Positron emission tomography computed tomography in oncology

The role of positron emission tomography computed tomography in oncological imaging has rapidly evolved. It has proven itself to be cost effective and alters patient management in a significant proportion of cases. This article discusses its current and future applications.

The role of positron emission tomography has evolved rapidly over the last two decades from primarily a research tool to a clinical mainstay in oncological imaging (*Table 1*). Several factors have contributed to this including the increasing availability of fluorine-18-fluoro-2-deoxy-glucose (^{18}F-FDG) from a network of medical cyclotrons and the arrival of hybrid positron emission tomography computed tomography scanners that allow faster scan acquisitions with the benefit of combined functional and anatomical data. This review will consider the background of positron emission tomography computed tomography imaging, its current indications and possible future clinical advances.

Positron emission tomography tracers

Fluorine-18-fluoro-2-deoxy-glucose

The half life of fluorine-18 (approximately 110 minutes) allows the transportation of ^{18}F-FDG between the ever-expanding cyclotron network and the imaging centres. Short half life positron emitters such carbon-11 (^{11}C) and oxygen-15, while potentially useful, are limited to the few sites with an on-site cyclotron and radiochemistry facility. FDG is a glucose analogue and, as such, targets increased glucose transport (via the GLUT 1 transport protein) and increased metabolism by neoplastic cell types. Unlike glucose, which once phosphorylated in the cell by hexokinase undergoes further metabolism, ^{18}F-FDG is effectively trapped after phosphorylation and does not undergo further metabolism. While all tissues take up glucose and FDG, the discrepancy between 'normal' and hypermetabolic tissues forms the basis of positron emission tomography computed tomography imaging. These hypermetabolic changes often occur before anatomical abnormalities become apparent – this potentially allows for earlier detection of neoplastic lesions and is an important factor in positron emission tomography imaging. It is important to note at this point that glucose metabolism is also increased in several inflammatory or infective conditions as macrophages and other activated white cells demonstrate increased glycolysis. Conversely, several tumour types do not characteristically demonstrate high glucose metabolism, e.g. prostate cancer, bronchioalveolar cell lung cancer. Owing to its urinary excretion, the role of FDG in the staging of primary urinary tract tumours is somewhat limited.

Several new tracers are gaining clinical acceptance, each group targeting a different metabolic pathway or receptor ligand in the malignant cell. Of these, the most widely used at present are fluoride-18 for bone imaging and those targeting choline metabolism in tumours. Imaging with gallium-68-labelled peptides is also likely to provide several clinical applications.

Fluoride-18

Fluoride-18 detects abnormal osteoblastic response in the skeleton and therefore can detect bony metastases (*Figure 1*). Although uptake is not specific for metastases, positron emission tomography computed tomography systems can provide higher diagnostic accuracy than conventional planar or indeed single-photon emission computed tomography methylenediphosphonate bone scans (Groves et al, 2007). While this is partly a result of the inherent resolution of positron emission tomography imaging and the morphological characterization gained from computed tomography, fluoride-18 also provides a significantly increased target to background ratio in detecting abnormalities when compared with conventional scintigraphic agents. The Society of Nuclear

Table 1. Indications for positron emission tomography computed tomography in oncological imaging

Primary presentation – unknown primary, differentiating benign from malignant lesions
Staging on presentation – certain tumour types, e.g. non-small cell lung cancer
Therapy planning – increasing role in radiotherapy planning
Response evaluation – following therapy
Restaging – in disease relapse and confirmation of relapse
Localizing disease – in cases with rising tumour markers of unknown cause
Guide for image-guided biopsy

Based on the European Association of Nuclear Medicine guidelines (Boellaard et al, 2010)

