Nuclear Medicine

Edited by Peter J Ell FMedSci, University Chair and Director, Institute of Nuclear Medicine, UCL; Clinical Director, University College London Hospitals NHS Trust, London

18F-fluorodeoxyglucose PET/CT in cancer imaging

Irfan Kayani MRCP FRCR, Specialist Registrar in Nuclear Medicine/Radiology

Ashley M Groves MRCP FRC MD, Senior Lecturer in Multimodality Imaging

Institute of Nuclear Medicine, University College London Hospitals NHS Trust, London

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The introduction of positron emission tomography (PET) and, more recently, integrated PET/computed tomography (PET/CT) has enhanced diagnosis and staging of a number of key cancers. PET provision is currently limited in the UK with only 11 fixed PET/CT scanners available for clinical use in the NHS, but there are plans for a major expansion in the UK for the near future.[1]

Positron emission tomography

PET scanners detect high energy annihilation radiation produced by positron emitting radionuclides. PET imaging allows mapping of abnormal biochemical processes with the use of key metabolic tracers.

Radiotracers

By far the most widely used and successful PET radiotracer is 18F-fluorodeoxyglucose (FDG). Most PET radiotracers, including FDG, require a cyclotron for generation. Other PET radiotracers have limited clinical usefulness as they have very short physical half lives (Table 1). Fluorine-18 has a physical half-life of 110 minutes, allowing distribution of FDG to sites in reasonable proximity to the supplying cyclotron. Metabolically active cells including tumours accumulate FDG within the cytoplasm. FDG is taken into cells via glucose transporter proteins and phosphorylated by hexokinase. It is then 'trapped' within the cell as it is resistant to further glycolysis; its strong negative charge prevents passage back across the cell membrane. FDG is also taken up by activated macrophages, leading to positive uptake in a range of benign infectious and inflammatory pathologies (Table 2).

Table 1. Some other positron tracers with applications in oncology.

- 18F-fluoride bone imaging agent
- 18F-fluorodeoxythymidine tumour cell proliferation
- ^{11}C-choline cellular proliferation
- ^{62}Cu-ATSM hypoxia ligand
- 18F-fluoromisonidazole hypoxia ligand

Table 2. Non-cancerous pathologies which can display 18F-fluorodeoxyglucose uptake.

Inflammatory:

- post-radiotherapy
- sarcoidosis
- vasculitis (eg Wegener's)
- reparative changes post-surgery

Infectious:

- active bacterial, mycobacterial and fungal infections

Diagnostic accuracy

PET has superior diagnostic accuracy to CT and magnetic resonance imaging (MRI) for the staging and restaging of a wide range of cancers.[2,3] In contrast to CT and MRI, which primarily rely on lesion morphology and contrast enhancement, PET reflects metabolic function. Metabolic behaviour typically precedes anatomical change so PET often allows more sensitive and earlier detection of cancer. PET is also valuable in evaluating response to therapy and is more accurate than CT or MRI in differentiating viable tumour from ablated tissue.

Combined positron emission tomography and computed tomography

It is clear, however, that functional and anatomic imaging modalities are complementary because FDG PET has

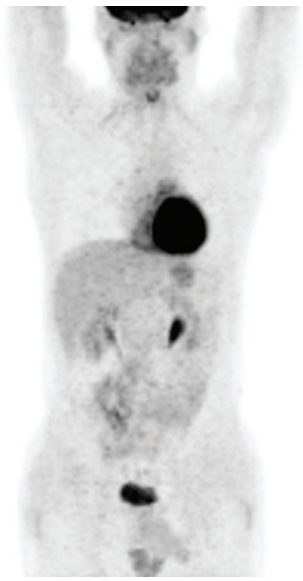

Fig 1. Positron emission tomography (PET)/computed tomography (CT) images demonstrating the normal biodistribution of 18F-fluorodeoxyglucose (FDG) in a patient in complete remission. There is avid FDG uptake in the brain, myocardium and urinary tract, with normal FDG uptake in salivary glands, liver, spleen and gastrointestinal tract.

Table 3. Advantages of positron emission tomography (PET)/computed tomography (CT) over PET.

Technical
Improved quality of PET scan
Faster PET scan, reducing examination times by up to 40% relative to PET
Clinical
Improved:
• lesion localisation
• lesion characterisation
• tumour staging
• patient management

Table 4. Patient preparation and procedure for positron emission tomography (PET)/computed tomography (CT).

