical staging Prior to metastatectomy
Assessment of response to treatment	Lymphoma	
Assessment of radiological abnormalities after treatment	Indeterminate radiological findings	Residual mass in lymphoma Scarring after surgery or radiotherapy
Assessment of recurrent disease	Lung cancer Colorectal cancer	Radiological abnormalities Increased levels of tumour markers

18-fluorodeoxyglucose is a radiolabelled analogue of glucose. It is taken up into cells by the glucose transporters (GLUTs) and is phosphorylated. As fluorodeoxyglucose contains deoxyglucose, it does not undergo further metabolism and thus acts as a 'microsphere.' For more than 70 years, it has been known that malignant cells, in general, have increased glucose metabolism because the GLUTs and hexokinase are upregulated, which is why 18-FDG works. The 18-FDG is taken up avidly by many malignant tissues and thus a functional image that enables differentiation from benign tissues is acquired. The difficulty with CT and magnetic resonance imaging (MRI) is that they produce anatomical images, which means that it is difficult to differentiate a scar from malignant tissue post-therapy.

Certain generic uses of PET are shown in Table 2. The precise role of PET for a particular type of tumour will depend on the clinical issues raised in its management. For example, if a patient with malignancy is being considered for curative surgery or radiotherapy, it is important to be sure the disease is localised; however, if the treatment is chemotherapy, this may not be so important.

Lung cancer

Suspected lung cancer is one of the most common reasons for which patients are referred for PET scans.[2] In general, lung cancers take up 18-FDG very avidly, with relatively low uptake in the surrounding, normally aerated lung parenchyma. However, two lung tumours – pulmonary carcinoid and bronchioloalveolar cell cancer – are well known to be less 18-FDG-avid and are frequently listed as causes of false negatives with 18-FDG-PET.

18-FDG-PET has major role in preoperative staging of non-small cell lung cancer (NSCLC) (Fig 1). Determination of nodal

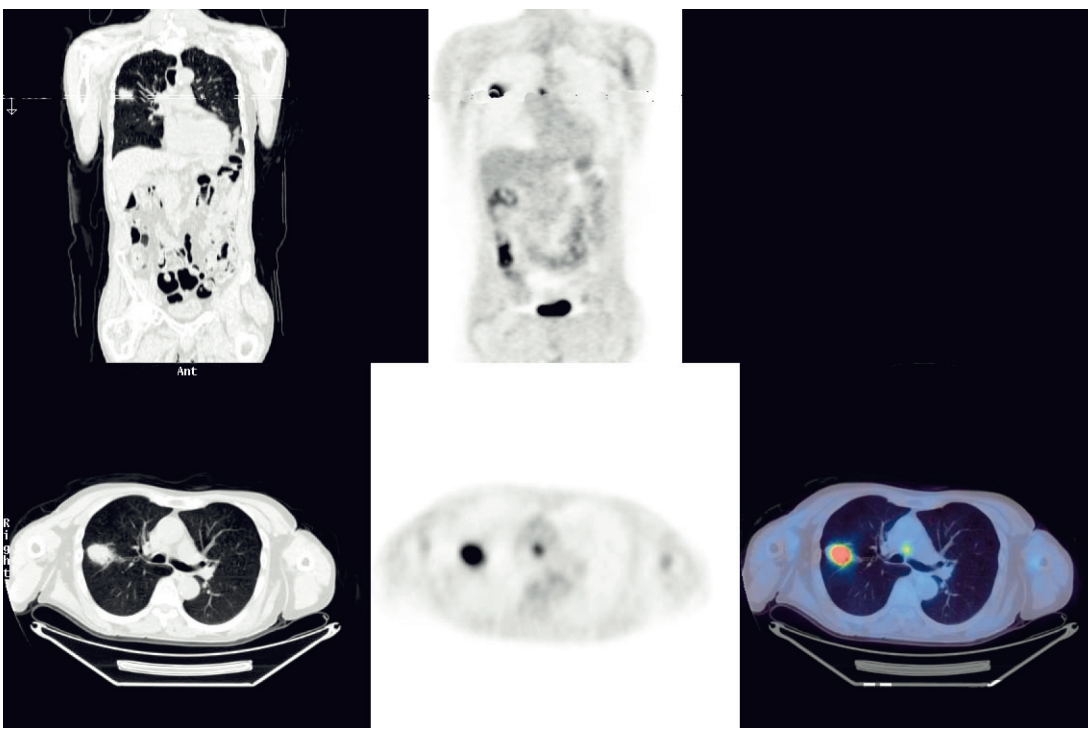

Fig 1. Images from 18-fluorodeoxyglucose positron emission tomography–computed tomography in a patient with potentially operable lung cancer. The image shows a subcarinal node, which renders the cancer inoperable.