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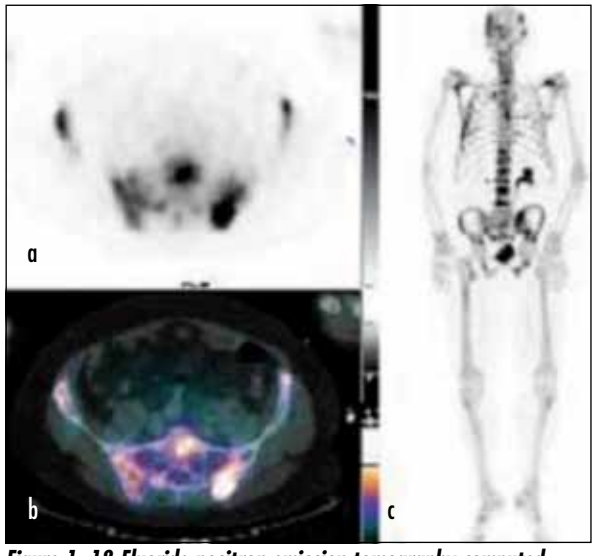


Figure 1. 18-Fluoride positron emission tomography computed tomography. a. Positron emission tomography only image of the pelvis demonstrating abnormal osteoblastic response in sacral and iliac metastases. b. Fused positron emission tomography computed tomography image at the corresponding level in the pelvis. c. Maximum intensity projection image of the whole body demonstrating multiple sites of metastases in the skull, scapulae, spine, ribs and pelvis.

Medicine has produced guidelines for the use of fluoride-18 indicating its potential applications in the localization of bony metastases and determining disease extent (Segall et al, 2010).

Choline

Choline is taken up into cells where it becomes integrated into cell membranes. This process is enhanced and upregulated in certain malignancies. ^{18}F-choline and ^{11}C-choline tracers are becoming more popular, particularly in cases of recurrent prostate cancer where they are used to identify morphologically occult disease in the presence of a rising prostate-specific antigen level. Because of the relatively low glycolytic rate of prostate cancer, ^{18}F-FDG has proven of limited benefit in these scenarios. ^{18}F-choline benefits from the relatively long half life of ^{18}F and therefore can be distributed to remote centres from the producing cyclotron and radiochemistry lab. However, it is excreted in the urine to a greater extent than ^{11}C-choline. In a recent review (Beer et al, 2011), choline positron emission tomography computed tomography demonstrated encouraging results in the management of recurrent prostate cancer although multicentre trials are needed to further validate these findings.

Gallium-68-labelled peptides

Unlike the other positron emission tomography radionuclides considered, gallium-68 (^{68}Ga) is generator produced. This means that production can occur directly at the imaging centre without the need for a cyclotron. Its properties allow its potential use in many clinical applications including in the imaging of neuroendocrine tumours by linking it to somatostatin receptor analogues. Srirajaskanthan et al (2010) demonstrated that imaging with ^{68}Ga-DOTATATE in patients with equivocal or negative conventional scintigraphic studies for neuroendocrine tumours led to a direct change in management in 70.6% of cases.

Standardized uptake values

Whatever the radiotracer used, positron emission tomography provides the ability to semi-quantify its accumulation by means of the standardized uptake value, which is defined as:

$$\frac{\text{activity concentration in tissue}}{\text{injected activity/body weight}}$$

This provides an indirect measurement of metabolic activity. The standardized uptake value may be useful in assessing biological tumour type (poorly differentiated or high grade cell types generally having a higher standardized uptake value), prognosis for certain tumours and response evaluation.

Multimodality or hybrid imaging with positron emission tomography computed tomography combines the ability to use these functional and metabolic parameters with improved anatomical localization and characterization.

Clinical applications

Table 1, based on the European Association of Nuclear Medicine guidelines, lists the main indications for positron emission tomography computed tomography imaging in oncology. This is a rapidly evolving field and, as such, this table should not be considered exhaustive. However, these indications provide a good basis to expand on the utility of positron emission tomography and will be considered below.

