Increasing access to positron emission tomography-computed tomography (PET-CT) has resulted in a shift towards functional imaging, being the primary tool in the assessment of viable tumour in oncology patients. In this review, we discuss the basic principles of this evolving technology and the radio-isotopes it employs. The main clinical applications of PET-CT are reviewed and some of the limitations of the technique are highlighted. Finally, we offer insight into possible future developments and how these modify current practice.

Introduction

Staging of tumours and assessment of their response to therapy have traditionally been based around assessment of structural change. The techniques of computed tomography (CT), magnetic resonance, ultrasound and plain film radiography are all employed, either alone or in combination, to evaluate structural abnormality. The most frequently used technique in terms of whole-body staging is currently CT. A variety of protocols have been developed that aim to standardize the interpretation of oncological CT imaging. A key feature of almost all such protocols is that it is the absolute size that of the tumour, lymph nodes or metastasis that is used to decide the presence or absence of malignancy or the change in size that is used to assess the degree of response to treatment. Of these protocols, the Response Criteria In Solid Tumours (RECIST) is one of the protocols more commonly used. RECIST takes into consideration the summation of uni-lateral measurements of suspected sites of disease. The size of a lesion or, in the case of treatment response, the percentage change in size since the previous scan dictates whether a CT is reported as showing active disease, response to treatment or progression of disease. Unfortunately, such methods are subject to considerable inter- and intra-observer variation and fail to differentiate post-therapy residual structural abnormality from viable malignancy. Functional imaging, in particular, positron emission tomography (PET), aims to overcome these weaknesses.
PET history and principles

The first recorded medical use of positrons was in 1951 when a simple sodium iodide detector probe was used to localize a brain tumour.3 Much of the initial work using PET centred on neuropsychiatric and cardiac research. Only in 1997 when FDA approval for the use of 18F-fluorodeoxyglucose (18FDG) as a radiopharmaceutical was granted and subsequently when reimbursement was approved, did whole-body scanning for clinical applications start to take off.

Traditionally, PET and CT have been seen as complementary technologies, which were used sequentially in the diagnosis of cancer. Such an approach required mental mapping of abnormalities seen on PET to the anatomical structures seen on CT. Software for retrospective fusion of PET and CT images is available. However, outside the brain, precise mapping is problematic due to the large potential variability in, for example, patient position between the two scans. These problems were resolved with the introduction of the PET–CT scanner. The first such scanner began to operate in 1998 and the first clinical machine began to operate in March 2001. An appreciation of the importance of this advance was rapidly gained and by 2004, PET–CT was reported to be the fastest growing imaging modality with up to 1000 systems installed worldwide in 2004 alone.4 In addition to limiting the spatial and temporal differences between the two sets of images, PET–CT has a number of other advantages over either PET or CT alone. The most significant of these is the use of the CT data (modified to allow for the difference in photon energy between CT and PET) for attenuation correction which improves image quality and is essential for quantitative accuracy of PET. Using this technique as opposed to the conventional rod-source attenuation correction on PET-only systems allows scan times to be reduced by 25–30%.4 Typically, a combined whole PET–CT scan is now completed in ~30 min and PET-reconstructed image resolution is of the order of 5–7 mm.

In addition to simply documenting the presence or absence of metabolically active tissue, there is also the potential for measurement of metabolic activity using PET. Such a measurement would be particularly appealing in the practice of oncology when assessing, for example, response of a tumour to treatment.5 The most widely used technique involves calculating the ratio of tumour activity concentration to that in the remainder of the body and is termed the standardized uptake value (SUV). It is recognized that SUV is far from perfect.6 There are several variables that can affect SUV, including time between injection and scanning, plasma glucose and patient body size (both habitus and body composition). Of particular relevance in
oncology patients are alterations in blood glucose and body size. Some centres advocate the use of SUV corrected for lean body mass and blood glucose level on the basis that it is common for oncology patients to suffer weight loss either as a result of their disease or treatment and chemotherapeutic agents may alter blood glucose levels over time (raised blood glucose has been shown to reduce SUV).

