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PET/CT in oncology

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Positron emission tomography (PET) is one of the important clinical molecular imaging techniques used in oncology. In contrast to anatomical imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI), molecular imaging gives information about metabolism and function at the cellular and molecular level, albeit at the expense of poorer spatial resolution.

Clinical applications of PET imaging in cardiology, neurology and infection are increasing rapidly but its major role lies in oncology. In the last decade, combined PET/CT scanners have been introduced to facilitate hybrid metabolic and anatomical imaging. Anatomical and functional images are acquired sequentially without moving the patient, giving optimal co-registration of the data for improved interpretation.

Positron emission tomography

PET is a nuclear medicine imaging technique with which tomographic images of the distribution of a radioactive tracer are acquired following intravenous administration of the tracer. Positron-emitters contain an excess of protons in the nucleus which produce a positive electron (positron). Positrons interact with neighbouring electrons in matter to produce paired 511 keV gamma rays (annihilation) which travel approximately 180° from each other. PET scanners are designed to detect the two gamma rays generated from the annihilation event. They can place the point of emission more accurately than standard single photon nuclear medicine gamma camera imaging, allowing better spatial resolution and quantitative accuracy in comparison with SPECT imaging. A commonly used parameter in clinical PET imaging is the standardised uptake value, a semiquantitative method to calculate the concentration of radioactivity in a tumour or organ.

^{18}F-fluorodeoxyglucose

^{18}F-fluorodeoxyglucose (^{18}F-FDG) is the most common tracer used in PET imaging for oncological disease. As a glucose analogue, it has a similar distribution to glucose. Increased glucose metabolism occurs in most cancers due to overexpression of membrane glucose transporters (eg GLUT 1) and high glycolytic enzyme expression and activity (hexokinase).[1,2]

^{18}F-FDG is phosphorylated by hexokinase to ^{18}F-FDG-6-phosphate which does not undergo further metabolism, is trapped and accumulates inside the cell. The half-life of ^{18}F-FDG is approximately 110 min, making it feasible to scan patients at sites distant from the cyclotron from which ^{18}F-FDG is produced.

Table 1. Indications for performing PET/CT in oncology.[3,4]

- Differentiate benign from malignant anatomical lesions
- Detect an occult primary in patients presenting with metastatic disease
- Cancer staging
- Assess treatment response
- Tumour recurrence
- Assess disease progression
- Select suitable site for biopsy
- Guide radiation planning
- Differentiate post-therapy changes (surgical, chemotherapy or radiotherapy) from residual disease

PET/CT in clinical oncology

The oncological applications of ^{18}F-FDG PET/CT imaging are wide (Table 1).[3] ^{18}F-FDG has high sensitivity but is not tumour-specific. In some low-grade cancers, for example, uptake may be poor or it may be difficult to differentiate between post-treatment inflammatory changes and residual disease.

The role of PET/CT has expanded in oncology over the last decade and is performed as a routine investigation in a number of common cancers.

Lung cancer

^{18}F-FDG-PET/CT is considered essential to exclude unsuspected distant metastases and avoid futile surgery in patients deemed candidates for curative treatment of lung cancer. Imaging of mediastinal lymph nodes allows targeted sampling and approximately 10% of patients may be found to have occult distant metastases. PET can be useful for restaging in patients suspected to have recurrence after curative therapy.

Characterisation of a solitary pulmonary nodule is a relatively common clinical problem faced by chest physicians. ^{18}F-FDG-PET/CT is superior to CT in characterising most of them. A metanalysis of 450 patients in 13 studies reported sensitivity and specificity of ^{18}F-FDG-PET in solitary pulmonary nodules of 92.4% and 83.3%, respectively.[5] False-positives can occur with active inflammatory or granulomatous lesions.

Occasionally, adenocarcinoma, bronchioalveolar carcinoma and lung carcinoid show minimal or low-grade ^{18}F-FDG activity. Subcentimetre lung nodules may be beyond the resolution of PET imaging and can be falsely negative.

