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PET/CT and breast cancer

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Abstract

This paper summarises the current status of PET/CT in relation to breast cancer.

Keywords: *PET/CT; Breast cancer.*

Introduction

Breast cancer is the most common cancer among women. The lifetime risk for the development of breast cancer is currently 1 in 8 (12%) in the developed world. The American Cancer Society predicts that over 250,000 cases of new breast cancer will be diagnosed in 2010. This is composed of about 207,090 new cases of invasive breast cancer and 54,010 new cases of carcinoma in situ. There will be about 40,000 deaths from breast cancer in the United States in 2010[1]. Breast cancer rates have shown a decline of about 2% per annum since 1999. Large nationwide screening programmes are in place in many countries. These programmes aim to detect cases of breast cancer early, provide prompt appropriate treatment and improve outcome.

Imaging techniques and tracers

Mammography, magnetic resonance imaging (MRI), ultrasound, computed tomography (CT) and bone scintigraphy play a significant role in breast cancer detection, assessment of treatment response, detection of recurrence and assessment of complications. Imaging with the positron emitting isotope ^{18}F attached to the glucose analogue fluorodeoxyglucose (FDG) and fusing it with CT (PET/CT) is becoming a standard imaging procedure in breast cancer. Fused PET/CT images are superior to PET or CT alone[2].

The intensity of [^{18}F]FDG uptake is related to the biological and histological characteristics with uptake being usually more marked in invasive ductal carcinoma than in invasive lobular carcinoma[3]. Uptake in ductal carcinoma in situ (DCIS) is usually poor or absent rendering it unsuitable for evaluation with FDG. Positive correlation between FDG uptake, tumour grade and tumour proliferation index has been demonstrated[4]. Likewise, p53 status is associated with increased uptake but no correlation has been demonstrated with c-erb-B2 overexpression[5]. A recent publication analysing FDG PET in 275 women with primary breast cancer demonstrated a positive relationship between standardised uptake value (SUV) and oestrogen receptor status ($p < 0.001$)[6]. A further study involving 88 patients demonstrated that triple negative breast tumours were associated with increased FDG uptake (100% sensitivity) consistent with a more aggressive biological status[7].

Other tracers studied clinically include fluorothymidine (FLT), a marker of cell proliferation, and fluoroestradiol (FES), a radioligand of oestrogen receptors. In one small study, FLT PET was able to detect changes in breast cancer proliferation as early as 1 week following chemotherapy[8]. A study involving 17 patients demonstrated good correlation between FES PET and oestrogen receptor expression, which might be useful in patients with multiple tumours or tumours that are difficult to biopsy[9]. The favourable imaging performance and clinical utility of [^{18}F]fluoride PET compared with conventional bone scintigraphy supports its use on a more routine basis for the assessment of skeletal metastases[10,11]. Radiolabelled antibodies targeting the HER-2/neu receptor and annexin V (a marker of apoptosis) have also been utilised[12,13].

Staging

The most important prognostic factor is the axillary lymph node status[14–16]. The 10-year survival rate ranges from 30% (>10 nodes) to 70% (1–3 nodes) compared with 90% in those with no nodal disease. Axillary

node clearance is usually restricted to levels I and II. A particular advantage of PET/CT is the identification of nodal disease in level III (superomedial to pectoralis minor) and extraaxillary regions[17]. In a study involving 111 patients, tumour size ($\leq$10 mm) and low tumour grade were independent factors predicting FDG uptake[18]. It is possible that improved detection may occur in this particular group with the development of PET mammography[19,20]. A recent study involving 36 women using prone FDG PET and MRI (90 lesions) demonstrated a reduced false-negative rate from 27% to 9% making it potentially useful in deciding which lesion to biopsy, particularly in women with multiple suspicious nodules on MRI[21].

Large breast tumours, locally invasive breast tumours and inflammatory breast tumours are associated with a high risk of nodal involvement and distant metastases[22]. In a prospective multicentre study involving 360 women with newly diagnosed invasive breast cancer analysis revealed a sensitivity of 61%, specificity of 80%, positive predictive value (PPV) of 62% and negative predictive value of 79% for the identification of axillary nodal metastases[23]. False-negative axillae had smaller and fewer tumour positive lymph nodes than true positive axillae ($p<0.005$). Finding 2 or more intense foci of tracer uptake in the axilla was highly predictive of axillary nodal disease (78–83% PPV). A prospective study involving 60 consecutive patients with breast tumours >3 cm found the primary tumour in 100% of patients with PET/CT and MRI[24]. Sensitivity and specificity of PET/CT for the detection of lymph node metastases was 70% and 100%, respectively. PET/CT diagnosed all extraaxillary lymph nodes. Overall sensitivity and specificity of PET/CT in detecting distant metastases was 100% and 98%, respectively (compared with 60% and 83% for conventional imaging). PET led to a change in the initial staging in 42% of patients.

A more recent study utilised FDG PET/CT in 61 patients as a triage tool for sentinel lymph node biopsy (SNLB) compared with axillary lymph node dissection[25]. The overall accuracy for PET/CT was 79% with a high specificity (92%) and PPV (82%) although only moderate sensitivity (58%). Patients deemed to have a 60% risk for axillary lymph node metastases (tumour diameter 4–5 cm) appear to be candidates for SNLB provided the axilla is clear on PET/CT. This approach has the potential to reduce the number of axillary lymph nodes dissections performed.