Primary presentation

Positron emission tomography computed tomography is often used in differentiating possible benign from malignant lesions, particularly where diagnostic histological confirmation cannot be safely achieved. This is particularly the case in assessing indeterminate solitary pulmonary nodules. A study in 2008 of 344 subjects with solitary pulmonary nodules between 7 mm and 30 mm compared FDG positron emission tomography with computed tomography characterization. Lesions were categorized as benign or malignant on positron emission tomography imaging based on standardized uptake value measurements (standardized uptake value greater than 2.5 is considered to be malignant). This study concluded that positron emission tomography was not only more accurate than computed tomography but led to fewer indeterminate results with less inter-

observer and intraobserver variability (sensitivity = 95.9% and specificity = 77.9% *vs* sensitivity = 96.3% and specificity = 36.1% respectively) (Fletcher et al, 2008b). Solitary pulmonary nodules with a maximum standardized uptake value of greater than 2.5 have an approximately 80% chance of representing a malignancy (Bryant and Cerfolio, 2006). While these results are impressive, it is important to note that tumour types such as bronchoalveolar cell carcinoma and carcinoid often demonstrate only low grade FDG uptake because of their low glycolytic rate (*Figure 2*). Furthermore, because of the partial volume effect whereby the standardized uptake value of small lesions will usually be underestimated, lesions categorized as probably benign still require follow up in order to exclude an occult malignant aetiology. However, a conservative management plan can be followed in these cases.

The principles of a high glycolytic activity in malignancy can be used in the majority of organ systems to differentiate between benign and malignant lesions with a few notable exceptions. The most commonly encountered of these is in the thyroid where both benign and malignant nodules may demonstrate increased FDG uptake. No uptake within a thyroid nodule virtually excludes malignancy (Giovanella et al, 2011).

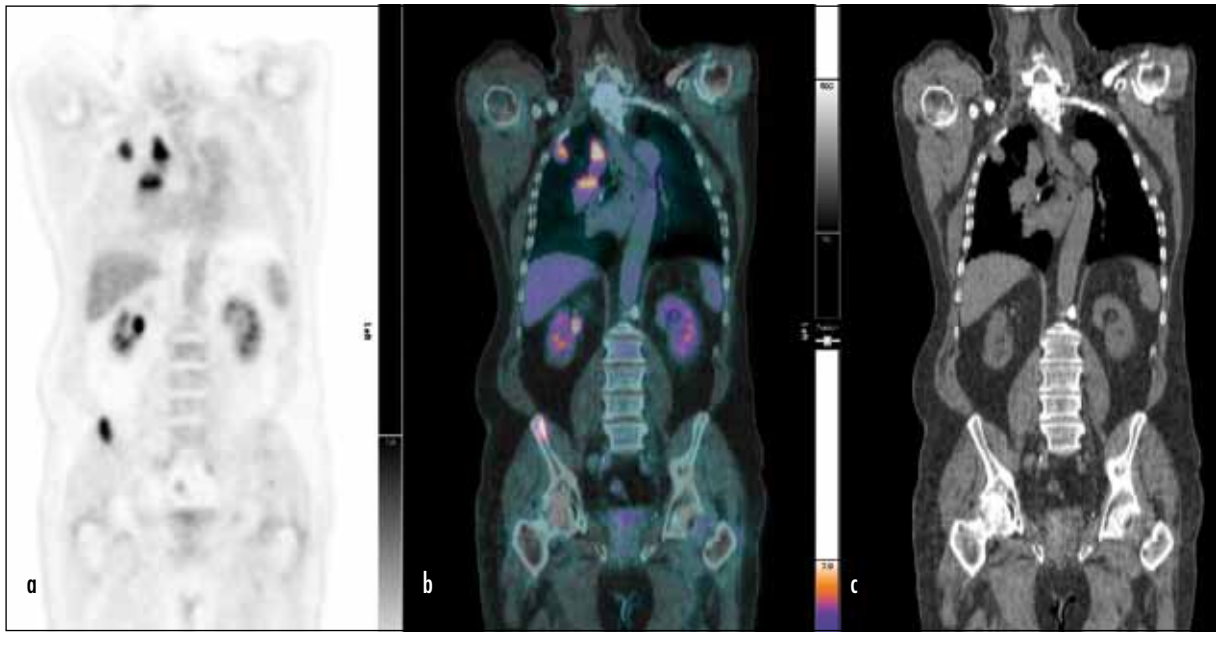
Positron emission tomography computed tomography often plays an important role in the detection of occult malignancies, discovered as a result of the presence of metastatic disease. Carcinoma of unknown primary is a heterogenous group of conditions with lung, oropharynx and pancreas representing the most likely primary sites (Kwee et al, 2010). Although there are rather variable results in the literature, positron emission tomography computed tomography demonstrates the primary site in approximately 31% of cases when conventional cross-sectional imaging has failed (Dong et al, 2008). This directly affects patient management and leads to the possibility of targeted therapy.

