Clinical Oncology (2007) **19:** 237–255
doi:10.1016/j.clon.2007.02.001

Overview

Positron Emission Tomography in Oncology: A Review

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ABSTRACT:
Positron emission tomography is an evolving imaging tool that is becoming increasingly available for use in clinical practice. This overview will look at the current evidence for the use of positron emission tomography in imaging different tumour types and the different radiotracers that are either available or being evaluated in an investigational setting. Wood, K. A. *et al*. (2007). *Clinical Oncology* 19, 237–255

Key words: Diagnosis, malignancy, PET, PET-CT, radiotracer, staging

Introduction

Positron emission tomography (PET) is a rapidly evolving imaging tool. It has been used for over 25 years in research and has had a clinical role for 15 years. The major clinical applications of PET are in the areas of cardiology and neurology, but over 90% of its workload is in oncology [1]. The most commonly used PET tracer available is 18F-fluorodeoxyglucose (18F-FDG), although there are many more tracers in development capable of imaging a wide array of tissue functions. In a large meta-analysis in 2001, PET was shown to change management in 30% of patients [2]. This was particularly so in patients with lung cancer, where PET helps define clinical management and prognosis, and in lymphoma, where PET already has a role [3–6]. This overview aims to look at some of the more validated tracers in development and the evidence available for the use of PET in clinical oncology.

PET in the UK has been severely restricted by the lack of availability of scanners and cyclotrons, but this situation will probably change over the next 5–10 years [7,8]. The Royal College of Radiologists has formed a working party that has published a document that details a strategy for the provision of PET-computed tomography (PET-CT) throughout the UK. In this document, they have outlined the need for a PET-CT scanner per 1–1.5 million population. They have recommended siting PET-CT scanners mostly with a cyclotron throughout the UK together with mobile or static satellite scanners as required. A two-phase implementation has been proposed that they have recommended take place over the next few years. This document has been presented to the UK Department of Health [9].

PET on its own lacks the fine anatomical detail one is able to achieve with CT. Most studies to date have been based on PET data alone. However, there is an increasing body of evidence to suggest that CT combined with PET details images with a much higher degree of accuracy. As a result, all future PET scanners purchased for clinical use in the UK will be combined PET-CT scanners.

Radiotracers for Clinical Use

The most widely available radiotracer is 18F-FDG. However, many more tracers are being evaluated (see Table 1).

Metabolism

18F-fluorodeoxyglucose

18F-FDG is the most commonly used and available tracer. The increased level of glycolysis within tumour cells led to the discovery that glucose could be used as a possible tracer for the identification of tumour cells within the body [10]. Brown *et al*. [11] showed that the uptake of glucose was directly related to the expression of glucose transporter-1 (GLUT-1). A number of other cell surface glucose transporters upregulated in malignant cells have since been implicated (GLUT-1–5, SGLT1). After the transport of FDG across the cell membrane it is phosphorylated to become FDG-6-phosphate. This compound is trapped intracellularly and is resistant to the further metabolic processes that would normally occur to glucose-6-phosphate. With the increased numbers of glucose transporters on the tumour cell membrane allowing an increased uptake of FDG and the trapping of FDG-6-phosphate, there is a gradual accumulation of FDG in these malignant cells, allowing a three-dimensional image of the tumour to be visualised. There is also evidence to suggest that glucose uptake is increased with worsening grade of malignancy [12].

FDG uptake can also occur in macrophages, neutrophils and muscle cells in tension. A common cause of a false-positive scan is uptake of FDG in areas of inflammation and infection. It can take up to 8 weeks for a surgical wound to

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Table 1 — Uses of radiotracers

Functional radiotracer	Uses
Metabolism	
18F-fluorodeoxyglucose (18F-FDG)	Diagnosis, staging, treatment response, diagnosis of relapse, prognosis
Hypoxia	
2-Nitroimidazoles	
18F-fluoromisonidazole (FMISO)	Low tumour to background ratio and long interval between administration and imaging
FETNIM, FETA, FAZA	Higher tumour to background ratio than FMISO but limited clinical evidence
EF-5	Immunohistochemical hypoxia marker in addition to PET radiotracer
Thiosemicarbazones	
Cu-ATSM	Promising. Response seen after treatment for carcinoma of the lung and cervix
Cellular proliferation	
Nucleoside radiotracers	
3-Deoxy-3-[18F]fluorothymidine (FLT)	Uptake in head and neck, melanoma, lung, breast and colorectal carcinomas
Amino acid radiotracers	
11C-methionine	Improved tumour to background ratio in brain imaging. No renal excretion therefore pelvic imaging possible
Others	
11C-acetate	Pelvic imaging, no renal excretion
11C-choline	Brain imaging. Pelvic imaging
Endocrine	
Hormonal	
18F-fluorodihydrotestosterone	Androgen receptor ligand. Possible role in prostate malignancy
18F-fluoroestradiol (FES)	Oestrogen receptor ligand. Possible role in breast cancer
Catecholamine activity	
11C-hydroxyephedrine	
11C-epinephrine	
11C-phenylephrine	
6-18F-fluorodopamine	Possible use in phaeochromocytoma
Amine precursors	
11C-hydroxytryptophan	
18F-fluorodihydrophenylalanine	Possible use in carcinoid tumours
Adrenocortical steroid synthesis	
11C-etomidate, 11C-metomidate	Distinguishing benign from malignant adrenal masses
Matrix metalloproteinase inhibitors	Investigated for breast cancer imaging
Integrins	
$\alpha_v\beta_3$ integrin	Potential use in melanoma
Monoclonal antibodies	
VG76e	Antibody to vascular endothelial growth factor (VEGF). Uptake in human fibrosarcoma xenografts
Apoptosis	
Annexin V	PET imaging may allow imaging
Bone metabolism	
18F-fluoride	Osteoblastic bone lesions. Possible use in breast and prostate cancer

PET, positron emission tomography; FETNIM, fluoroerythronitroimidazole; FETA, fluoroetanidazole; FAZA, fluoroazomycin arabinoside; EF-5, 2-(2-nitro-1[H]-imidazol-1-yl)-*N*-(2,2,3,3,3-pentafluoropropyl)-acetamide; Cu-ATSM, copper (II)-diacetyl-bis(*N*(4)-methylthiosemicarbazone).

be amenable to PET scanning without the risk of a false-positive report. False-positive scans can also occur as a result of physiological uptake in the smooth and striated muscles, brain, urinary system and the thymus in patients under the age of 25 years [13]. PET imaging after the completion of cancer therapy can result in false positives. This is in part thought to occur as a result of the activation of energy-dependent cellular repair mechanisms after insult to the tumour cell from chemotherapy or radiotherapy. Uptake in the bone marrow and spleen can occur after chemotherapy, this is particularly the case after granulocyte-colony stimulating factors, although this effect is thought to diminish at 3 weeks [14]. Radiotherapy may increase FDG uptake for up to 6 months after therapy, particularly in certain tumour types, i.e. head and neck, and brain.

False-negative scans can occur in tumours that are growing slowly, i.e. mucosa associated lymphoid tissue (MALT) lymphomas. These have a low metabolic rate and therefore require less glucose. Consequently, the FDG uptake is low. Small tumours can fail to be detected on PET scanning due to the limit of the resolution of the scanner and relatively lower sensitivity for detecting smaller tumours. At present, the resolution of most PET scanners is 5—6 mm. However, with developing scanner hardware and software, this limit of resolution will probably improve. Chemotherapy can cause the stunning of tumour cells, resulting in reduced uptake and

false negatives. Artefacts can be seen on images that have not undergone attenuation correction. Whole-body images are generally not attenuation corrected and artefactual lesions can occur, which may subsequently be reported as falsely positive or negative.

Hypoxia

2-Nitroimidazoles

In viable hypoxic cells, 2-nitroimidazole compounds are reduced by nitroreductases to become covalently bound to intracellular protein thiols. In the presence of oxygen, this reaction is reversed and the nitroimidazole is cleared [15]. The use of nitroimidazoles to image regions of tumour hypoxia is under investigation. Knowledge of tumour hypoxia is useful for prognostic information and may help identify regions within a tumour that can be dose escalated with radiotherapy.

18F-fluoromisonidazole. 18F-fluoromisonidazole (FMISO) is a lipophilic compound that enters cells by passive diffusion. In hypoxic cells it is reduced and binds covalently to intracellular macromolecules trapping the FMISO. In normoxic cells, intracellular reduction does not occur and the compound moves freely out of the cell. Numerous studies have validated the use of FMISO as an agent to image hypoxia. However, its low tumour to background ratio and slow washout from normoxic cells have limited its use [16].

18F-fluoroerythronitroimidazole, 18F-fluoroetanidazole, 18F-fluoroazomycin arabinoside. These nitroimidazoles are hypoxic tracers that are trapped in hypoxic tissue by the same mechanism as FMISO. They have a higher tumour to background ratio than FMISO [17] and so may have greater clinical utility. There are no clinical trials that support their use at present.