Lymphoma

^{18}F-FDG-PET/CT is recommended for initial staging in lymphomas that are typically ^{18}F-FDG-avid (eg Hodgkin's lymphoma (Fig 1), diffuse large B cell lymphoma and stage 1 follicular lymphoma). Multicentre and multinational trials are underway to determine if early assessment of chemotherapy response (eg after two or three cycles) will allow escalation or de-escalation of treatment. ^{18}F-FDG-PET/CT can be useful at the end of chemotherapy to characterise residual masses identified on CT to determine whether they are metabolically active, implying residual disease requiring further treatment.[6]

Head and neck tumours

^{18}F-FDG-PET/CT can be particularly helpful when recurrent disease is suspected in head and neck cancers. Previous surgery and radiotherapy may have distorted normal structures, making interpretation

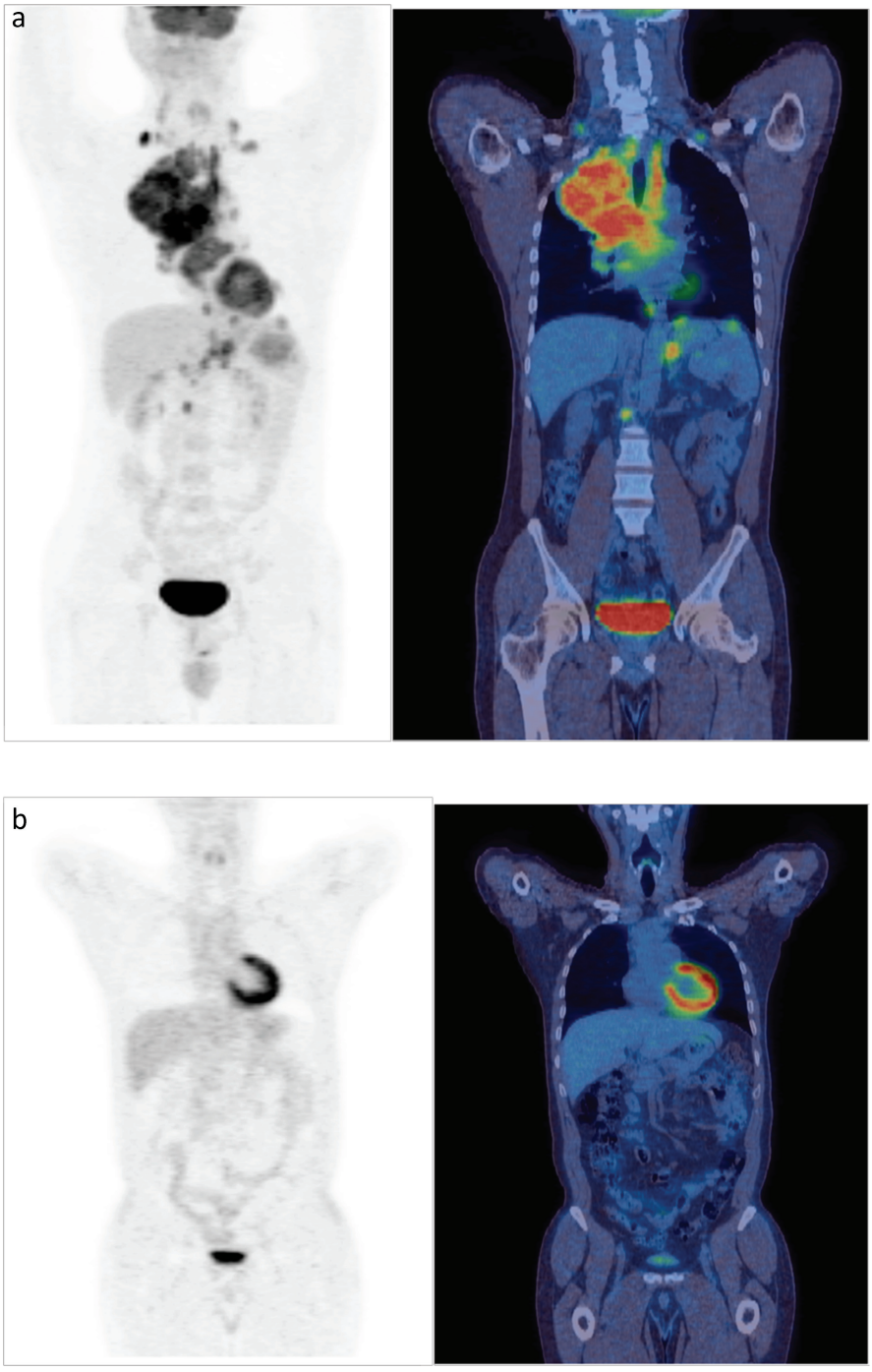


Fig 1. Hodgkin's disease: (a) Coronal images show increased metabolic activity in multiple lymph nodes above and below the diaphragm and a large anterior mediastinal mass. (b) Post-chemotherapy, there is complete resolution of ^{18}F-FDG uptake in lymph nodes and mediastinal mass, in keeping with a complete metabolic response.

