^{18}F-FDG dual-headed gamma camera PET in detection of axillary nodal disease in patients with large or locally advanced breast cancer: Possible alternative staging of axilla

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Abstract. Positron emission tomography (PET) has been used in staging the axilla. Gamma Camera PET (GCPET) is a cost effective alternative, but poorly studied. The aim of this study was to assess GCPET in demonstrating metastatic deposits in axillary nodes in patients with a high likelihood of nodal disease. Twenty-seven women with large (T2, T3 or T4) or advanced breast cancer (N1, N2 or M1) were recruited. All patients underwent axillary lymph node removal or biopsy (fine needle aspiration cytology (FNAC) or core cut) and whole body GCPET imaging. Images were reported anonymously and compared with the histological findings. Twenty-one patients proceeded to surgery and 10 had tumour-involved axillary nodes; GCPET was positive in 8 of these. The remaining 6 patients underwent core cut or FNAC of the axillary nodes, 2 of which contained a tumour. GCPET was positive in both cases. Thus, the diagnostic values were: sensitivity 83%, specificity 100%, positive predictive value 100%, negative predictive value 88% and accuracy 93%. In conclusion, GCPET is a reliable method and can be performed in a district general hospital and detecting disease in axillary nodes in certain patients, possibly obviating the need for surgery.

Introduction

Axillary lymph node metastasis is the most important prognostic factor in breast cancer. The 10-year survival for patients with tumour-free lymph nodes is 65%, compared with 25% for those who have axillary lymph node involvement (1). Determination of axillary nodal status is crucial in deciding the need for both systemic and locoregional treatment (2,3). The 'gold standard', currently, for assessment of nodal status is axillary surgery. This procedure exposes patients to potential complications and morbidity including lympho-edema, damage to nerves, haematoma, seroma, cellulitis and limitations of shoulder movement (4-8).

The likelihood of nodal metastases depends on various factors but tumour size is a key factor. Tumours between 2-5 cm have 40-60% likelihood of nodal invasion, compared with less than 10% if the tumour is less than 0.5 cm (9-11). It has been estimated that, even in the large and locally advanced breast cancers (LABCs), up to 60% of such patients have an unnecessary axillary dissection (12). As a result, in recent years, there has been a growing interest in non-invasive or minimally invasive techniques (e.g. sentinel node biopsy) in staging the axilla, to reduce the significant morbidity which may be associated with unnecessary axillary dissection (13,14). Various non-surgical imaging techniques including mammography, ultrasonography, computerised tomography (CT) scanning and magnetic resonance imaging (MRI) have been used to detect metastatic deposits in axillary lymph nodes, but none has proven to be very effective (15-18). These imaging modalities, however, are evaluating anatomical characteristics only. Recently, positron emission tomography (PET) scanning has emerged as a unique non-invasive method of imaging tissues based not on anatomical features but on the metabolic activities of the cancers. PET makes use of radiopharmaceuticals that are made up of biologically relevant molecules (monosaccharides, amino acids, etc.), labelled with positron-emitting isotopes.

Malignant cells have a higher rate of glycolysis and are estimated to have a five times higher uptake of glucose than normal cells, primarily due to higher expression of the glucose transporter, Glut-1 (19). Fluorine-18 labeled fluoro-deoxyglucose (^{18}F-FDG), a radioactive derivative of glucose, is a radiopharmaceutical agent most commonly used with PET. ^{18}F-FDG, like glucose, is taken up by malignant cells but is incompletely degraded and, thus, is trapped intra-cellularly as ^{18}F-FDG-6-PO_4 which is detected by the PET scanner (19,20).

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Currently, PET can be performed using either a dedicated or a coincidence gamma camera (GCPET). The development of new electronics and software has enabled double-headed gamma cameras, sited in Nuclear Medicine Departments, to be used in a similar mode as a dedicated PET scanncer, although the sensitivity of these systems is not as high as the multiple detector scanners (21,22). Previously, we successfully reported the use of GCPET in the detection of primary breast tumours with a superior sensitivity, compared with mammography and ultrosonography (23). Comparable results were found in a study using GCPET to detect primary lesions in 26 women with a sensitivity of 84.6% (24). However, in the same study, GCPET detected axillary lymph node metastases with a sensitivity of 40% and specificity of 100% (24).

In early breast cancers, PET scans showed high specificity but lack of sensitivity in the detection of axillary nodal invasion (22,25-28). However, in women with large or LABCs, both the sensitivity (93%) and specificity (100%) are significantly enhanced, and their use to stage the axilla is a realistic option (21). The objectives of this study were to highlight the possibility of using GCPET (not dedicated PET), particularly in a district general hospital setting, and to establish the effectiveness of GCPET in demonstrating axillary lymph node involvement in large or LABCs with a high probability of regional tumour spread.

Materials and methods

Patients. The study was approved by the local Ethics Committee of the United Lincolnshire Hospitals NHS Trust and conducted in accordance with the Helsinki Declaration. The research was certified by ARSAC.