In occult head and neck primaries with cervical nodal disease, positron emission tomography demonstrates the primary lesion in approximately 27% of cases. While this number may seem relatively low, it should be noted that this patient population have already had negative nasal endoscopies and magnetic resonance imaging studies.

Staging

The use of positron emission tomography computed tomography in primary disease staging has long been recognized. While its main role was primarily in non-small cell lung cancer and lymphoma, its indications increase on almost every review. In 2008 the *Journal of Nuclear Medicine* published recommendations for ^{18}F-FDG positron emission tomography in oncology (Fletcher et al, 2008a). At this time it was reported that positron emission tomography had a role in staging oesophageal, head and neck, lymphoma, lung cancer, high risk colorectal cancer and melanoma. Subsequent studies have provided increasing evidence as to its role in these patient groups but also indicated potential applications for positron emission tomography computed tomography in the staging of gynaecological malignancies (particularly locally advanced cervical cancer) and upper gastrointestinal and/or pancreatic malignancies (Gold, 2008; Buchs et al, 2011) (*Figure 3*).

Figure 2. A 77-year-old man with possible T1b N2 M0 lung cancer on conventional imaging. 18-Fluoride positron emission tomography computed tomography demonstrates hypermetabolic right lung lesion with separate tumour nodule and right iliac crest metastasis T3 N2 M1 (proven to be squamous cell carcinoma on subsequent biopsy). a. Coronal positron emission tomography only imaging. b. Fused positron emission tomography computed tomography data set. c. Computed tomography only.