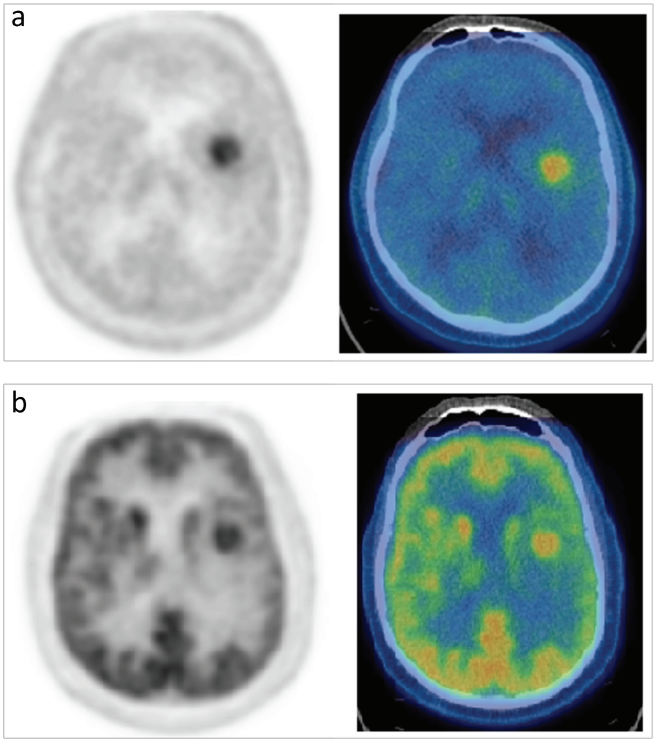


Fig 2. High-grade glioma: (a) Transaxial brain scan shows increased ^{11}C-methionine in a left frontal lobe lesion; (b) ^{18}F-FDG PET/CT shows increased metabolic activity at the same site indicating a high-grade tumour.

of both CT and MRI more problematic. It can also be useful in detecting unknown primary tumours (Fig 2).[7]

Breast cancer

^{18}F-FDG-PET and PET/CT have no routine role in characterising breast masses but may be helpful in patients with prostheses when mammography is difficult. PET shows only modest accuracy in staging the axilla and, again, has no routine role in local staging. However, in patients with advanced disease ^{18}F-FDG-PET/CT can detect distant metastases with high sensitivity whether they are nodal, visceral or skeletal. There are also some early data to suggest it may be a good method to determine treatment response in bone metastases that are characteristically difficult to assess by conventional skeletal imaging methods.