- Patients fasted for 6 hours prior to imaging
- Hyperglycaemia reduces the sensitivity of the scan, therefore diabetics should be reasonably well controlled (BM<10 mml/l)
- FDG is injected 1 hour before the scan
- The patient should be calm and relaxed during the scan; 5 mg diazepam po is often given to try to reduce anxiety and muscle and fat uptake of glucose
- A whole-body scan (mid-brain to mid-thigh) is acquired with CT and PET in sequence
- CT images take ca 30 sec and PET images 15–25 min to acquire; the CT protocol typically uses a low radiation dose of reduced quality relative to conventional CT
- The overall effective radiation dose for whole-body PET/CT is 20 mSv

BM = blood glucose; FDG = 18F-fluorodeoxyglucose; po = by mouth.

limited spatial resolution. Precise localisation of lesions is therefore often impossible and physiological uptake of tracer (eg in bowel, urinary tract; Fig 1) may be difficult or impossible to distinguish from adjacent pathology. Integrated PET/CT combines the benefits of separate PET and CT scans while minimising the limitations of either modality in isolation (Table 3). Separate PET and CT scans are acquired on the same instrument without the patient moving, thus enabling precise fusion of the anatomic and functional images. PET/CT improves the classification and localisation of lesions and tumour staging, thereby improving clinical management over PET alone. Patient preparation and the procedure are described in Table 4.

PET/CT is still a relatively new technology with an evolving role in oncology but it is likely to become a leading imaging modality. A summary of the major applications of PET/CT in oncology is provided in Table 5.

Major indications of positron emission tomography/computed tomography in oncology

Lung cancer

Solitary pulmonary nodule. FDG PET and PET/CT are useful in evaluating patients with solitary pulmonary nodules,[3] especially those with difficult to biopsy lesions or equivocal biopsy results. PET has a high accuracy in discriminating carcinomas from benign pathology in lesions larger than 1 cm in diameter.

Non-small cell lung cancer. FDG PET/CT has been shown to be the most accurate imaging modality in staging non-small cell lung cancer (NSCLC):[4,5] 70–97% accuracy for tumour staging, 78–93% for nodal staging and 83–96% for overall tumour node metastasis (TNM) staging. PET/CT is superior for tumour staging compared with CT, being able accurately to discriminate tumour bulk from adjacent atelectasis and also in overall nodal and TNM staging relative to PET and CT.

According to the recently issued National Institute for Health and Clinical Excellence guidelines on NSCLC,[6] FDG PET imaging should be readily available and performed in the great majority of patients with NSCLC. FDG PET has a high negative predictive value for nodal involvement. Nodes with negative FDG uptake do not require surgical confirmation even if they are enlarged by CT criteria. The specificity of PET (89%) for nodal disease is more limited due to inflammatory change causing FDG uptake; therefore, if in doubt, involved N2 and N3 nodes should be confirmed with histology. PET/CT is useful for monitoring the response to radiotherapy and chemotherapy in NSCLC.

Table 5. Indications for 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT).

Major indications	Primary staging of NSCLC and lymphoma Restaging of lymphoma following therapy Detection of recurrence in colorectal cancer and lymphoma
Secondary indications	Detection of recurrent head and neck cancer Staging of advanced melanoma (stage III and IV) and breast cancer Staging of bladder cancer and metastatic renal cancer Detection of unknown primary cancers, especially with occult head and neck cancers Paraneoplastic syndrome
Emerging indications for PET	Radiotherapy planning Early interim treatment assessment, especially in lymphoma and NSCLC to guide response-adapted therapy
FDG PET/CT of use in selected patients (mainly for evaluation of response to therapy and detection of recurrence)	Testicular cancer Oesophageal cancer GIST Gynaecological tumours Thyroid cancer (with negative I-123 and I-131 scans) Neuroendocrine tumours (with negative octreotide scans) Pancreatic cancer

GIST = gastrointestinal stromal tumour; NSCLC = non-small cell lung cancer.