involvement by CT relies on size-based criteria that are known to be inaccurate. 18-fluorodeoxyglucose PET can identify small positive nodes and large negative nodes. Metastasis of NSCLC to the adrenal glands, liver, and bones is common, and 18-FDG-PET has an important role in identifying these stage IV cases. A review of the literature in 2001 showed that PET was more sensitive and specific than CT in the assessment of patients being worked up for surgery.[3] Another finding common to many studies is that PET upstages 10–15% of patients, thus avoiding unnecessary surgery. On the other hand, disease is downgraded in 5–10% of patients, who thus can be offered potentially curable treatment. For a comprehensive recent review, see Ref 2. The PET in lung cancer staging (PLUS) study randomised patients into two groups – one who underwent conventional imaging only and the other conventional imaging plus PET – and found that the use of PET can avoid unnecessary surgery in one in five patients.[4]

The NICE recommendations for the use of 18-FDG-PET in lung cancer are as follows:[5]

- every cancer network should have a system of rapid access to 18-FDG-PET for eligible patients
- 18-FDG-PET should be performed to investigate solitary pulmonary nodules in cases where a biopsy is not possible or has failed, depending on nodule size, position, and CT characterisation
- 18-FDG-PET should be performed in patients staged as candidates for surgery by CT to look for involved intrathoracic lymph nodes and distant metastases
- 18-FDG-PET should be performed in patients who are candidates for radical radiotherapy according to CT
- when 18-FDG-PET for N2/N3 disease is negative, biopsy is not required even if the patient's nodes are enlarged according to CT. Consequently, if 18-FDG-PET is not available, suspected N2/3 disease, as shown by CT scan (nodes with short axis >1 cm) should be histologically sampled in patients being considered for surgery or radical radiotherapy.

18-FDG-PET is highly sensitive in the detection of residual or recurrent disease when compared to the non-specific appearance on images from CT. This is important for offering salvage treatment or changing treatment altogether. 18-fluorodeoxyglucose PET has a growing role in planning and monitoring treatment. Radiotherapy can be planned effectively with the knowledge of the extent of the tumour. In patients being considered for radiotherapy with curative intent, therefore, PET will aid delineation of the tumour boundaries (for instance, by separating the tumour from adjacent consolidated lung). Interest in the role of PET in assessing the response to treatment early in the course of chemotherapy is increasing. This could enable treatments that are ineffective to be stopped before unnecessary toxicity occurs.

A solitary pulmonary nodule (SPN), detected incidentally by screening or by symptom-directed work up, is another frequent referral for 18-FDG-PET. The task is to determine whether or not the nodule is malignant or benign. A meta-analysis documented a sensitivity of 96.8% and a specificity of 77.8% for 18-FDG-PET for differentiating benign from malignant lesions.[6] The size of a SPN is not a reliable criterion for its benignity; however, a negative 18-FDG-PET means that a lesion is markedly less likely to be malignant and a surveillance policy is appropriate in many cases. This fact is not without caveats, however, such as poorly avid tumours, lesions smaller than the resolution of PET scanners, and those located close to the moving diaphragm. 18-fluorodeoxyglucose PET is not a tumour marker *per se* as it is also taken up in inflammatory lesions. The most common 'false positive' cause of uptake in the lung is infection, particularly tuberculosis, as this can mimic malignancy radiologically. Although most SPNs in the USA are benign, this is not the case in the UK. The use of PET in the two countries therefore is different: instead of a test performed to determine whether a biopsy is needed, as in the US, PET is used in the UK in patients in whom a biopsy is felt to be hazardous or in those patients in whom the biopsy gave indeterminate results.

Positron emission tomography has established usefulness in more prevalent NSCLCs, which constitute 80% of lung cancers,