Gastrointestinal tract malignancies

Oesophageal cancer

The tumour staging of oesophageal tumours is usually best evaluated by endoscopic ultrasound and CT (Fig 3). ^{18}F-FDG-PET/CT is of added value in the initial staging of oesophageal cancer to exclude distant metastases, avoid futile surgery and assess response to neoadjuvant therapy.[8]

Colorectal cancer

^{18}F-FDG-PET/CT is frequently able to detect the source of rising tumour markers in patients with previously treated colorectal cancer, often when the patient is still suitable for radical therapy. MRI methods are more sensitive for small subcentimetre liver metastases, but ^{18}F-FDG-PET/CT often detects occult extrahepatic metastatic disease that precludes liver surgery.[9]

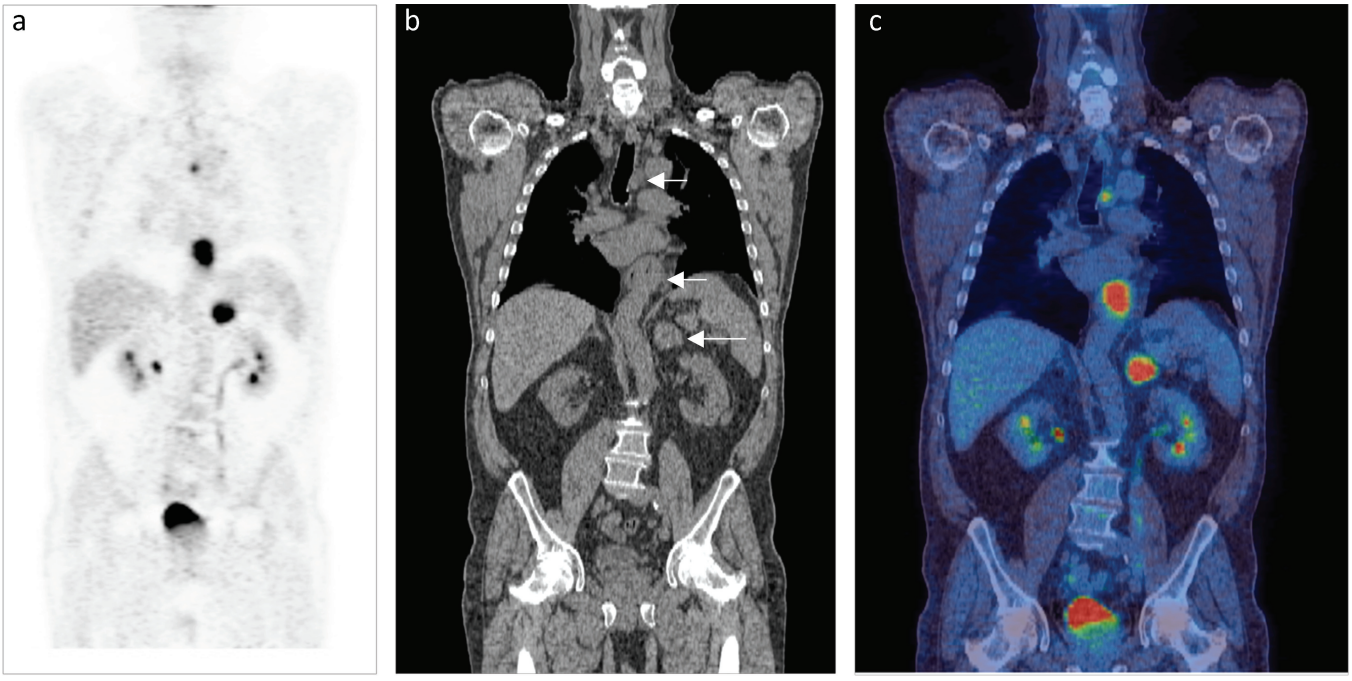
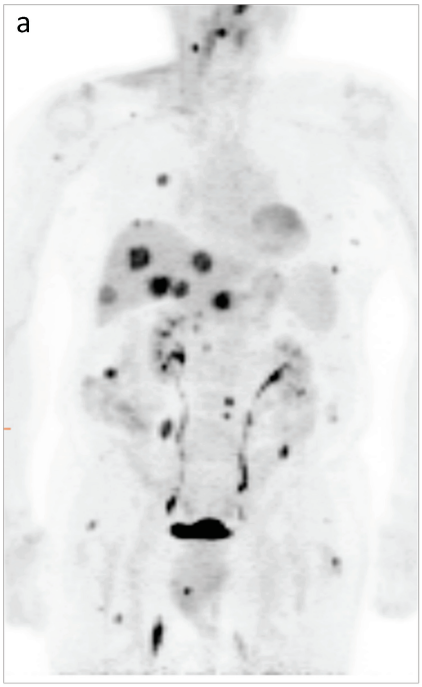
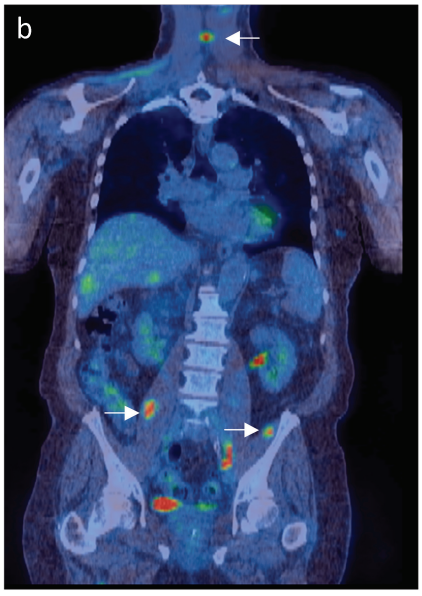