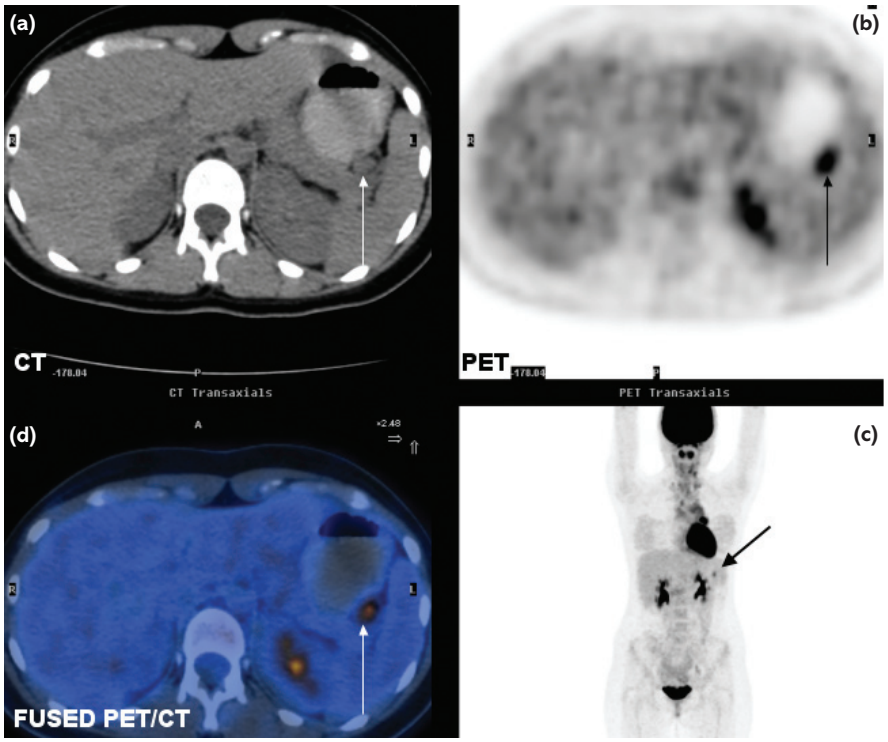

Fig 2. A 13-year-old boy with newly diagnosed non-Hodgkin's lymphoma, showing multiple sites of abnormal 18F-fluorodeoxyglucose (FDG) uptake in cervical and mediastinal lymph nodes. On **(a)** computed tomography (CT) alone and **(b)** and **(c)** positron emission tomography (PET) alone it is impossible confidently to localise the focus of FDG activity (arrow) in the upper abdomen; **(d)** combined PET/CT clearly demonstrates that FDG uptake here is due to a lymph node adjacent to greater curve of stomach. In this case, the PET/CT finding leads to upstaging of lymphoma from stage II to stage III.

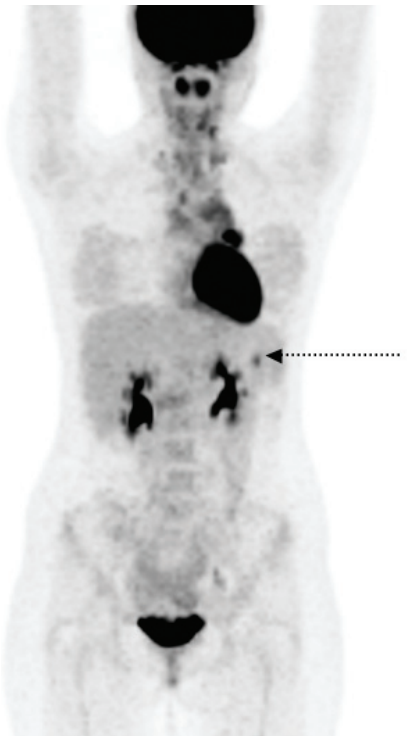

Fig 3. Fig 2c enlarged.

Small-cell lung cancer. The role of FDG PET and PET/CT in patients with small-cell lung carcinoma has yet to be established.

Colorectal cancer

Positron emission tomography. PET has limited use in the primary diagnosis of colorectal cancer due to FDG uptake in normal bowel, adenomatous polyps and inflammatory bowel lesions.[3] However, it is particularly useful in detecting recurrent cancer post-surgery or post-radiotherapy. PET can also improve survival rates after resection of liver metastases by excluding patients with unresectable extrahepatic tumour.[7] PET has limited sensitivity in detection of very small liver metastases and does not provide adequate anatomical information for the surgeon prior to hepatic resection.