2-(2-Nitro-1[H]-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)-acetamide. 2-(2-Nitro-1[H]-imidazol-1-yl)-*N*-(2,2,3,3,3-pentafluoropropyl)-acetamide (EF-5) is an agent that has been used for the detection of hypoxia in tissue sections. Labelled with 18F it can be used to generate PET images of hypoxia. Furthermore, it can be detected in tissue using immunohistochemical methods, allowing the correlation of imaging with hypoxia staining. Unfortunately, the images produced are relatively poor because of a low tumour to background ratio [16].

Thiosemicarbazones

Copper-labelled Diacetyl-bis(N(4)-methylthiosemicarbazone). Positron-emitting isotopes of copper compounds based on thiosemicarbazone ligands have been investigated for use as surrogate markers for hypoxia. One such compound, copper (II)-diacetyl-bis(*N*(4)-methylthiosemicarbazone) (Cu-ATSM) has been shown to be an effective marker for delineating hypoxic, viable tissue [18].

Pre-clinical [19] and preliminary clinical studies [20] have shown Cu-ATSM to be a promising surrogate marker for hypoxia within tumours. These initial studies suggest that Cu-ATSM will supply new information regarding tumour function that 18F-FDG cannot reflect. Cu-ATSM is selectively trapped in hypoxic tissue, but is rapidly washed out from normoxic cells. Once given to a patient, it diffuses into normoxic and hypoxic cells, but is retained in substantially higher concentrations within hypoxic cells, which can then be detected by PET. There is quick uptake and slow release from hypoxic tissue and this, together with a rapid loss from normoxic tissues, gives a good signal to background ratio, allowing clear images to be obtained. The mechanism of Cu-ATSM retention within viable tumour cells is thought to be related to the reduced environment of the hypoxic cell. This causes a reduction in the bound copper from copper(II) to copper(I), which dissociates from the ATSM complex and remains in the cell. Two clinical studies in lung and cervical cancer have looked at tumour to muscle ratios of 60Cu-ATSM, which have shown it to have prognostic significance [20,21].

Cellular Proliferation

Nucleoside Radiotracers

3-Deoxy-3-[18F]fluorothymidine. 3-Deoxy-3-[18F]fluorothymidine (FLT) is a thymidine analogue. It is taken into cells and undergoes phosphorylation by thymidine kinase 1. Once it is phosphorylated it becomes trapped intracellularly. Although it is not incorporated into DNA, it is thought to reflect cellular proliferation because thymidine kinase 1 levels increase 10-fold during DNA synthesis. FLT uptake has been shown in a number of malignancies, including lung, colorectal, melanoma and breast cancer. A prospective study of FLT in suspicious lung nodules was carried out by Halter *et al*. [22] who found that although the sensitivity of FDG and FLT PET were similar for the detection of the primary tumour (94% and 90%, respectively), the specificity of FLT (100%) was much greater than FDG (73%). FLT uptake correlates with proliferation markers in colorectal cancer and non-small cell lung cancer (NSCLC) [23].

Amino Acid Radiotracers

11C-methionine. 11C-methionine is a tracer used to assess changes in cell membrane synthesis. It is incorporated into the cell membrane after being transported into the cell. 11C-methionine imaging reflects increased amino acid transport, protein synthesis and cellular proliferation. In cancer, it reflects viable tumour tissue [24]. Methionine is not excreted by the kidneys, it is metabolised in the liver and pancreas. Therefore, it is thought to be a better tracer for imaging tumours of the urogenital tract when compared with FDG. One study comparing 18F-FDG PET with 11C-methionine PET in patients with prostate cancer showed that 11C-methionine PET identified significantly more lesions than 18F-FDG PET [25]. This may be as a result

of the better tumour to background ratio achievable with 11C-methionine. Methionine also has the added advantage over FDG in that it is not taken up by inflammatory cells to the same extent as FDG, because inflammatory cells have a lower protein metabolism than glucose metabolism.

Because of the high rate of cellular proliferation in tumours, it was felt that it would be more specific for malignancy than FDG. However, despite its potential use in imaging urogenital malignancies, it has a similar distribution in lung cancer to FDG [26]. 11C-methionine imaging has not been useful for imaging lymphomas or squamous cell carcinomas of the head and neck [16].

Others

11C-choline. Choline is needed for the synthesis of cell membrane phospholipids, transmembrane signalling, lipid-cholesterol transport and metabolism and methyl metabolism. In cancer cells, choline uptake is increased together with its intracellular metabolism products downstream. High levels of choline metabolites have been found in prostate cancer cells, although in non-cancer cells these metabolites are only present in very low concentrations [27]. 11C-choline uptake into cells after injection is very rapid, allowing imaging to take place as early as 3—5 min after injection [28]. There is very little urinary excretion.

Choline is not cancer specific, showing uptake in benign prostatic hypertrophy that is higher than normal prostate tissue but not as high as prostate carcinoma. This means it cannot be used to reliably distinguish benign from malignant changes [28]. In one particular study, the uptake of FDG and 11C-choline was directly compared. These investigators looked at a variety of malignancies and suspected malignancies. They found that uptake was increased for both markers in malignant vs benign tumours and that although FDG uptake was significantly higher in brain, head and neck, and lung malignancies, the ability to distinguish tumours from background was better with 11C-choline in brain tumours due to lower background levels [29].

11C-acetate. Acetate is metabolised and incorporated into the lipid pool as mostly phosphatidylcholine (a building block for cellular membranes) and neutral lipids. Its incorporation into lipids correlates with cellular growth [30]. It is not renally excreted and therefore can produce images with a good tumour to background ratio in the pelvic region.

Endocrine Markers

18F-fluorodihydrotestosterone

18F-fluorodihydrotestosterone (FDHT) is a radiolabelled ligand of the prostate androgen receptor. The prostate androgen receptor is involved in the growth and proliferation of prostate cancer cells. This ligand is currently being investigated for its role in prostate cancer management, although its use as a tracer may be short lived by virtue of its relatively low uptake in prostate tumour tissue compared with its much higher uptake in normal prostate tissue. Despite this, FDHT is accumulated by most prostate cancer metastases and treatment with the hormonal agent flutamide for 1 day has been shown to reduce FDHT uptake by 50% [31].

18F-fluoroestradiol

18F-fluoroestradiol (FES) has been used for imaging oestrogen receptor-positive breast cancers, although 25% of oestrogen receptor-positive tumours are negative for FES uptake [31]. This has so far been investigated for predicting an early response to tamoxifen treatment in patients with metastatic breast cancer [16]. A decline in FES uptake early after commencing tamoxifen has been shown to be predictive of a response.

11C-hydroxyephedrine, 11C-epinephrine, 11C-phenylephrine, 6-18F-fluorodopamine

These markers take advantage of the tumour-specific catecholamine transport and storage mechanisms that phaeochromocytoma cells retain. After cellular uptake, the radiopharmaceuticals are concentrated and stored in granules. Tumour visualisation can be accomplished within minutes. These agents are also taken up by salivary tissue, heart, liver, pancreas, spleen, gall bladder, kidney and bladder, which may cause difficulties with regard to image interpretation. Direct comparison with 131I-metaiodobenzylguanidine (MIBG) single photon emission computed tomography (SPECT) has not yet occurred [31].

11C-hydroxytryptophan, 18F-fluorodihydrophenylalanine

Carcinoids synthesise amine precursors. Therefore, the administration of 11C-hydroxytryptophan or 18F-fluorodihydrophenylalanine can be used to visualise these tumours. Although these tracers are very specific, false-negative scans may occur in undifferentiated tumours [31].

11C-etomidate and 11C-metomidate

11C-etomidate and 11C-metomidate both bind to 11-beta-hydroxylase, which is involved in the synthesis of cortisol and aldosterone. These can be used to identify adrenocortical cells and aid in the diagnosis of adrenal masses. These tracers are specific for the identification of adrenocortical cells. However, they fail to identify if the cell is benign or malignant. Addition of an 18F-FDG PET scan improves the accuracy of distinguishing benign from malignant lesions in this context [32].

Angiogenesis

Matrix Metalloproteinase Inhibitors

Matrix metalloproteinases are important in the facilitation of tissue invasion and angiogenesis. Inhibitors of matrix metalloproteinases are being investigated for cancer

imaging, bound to positron-emitting isotopes 11C, 18F and 64Cu in breast cancer [16].

Integrins

$\alpha_v\beta_3$ integrin is a transmembrane glycoprotein that mediates the migration of activated endothelial cells through the basement membrane during angiogenesis. Its expression is highly restricted in resting endothelial cells and most normal healthy tissues, although it is expressed in a variety of tumour cells, notably melanoma. This integrin binds to the arginine—glycine—aspartic acid sequence in extracellular matrix proteins such as vitronectin, fibronectin and fibrinogen. A number of tracers that incorporate this arginine—glycine—aspartic acid sequence have been developed labelled with 18F and have shown potential [16].