Fig 3. Oesophageal cancer. Coronal ^{18}F-FDG images show intense abnormal activity in a left paratracheal lymph node (top arrow), distal thickened oesophagus (middle arrow) and a left adrenal metastasis (bottom arrow).





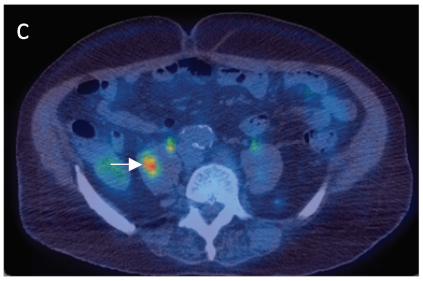


Fig 4. Melanoma: (a) Coronal views of ^{18}F-FDG PET/CT show multiple metastases in lynph nodes, lungs, skeleton and liver. (b) Coronal and axial fused PET/CT images also localise abnormal uptake in various muscles (arrows).

Pancreatic cancer

The sensitivity and specificity of ^{18}F-FDG-PET/CT is diminished in patients with pancreatic masses when inflammatory markers are raised (false-positives with pancreatitis) and in diabetic patients (higher false-negative rate). The technique is, however, valuable as a problem-solving tool when conventional imaging is equivocal, particularly in patients with suspected recurrence but indeterminate CT or MRI findings, or rising tumour markers but no obvious abnormality on conventional imaging.

Gynaecological cancer

^{18}F-FDG-PET/CT may be helpful in determining whether high-risk primary cervical and uterine tumours have nodal spread outside the pelvis and in detecting recurrent disease when other imaging is equivocal. There is no role for characterising ovarian lesions, but ^{18}F-FDG-PET/CT may be helpful in detecting occult disease in patients with established ovarian cancer, particularly when tumour markers are rising but conventional imaging is negative.[3]

Genitourinary cancers

Urinary tract tumours

^{18}F-FDG-PET/CT is not usually the first-line imaging technique in the investigation of urinary tract tumours. Fewer than 50% of renal cancers are ^{18}F-FDG avid and, in addition, ^{18}F-FDG is excreted through the urinary tract which may mask tumour uptake.

Prostate tumours

^{18}F-FDG shows low uptake in the majority of prostate tumours but choline-based tracers show superior sensitivity (see below).