Positron emission tomography/computed tomography. Early papers evaluating PET/CT have shown reduction in the number of false-positive and equivocal lesions and a higher diagnostic accuracy in the pelvis compared with PET alone.[8,9] The regional sensitivity and specificity of PET/CT in recurrent colorectal cancer are 89% and 98%, respectively, with a superior overall diagnostic accuracy (88% vs 71%) relative to PET alone. PET/CT is more sensitive and specific than PET in detecting recurrence in patients with a residual presacral mass.[8] Comparison of contrast-enhanced CT and PET/CT has shown comparable sensitivity in detecting liver metastases, but PET/CT is superior for the detection of recurrent liver tumour after hepatectomy.[10]

Lymphoma

FDG PET imaging is indicated in the initial staging and restaging of patients with Hodgkin's lymphoma (HL) and high-grade non-Hodgkin's lymphoma (NHL).[3] FDG PET has now superseded Ga-67 imaging for staging and restaging in lymphoma.[3] FDG PET overcomes problems associated with contrast-enhanced CT, namely the inability to detect disease in normal sized lymph nodes and partial or slow response of tumour volume to therapy. PET is more accurate than CT in assessing remission and estimating prognosis following treatment. FDG PET is particularly effective in evaluating patients with residual mass post-therapy. Early FDG PET scanning following only two cycles of chemotherapy accurately predicts long-term outcome in HL and aggressive NHL. An exciting potential application of this is early response-adapted treatment to target non-responsive tumours with more intensive toxic treatment.

Results. Initial studies with PET/CT in lymphoma have shown promising results. Improved staging is achieved compared with contrast-enhanced CT[11,12] or stand-alone PET.[13] PET/CT has a sensitivity of 91–94% and specificity of 88–100% in lymphoma.[11–13] PET/CT reduces false-positive findings on PET-only scans due to asymmetrical

Key Points

Non-small cell lung cancer:

18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) (or PET/computed tomography (CT)) should be performed following staging CT scan for all patients with potentially operable cancer

Colorectal cancer:

PET/CT is not currently indicated for the diagnosis of primary colorectal cancer (CRC)

PET/CT should be used where available as the initial staging modality in patients with suspected recurrent CRC

Lymphoma:

PET/CT should be used in initial staging of all patients with Hodgkin's lymphoma and aggressive non-Hodgkin's lymphoma (NHL) but not low-grade NHL

PET/CT FDG uptake is more accurate than CT in determining response to therapy and prognosis following therapy

Early interim treatment PET scans appear to be accurate predictors of long-term outcome in Hodgkin's lymphoma and NHL

KEY WORDS: 18F-fluorodeoxyglucose, oncology imaging, positron emission tomography (PET)/computed tomography (CT)

tracer activity within cervical fat, salivary glands or intercostal muscles.[13] PET/CT further changes lymphoma staging relative to PET in approximately 10% of patients due to both upstaging and downstaging of disease (Fig 2; Fig 3).[11,13]

Head and neck cancer

Although at present MRI is probably the first-line imaging modality for primary staging of head and neck cancer, PET is useful in patients with locally advanced, high-stage tumours and in depicting recurrent head and neck cancer.

Detection and resection of occult head and neck primaries in patients with cervical nodal metastases improves outcome. PET has a higher sensitivity than MRI or CT and is able to depict occult primaries in approximately one-quarter of patients with negative CT and MRI scans.

Positron emission tomography/computed tomography. The advantage of PET/CT over PET alone will probably be most relevant in head and neck cancer due to the complex anatomy and the difficulty in distinguishing post-surgical changes and multiple sites of physiological FDG uptake from adjacent pathology. PET/CT is more accurate in depicting tumours than PET alone,[14] it improves the reporter's confidence compared with PET, reduces the number of lesions classified as equivocal and improves interobserver variability.[14]

Other cancers

PET/CT has a valuable role in evaluating response to therapy and detecting recurrence in a range of metabolically active tumours such as gastrointestinal stromal tumour, oesophageal and testicular tumours. It also has a useful role in selected patients with advanced breast cancer, stage III or IV melanoma, metastatic renal and bladder cancer, gynaecological cancers and poorly differentiated neuroendocrine and thyroid cancers. The role of PET/CT in hepatoma, primary staging of renal cancer, early stage breast cancer, stage I and II melanoma, prostate cancer and well differentiated neuroendocrine and thyroid tumours is yet to be established.