Monoclonal Antibodies

VG76e is a monoclonal antibody that targets VEGF, which plays a central role in promoting angiogenesis. Labelled with 125I it shows a high tumour to background ratio in human fibrosarcoma xenografts [16].

Apoptosis

Phosphatidyl serine is externalised during apoptosis. Annexin V binds to phosphatidyl serine with a very high affinity. SPECT imaging of technetium-99m-labelled annexin V in order to monitor the response to chemotherapy and radiotherapy has been disappointing because the signal is small and difficult to detect. Labelling of annexin V with a positron emitter such as 18F or 124I would allow PET, which should provide more sensitive imaging with a better resolution.

18F-fluoride

Fluoride diffuses through the capillaries into extracellular fluid in bone. Hydroxyapatite crystals in bone exchange with fluoride ions to form fluoroapatite. The extraction of fluoride into bone is almost 100%. Fluoride uptake in osteoblastic metastatic bone lesions can be three times greater than normal bone and 5—10 times greater in breast cancer metastases. One of the problems with 18F-fluoride is that it is a very sensitive tracer and as such can give false positives with minimal inflammatory change. There are some data to suggest that 18F-fluoride has a greater accuracy for the detection of breast cancer metastases than a conventional bone scan. However, the data so far are not statistically significant [33].

Reporter Gene Imaging

Reporter genes encode proteins in cells that have been treated. These proteins interact with radiolabelled reporter probes that can be imaged with PET. Some of the treatment genes can be directly imaged with a designated PET tracer, others require a reporter gene linked to the therapeutic gene in order for identification by the tracer. This type of imaging can be used to assess successful gene transfer and to monitor the duration of therapeutic gene inclusion [31].

Clinical Indications for Positron Emission Tomography Scanning

PET has a role in the imaging of lymphoma, lung cancer, head and neck cancer, breast cancer, prostate cancer, renal cancer, cervical cancer, endometrial cancer, ovarian cancer, colorectal cancer, oesophageal cancer, thyroid cancer and other endocrine malignancies, sarcoma, melanoma, brain tumours and germ cell tumours, as shown in Table 2.

Lymphoma

FDG PET is a very sensitive imaging modality in both Hodgkin's and non-Hodgkin's lymphoma (NHL). It can be used for identifying extranodal disease in soft tissue [34], spleen [6,34], bone [35] and bone marrow [34,36]. FDG PET has a higher sensitivity (94—100%) in the detection of disease than CT (77—91%) [37]. Several studies have shown that FDG PET has a higher specificity than CT. It identifies more sites of disease, potentially altering staging and management [34,37]. In the staging of lymphoma, PET will probably upstage than downstage when compared with conventional imaging modalities [37]. Young *et al.* [38] looked at the effect of FDG PET on the staging of Hodgkin's lymphoma with CT alone. In this study, 21/38 patients were upstaged, 16/38 had concordant staging and 1/38 was downstaged. The use of FDG PET for staging has shown that focal abnormalities in the bone marrow probably represent disease at presentation, but the absence of uptake cannot be used to exclude the presence of disease in low-grade disease, as this is often not seen. FDG PET can detect lymphoma in nodes less than 1 cm in size and can therefore be used to differentiate equivocal nodes on CT [37]. FDG PET gives additional information in the initial staging of lymphoma. However, it can also be useful for diagnosis, the assessment of a response to treatment, prognosis and the diagnosis of relapse.

Non-Hodgkin's Lymphoma

FDG PET scanning is useful for staging intermediate and high-grade NHL. It is less useful for low-grade NHL. Low-grade NHL has variable uptake depending on the type of histology. MALT lymphomas and small lymphocytic lymphomas are not FDG avid, whereas follicular lymphoma is [37]. Despite this, PET scans in initial staging can be important. If a PET scan is requested after treatment, or at a later stage for the investigation of a possible relapse, a baseline scan will help determine if the lymphoma can be imaged with FDG PET. A negative scan may be difficult to interpret if it is unclear if the patient has disease that concentrates FDG.

FDG PET after therapy may be predictive of a treatment response. Spaepen *et al.* [39] found that 56/67 patients with a negative PET scan after treatment did not relapse, whereas 26/26 of those with a positive PET scan did

Table 2 — Current possible uses of 18F-fluorodeoxyglucose positron emission tomography depending on tumour type

Tumour type	Diagnosis	Staging	Radiotherapy planning	Prognosis	Response to treatment	Assessment of residual disease	Diagnosis of recurrence
Non-Hodgkin's lymphoma	No	Yes	No	Yes	Yes	No	Yes
Hodgkin's disease	No	Yes	No	Yes	Yes	Yes	Yes
Non-small cell lung cancer	Yes	Yes	Yes	Yes	Yes	No	Yes
Head and neck	Yes	No	Yes	Yes	Yes	Yes	Yes
Breast carcinoma	Yes	Yes	No	Yes	Yes	No	Yes
Germ cell tumours	No	No	No	No	No	Yes	Yes
Prostate carcinoma	No	Yes	No	No	No	No	No
Renal carcinoma	No	Yes	No	No	No	No	No
Cervical carcinoma	No	Yes	Yes	Yes	No	No	No
Endometrial carcinoma	No	No	No	No	No	No	Yes
Ovarian carcinoma	No	Yes	No	Yes	No	No	Yes
Sarcoma	Yes	Yes	No	Yes	Yes	No	No
Colorectal carcinoma	Yes	No	No	Yes	Yes	No	Yes
Melanoma	No	No	No	No	No	No	Yes
Brain	No	No	Yes	No	No	No	Yes
Oesophageal carcinoma	Yes	Yes	Yes	Yes	Yes	No	No
Thyroid carcinoma	No	Yes	No	No	Yes	No	Yes
Phaeochromocytoma	Yes	No	No	No	No	No	No
Carcinoid tumours	Yes	Yes	No	No	No	No	No
Adrenocortical tumours	Yes	No	No	No	No	No	No

relapse. Of these, only 12 could have been predicted to relapse based on conventional diagnostic methods. There is evidence to suggest that an interim scan between the second and third cycles or third and fourth cycles of chemotherapy may be a better predictor of relapse than a scan carried out at the end of a course of treatment [40]. Spaepen *et al*. [41] showed that a mid-cycle PET is the best indicator of progression-free survival and overall survival in NHL. Seventy patients were scanned between cycles three and four of their chemotherapy. Thirty-seven patients had a complete response. Of these, 31 remained disease free up to a median follow-up of 1017 days. Of the 33 patients who were PET positive at this point, none was able to maintain a complete remission. Mikhaeel *et al*. [42] completed a similar study in 121 patients with NHL. FDG PET scans were carried out after two to three cycles of chemotherapy. The estimated 5-year survival for the PET-negative group was 88.8%, whereas this was 16.2% for the PET-positive group. This could have major implications with regard to an early change in therapy if there is little or no response to treatment, resulting in a reduction in unnecessary toxicity and improved disease control. False positives may occur after chemotherapy. However, this does not seem to be the case if there is an interval of 7—10 days between chemotherapy and scanning. Scans carried out at this time resulted in good predictions of disease-free survival.

Hodgkin's Disease

Several studies have suggested that the use of FDG PET for the staging of Hodgkin's disease is as good, if not better, than conventional imaging [37]. The addition of FDG PET to conventional staging can result in a change in management in up to 25% of patients [34].

There is some evidence that obtaining an FDG PET scan during treatment can predict outcome. A Danish group [43] showed that an FDG PET scan carried out after two cycles of chemotherapy predicted progression-free survival and overall survival. In this study of 77 patients, 61 had negative FDG PET scans and 16 had positive scans. Eleven of the 16 positive patients went on to develop disease progression, as did three of the 61 negative scan patients. Again, this may indicate a role for an early change in management in patients who have positive FDG PET scans at this time.

The diagnosis of residual masses after treatment can represent a management problem. Several studies have shown the utility of PET scanning if a residual mass is present on the completion of treatment. Positive PET findings on the completion of treatment are associated with a high relapse rate (60—100%), whereas negative findings are associated with a very low relapse rate (0—16%) [37].

Lung Cancer

FDG PET can be useful for the diagnosis, staging, prognosis and radiotherapy planning of NSCLC.