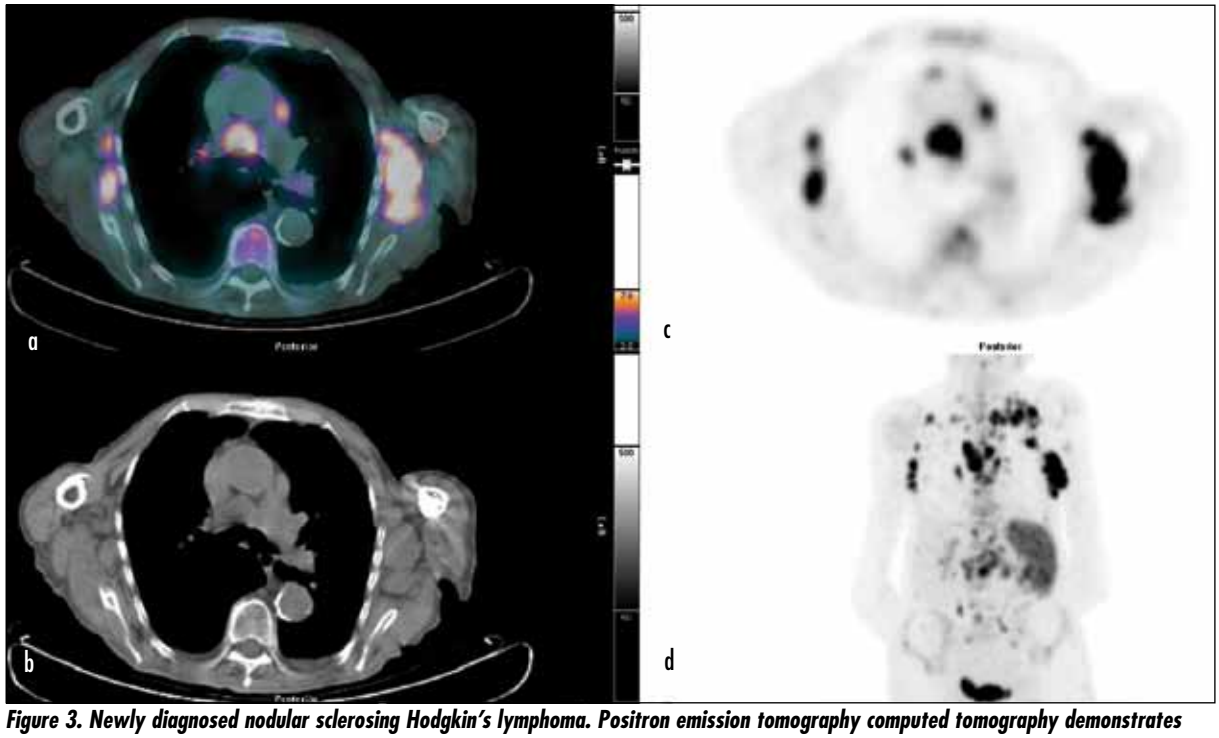


Figure 3. Newly diagnosed nodular sclerosing Hodgkin's lymphoma. Positron emission tomography computed tomography demonstrates hypermetabolic nodes above and below the diaphragm, splenic and osseous involvement (stage IV). a. Fused positron emission tomography computed tomography dataset demonstrating involved bilateral axillary, precarinal, right hilar and prevascular nodes. b. Corresponding computed tomography only image and (c) positron emission tomography only image. d. Maximum intensity projection image showing widespread involvement above and below the diaphragm.

Although in the majority of solid tumours positron emission tomography computed tomography imaging does not tend to alter the T stage, it is important to recognize some of the potential benefits. First, the metabolic dimensions derived from positron emission tomography computed tomography often mirror the pathological specimen more closely than conventional imaging, particularly in oesophageal and rectal carcinomas (Lambrecht and Haustermans, 2010; Buijsen et al, 2011). Second, because positron emission tomography is a functional imaging tool it is able to delineate tumour from less active surrounding tissue. This is particularly important in the T staging (and potential treatment) of non-small cell lung cancer where adjacent atelectasis can mask the true dimensions of the pulmonary lesion. Furthermore, FDG uptake can provide clues to the characteristics of the primary tumour, particularly the potential aggressiveness of the lesion (Jadvar et al, 2009). It is therefore unsurprising that standardized uptake value measurements have been assessed as a prognostic indicator.

A meta-analysis of 21 studies concluded that patients with non-small cell lung cancer with a high standardized uptake value have shorter survival than those with a lower glycolytic rate. However, it was unable to confidently identify a threshold standardized uptake value (Paesmans et al, 2010). Similarly, a meta-analysis of standardized uptake value measurement in head and neck cancers demonstrated a statistically significant survival benefit in patients with a low pre-treatment standardized uptake value compared to those patients with a high standardized uptake value (Xie et al, 2011). It is therefore evident that positron emission tomography computed tomography of the primary, untreated lesion in several tumour types may act as a prognostic indicator. This in itself may lead to changes in patient management. While assessment of the primary tumour by positron emission tomography computed tomography may provide additional information, it is in the nodal (N stage) and assessment of distant disease (M stage) that the benefits of positron emission tomography computed tomography become most apparent.

Because positron emission tomography is a functional imaging tool, it does not rely on lymph node size as a criterion for detecting tumour involvement. This means that disease can be detected in nodes which would have been called normal based on computed tomography criteria. Alternatively, large nodes which are positron emission tomography negative can be classified as benign. Whole body imaging using positron emission tomography also allows the detection of distant metastases. It is well documented that, as a result of these factors, imaging with positron emission tomography significantly limits the number of so-called 'futile' thoracotomies in lung cancer. Because of its relatively high sensitivity in both N and M staging, the new draft National Institute for Health and Clinical Excellence (2011) guidelines for the diagnosis and treatment of

lung cancer state that all patients potentially suitable for treatment with curative intent should be offered a positron emission tomography computed tomography scan before treatment. There is, however, a continued need to evaluate positron emission tomography positive nodes with mediastinoscopy unless there is obvious metastatic disease or high probability of N2 or N3 disease on the positron emission tomography study. This is because of the variability in specificity within the literature examined by National Institute for Health and Clinical Excellence (37.5–100%). It is important to note that reactive nodes can be positron emission tomography positive, especially in the presence of coexisting pneumonitis.