Testicular cancer

^{18}F-FDG-PET/CT can contribute significantly to the management of patients with rising tumour markers and normal conventional imaging in testicular cancer. It may also be used to differentiate active tumour from scar tissue in a post-treatment residual mass.

Melanoma

^{18}F- FDG-PET/CT is of limited use in early stage disease where sentinel lymph node

Table 2. Other ^{18}F-PET tracers in oncology.[11]

- ^{18}F-fluorothymidine (^{18}F-FLT), useful for imaging cellular proliferation
- ^{18}F-fluoromisonidazole (^{18}F-MISO) for tumour hypoxia
- ^{18}F-FDOPA which has shown promising results in neuroendocrine tumours, medullary thyroid cancer and phaeochromocytomas
- ^{18}F-RGD for non-invasive imaging of integrin expression in tumour angiogenesis
- ^{18}F-choline (or ^{11}C-choline) for detecting metastases in prostate cancer

Key points

- The role of ^{18}F-FDG-PET/CT is well established in oncology
- ^{18}F-FDG is the most common radiopharmaceutical used for imaging cancer
- PET/CT is invaluable in cancer staging, therapeutic planning and response assessment
- Some cancers show low-grade or no metabolic activity with ^{18}F-FDG; other tracers are available for these indications
- Other, non-^{18}F-FDG, tracers which image other aspects of tumour biology are likely to have an increasingly important role in oncological imaging

KEYWORDS: cancer, PET/CT, ^{18}F-fluorodeoxyglucose (FDG), molecular imaging, non-^{18}FDG tracers

biopsy is regarded as the gold standard locoregional staging technique. PET/CT has reported sensitivity of 87% and a positive predictive value of 90% in stage 3 disease, however, and changes management in 15% of cases with stage 4 disease (Fig 4).[10]

Non-^{18}F-FDG tracers

^{18}F-fluoride

^{18}F-fluoride is a bone-specific agent. ^{18}F-fluoride PET/CT imaging tends to be more accurate than conventional bone scintigraphy in view of higher spatial resolution, tomographic images and ability to correlate tracer uptake with the CT component of the study. However, as with the conventional bone scan, uptake is not tumour-specific (Table 2).

Choline

Choline is transported into tumour cells and phosphorylated by choline kinase, leading to the manufacture of phospholipids incorporated into cell membranes. It has proved particularly useful in prostate cancer which is typically associated with poor ^{18}F-FDG uptake. Both ^{11}C-choline and ^{18}F-choline are increasingly used for PET imaging in prostate cancer to detect occult metastases before radical treatment or to ascertain the cause of biochemical failure when conventional imaging is negative.

68 Ga-peptides (eg Dotatoc, Dotanoc, Dotatate)

^{68}Gallium can be produced from a generator, thus does not require proximity to a cyclotron. ^{68}Ga-labelled peptides such as octreotide analogues that target somatostatin receptors (eg ^{68}Ga-Dotatoc) are the most widely used PET agents for imaging neuroendocrine tumours (NET). ^{18}F-FDG can be useful in poorly differentiated NETs but ^{68}Ga-peptides are extremely sensitive for imaging most well differentiated tumours. Hoffman *et al*[12] showed that ^{68}Ga-Dotatoc PET detected 100% of the lesions not seen on CT/MRI and 85% of those not recognised on ^{111}In-octreotide SPECT.

The future

It is likely that PET/CT will have an increasing role in radiotherapy planning, allowing better tumour coverage and minimising toxicity to normal tissues. PET/MRI scanners have only recently become commercially available. Initially, it is likely that they will be primarily used for research purposes but clinical applications will inevitably follow, possibly in cancers where MRI already shows benefit over CT (eg brain, head and neck, liver and pelvis).

Conclusions

PET/CT is one of the most common and rapidly expanding medical imaging techniques used in oncology. It has proved cost-effective and clinical use will continue to grow with the increased use of new tracers.

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