Radiotherapy and PET/CT

The incorporation of functional imaging has great potential to optimise radiotherapy. PET/CT can alter standard pretherapy CT-based fields: for example in lung cancer, by discriminating tumour from adjacent atelectasis and detecting unsuspected distant nodal metastases. The distribution of viable cells is usually not uniform within tumour masses (eg tumour necrosis). Most of the initial studies utilising PET/CT have been in NSCLC and head and neck cancer.[14,15] PET/CT has been shown to change the radiation field relative to CT in more than half of patients.[14]

By improving tumour delineation, PET/CT can be used to modify radiotherapy to reduce radiation dose to normal tissues and allow selective dose escalation to metabolically active areas within tumour bulk. In this way, the probability of in-field and marginal field recurrence may be reduced. The results of prospective trials currently underway will help determine the impact of FDG PET/CT-based radiation fields on tumour recurrence and patient survival.

Future developments

Some ongoing trials which will help define the role of PET/CT in oncology in the future include the evaluation of:

- the impact of early PET/CT response-adapted radiochemotherapy regimens on patient outcome
- PET/CT-based radiation fields on patient outcome in radio-oncology, and
- the role and incremental benefit of utilising diagnostic quality CT in FDG PET/CT protocols (for tumour staging).

Conflicts of interest

None.

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Renal imaging

Sharon F Hain BSc MBBS FRACP, Consultant Physician in Nuclear Medicine, *Institute of Nuclear Medicine, University College London Hospitals NHS Trust, London*

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Renal imaging with compounds labelled with the radionuclide technetium-99m (^{99m}Tc) is widely performed to evaluate the renal system and provide mainly functional but also some anatomical information. There are primarily two types of imaging: static and dynamic.

Static renal imaging

^{99m}Tc-dimercaptosuccinic acid (DMSA) is the tracer used in static imaging. Following intravenous (iv) injection, it is taken up in the proximal tubules where it is fixed. Imaging is performed three hours later and should include anterior, posterior and right and left lateral oblique views to give the best depiction of outline. The scan gives good definition of the cortical outline of the kidney.

A normal study shows smooth homogeneous uptake of tracer with a lower concentration in the collecting system (Fig 1). Normal variants include prominent columns of Bertin and flattening of the left superolateral aspect due to splenic impression. DMSA studies can be used to identify and diagnose many conditions, including horseshoe kidney (Fig 2), cross-fused renal ectopia, duplex systems and kidneys outside the normal anatomical location (eg pelvis), all of which may have been missed on ultrasound.

The main abnormality assessed with DMSA is cortical scarring due to reflux and infection. This appears as areas of decreased uptake in the cortex, with cortical thinning and volume loss (Fig 3). The major pitfall is that acute pyelonephritis may give this appearance for up to three months following infection. It is therefore necessary to know whether there has been a recent urinary tract infection; if so, follow-up studies at 3–6 months should be performed. Defects due to the acute infection will resolve, whereas scars are permanent.

DMSA also provides non-invasive accurate assessment of the differential function of the kidneys (normal range for each 45–55%) (Fig 1); it may also be used to measure the differential function within one side (eg a duplex).

Single-photon emission computed tomography or pinhole imaging is sometimes performed; this enables visualisation of smaller lesions/scars and may increase the level of certainty.[1,2]

Dynamic renal imaging

The two most commonly used tracers in dynamic renal imaging are ^{99m}Tc-mercaptoacetyltriglycine (MAG-3) and

Key Points

- **Nuclear medicine renal imaging provides important functional information on the kidneys**
- **Dynamic renography can be used to evaluate many conditions, including obstruction, renal artery stenosis and vesico-ureteric reflux**
- **^{99m}Tc-dimercaptosuccinic acid identifies renal scarring and gives differential function**
- **In renal transplants, acute rejection can be differentiated from acute tubular necrosis**
- **Glomerular filtration rate can be evaluated by non-imaging studies with low radiation dose**

KEY WORDS: captopril renogram, ^{99m}Tc-dimercaptosuccinic acid (DMSA), glomerular filtration rate, ^{99m}Tc-mercaptoacetyltriglycine (MAG-3), obstructive uropathy, renal scarring