**Radiopharmaceuticals**

Functional imaging using PET may take many forms. Although initial experimental laboratory work used a variety of radioisotopes, for example, $^{14}$C labelled deoxyglucose, the most widely used imaging technique in clinical practice today is $^{18}$FDG PET. $^{18}$FDG acts as a glucose analogue. Following its intravenous (IV) injection, $^{18}$FDG localizes to sites where there is active metabolism and increased glucose uptake. Malignant neoplasms have, for many years, been known to be highly metabolically active with several tumour types overexpressing the GLUT-1 membrane glucose transporter protein. Consequently, many malignancies display avid uptake of $^{18}$FDG. Once within the cell, $^{18}$FDG undergoes phosphorylation by hexokinase to form $^{18}$FDG-6-phosphate. Unlike glucose, $^{18}$FDG-6-phosphate is subsequently subjected to minimal enzymatic reactions and as a result will accumulate within the cell at a rate proportional to glycolysis. Other factors that modulate the amount of $^{18}$FDG uptake include the number of viable tumour cells and blood flow to and within the tumour. Enhanced blood flow is of particular importance since without this, a tumour will rapidly outgrow its blood supply and necrosis will occur. Much interest has, therefore, been centred on the subject of angiogenesis. Although primarily a research tool, PET may be employed to assess tumour angiogenesis. Two approaches have been used to achieve this. The first measures the accumulation of a freely diffusible tracer ($^{15}$oxygen–water) to indirectly assess blood flow. The second detects the markers of angiogenesis (such a vascular endothelial growth factor receptor) using isotope-labelled monoclonal antibodies directed against the target detected with PET.

Recently, interest has grown in the potential for use of a variety of radiopharmaceuticals other than $^{18}$FDG in oncological imaging. For example, research has demonstrated the accumulation of derivatives of choline and $^{11}$C-acetate in prostate cancer. Although $^{11}$C-acetate is unlikely to be of widespread clinical use due its short half-life (20 min), $^{18}$F-based (half-life 110 min) choline compounds may prove to be of use and currently being investigated. Other examples include the use of $^{18}$F-DOPA in the investigation of neuro-endocrine tumours,
$^{18}$F-thymidine as a marker of cellular proliferation and labelled antibodies targeted against specific tumour proteins. As yet, all these remain as research tools, with $^{18}$FDG PET–CT being used for the bulk of clinical work.

**PET–CT image interpretation and artefacts**

An appreciation of sites of normal physiological uptake together with an understanding of potential artefacts and limitations must be gained in order to accurately interpret either PET or PET–CT scans.

**Normal uptake**

There are many sites of relatively high metabolic uptake in the body which must not be misinterpreted as pathological uptake of tracer.

As the brain primary substrate for metabolism is glucose, there is predictably high $^{18}$FDG within the cortical tissue, brain’s stem and basal ganglia. This limits the sensitivity of $^{18}$FDG PET–CT for the detection of intra-axial malignant disease.

The liver spleen and bone marrow demonstrate homogeneous low-grade uptake, but this does not usually obscure the presence of avid malignant processes within these organs.

Myocardial uptake is variable, although, in general, the left ventricular myocardium will be greater than the background blood pool.

Moderate uptake may be seen in normal-sized lymphoid tissue in Waldeyer’s ring and thymic tissue of children. In addition, post-chemotherapy thymic rebound may occasionally be seen in children and young adults.

Pre-menopausal women may display moderate uptake in glandular breast tissue, which can become marked during lactation. Cyclical ovarian and uterine activity may also be seen.

Uptake within the gastro-intestinal tract ranges from almost undetectable to diffuse high uptake. Diffuse low-grade uptake within the oesophagus is most commonly due to oesophagitis. Similarly, gastritis due to *Helicobacter pylori* infection within the stomach may result in diffuse uptake within the gastric mucosa, although some uptake is normally seen. Minimal uptake is usually seen within the small bowel. In contrast, the large bowel and, in particular, the caecum may display avid uptake. The cause of this avid uptake is likely to be multi-factorial and includes mucosal activity, regional lymphatics and bacterial activity within the lumen of the bowel.
\[^{18}\text{FDG}\] PET–CT has limited sensitivity for detection of tumours within the urinary tract since \[^{18}\text{FDG}\] is, unlike glucose, subject to renal excretion. Consequently, the renal collecting systems, ureters and bladder frequently show high activity, and detecting a renal or bladder tumour against this background activity is difficult. Some advocate catheterization of patients and washout of the bladder to enhance the detection of pelvic malignancy; however, generally, if the patient is well hydrated and the \[^{18}\text{FDG}\] within the bladder is therefore diluted, this is not necessary.