FDG PET can be used as a diagnostic aid for the accurate determination of indeterminate pulmonary nodules (see Fig. 1). Its use is limited in lesions smaller than 1 cm in diameter [44]. When compared with CT [45], FDG was more accurate in distinguishing benign from malignant lesions (87% vs 80%) and was significantly more specific (83% vs

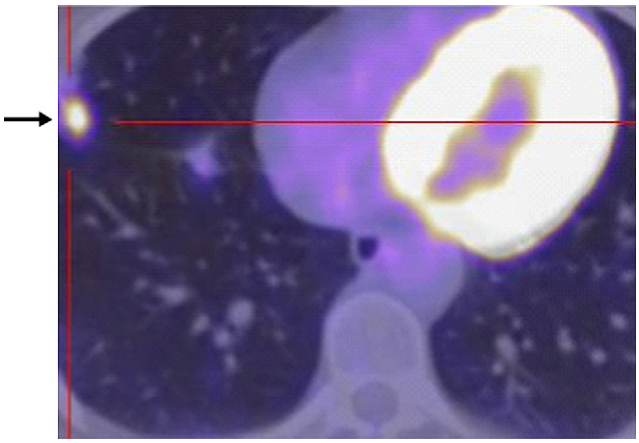

Fig. 1 — Positron emission tomography-computed tomography (PET-CT) image showing fluorodeoxyglucose (FDG) uptake in a suspicious lung nodule at the lung periphery. Note the avid uptake in the myocardium (image courtesy of Dr Wai-Lup Wong, Paul Strickland Scanner Centre, Mount Vernon Hospital, Northwood, UK).

52%). A further study comparing fine needle aspiration cytology (FNAC) with FDG PET showed comparable efficacy of FDG PET with FNAC, but without the potential complications of pneumothorax. In this study, the sensitivity, specificity and overall accuracy for PET vs FNAC were 100% vs 81%, 78% vs 100%, and 94% vs 86%, respectively [46]. The use of FDG PET in the work-up of NSCLC has resulted in a reduction in the number of futile thoracotomies carried out either for primary treatment or diagnosis of lung nodules. Data from a regional Dutch Cancer Centre Registry indicated a 20% drop in the need for resections with the addition of PET imaging. This is of great importance, given the morbidity of this procedure and the patient population who are usually elderly smokers [47].

FDG PET has a greater sensitivity for the detection of more aggressive lung cancers with increased glucose utilisation in comparison with more slower growing, indolent tumours, such as bronchioalveolar carcinomas or carcinoid tumours [48]. In terms of staging, FDG PET is more sensitive (85% vs 61%) and specific (90% vs 79%) than CT for detecting mediastinal disease. Despite this, mediastinoscopy remains the gold standard for mediastinal disease staging [49].

Prognostic information may be derived from FDG PET. A study by Sasaki *et al*. [50] evaluated 162 patients with stage I—IIIb NSCLC. Each patient had an FDG PET scan before either surgery or radical radiotherapy. The standardised uptake value (SUV) of the primary tumour was determined and a cut-off of 5.0 was found to be a significant prognostic factor for overall survival ($P = 0.03$) and disease-free survival ($P = 0.001$). FDG uptake may be of use in assessing treatment response during or after chemotherapy. Fifty-seven patients with stage IIIb or IV NSCLC had FDG PET scans before and after their first cycle of a platinum-based chemotherapy. There was a significant correlation between a reduction in FDG uptake and the response to chemotherapy, the median time to progression and overall survival [51]. This could be used to determine early tumour response to chemotherapy, thereby allowing an early change in management in non-responders and a reduction in unnecessary morbidity. PET-detected metastatic disease burden before treatment with surgery, radiotherapy or chemotherapy has been significantly associated with survival in patients with a single metastasis vs more than one metastasis [52].

PET-CT is a promising tool for planning radiotherapy in NSCLC. FDG PET is better able to discriminate between atelectasis and tumour, allowing increased confidence in tumour delineation and a reduction in the irradiation of normal lung tissue (see Fig. 2). Radiotherapy planning of nodal disease may be improved because of the more sensitive imaging of this area. One study assessed the contribution of FDG PET in the planning of radical radiotherapy for 24 patients with NSCLC. Fourteen patients had their CT-planned volumes altered after information was obtained from a FDG PET scan. In four of these, the volume was decreased due to the inclusion of atelectasis and 10 of these had volume increases due to the presence of unsuspected nodal disease [53].

There is less information on the use of FDG PET in small cell lung cancer. However, in one study, 8/25 patients had more extensive disease than conventional imaging had shown [54].

Head and Neck Tumours

Many structures in the head and neck accumulate FDG, although this tends to be symmetrical with low to moderate uptake. Uptake can be seen at the base of the tongue and tonsils due to accumulation in the lymphatic tissue of Waldeyer's ring. There is also increased uptake in the

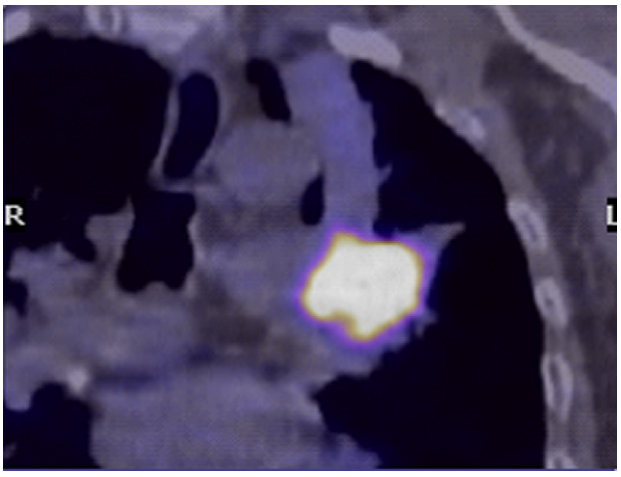

Fig. 2 — Positron emission tomography-computed tomography (PET-CT) image showing uptake in a proximal non-small cell lung cancer (NSCLC) with an area of collapse distally. It would have been difficult to determine if this area was infiltrated with NSCLC in the absence of a PET scan (image courtesy of Dr Wai-Lup Wong, Paul Strickland Scanner Centre, Mount Vernon Hospital, Northwood, UK).

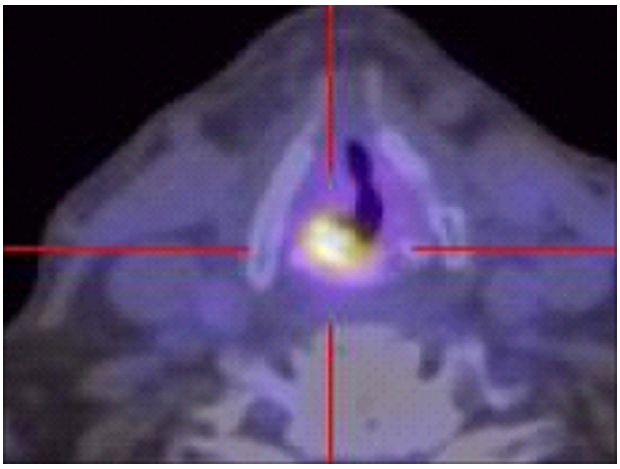

Fig. 3 — Fluorodeoxyglucose (FDG) uptake in a primary squamous cell carcinoma of the larynx (image courtesy of Dr Wai-Lup Wong, Paul Strickland Scanner Centre, Mount Vernon Hospital, Northwood, UK).

genioglossus muscle, the masticator muscles, the tip of the tongue, and the larynx in patients who speak during FDG uptake. Muscles of the eyes and eyelids can show uptake if the patient does not close their eyes.

Head and neck cancers are FDG avid. Between 90% and 100% of known cases can be identified by FDG PET (see Fig. 3). There are occasional difficulties in identifying disease due to the proximity of FDG-avid normal tissue, such as salivary tissue or Waldeyer's ring, but to the experienced eye the site of the primary is usually obvious. FDG PET can be used for the diagnosis of carcinoma of unknown origin. Imaging with FDG PET has resulted in finding a primary tumour in 47% of patients with involved cervical neck nodes and no evidence of a primary tumour site on conventional imaging [55], although one needs to beware of false positives that can result from infection and surgical interventions (i.e. biopsy) carried out before imaging. FDG PET could be a useful screening tool for the detection of synchronous primaries in this at-risk population, although probably not feasible at this time.

There is no definitive proof that the addition of FDG PET scanning provides more accurate staging than conventional imaging of head and neck cancer. There is controversy surrounding the use of FDG PET for staging cervical lymph node disease. Some studies have shown an improved specificity for determining cervical lymph node involvement, whereas others have shown no improvement at all. Adams *et al*. [56] compared FDG PET, CT and magnetic resonance imaging (MRI) with the histopathological staging of 60 neck dissection specimens. In this surgical study, FDG PET was found to be a more accurate method of staging than the other imaging modalities. CT and MRI overstaged or understaged disease in 25%, whereas FDG PET overstaged and understaged disease in 10% of cases.