The value of functional imaging is also seen in the staging of lymphomas where reported sensitivity and specificity are high (median sensitivity 90.3%, median specificity 91.1%) (Isasi et al, 2005).

While improved N and M staging are seen in a variety of solid tumours, the role of positron emission tomography computed tomography in the initial staging of all but high risk colorectal cancer remains limited. Furthermore, because of the low glycolytic rate, staging prostate cancer with FDG positron emission tomography computed tomography is not feasible. Although several articles have suggested a possible role in primary breast cancer, particularly in axillary nodal staging (Heusner et al, 2009), further research is needed as others have found no added benefit and at present positron emission tomography computed tomography cannot replace invasive sentinel node sampling. There is still, therefore, no convincing evidence for the use of FDG positron emission tomography in the primary diagnosis and staging of breast cancer at this time, particularly as lobular carcinomas tend to exhibit low FDG avidity.

Therapy planning

The detection of loco-regional and metastatic disease is important in surgical planning. The efficacy of positron emission tomography computed tomography in primary staging has already been demonstrated which directly impacts upon surgery. In addition, these principles are also becoming increasingly important in radiotherapy planning. Positron emission tomography negative nodes and tissues can be excluded from the radiation field thereby limiting the target volume and potentially reducing toxicity. Positron emission tomography computed tomography radiotherapy planning is already in clinical use in the treatment of non-small cell lung cancer in some European centres.

There is evidence of reduction in the incidence of acute oesophagitis secondary to the smaller target volume produced by positron emission tomography in the assessment of nodal disease (Fernandes et al, 2010). By using the metabolic dimensions of the tumour, positron emission tomography computed tomography has also been shown to affect the radiotherapy target volumes in oesophageal and anal cancers. More work is needed in these areas. At present, trials involving positron emission tomography computed tomography in radiotherapy planning are underway in brain tumours, head and neck cancers, non-small cell lung cancer, oesophageal cancer, rectal or anal cancer, sarcomas and gynaecological malignancies (Bussink et al, 2011). The use of positron emission tomography in radiotherapy planning is likely to continue to expand in the next few years. Indeed the new generation of wide bore scanners have been developed with this indication in mind.

There is also increasing interest in assessing tumoural metabolic heterogeneity. It is known that relative hypoxia increases the resistance of tumours to chemotherapy and radiotherapy and positron emission tomography hypoxia markers such as ^{18}F-fluoromisonidazole (^{18}F-FMISO) can assess this. Tumoural assessment with these metabolic imaging agents could allow a heterogenous radiation field to the tumour, such that areas with relative radio-resistance would have an increased dose (Bussink et al, 2011).

Response evaluation

While anatomical imaging can only rely on volumetric data in order to assess tumoural response to chemotherapy and radiotherapy, positron emission tomography computed tomography allows the assessment of metabolic response. The assessment of residual nodes and/or nodal masses following chemotherapy for lymphoma has proven the efficacy of positron emission tomography computed tomography in this area and is in widespread clinical use. By categorizing residual FDG uptake into a 5-point scale following chemotherapy (Barrington et al, 2010) it is possible to assess treatment response and delineate areas of residual lymphomatous disease for further therapy (*Figure 4*).

The use of early positron emission tomography computed tomography in therapy monitoring can also lead to so-called 'response adaptive therapy', whereby therapeutic interventions can be escalated, changed or continued based on early metabolic imaging findings. This leads to personalized treatment and ensures ineffective therapies are withdrawn at an early stage. These principles have been adopted by pharmaceutical manufacturers assessing novel drugs leading to cost savings from the early shelving of ineffective therapies.