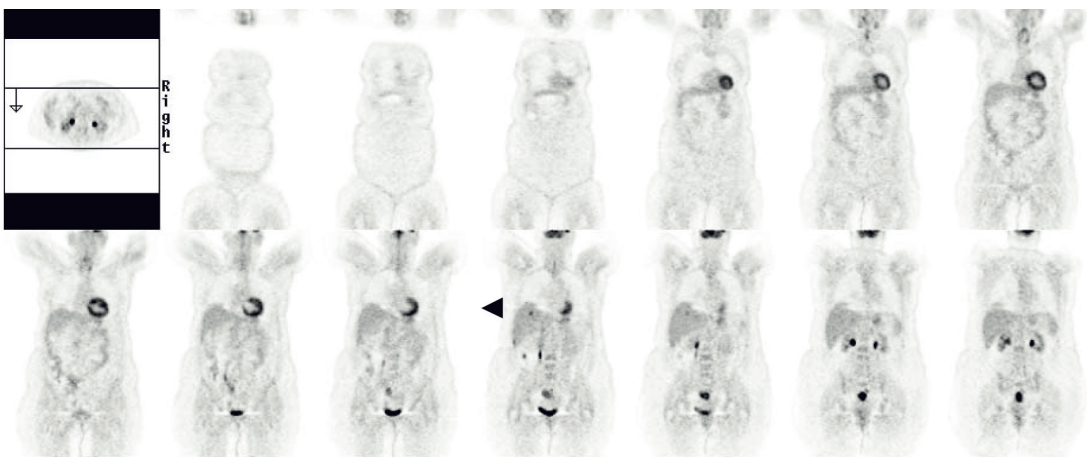

Fig 2. 18-fluorodeoxyglucose positron emission tomography (PET) scans showing PET only images of a patient with possible recurrent colorectal cancer. The images show recurrent disease in the pelvis and a small liver metastasis.

and limited use in small cell lung cancers (SCLC), which constitute 20% of lung cancers. This is because SCLC is managed primarily with chemotherapy, so precise definition of the tumour sites is less important. In the occasional patient with SCLC who is being considered for surgery, PET–CT is performed to confirm that the disease is localised.

Colorectal disease

Positron emission tomography is not used in the primary staging of colorectal cancer because the staging is usually surgical. The best-established use of PET in colorectal cancer is to detect recurrent disease. The most common scenario is rising levels of carcinoembryonic antigen (CEA) in patients with recurrence of colorectal cancer with negative conventional radiological work up (Fig 2).[7] Carcinoembryonic antigen has a sensitivity to detect recurrence of 60–70% and a specificity of 84%.[8] Computed tomography can fail to demonstrate hepatic metastases in about 7% of cases. Furthermore, deposits in the peritoneum, mesentery, and lymph nodes can be missed on images from CT. Differentiation between post-surgical scarring and local recurrence is also not possible on images from CT. A review of the literature on 2,244 patient studies showed sensitivity and specificity of 94% and 87%, respectively, for PET compared with 79% and 73%, respectively, for CT.[9]

A meta-analysis of 577 patients showed the sensitivity and specificity of 18-FDG-PET in the detection of recurrent colorectal cancer to be 97% and 76%, respectively. The overall calculated change in management was 29%.[10] Some other studies have shown the utility of 18-FDG-PET in predicting response to treatment. Response to radiation therapy should be assessed several months after treatment, as the standard uptake value (PET signal) declines only slowly, whereas the decrease in the signal occurs more rapidly with chemotherapy. Likewise, differentiating responders from non-responders in monitoring liver metastases can be achieved with PET earlier than with anatomic means.[7] Positron emission tomography has also been used prior to hepatic metastatectomy. Fernandez *et al* compared the survival of patients who had preoperative PET to rule out disseminated disease with a series of conventional survival curves from historical studies. They showed that the five-year survival increased from 30% to 58% when PET was used to separate those with localised disease.[11]

False-negative results with 18-FDG-PET are well recognised in mucinous adenocarcinoma because of the relative hypocellularity of these tumours.[7] Sensitivity of PET is lower for mucinous tumours than for non-mucinous tumours (58% *v* 92%).

In summary, the current clinical indications are:

- when a patient has increasing levels of CEA after primary treatment or local or systemic symptoms with no increase in CEA
- prior to resection of limited recurrence
- when there is a residual mass after abdominoperineal resection
- for primary staging in selected patients
- for evaluation of radiological abnormalities.

Lymphoma

In many ways, the role of PET in the management of lymphoma is the prime example of the use of PET in malignancy. The management of patients with malignancy can be divided into diagnosis, staging, assessment of response to treatment, evaluation of post-treatment abnormalities (such as residual masses), assessment of recurrence, and, finally, surveillance.