The importance of SUV as a means for predicting tumour behaviour and prognosis is uncertain at present. One retrospective analysis of 143 patients who had a FDG PET scan at some point after treatment with surgery, radiotherapy and/or chemotherapy for squamous cell carcinoma of the head and neck showed that PET was a highly sensitive method of detecting recurrent disease and providing information about prognosis. The use of PET for detecting recurrent disease in this study had a sensitivity of 96% and a specificity of 72% because of false positives occurring due to tissue inflammation as a result of treatment. The mean SUV in patients who developed a recurrence was 5.8 ± 3.7 vs 2.0 ± 2.3 in those who did not. The prognostic utility of PET scanning these patients was shown, in that patients with an SUV of less than 2.0 had a 2-year relapse-free survival of 85%, those with an SUV of 2.0—6.0 had a relapse-free survival of 45% and an SUV of greater than 6.0 resulted in a relapse-free survival of 10% [57]. Lonneux *et al*. [58] found that accuracy for the detection of residual disease was greatest if the scans were carried out 12 weeks or more after the completion of radiotherapy compared with before 12 weeks. The sensitivity and specificity for the diagnosis of residual disease before and after 12 weeks following the completion of therapy were 100% and 25% vs 96% and 90%, respectively. The low specificity of the early scan represents a high false-positive rate from the effects of treatment.

Breast

FDG PET has shown promise in the diagnosis of primary and recurrent disease, staging, prognosis and therapy response of breast cancer.

Large prospective studies have looked at the use of FDG PET in the diagnosis of primary breast cancer and have shown its potential utility, although tumours smaller than 1 cm, lobular carcinomas and well-differentiated subtypes limit its diagnostic ability. In one study evaluating 185 breast masses in 144 patients, FDG PET scans were done before histological evaluation. The sensitivity for detecting a tumour less than 1 cm in diameter was 57% vs 91% for tumours larger than 1 cm [59]. Carcinoma *in situ* was detected with a sensitivity of 25% and the false-negative rate for the detection of infiltrating lobular carcinoma was 65% vs 24% for infiltrating ductal carcinoma. The specificity for the differentiation of malignant from benign lesions was 90% in several studies [60,61]. Currently, for breast cancer screening, FDG PET scanning would be too expensive and associated with an unacceptable whole-body radiation dose. In terms of diagnosis, it is not as accurate as mammography. So at present it is unlikely to replace mammography for screening purposes.

FDG uptake may have a role in predicting prognosis. One study divided 70 breast cancer patients (68 with invasive ductal carcinoma, one with invasive lobular carcinoma, one with mucinous carcinoma) into two groups. The group with an SUV of greater than or equal to 3.0 had a significantly worse relapse-free survival than the patients with an SUV of less than 3.0 [62].

The use of FDG PET for axillary lymph node staging is limited by its inability to detect small lymph nodes. FDG PET should therefore certainly not replace conventional axillary staging. However, it may provide complementary

information in sentinal lymph node sampling, thereby reducing false negatives from this procedure. FDG PET scanning can be used to identify if patients have involved internal mammary nodes at the time of presentation. Up to 25% of patients with breast cancer have involved internal mammary nodes at the time of presentation, resulting in a worse survival probability [63]. At present, controversy surrounds the effect that treatment of these nodes has on survival. New radiation techniques that allow more focussed therapy or the addition of adjuvant chemotherapy to patients with internal mammary node disease may now alter the natural history of the disease and improve survival. Therefore, knowledge of their involvement may become important.

FDG PET has been shown to be both sensitive and specific in the staging of breast cancer, with Moon *et al*. [64] quoting values of 93% and 79%, respectively. A restrospective study comparing CT with FDG PET in asymptomatic patients with a rise in tumour markers found that FDG PET-detected recurrences in 94% of patients, whereas CT detected recurrences in only 18% [65]. In particular, FDG PET identified 10 sites of bony recurrence that were subsequently confirmed by MRI, whereas bone scanning identified only two. The diagnosis of bony metastases is currently made after a bone scan or MRI. However, if a bone scan is equivocal due to the presence of lytic metastases, FDG PET can be useful for determining the presence of tumour. Lytic lesions may be difficult to identify by bone scanning because of the absence of an osteoblastic response. Additionally, a false-negative bone scan can occur if there is involvement of the bone marrow without cortical bone erosion. FDG PET scanning can identify these lesions, thereby making it a useful tool for the investigation of equivocal scans.

FDG PET has a potential role in the diagnosis of recurrent disease. Brachial plexopathy occurring some time after treatment of a primary tumour may represent either tumour recurrence or a late effect of radiotherapy. Hathaway *et al*. [66] demonstrated the value of combining FDG PET with MRI in this scenario in order to diagnose tumour and identify patients who would benefit from further surgery.

There are emerging data that PET scanning could be used as an early indicator of the response to treatment [67]. The rationale is that a functional change in tumour predates anatomical change. Schelling *et al*. [68] looked at changes in the uptake of FDG after one to two cycles of neoadjuvant chemotherapy. All patients who were found to have a pathological response at the time of surgery had a marked reduction in FDG uptake at the time of the second scan, often down to background. In a further study [69], FDG PET scanning was carried out at the beginning and end of an entire course of neoadjuvant chemotherapy. In these patients, a clinical response was determined after completion of the therapy together with a pathological response and compared with the reduction in SUV. In terms of the clinical response, there was no significant difference in SUV reduction between complete responders, partial responders and non-responders. However, for the pathological response, the reduction in SUV was significantly different between complete, partial and non-responders. The results from these two studies suggest that FDG PET may have a role in evaluating the response to neoadjuvant chemotherapy. Scanning early may identify patients who are not responding to their treatment and who may benefit from a change in therapy, thereby reducing the unnecessary side-effects of ineffective therapy.

Germ Cell Tumours

The use of FDG PET in the management of germ cell tumours is in its infancy. There does seem to be reasonable evidence for the use of FDG PET in the identification of residual disease after therapy. However, the use of FDG PET in other clinical scenarios should be in the context of a clinical trial [70].

FDG PET has been used in an effort to identify patients with clinical stage I non-seminomatous germ cell cancer who are at high risk of recurrence for adjuvant therapy. Currently, there is no evidence to suggest that FDG PET scanning is a more reliable method of identification of patients with true stage I non-seminomatous germ cell tumour disease than CT [71]. Accurate identification of this group would mean that patients with true stage I disease could be placed under observation rather than treated prospectively. The European Germ Cell Cancer Consensus Group have recommended that the use of FDG PET in this situation should be in the context of a clinical trial [72]. A prospective Medical Research Council trial is underway to evaluate the role of FDG PET scanning in stage I non-seminomatous germ cell tumours.

FDG PET can be used to evaluate the presence of residual disease after therapy in both seminoma and non-seminomatous germ cell cancer. In non-seminomatous germ cell tumour, FDG PET scanning can be a highly reliable method of determining the presence of residual disease if the scan is positive [73]. There is a high correlation with FDG uptake and viable tumour tissue. Negative FDG studies do not exclude residual disease because a differentiated teratoma may not be FDG avid. These scans must therefore be interpreted with caution and surgical resections should be carried out as planned. Determination of residual disease after chemotherapy in patients with seminoma can be carried out with FDG PET, particularly in lesions greater than 3 cm. De Santis *et al*. [74] evaluated 56 FDG PET scans in 51 patients and found that residual disease was correctly predicted in all lesions greater than 3 cm in diameter and in 95% of those lesions less than or equal to 3 cm in diameter. FDG PET scanning has been used for the diagnosis of relapse in patients with a mismatch of serum marker levels and absence of visible disease on CT imaging, although larger clinical trials are needed to confirm this.

Prostate

Imaging of the prostate with FDG PET has been disappointing [75]. The limitations of using FDG PET to image the pelvis are as a result of urinary excretion of FDG into ureters and

bladder. Therefore, potentially obscuring pelvic lymph nodes and prostate tissue. With the advent of PET-CT, however, anatomical delineation has improved in comparison with PET scanning alone. As a result of this, FDG PET-CT can now be used for the identification of locoregional disease, as well as more widespread metastatic disease. 11C-acetate [30], 11C-choline [27,28] and 11C-methionine [25] have all been investigated as potential pelvic PET tracers, due to their non-renal route of excretion.

The diagnosis of recurrent prostate cancer is often based on prostate-specific antigen (PSA) rise alone. Frequently, imaging is used to identify the site if there is recurrence, but this is often negative due to the low burden of disease. PET scanning has therefore been investigated to see if it can provide more of a clue as to the probable source of recurrent disease. Hermann *et al*. [76] investigated the use of FDG PET for diagnosing recurrent disease after prostratectomy. This study suggested that a PSA of 2.4 ng/ml seems to provide the level at which the results of FDG PET scanning start to become reliable. At PSA levels less than 2.4 ng/ml, sensitivity and specificity decline. 11C-acetate has shown greater promise than FDG PET for the detection of locoregional recurrence. A study by Fricke *et al*. [77] compared FDG with 11C-acetate uptake in prostate cancer patients with suspected recurrence. 11C-acetate showed a higher sensitivity for the detection of local recurrence (70% vs 43%) and nodal metastases (75% vs 30%), although FDG had a higher sensitivity (75% vs 50%) for the diagnosis of distant metastatic disease, which was mostly bone. Picchio *et al*. [78] compared 11C-choline with FDG PET in 100 patients with a biochemical PSA relapse after either radical prostatectomy or radiotherapy. Choline PET was found to be more accurate for the diagnosis of locoregional and distant metastatic disease than FDG PET. The choline PET images were subsequently compared with conventional imaging. Forty-seven choline scans were found to have areas suspicious for metastatic disease. In 35 of these scans abnormalities were also found on conventional imaging. However, in only one conventional scan was disease found in the absence of uptake on an 11C-choline PET. 11C-methionine is also a promising marker for the diagnosis of metastatic disease in prostate cancer. Nunez *et al*. [79] compared 11C-methionine and 18F-FDG PET scanning with conventional imaging using bone scintigraphy, MRI and CT for staging newly progressive metastatic prostate cancer. The sensitivity for the detection of soft tissue and bony metastases was 70% and 70%, respectively, for methionine and 48% and 34% for FDG PET.