Testicular activity is variable and tends to be higher in younger patients.

Foci of active brown fat are occasionally seen in children and young adults and are typically symmetrical and located around the lower neck and scapulae. Brown fat is known to be highly metabolically active and is responsible for thermogenesis and, consequently, is often seen as areas of avid tracer uptake on PET–CT, particularly in cold weather (Fig. 1).

Following the injection of \[^{18}\text{FDG}\], patient movement and speech should be limited in order to minimize skeletal muscle uptake, which may otherwise be misinterpreted as abnormal uptake.

**Benign causes of \[^{18}\text{FDG}\] uptake**

In addition to physiological uptake, there are numerous benign causes of uptake that may mimic malignancy.\(^{15}\) Typically, these benign causes are sites of inflammation or infection and include the following.

Osteoblastic activity together with granulation associated with bone healing, whether it be of iatrogenic or traumatic origin, results in an elevated \[^{18}\text{FDG}\] uptake in the acute or subacute phase of healing. In the case of rib fractures or a healing sternotomy, the linear nature of the uptake makes delineation from malignant causes relatively easy. Conversely, an isolated fracture with florid callus may be very difficult to differentiate. Similarly, degenerative or inflammatory arthritis can result in increased tracer uptake. This may be markedly asymmetrical, e.g. the acromioclavicular joint on the side of the dominant hand, but is rarely mistaken for malignancy.

Detection of infiltrated lymph nodes is of great importance to cancer staging and therefore treatment. The absolute size of a node gives some indication of the likelihood of malignant infiltration as opposed to reactive enlargement; however, there is inevitably a ‘grey area’ of overlap between the two groups. A major advantage of PET–CT is its ability to detect malignant infiltration in nodes that are not size
Fig. 1 (A) Coronal PET images reveal avid bilateral FDG uptake both at the anterior and at the posterior aspects of the neck. (B) CT and fused PET–CT images demonstrate this FDG uptake to be within the sterno-cleidomastoid muscles (due to patient movement) and metabolically active brown fat.
significant (Fig. 2). Unfortunately, granulomatous conditions such as tuberculosis or sarcoidosis can cause increased tracer uptake. In addition, recent infection, surgery or extravasation of tracer at the injection site may all cause varying degrees of increased tracer uptake in draining lymph nodes.

Sites of localized soft tissue infection or inflammation/granulation may result in tracer uptake. Examples include abscesses, stoma sites and pancreatitis. Distinguishing such abnormalities from malignant deposits can be problematic but is often resolved through reference to the CT component of the image.

Problems specific to PET–CT

Although a single machine, the CT and PET components of a PET–CT examination are acquired separately. Modern multi-slice CT potentially allows whole-body scanning within a single breath-hold. In contrast, a whole-body PET requires ≥20 min to acquire and is, therefore, subject to breathing movement artefact. Mis-registration between the two sets of images may therefore occur, particularly in the thorax and around the diaphragm. Some advocate acquiring the CT data during normal expiration. However, in practice, patients may find this difficult to achieve. Such mis-registration is a factor that limits the sensitivity of PET–CT in the detection of focal lung nodules. It is a common belief among many that PET–CT is not appropriate for the assessment of subcentimetre pulmonary nodules due to the poorer spatial resolution of PET when compared with CT and the movement of nodules during the PET image acquisition. Although this is in part true, in reality, if a nodule is highly FDG avid, it is likely to be visualized even if it is <1 cm in diameter. However, on average, the sensitivity for subcentimetre metastases has been reported to be <80 or <40% when 5–7 mm. Using the CT data for attenuation correction may lead to artefactual overestimation of tracer uptake. This typically occurs when highly attenuating materials, e.g. prosthetic metal devices or high density oral contrast, are present. PET–CT is commonly performed in the absence of IV contrast. Although some have suggested that IV contrast may improve diagnostic accuracy, it is likely that a concentrated intravascular bolus of contrast (which will have dissipated by the time the PET component is acquired) would lead to artefactual activity in the attenuation corrected image. This is unlikely to lead to misinterpretation; however, newer reconstruction algorithms can overcome this artefact.
Fig. 2 Contrast-enhanced staging CT revealed a patient with breast cancer to have a solitary left upper lobe pulmonary metastasis. Prior to resection of the pulmonary metastasis, PET–CT was performed. Coronal PET images (A) reveal there to be multiple sites of abnormal FDG uptake. Axial fused PET–CT images confirm these to include avid axillary and mediastinal nodes (B) (considered borderline significance by size criteria on the staging CT) together with disease within the liver (C) and bones (D).
Common uses of PET–CT in current oncology practice