Several studies have now been published demonstrating the value of positron emission tomography computed tomography in therapy response. These include lung, oesophageal, gastric, rectal and breast cancer as well as in the assessment of metastatic disease (Nannini et al, 2009; Bussink et al, 2011). Lordick et al (2007) showed that patients with oesophageal cancer with a decrease in standardized uptake value of 35% 2 weeks after induction chemotherapy had a significantly longer median event-free survival and overall survival.

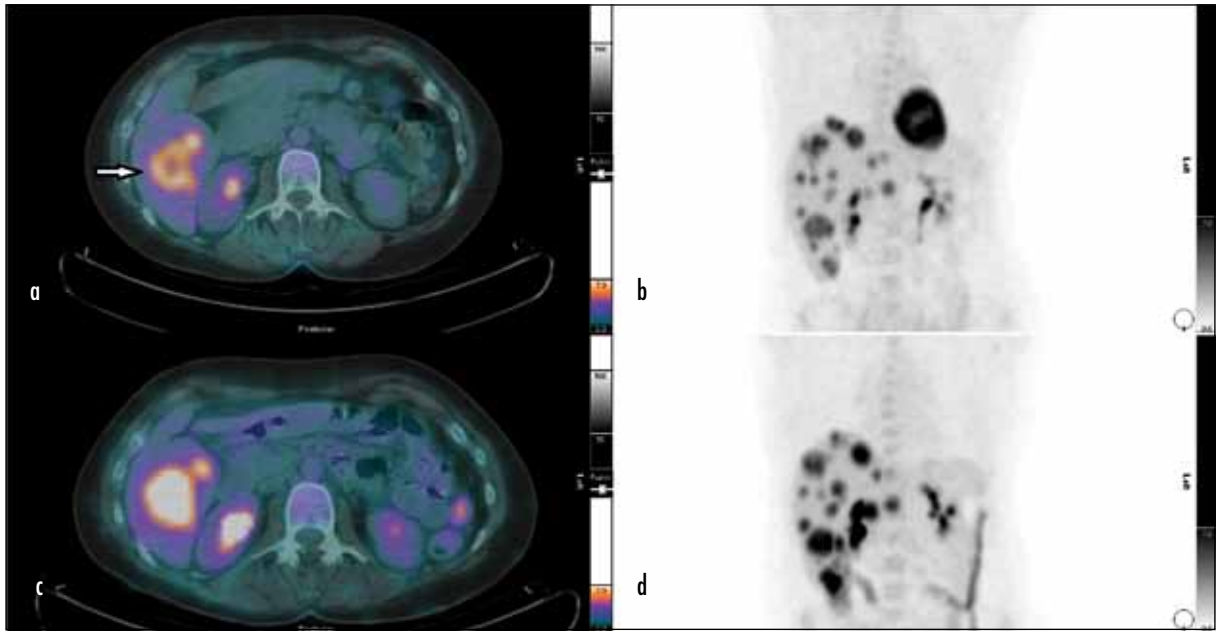


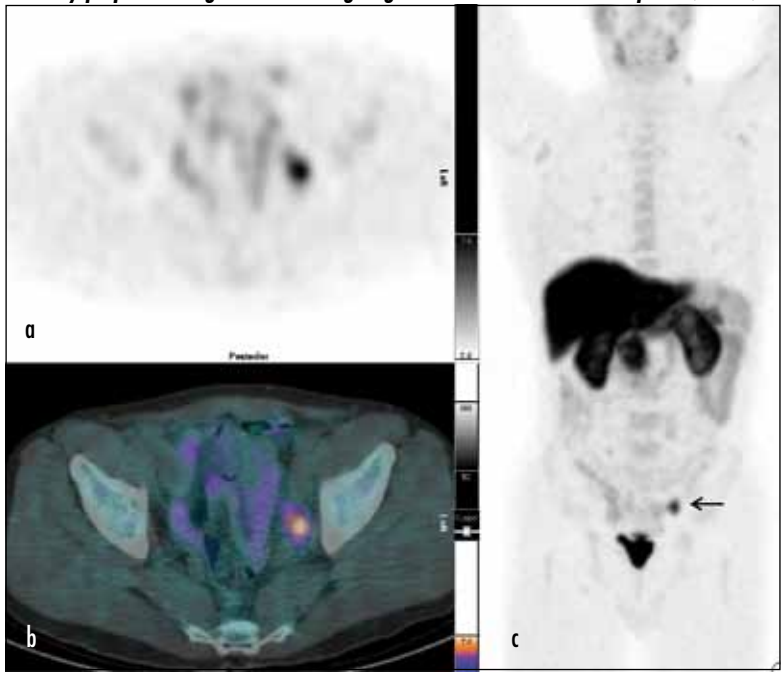
Figure 4. Breast cancer with liver metastases post two cycles of chemotherapy. a. Fused positron emission tomography computed tomography dataset and (b) maximum intensity projection images showing central necrosis (arrow) and decreased fluoro-2-deoxy-glucose uptake of the liver metastases when compared with (c) the pre-treatment fused dataset and (d) maximum intensity projection images.

Disease recurrence (restaging and localizing occult disease)

While the role of positron emission tomography computed tomography in the primary staging of breast cancer is limited and controversial, there is no argument as to its value in the detection of loco-regional recurrence or distant metastases with positron emission tomography proving more sensitive than either computed tomography or tumour markers (Evangelista et al, 2011).

Indeed, with the exception of prostate cancer, FDG positron emission tomography computed tomography is of value in assessing disease recurrence within most other tumour types (Papathanassiou et al, 2009). The assessment of known or potential disease recurrence is one of the commonest indications for positron emission tomography computed tomography at present. Furthermore, positron emission tomography computed tomography is of increasing use in localizing occult disease in the presence of rising levels of tumour markers. This is again true of most tumour types. Even in prostate cancer, radiolabelled choline has been successfully used in detecting previously occult disease at low levels of prostate-specific antigen (Beer et al, 2011) (*Figure 5*).