The initiation of hormonal treatment in patients with prostate cancer would seem to diminish the uptake of FDG into these tumours, reflecting a reduced requirement for glucose in these cells. In a series of 10 patients, an FDG PET scan was carried out before the initiation of treatment [80]. A second scan was carried out 1—5 months later to assess the effect of treatment on FDG uptake. In each case the prostate SUV and PSA levels declined. SUV fell by 12—77% and PSA levels fell by 70—99%. This result may show a potential role of FDG PET scanning in determining the biological behaviour of these tumours and their response to hormonal agents.

Bladder

FDG PET does not currently have a role in the primary staging of bladder cancer due to the renal excretion of FDG. The collection of FDG in the bladder and pooling in the lower ureters impair the visibility of bladder wall uptake, therefore making scans difficult to interpret. The addition of CT to FDG PET may improve the imaging utility of PET scanning in local bladder cancer imaging. However, it is unlikely to supersede the capabilities of MRI or CT on its own at present. FDG PET can, however, be used for the identification of metastatic disease and PET-CT will probably further improve this.

11C-methionine and 11C-choline are being investigated as alternative tracers for bladder cancer as they are not renally excreted. Ahlstrom *et al*. [81] showed that methionine uptake was related to tumour grade. However, this was only taken up by 78% of tumours and did not improve local staging of the disease. 11C-choline scans were carried out in 18 patients before cystectomy and in five healthy volunteers [82]. There was little uptake of choline in normal bladders, but uptake in patients with residual carcinoma, suggesting a possible future role in bladder cancer staging. However, more studies are required.

Renal

FDG PET may have a role in the staging of metastatic disease in renal carcinoma. This is limited, however, by small volume disease, although PET-CT may improve this. In a study by Ramdave *et al*. [83], FDG PET changed management in four of eight patients with suspected local recurrence or metastatic disease. PET was true positive in seven patients and true negative in one patient with suspected recurrence. CT of these patients suggested potentially resectable disease in all. However, PET showed widespread metastases in four, making surgical management inappropriate. In a retrospective study by Kang *et al*. [84], FDG PET was compared with conventional imaging in the staging of renal cell carcinoma. The results of imaging were confirmed either histologically or by follow-up of at least 1 year. Conventional imaging was more sensitive than PET. However, PET was more specific, suggesting a complementary role in equivocal cases. CT imaging can result in false-positive reporting due to the presence of benign processes, such as reactive inflammatory processes, scar tissue, normal anatomy variation and artefact. The sensitivity of PET will probably be improved further with combined PET-CT scanning.

Cervix

FDG PET scanning may have a role in the staging of cervical cancer. Although its sensitivity for detecting lymph nodes is poor, it is superior to CT and has the advantage of being rather specific [85]. In addition, the acquisition of FDG PET imaging before therapy can provide information with regards to prognosis.

Grigsby *et al*. [85] carried out a retrospective study of 101 patients with carcinoma of the cervix. These patients

had both CT lymph node staging and whole-body FDG PET imaging before treatment with radical radiotherapy with or without concomitant chemotherapy. CT showed pathologically enlarged pelvic nodes in 20% of patients and para-aortic nodes in 7%. PET images showed abnormal FDG uptake in pelvic nodes in 67% and para-aortic nodes in 21%. In 8% of patients there was uptake of FDG in the supraclavicular nodes, which was confirmed pathologically in all cases. Neither pelvic nor para-aortic nodes were sampled histologically. The 2-year progression-free survival based on para-aortic lymph node recurrence alone was 64% in the CT- and PET-negative patients, 18% in the CT-negative, PET-positive patients and 14% in the CT- and PET-positive patients ($P < 0.0001$). Multivariate analysis of these data showed that the presence of para-aortic lymph nodes as demonstrated by PET was the most significant prognostic factor for progression-free survival. Although this study sounds promising, an alternative retrospective study by Wright *et al*. [86] showed the poor sensitivity of PET by comparing preoperative PET imaging with histological lymph node status in 59 patients with cervical cancer. Pelvic lymph node disease was confirmed pathologically in 32% of patients, which was detected by PET with a sensitivity of 53% and a specificity of 90%. Para-aortic lymph node disease was confirmed pathologically in 9% of patients. PET detected these nodes with a sensitivity of 25% and a specificity of 98%. The mean size of lymph nodes was greater in the PET-positive nodes, with a mean of 15.2 mm (range 2—35 mm), compared with the involved but PET-negative nodes, with a mean size of 7.3 mm (range 0.3—20 mm).

After the completion of therapy, PET imaging may be able to provide information about prognosis. A retrospective review [87] looked at PET scanning after treatment in 152 patients with carcinoma of the cervix treated with radiotherapy or chemoradiotherapy. These patients had post-treatment FDG PET scans 1—12 months (mean 3 months) after treatment was completed. The patients who had no abnormal FDG uptake had a 5-year cause-specific survival estimate of 80%, whereas those with uptake in the irradiated region or outside the irradiated region had cause-specific survival estimates of 32% and 0%, respectively. This study indicates that PET may be useful for prognostic information in this situation. However, further evidence is warranted in terms of a prospective study.

Endometrium

The use of FDG PET to detect recurrence in patients who have undergone treatment for endometrial cancer has been helpful. These scans have shown sensitivities and specificities of 96—100% and 78—88%, respectively [88]. Specificity is typically lower in pelvic malignancies due to the occurrence of false-positive scans occurring as a result of uptake by benign pelvic processes, such as uterine fibroids, endometriosis and cyclical changes in endometrial uptake with the menstrual cycle. Physiological ovarian FDG accumulation can be found around the time of ovulation and during the early luteal phase of the menstrual cycle in pre-menopausal woman. It is therefore recommended that FDG PET scanning in pre-menopausal patients should be scheduled for the interval after menstruation.

Ovary

The use of FDG PET scanning in carcinoma of the ovary shows some promise. It is capable of yielding information with regards to the staging, prognosis and diagnosis of recurrent disease. The addition of FDG PET to abdomino-pelvic CT staging improved the accuracy of staging from 53% with CT alone to 87% when compared with surgical staging [89].

The degree of uptake of FDG has been shown to correlate with the immunohistochemical prognostic indices GLUT-1 and MIB-1 (a proliferation index marker). Its uptake has also been shown to be predictive of histological grade [90] in carcinoma of the ovary. These features may be a further reason for the use of FDG PET in initial staging as an FDG PET scan may be capable of providing not only anatomical information but information on the probable behaviour of disease.

One study has shown that FDG PET may have a role in the diagnosis of recurrent disease not visualised on CT. Bristow *et al*. [91] looked at 22 patients with a rising CA-125 and negative or equivocal CT imaging. All the patients went on to have surgical assessment of their disease after an FDG PET-CT scan. The PET-CT scan was found to have a sensitivity of 83.3% for recurrent disease greater than or equal to 1 cm. The use of PET-CT in this clinical context is supported by a number of studies.

Sarcoma

FDG PET is a promising imaging tool for the diagnosis of primary and recurrent soft tissue sarcoma. There are few data comparing PET scanning directly with conventional imaging, so at present it is recommended that FDG PET should be carried out to elicit additional information about a tumour rather than replace conventional imaging. FDG PET may also be useful for providing information on the biological behaviour of sarcomas and their response to treatment.

A meta-analysis [92] to assess the diagnostic and grading ability of FDG PET in soft tissue sarcoma was carried out by evaluating 441 soft tissue lesions in 15 studies. This showed that 18F-FDG PET can be used to differentiate intermediate and high-grade tumours from benign and low-grade tumours based on SUV. An SUV of greater than or equal to 2.0 will probably represent an intermediate to high-grade tumour and an SUV of less than 2.0 will probably represent a benign or low-grade malignancy. Schwarzbach *et al*. [93] carried out a prospective study on 74 patients with soft tissue sarcoma. This study showed a significant association between preoperative FDG uptake and prognosis. Patients with an SUV of less than 1.59 had a significantly better local control, overall and recurrence-free survival than patients with an SUV of greater than or equal to 1.59.