Differing arrangements for reimbursement are a factor for differences in practice between regions. The following are common uses of PET–CT in current practice in the UK.

Thoracic malignancy

PET–CT is now integral to the evaluation of pulmonary nodules, staging of lung cancer, planning of therapy and diagnosis of recurrent disease with its use being advocated by the British Thoracic Society.\(^20\) Furthermore, PET–CT is proved to be better than PET alone, CT alone or PET and CT performed separately and viewed together. Indeed, PET–CT provided additional information in 41% of cases reviewed.\(^21\) Examples of such information include evaluation of chest wall invasion by a tumour which is difficult with PET alone due to the limited anatomical accuracy but can be more easily evaluated with combined PET and CT. One area in which PET–CT is likely to be of benefit over PET alone is in the detection of small pulmonary nodules, although at present the data to support this are lacking.

In primary lung malignancies where there is associated bulky mediastinal lymph node enlargement, the nodal staging (N-staging) component of tumour, nodes, metastasis (TNM) staging is rarely problematic. Difficulty arises when there are nodes that are not significant by CT criteria but which if found to be infiltrated with malignancy would significantly alter the course of treatment (usually affecting whether curative surgery should be contemplated or not). This is particularly true of small hilar nodes since infiltration of these nodes is pivotal in deciding whether nodal status is N1 or N2. PET has proved to be highly effective in such cases with a specificity of 93% and a sensitivity of 88% for the delineation of infiltration of mediastinal nodes.\(^22\)

Tumour recurrence within the thorax in the context of distorted anatomy following surgery and radiotherapy can be difficult to detect. PET–CT may be extremely useful in such a setting since viable tumour can be appreciated as separate from the surrounding post-therapy changes seen on the CT.\(^23\)

Although clearly a useful tool for the assessment of malignancy in the thorax, PET–CT does have limitations. Examples include poor delineation of bronchioalveolar cell carcinomas and malignant pleural effusions. Its use in the evaluation of thoracic malignancies other than primary lung cancer remains under evaluation. One area of particular interest is the assessment of malignant pleural mesothelioma in which
PET–CT has been shown to be of benefit in the assessment of chest wall invasion and nodal involvement.24

**Gastro-intestinal malignancy**

Colorectal malignancy is second only to lung cancer in terms of malignancy-related deaths in Western countries. Although PET–CT has not yet been fully evaluated as a means of primary diagnosis, PET is of proven benefit in the staging and subsequent re-staging of colorectal carcinomas.25 A recent study,26 has shown PET to be sensitive for the detection of the primary colonic tumour (96%) and distant metastases (78%), but to have relatively low sensitivity for abdominal and pelvic lymph node staging (29%). It is, however, important to remember that PET is unlikely to be used in isolation for the staging of colorectal malignancy. More likely is that there will be multiple modalities used in the disease staging. Current common practice is to use magnetic resonance imaging (MRI) for local tumour staging and pelvic lymph node staging of rectal tumours and CT or PET–CT to detect disseminated malignancy from a colorectal tumour. In addition, MRI and ultrasound (including micro-bubble contrast-enhanced ultrasound) may be used to characterize focal liver lesions.