Positron emission tomography is more sensitive than CT in the staging of lymphoma and identifies significantly more sites of disease than CT. Although this may not change the stage very often, it can change the management by better identifying the radiotherapy field or clarifying equivocal lesions. Moog *et al* compared CT and PET in the identification of sites of disease in patients with Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL).[12] Overall, 160 sites were positive on both PET and CT and 25 positive on PET alone (seven truly positive, two false positive, and 16 equivocal because biopsy was not possible). Partridge *et al* studied 44 patients with HD in a retrospective study and identified 159 sites with PET and 84 with CT. As a result, 18 patients were upstaged (nine in extranodal sites), three were downstaged, and 11 had treatment changes. Identifying more sites of disease in a patient who is otherwise known to be at stage 4 obviously has little value, but PET is helpful in confirming that patients who are being considered for radiotherapy are truly at stage 1 or 2. In addition, the boundaries of disease in patients at stage 2 can be determined more accurately with PET than with CT.

The main role of PET in patients with lymphoma lies in the early identification of response or non-response to treatment. Several studies have shown that early complete resolution of abnormalities seen with PET after two cycles,[13,14] or three or four cycles[15] is associated with a prolonged disease-free period. These authors also showed that failure to achieve an early complete response was associated with short disease-free survival.

Radiological masses can remain for years, and this led to the concept in staging of complete remission unknown (CRU). This is another example of the generic role of PET in assessing radiological abnormalities after treatment. Mikhaeel *et al* studied 32 patients: 15 with HD and 17 with aggressive NHL. The median follow up was 38 months. Eight of the nine patients with positive images from PET relapsed. No patient with HD with a negative scan relapsed; however, 2/12 patients with NHL with a negative scan did.[16]

Oesophageal cancer

Although PET has difficulty in identifying local involvement of the lymph nodes in patients with oesophageal cancer, it does identify distant disease. Rankin *et al* identified 3/8 perioesophageal nodes (compared with 4/8 identified with CT) but also found one liver metastasis and seven other distant metastases not previously found.[17] In a prospective study, Duong *et al* found that the use of PET in the preoperative work up of patients with oesophageal cancer had a high impact on 40% of patients.[18] Out of 68 patients, 22 had a significant change in the mode of treatment (for example,

from surgery to radiotherapy or from curative intent to palliation) and five had a change in radiotherapy field as a result of the PET scan. The recent use of combined PET–CT cameras has increased the accuracy of PET and promises to be especially useful in the characterisation of local nodal involvement. Bar-Shalom *et al* found that image fusion was particularly useful in the detection of locoregional nodes and the interpretation of neck and pelvic abnormalities on images from PET, which are two regions of the anatomy that are known to be complex.[19]

Other uses of PET–CT

In gynaecological cancer, PET is of use in restaging. Simcock showed that PET–CT produced a significant change in the management in 34/56 women.[20] Furthermore, Tsai *et al* found that PET–CT image fusion was helpful in directing biopsy and led to a change in management in 22% of patients.[21]

The head and neck is probably the most difficult part of the body to study radiologically, so PET–CT has obvious potential. Shoder *et al* showed that PET–CT had a marginally higher accuracy than PET (96 *v* 90%), but the addition of CT was essential for accurate localisation. Overall, the management was altered in 18% of patients as a result of PET–CT.[22]

Melanoma can metastasise to any organ, including unusual sites such as the gastrointestinal tract, myocardium, and leptomeninges; however, spread to the regional lymph nodes, lung, liver, bone, and brain is more common. 18-fluorodeoxyglucose PET–CT can highlight and localise metastases at unusual sites that are easily missed by conventional imaging modalities.[23] The utility of PET in melanoma at American Joint Committee on Cancer (AJCC) stages III and IV is well established, and PET has proved to be superior to standard diagnostic procedures for the detection of distant nodal and visceral metastases. It has a role in staging, treatment planning, follow up, and assessment of recurrence and response. Studies and meta-analysis reported in literature show the sensitivity, specificity, and accuracy of 18-FDG-PET for detecting recurrent melanoma at 70–100%.[24] In a prospective study, the results of 18-FDG-PET impacted on the management of 40% of patients with suspected recurrent melanoma.[25] 18-fluorodeoxyglucose PET is also shown to detect disease up to six months earlier than conventional techniques.

Summary

This paper shows that PET–CT has a considerable role in the management of patients with cancer. Current access to PET–CT in the UK is extremely limited, but this situation is improving and the 'system of rapid access to PET' called for by NICE should be available in the next few years.[4] To detail all the indications is not possible, but PET is also of use in patients with, for example, thyroid cancer, carcinoma of unknown origin, and paraneoplastic syndromes. Interest in the use of PET in the early assessment of response to chemotherapy is increasing. Positron emission tomography has been shown to predict response in lymphomas and lung cancer after two cycles of chemotherapy. As quite toxic new therapies become available, it is expected that PET will have a role in differentiating responders (who should continue with the treatment) from non-responders (who can stop taking it and be fast tracked to another form of treatment).

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