FDG PET may have a role in the evaluation of response to neoadjuvant treatments. In one small study, FDG PET images

were obtained in patients with soft tissue and musculoskeletal sarcoma having neoadjuvant treatment before surgery. This early study found a correlation between FDG response and tumour pathology at the time of surgery [94].

In Ewing's sarcoma, FDG PET is more sensitive at detecting bone metastases when compared with conventional bone scanning [95]. It may also be of use in determining prognosis. Hawkins *et al*. [96] looked at 36 patients with Ewing's sarcoma and arranged for a PET scan both before and after chemotherapy. An SUV of less than 2.5 after chemotherapy was found to be predictive of progression-free survival independent of the initial disease stage.

Colorectal

FDG PET has a role in the diagnosis of recurrent colorectal cancer. However, there is increasing evidence to suggest that it may be of use in the assessment of disease to neoadjuvant therapies and in the making of a primary diagnosis.

Primary carcinomas of the colon and rectum concentrate FDG, making PET a possible means of identifying disease in the future. Despite FDG uptake, physiological uptake in the bowel can create difficulties with scan interpretation. Sensitivity is dependent on the size of the primary tumour, increasing with tumour size and the grade of dysplasia, becoming increasingly sensitive as cells become increasingly undifferentiated [97—100]. Inflammatory bowel disease, diverticulitis, physiological uptake in colonic mucosa, lymphoid tissue and smooth muscle are non-malignant causes of increased FDG uptake in the bowel. Often the pattern of uptake with such benign causes is widespread or segmental, unlike the focal uptake of FDG with malignancy.

FDG PET is a very useful tool for the diagnosis of recurrent colorectal cancer. After a rise in carcinoembryonic antigen it can take, on average, several months for conventional imaging methods to localise disease relapse. Often metabolically active tumours can be identified before their anatomical identification by conventional imaging and this has been illustrated by PET. In a meta-analysis of 577 patients [101], FDG PET had a sensitivity of 97% and specificity of 76% for the diagnosis of recurrent colorectal disease. For the evaluation of liver metastasis, FDG PET had a sensitivity of 95% vs CT (65%) and MRI (76%). Further smaller studies have been carried out that illustrate the utility of FDG PET in the diagnosis of recurrent disease. Despite the small patient numbers, the effect on patient management is clear, with one study showing FDG PET to have a positive predictive value of 95% and a negative predictive value of 85% [102]. In a prospective study of 102 patients, FDG PET scanning influenced management in 59% of patients with suspected disease recurrence [103], showing the profound effect that FDG PET scanning has in this group of patients.

The use of FDG PET is being investigated for the assessment of patients with unresectable rectal tumours after neoadjuvant chemoradiation before surgery. A prospective study by Guillem *et al*. [104] compared PET scans before chemoradiation with PET scans 4—5 weeks after chemoradiation but before surgery. These patients were followed up for a median of 42 months. A reduction in SUV of greater than 62.5% predicted an improved disease-specific and recurrence-free survival.

Melanoma

Although there is limited evidence to suggest that FDG PET should have a role in the primary disease staging of melanoma, it can be of great help in the detection of recurrent or metastatic disease.

In the diagnosis of relapsed melanoma, several studies have shown FDG PET to have a sensitivity, specificity and accuracy of 70—100% [105]. FDG PET is particularly useful for detecting soft tissue and lymph node metastases. Most lesions missed by PET are usually less than 1 cm in diameter and are either pulmonary, hepatic or brain metastases, which are better detected by CT or MRI, although improvements in the sensitivity of PET are expected with combined PET-CT.

FDG PET is not particularly helpful for staging early disease. Studies have looked at its utility for detecting sentinel lymph node metastases and have shown very low sensitivities. One study by Wagner *et al*. [106] found that the sensitivity for the detection of regional lymph node metastases in early stage melanoma was 21%. This is probably due to the limit of resolution of PET scanners. Nodal metastases smaller than 5 mm in diameter are unlikely to be seen.

Brain

Gliomas demonstrate the uptake of FDG, as does normal brain tissue. The degree with which this occurs has been shown to reflect the tumour grade and survival in both primary and recurrent gliomas [107,108]. The uptake of FDG in normal brain and glioma can be similar, which can make images of gliomas difficult to interpret. As a result of this, a number of other tracers are under investigation to see if they are better at differentiating tumour from non-tumour.

Radiolabelled amino acids methyl-11C-L-methionine, 11C-tyrosine and *O*-(2-18F-fluoroethyl)-L-tyrosine [109—112] are more specific tracers for the detection of brain tumours than 18F-FDG due to their low uptake in normal brain. Methyl-11C-L-methionine uptake correlates with cellular proliferation and has been found to differentiate World Health Organisation grade II gliomas from grade III/IV gliomas [113]. However, one of the problems with this tracer is its uptake in acutely ischaemic tissue and inflammatory tissue, which is clearly a problem for brain imaging.

18F-FLT is a promising tracer. It illustrates the incorporation of nucleosides into DNA in proliferating cells [114]. The relative uptake of 18F-FLT seems to be greater than that of 18F-FDG and methyl-11C-L-methionine, indicating that it may be a more specific tumour marker. Chen *et al*. [115] showed that 18F-FLT uptake was better at predicting tumour progression and survival vs 18F-FDG. Grade II tumours and those that were stable had poor uptake of FLT, reflecting the functional nature of the tracer.

PET may find a role in the diagnosis of primary or recurrent pituitary tumours. Both 11C-methylspiperone and

11C-raclopride bind to dopamine type 2 receptors in pituitary tumours. Although their use is investigational at present, they represent agents that may be useful in the future. Often quite a marked endocrine disturbance can occur before the tumour can be seen on CT or MRI. PET may be useful in this respect, as functional changes probably predate anatomical change.

Oesophagus

FDG concentrates in oesophageal tumours, reflecting its high sensitivity for the detection of primary tumours. In terms of nodal staging, FDG PET is more accurate than CT and endoscopic ultra-sound scan (USS) [116], although the differentiation of involved local lymph nodes from primary tumour can be difficult, resulting in false negatives. Combined PET-CT may improve accuracy in this context. For the detection of metastatic disease, FDG PET has an accuracy of 82% compared with the 64% accuracy of CT and endoscopic USS [117].

The use of FDG PET in the assessment of the response to neoadjuvant chemoradiation has been evaluated in a number of studies. In one study, FDG PET scans were obtained before chemoradiation and 3 weeks after chemoradiation before surgical resection. A reduction in FDG uptake correlated with tumour response histologically. In addition, patients with no response on PET imaging had a significantly worse survival than responders [118]. A similar study by Flamen *et al*. [119] looked at the FDG PET response to neoadjuvant chemoradiation before surgery. In this study, patients were defined as having a major response if FDG uptake in the primary tumour on the second scan showed a greater than 80% diminution in uptake when compared with the initial scan and an absence of FDG uptake elsewhere. The median survival for major responders was 16.3 months vs 6.4 months in non-major responders. They found that the FDG response was a stronger prognostic factor for overall survival than the extent of lymph node involvement as seen on the initial scan.

Thyroid Carcinoma

After surgery, 20% of well-differentiated thyroid cancers relapse. Up to 50% of these fail to be identified with radioiodine due to poor iodine uptake or tumour size. In the context of a rising serum thyroglobulin and a negative radioiodine scan, FDG PET can detect metastases not seen on MRI or CT with a sensitivity of 82–95% and a specificity of 83–95% [120–123]. Recombinant thyroid stimulating hormone (TSH)-stimulated FDG uptake improves the detectability of occult thyroid metastases using FDG PET, although the need for an elevated TSH as routine requires clarification.

Tumour cell variants that do not concentrate iodine, such as Hurthle cell, can be imaged with FDG, whereas before the advent of PET scanning these tumours were very difficult to follow-up. FDG PET may also find a use in the staging and diagnosis of medullary carcinoma of the thyroid and anaplastic thyroid cancer.

Phaeochromocytoma

These tumours are relatively well differentiated. Therefore, tracer molecules that are recognised by the amine precursor uptake and decarboxylation (APUD) pathway are currently under evaluation. Sometimes these tumours can dedifferentiate, so it may not be possible to image these agents dependent on catecholamine uptake and storage. In these undifferentiated tumours, radiolabelled FDG or fluorodihydroxyphenylalanine may be used as an alternative. The sensitivity of FDG PET for the detection of a benign or malignant phaeochromocytoma is 70% [124], whereas for fluorodihydroxyphenylalanine the sensitivity is 100% [125]. Currently, the use of PET for phaeochromocytomas is more an adjunctive imaging tool to be used if CT, MRI or 131I-MIBG scintigraphy is inconclusive or equivocal.

Carcinoid Tumours

MRI, CT and 111In-octreotide are initially carried out for the diagnosis and localisation of carcinoid tumours. However, PET scanning with a variety of agents can be used if the above tests are inconclusive. Carcinoids synthesise amine precursors. Therefore, the administration of 11C-5-hydroxytryptophan [126] or 18F-fluorodihydrophenylalanine [127] can be used to visualise these tumours. For undifferentiated carcinoid tumours, FDG can be used. FDG is often not useful for imaging more differentiated carcinoids.