Even with the use of pelvic MR, whole-body CT, tumour markers and clinical examination, detection of recurrent colorectal malignancy is often problematic. This is commonly due to the difficulty in differentiating recurrent disease from post-surgical change. Several studies have demonstrated PET to be helpful in detecting recurrent disease.4 Furthermore, when compared with PET alone, PET–CT improves diagnostic accuracy27 (likely due to the enhanced localization of lesions that CT component allows).

Gastro-intestinal stromal tumours (GISTs) are mesenchymal tumours that arise most commonly from the stomach or small bowel. GISTs demonstrate heterogeneous 18FDG uptake between patients and even between different tumour sites within the same patients. Consequently, the role of PET–CT in the assessment of GIST was initially uncertain. This view has in part been altered by recent evidence proving the benefit of PET–CT over contrast-enhanced CT in the assessment of response of GIST to the tyrosine kinase inhibitor imatinib mesylate.28

**Lymphoma**

Given the curative intent in a high percentage of lymphoma patients, accurate diagnosis, staging and follow-up in this group of patients is
essential. Current practice for staging of lymphoma will usually include contrast-enhanced CT from base of skull to upper thighs. Almost every healthy individual will have some lymph nodes commonly in the head and neck, axillae and inguinal regions and it can be difficult to differentiate on the basis of size alone that which of these nodes are infiltrated with disease. Since this decision is critical in determining whether local or systemic therapy will be employed, accurate assessment is of paramount importance. Fortunately, both Hodgkin and non-Hodgkin lymphomas will usually demonstrate avid $^{18}$FDG uptake at the time of diagnosis. Studies have indicated PET–CT to be more sensitive and specific in the evaluation of nodal and extra-nodal disease in patients with lymphoma. In particular, the sensitivity of detection of extra-nodal disease is improved by the use of PET–CT as opposed to CT alone (88 and 50%, respectively). Following treatment, up to 64% of patients display some residual abnormality, and differentiating fibrosis and necrosis from viable tumour cells is notoriously difficult. FDG PET–CT is one of the most accurate non-invasive methods for differentiating viable from non-viable residual masses. PET–CT also plays an important role in the evaluation of response to treatment. Patients in whom there is no detectable FDG uptake post-treatment generally have a better prognosis than those in whom there is residual uptake.

**Head and neck malignancy**

Despite the use of a variety of imaging techniques, including contrast-enhanced MR, CT and ultrasound, the accurate staging and detection of disease recurrence in head and neck cancers remain problematic. The limitations of these structural imaging techniques in the head and neck are that the anatomy is complex and when distorted by either tumour or treatment, defining viable disease can be difficult. Furthermore, the large number of physiological or reactive nodes around the head and neck can result in equivocal reports. An additional problem for CT and MR interpretation is the widespread use of metallic dental amalgam, resulting in streak and susceptibility artefact, respectively. PET has been shown to improve accuracy of staging of head and neck malignancy when compared with CT or MR and PET–CT is more accurate than PET or CT alone. In addition to staging of head and neck cancers, PET–CT is finding increased use for the detection of occult sites of primary malignancy in the head and neck. Owing to several sites of normal physiological uptake, e.g. salivary glands, and the potential for artefact, e.g. muscle uptake from talking or chewing, care must be employed when reporting PET–CT of the head and neck.
Breast cancer

Uptake of FDG in primary breast cancer is variable, with some showing very little uptake and others being avid. Even tumours of the same histological type may differ in uptake of FDG. Furthermore, PET sensitivity for the detection of small lesions within the breast is likely to be limited. Consequently, PET–CT is not generally used in the assessment of the primary breast mass and axillary nodes. Where it is of use is in the assessment of systemic metastatic disease, detection of disease recurrence and the monitoring of therapy. One recent study has demonstrated PET to have a sensitivity of 89% and a specificity of 88% for the detection of disease recurrence with 30% of patients originally thought only to have local disease recurrence found to have more distant disease on PET.34

Pancreatic and hepatic malignancy

Current practice is to use ultrasound, contrast-enhanced CT or contrast-enhanced MR for the detection of focal liver lesions and then, if necessary, to use triple phase CT, dynamic MR or possibly contrast-enhanced ultrasound to further characterize a lesion. Such an approach is generally robust and PET–CT has a limited role to play in the assessment of a primary hepatic malignancy. Where PET–CT is in of use is the detection of disseminated malignancy from a hepatic primary since this is likely to significantly modify treatment options, for example, if segmental resection or orthotic liver transplantation is being considered.