PET is useful for detecting lytic bone deposits and marrow infiltration but has limitations in the detection of osteoblastic deposits. A study involving 89 patients who had undergone FDG PET, conventional bone scintigraphy and multislice CT revealed that PET was superior in detecting lytic deposits (100%) and marrow infiltration (87%) but inferior in detecting sclerotic deposits (56%)[26]. A recently published study comparing PET/CT and bone scintigraphy in 163 women found high concordance (81%) between the 2 techniques for reporting bone metastases[27]. Of the discordant studies (19%) just over a third had pathologically confirmed bone metastases, most of which were detected by PET/CT. A meta-analysis involving 23 studies for the diagnosis of bone metastases in breast cancer revealed a pooled sensitivity for MRI (97%) to be higher than PET (83%) or bone scintigraphy (87%) ($p<0.05$)[28]. No significant difference between bone scintigraphy and PET was demonstrated. The pooled specificity for PET (94.5%) and MRI (97%) were both significantly higher than bone scintigraphy (88%) ($p<0.05$).

PET is also accurate in identifying metastatic disease in the pleura, mediastinum and abdomino-pelvic regions[24]. It is also useful in confirming benign lesions at sites where metastatic disease is suspected on conventional imaging[29]. As with other cancers detection of small intracranial deposits is not possible because of the high background uptake of glucose within brain parenchyma; MRI is the preferred imaging technique. Comparison of whole-body diffusion-weighted imaging (DWI) and FDG PET/CT for staging breast cancer in 20 patients revealed an overall accuracy of 98% for PET/CT compared with 76% for DWI[30]. Of the lesions visualised on DWI only, 82% were false-positive compared with 11% on PET/CT. The data indicate that DWI is a sensitive but non-specific technique for the detection of locoregional or metastatic disease. Use of the apparent diffusion coefficient to quantitatively differentiate lesions was not possible.

The cost-effectiveness of PET regarding detection of locoregional lymph node metastases from breast cancer has been studied in Australia with a reported cost benefit[31]. However, there is also a need for prospective randomised clinical trials with high patient numbers to evaluate the cost-effectiveness of PET/CT[32].

Monitoring therapy

Neoadjuvant therapy plays an important role in the treatment of breast cancer. The aims are to reduce tumour burden thereby making inoperable tumours operable and to offer breast-conserving surgery to those patients where a sufficient reduction in tumour size has been achieved. Axillary response after neoadjuvant therapy yields prognostic information with a complete remission a strong predictor of disease-free survival[33]. Choi *et al.*[34] analysed results from PET/CT and other imaging techniques before and after neoadjuvant therapy in 41 patients and found that MRI was superior to PET/CT. In contrast, Kumar *et al.*[18] evaluated the role of PET/CT after 2 cycles of neoadjuvant therapy in 23 patients. PET/CT demonstrated that 16 were responders and 7 were non-responders. Analysis revealed a sensitivity, specificity and accuracy of 93%, 75% and 87%, respectively, enabling PET/CT to differentiate responders from non-responders. A more recent study involving 38 patients indicated that PET/CT was suitable to monitor axillary response

especially in triple negative tumours[35]. However, it is worth remembering that the optimum time for assessment of treatment response has yet to be established and the best results are obtained in those whose SUV is increased at the outset. As a result, PET/CT cannot be considered yet as the technique of choice for monitoring disease response in the neoadjuvant setting[17].

In monitoring disease response for metastatic cancer, a study involving 20 patients demonstrated that 75% of patients showing a metabolic response on visual analysis responded well to therapy[36]. Analysis using the average SUV showed that changes measured after 3 cycles of chemotherapy predicted the clinical response to chemotherapy and overall survival. In a large study utilising PET/CT in 102 women comparing morphological and metabolic changes in bone metastases following systemic therapy found that a decrease in SUV after treatment was an independent predictor of response duration in patients with metastatic breast cancer who had bone metastases[37]. A large multicentre trial involving 272 PET scans in 104 patients demonstrated that patients with a baseline SUV <3.0 did not achieve a histopathological response[38]. A threshold of 45% decrease in SUV correctly identified 73% of responders after the first cycle with a similar result after the second cycle when a 55% threshold was applied. However, more data are required before this becomes routine practice.

Recurrent disease

The evaluation of local recurrence in the breast, skin or chest wall with PET or PET/CT can be a problem with both false-positive and false-negative cases as a result of inflammation or small volume disease[39]. Differentiating brachial plexopathy from axillary or supraclavicular recurrence can be difficult and PET is useful in this scenario[40,41]. Isasi *et al.*[42] performed a systematic review involving 808 patients which showed that PET had a sensitivity of 90% and specificity of 87%. A multidisciplinary expert panel convened by the American Society of Clinical Oncology (ASCO) found moderate evidence that PET should routinely be added to the conventional work-up in detecting recurrent breast cancer[43].They concluded that the evidence was also moderate for FDG PET to improve health-care outcomes and that its main benefit was avoiding futile surgery. A meta-analysis of 42 studies comparing the accuracy of multiple imaging techniques in the detection of recurrent breast cancer found that MRI and PET were superior to ultrasound or CT ($p < 0.05$) with no statistical difference between PET or MRI[44]. Grassetto *et al.*[45] using FDG PET/CT in 89 women with rising serum Ca 15.3 levels, negative clinical examination and negative conventional imaging, found sites of active disease in 40 patients in the chest wall, internal mammary nodes, lungs, liver and bony skeleton.

Conclusion

PET/CT is particularly helpful in detecting extraaxillary nodal disease and occult metastases in patients with locally advanced breast cancer. It also has an evolving role in evaluating response to chemotherapy in the neoadjuvant or adjuvant setting. It is more efficient than conventional imaging in detecting suspected recurrence. It has no role in detecting micrometastases in axillary nodes or subcentimetre breast tumours.

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