Adrenocortical Tumours

Many tumours metastasise to the adrenal glands and benign adenomas can often be difficult to differentiate from metastatic disease. CT or MRI is often helpful in determining if an adenoma is benign or malignant. However, FDG PET can be used to provide additional information if the scans are equivocal.

Use of Positron Emission Tomography in Radiotherapy Planning

There are large interobserver differences in defining volumes based on CT and MRI. The addition of PET to planning images has resulted in a smaller interobserver variability and, on the whole, a smaller gross tumour volume (GTV) with a reduction in the standard deviation [128].

Lung

An increase and a decrease in GTV have been noted using FDG PET in planning radiotherapy volumes for the treatment of lung tumours. An increase in GTV will probably occur because of the inclusion of nodal disease not detected on CT; a decrease in GTV may occur by being able to differentiate atelectasis and collapse from active tumour on an FDG PET planning scan [129].

FDG PET has a higher sensitivity for the detection of mediastinal nodal disease than CT. A large study looked at

the pathology of 988 mediastinal lymph nodes and their interpretation on CT and FDG PET-CT. On the basis of CT criteria alone, 75% of the pathologically involved nodes would have been covered by the GTV, whereas 89% of involved nodes would have been covered by the PET-CT planned GTV [130]. Conversely, one study showed that irradiation field sizes to the involved mediastinal nodes alone were smaller if PET-CT planning was used ($9.9 \pm 4.0\,cm^3$) vs CT planning alone ($13.7 \pm 3.8\,cm^3$) ($P = 0.011$) [131]. De Ruysscher *et al*. [132] showed that irradiating these PET-positive nodes alone resulted in only a single treatment failure in 44 patients.

The use of FDG PET scanning in small cell carcinoma of the lung can lead to upstaging in up to one-third of patients [133]. In a study by Kamel *et al*. [134], FDG PET scanning changed treatment in 19% (eight) of patients. Three of the patients had their adjuvant radiotherapy cancelled and five patients had their radiation fields changed.

Head and Neck

Daisne *et al*. [135] looked at the use of FDG PET for the delineation of disease extent in comparison with CT and MRI. In each case, these images were compared with the pathology. The GTVs delineated on CT and MRI were similar, whereas the GTV delineated using FDG PET was smaller. The volume of the resected specimens was smaller still, reflecting an overestimation of all imaging modalities. This is the only study directly comparing FDG PET imaging with pathology. However, a number of other studies have compared radiotherapy volumes based on PET-CT vs CT alone. These studies showed both an increase and a decrease in GTV planned using PET-CT over CT alone [136].

Schwartz *et al*. [137] investigated the correlation between pathological nodal status and PET-CT or CT alone. In this study, FDG PET seemed to correlate with pathological nodal disease better than CT, although there was no difference in GTV delineated using either imaging modality, which would suggest that current practises based on CT planning alone are satisfactory for radiotherapy planning of the neck.

Cervical Tumours

The role of FDG PET in brachytherapy treatment planning is currently being evaluated. One study has already shown its feasibility [138]. A further study has shown that while it is feasible, three-dimensional PET volumes are larger than those that are clinically estimated [139].

In a study investigating the effect of FDG PET on treatment planning, Tsai *et al*. [140] found that five of 18 irradiation fields had to be enlarged in order to include areas of FDG uptake in the para-aortic region.

Brain

There are no data correlating the volume of FDG uptake with the pathology of brain tumours. However, the imaging of different grades of glioma will probably be better with different radiotracers. Methionine PET scanning is probably better for the delineation of low-grade tumours than FDG. FDG uptake is lower in these tumours than the normal surrounding tissue, which would make the delineation of tumour borders difficult. In a study of 13 patients, planning with methionine PET resulted in a smaller GTV than MRI. This occurred as a result of improved confidence in the tumour outline [141].

Treatment failure after radiotherapy will most probably occur in the area of FDG uptake for a glioblastoma multiforme. In a study of 27 patients, the GTV was reduced with FDG PET planning vs MRI planning [142]. Using intensity-modulated radiotherapy to plan this smaller GTV based on FDG uptake, the dose to the glioblastoma multiforme can be escalated by 10–20% [143]. This dose escalation may help to improve local control after radiotherapy.

Oesophageal Tumours

FDG PET can be used in the planning of oesophageal tumours by improving the ability to define cranial and caudal extent, which can be difficult using CT alone. A study of the effect of FDG PET on the CT planning of oesophageal tumours showed that FDG PET upstaged eight of 21 patients by revealing metastatic or nodal disease. Radiotherapy planning based on CT alone would have resulted in the exclusion of FDG-avid disease in 11 of the 16 patients eligible, which was mainly due to discordance in the cranial and caudal extent of disease [144].

Conclusion

PET scanning has been around for many years as a research tool, with a body of evidence that reflects this. Despite this, it is only relatively recently that it has gained widespread acceptance in clinical practice. Its one failing was the lack of anatomical detail, which has been rectified with the combination of CT with PET (see Fig. 4). The increase in the availability of PET scanners, growing clinical expertise and an abundant and growing evidence base have resulted in PET becoming an invaluable clinical resource. Its ability to provide images that reflect tissue function have led to a surge in the development of tracers that can be used to provide a map of biological activity. FDG is the most widely used and readily available PET tracer. This labelled glucose analogue has a proven role in the diagnosis of primary and relapsed disease, staging, treatment response and radiotherapy planning of a number of malignancies. FDG is a relatively non-specific tumour tracer, yet its success as a functional imaging marker is clear.

More specific tracers that have been rationally designed to illustrate tissue function are currently undergoing scrutiny in pre-clinical and clinical investigations. However, beyond the confines of a trial, these novel markers are not generally available. As these new tracers are developed they will probably have a profound effect on imaging, not only in the speciality of oncology, but in medicine as a whole. With evidence and clinical experience gathering, together with the growing provision of PET services, this imaging technique will undoubtedly continue to go from strength to strength.

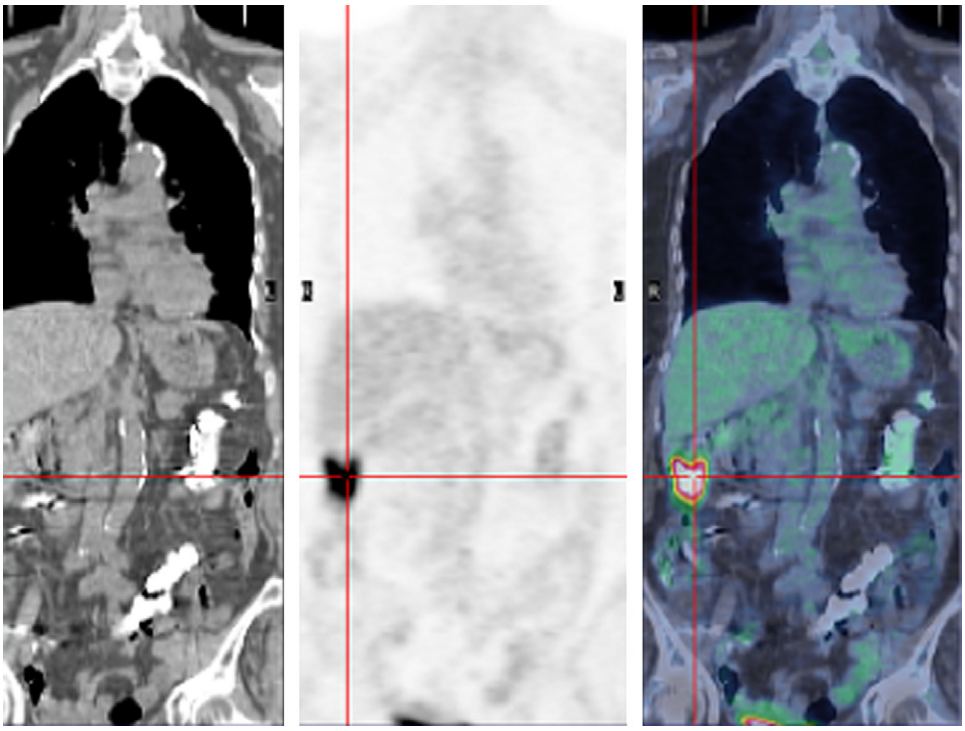

Fig. 4 — Computed tomography (CT) image (left) and fluorodeoxyglucose positron emission tomography (FDG PET) image (middle) of an abdominal malignancy. The combination of PET-CT (right) shows the improved anatomical detail of PET and the higher sensitivity of CT (images courtesy of Dr Wai-Lup Wong, Paul Strickland Scanner Centre, Mount Vernon Hospital, Northwood, UK).

Acknowledgements. The authors would like to thank Dr Wai-Lup Wong for the images he has provided for this overview.

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Received 11 January 2007; accepted 1 February 2007

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