Figure 5. Rising prostate-specific antigen level post radical prostatectomy. Magnetic resonance imaging and computed tomography unremarkable. Choline positron emission tomography computed tomography demonstrates a small pelvic sidewall node (arrow) with intense choline uptake at site of disease recurrence. a. Positron emission tomography only image demonstrating uptake in the left pelvic sidewall node. b. Fused positron emission tomography computed tomography dataset at corresponding level. c. Maximum intensity projection image demonstrating single focus of abnormal nodal uptake (arrow).



Guide for image-guided biopsies

While computed tomography or ultrasound-guided biopsy is usually successful in providing histological confirmation of disease, there are occasions where positron emission tomography computed tomography can provide additional information and lead to a more targeted biopsy. Areas of highest standardized uptake value uptake within tumours can be targeted to assess the most metabolically active component of tissue and therefore potentially assess the most 'aggressive' tissue within the tumour.

Conclusions

The role of positron emission tomography computed tomography in oncology has moved from a research tool to a mainstay of oncological imaging. It is not only a staging tool in primary or recurrent disease but has become invaluable in the assessment of therapeutic planning and response. It is highly likely the clinical use of positron emission tomography computed tomography will continue to grow as it has proven itself cost effective (Langer, 2010). A recent Danish study assessing the use of positron emission tomography computed tomography without capacity limitations clearly demonstrated its utility with the number of studies requested increasing strikingly over a 3-year time frame. In this study, positron emission tomography computed tomography altered diagnosis, stage or management in 36% of cases (Hoilund-Carlsen et al, 2011). With this kind of impact the future of positron emission tomography computed tomography is assured. **BJHM**

Conflict of interest: none.

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KEY POINTS

- The role of positron emission tomography computed tomography in oncology continues to expand.
- Novel tracers can target different metabolic pathways allowing additional tumour detection and characterization.
- Positron emission tomography computed tomography has proven efficacy in primary disease characterization, staging and restaging, therapy planning and response, disease detection in cases of rising tumour markers and as an additional aid in targeted biopsies.