Detection of primary pancreatic malignancy in its early stage is problematic, regardless of the imaging modality used. Currently, contrast-enhanced multi-slice CT is the primary technique for the assessment of a suspected pancreatic tumour. PET has been shown to be superior to structural imaging techniques for the detection of distant metastasis and local recurrence following treatment35.

Thyroid malignancy

Radioiodine scintigraphy is the main modality used in the assessment of thyroid malignancy. Dedifferentiation of a thyroid malignancy may result in failure of the tumour cells to accumulate iodine and consequently inability to image or treat the tumour with radioiodine. PET plays a role in such cases and has been shown to be up to 94% sensitive in the detection of recurrent local tumour or metastasis.36 PET–CT has advantages over PET alone when imaging neck in search of recurrent thyroid disease due to the added anatomical information making it easier to differentiate recurrent tumour from, for example, muscles around the vocal cords.
Gynaecological malignancy

Ovarian cancer and cervical cancer together are a major cause of mortality and morbidity in the female population. Although PET–CT is not commonly used in the assessment of these malignancies, a recent small study suggests that it may have a role to play particularly in the detection of disseminated disease when potentially curative surgery is being considered (Fig. 3). Of particular note is the improved accuracy of detection of pelvic lymph nodes in cervical carcinoma with PET relative to CT since this is likely to modify therapy and serve as a predictor of survival.

Melanoma

Melanoma is characterized by its avidity for FDG and its ability to metastasize to unusual sites. Melanoma is potentially curable by surgery if the disease is at an early stage in its growth. Although there are no data to suggest that PET is of benefit in the initial diagnosis of melanoma, it is of proven benefit in the subsequent staging. PET is proven to be more sensitive than CT in the detection of metastasis within the skin, abdomen and lymph nodes, with CT more sensitive than PET in the detection of pulmonary lesions. It is, therefore, likely that PET–CT will be particularly effective in the staging of melanoma.

Unknown primary malignancy

Between 5 and 10% of all patients diagnosed with malignancy have no known primary at the time of diagnosis. Establishing the site and histological type of a primary tumour is important because it facilitates directed therapy and improves survival. The case for the use of PET–CT to detect a primary tumour in patients with metastasis of unknown origin would seem compelling. Unfortunately, evidence suggests that PET–CT is not significantly better than PET, CT or CT and PET read together (sensitivities of 33, 24, 18 and 29%, respectively). Even though the advantage of PET–CT is small, it is becoming established as the investigation of choice in these difficult cases.

Conclusion

In a short space of time, PET–CT has established itself as an essential component in the assessment of malignancy. There is little doubt that as understanding of PET–CT grows among the medical community as a whole, indications for PET–CT will grow. Furthermore, much
Fig. 3 Patient with known ovarian carcinoma was shown to have a solitary liver metastasis on IV contrast-enhanced CT. PET–CT was requested to confirm this to be a solitary site of disease prior to segmental hepatic resection. Coronal PET images (A) show several sites of abnormal FDG uptake in addition to that within the liver. Fused PET–CT reveals the presence of both left (B) and right (C) metabolically active para-aortic lymph nodes which were not appreciated on the staging CT. In addition, an avid disease deposit within the left hemi-pelvis (D) was misinterpreted on staging CT as a loop of bowel.
research into the potential uses of this technology is currently being undertaken. Of particular interest are developments regarding the application of PET–CT in the planning of radiotherapy and intensity-modulated radiotherapy, new radiopharmaceuticals and potential uses of PET–CT aside from malignancy. It is likely that as access improves and our understanding grows, PET–CT may be the only imaging test required in the initial investigation of oncology patients in some circumstances.

References

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