Twenty-seven women with large and LABCs presenting to the Breast Clinic, Lincoln County Hospital were invited to take part in this study. The study recruited women with primary tumours larger than 2 cm (T2, T3), tumours which had invaded skin or the chest wall (T4) and tumours with ipsilateral palpable and clinically involved axillary lymph nodes (N1, N2). This study also included two patients who had recurrent disease. The size of the breast cancer was measured by callipers in two dimensions. Locoregional metastases was also assessed in all patients before staging according to the TNM classification. After histological confirmation of breast cancer, and prior to commencing treatment, patients were referred to the Nuclear Medicine Department for PET scan imaging.

^{18}F-FDG PET imaging. All patients were scanned after injection of 140 MBq of ^{18}F-FDG. Details of the technique used was described in our previous study (23).

Axillary node evaluation. Twenty-one of the 27 patients underwent surgery to the breast and axilla without any prior treatment. After careful discussion between the consultant breast surgeon, the patients and her relatives/carers, either wide local excision or mastectomy was carried out, with axillary lymph node sampling (removal of 4 or more nodes) or lymph node clearance (level 3). Histopathological staging of the primary tumour and the axilla was obtained.

The remaining 6 patients (including two patients who had locoregional recurrent disease) were treated with chemotherapy/hormonal therapy before proceeding to surgery and/or radiotherapy. The axillary lymph node status in these 6 patients was obtained either by ultrasound-guided FNAC (n=4) or core cut biopsy (n=2), prior to commencing systemic treatment.

Table I. Patient demographics and tumour characteristics.

Total no. of patients	27
Age (years)	
Mean	68
Range	43-83
Primary tumour type (two patients who had recurrent disease not included)	
Invasive ductal	19
Invasive lobular	2
Invasive lobular/ductal	2
Invasive metaplastic (no special type)	1
Mucinous carcinoma	1
Primary tumour stage (two patients who had recurrent disease not included)	
T1	0
T2	22
T3	1
T4	2
Axillary node status (two patients who had recurrent disease not included)	
N0	18
N1-N2	7
Metastatic status (two patients who had recurrent disease not included)	
M0	22
M1	3

Data analysis. ^{18}F-FDG-PET was evaluated and reported by a consultant radiologist (DCW) and two clinical scientists (CM and PAG) who were anonymised to all clinical data. Also, the surgeon and pathologists who were involved in this study were blinded to the ^{18}F-FDG-PET results. Histopathological or cytological description of the axillary lymph nodes was reported by experienced breast pathologists/cytologists. The presence of metastasis in axillary nodes documented by GCPET scanning was compared with the pathological assessment. The sensitivity, specificity, accuracy, and positive and negative predictive values were calculated relative to the definite histopathological status of the axillary lymph nodes. Calculation of these parameters was as follows: sensitivity = TP/(TP+FN); specificity = TN/(TN+FP); positive predictive value = TP x 100/(TP+FP); negative predictive value = TN x 100/(TN+FN); Accuracy = (TP+TN)/(TP+FP+FN+TN). (TP is true positive, TN is true negative, FP is false positive and FN is false negative).

Table II. Axillary lymph nodes status.

	Total	Percentage
Diagnosis of axillary lymph node metastases		
Histopathological assessment of operative specimens	21	78
Histopathological/cytological assessment by core cut/FNAC	6	22
Axillary lymph node status		
Evidence of tumour invasion	12	44
No evidence of tumour invasion	15	56

Results

Twenty-seven women recruited in this study had a mean age of 68 years. Among the 27 patients, 25 had tumours clinically assessed to be larger than 2 cm (T2 or more) and two patients had locoregional recurrent disease. Seven patients had clinically palpable axillary lymph nodes (N1, N2). Clinically, pre-treatment staging was classified according to the TNM classification and is shown in Table I.

Twelve of these 27 patients (44%) were shown from either the final histopathological or cytological report to have metastatic nodal disease (10 of 21 patients from histology and 2 of 6 patients from FNAC). The histopathological/cytological findings of the 27 specimens of the axilla are summarised in Table II.

A typical GCPET scan is shown in Fig. 1 demonstrating increased uptake of 18F-FDG in the involved axillary node. Increased axillary uptake was found in 10/12 patients with proven axillary disease (10 true positive). The other 15 patients showed no sign of tumour involvement in both PET uptake and histopathological evaluation (15 true negative). In the 2 patients with negative scans, histopathological examination confirmed ipsilateral axillary involvement (2 false negative) in 1 out of 20 and 1 out of 6 nodes, measuring 5 and 4 mm, respectively. No false positive results were obtained. The results are summarised in Table III. Overall, the sensitivity, specificity, accuracy, positive predictive and negative predictive value of GCPET to detect axillary invasion were 83, 100, 93, 100 and 88%, respectively.

Discussion

The incidence of axillary nodal metastases in patients with breast cancer depends on a range of factors but, in particular, on the size and grade of the primary tumour (10,11). In this series, where patients either had tumours which clinically were

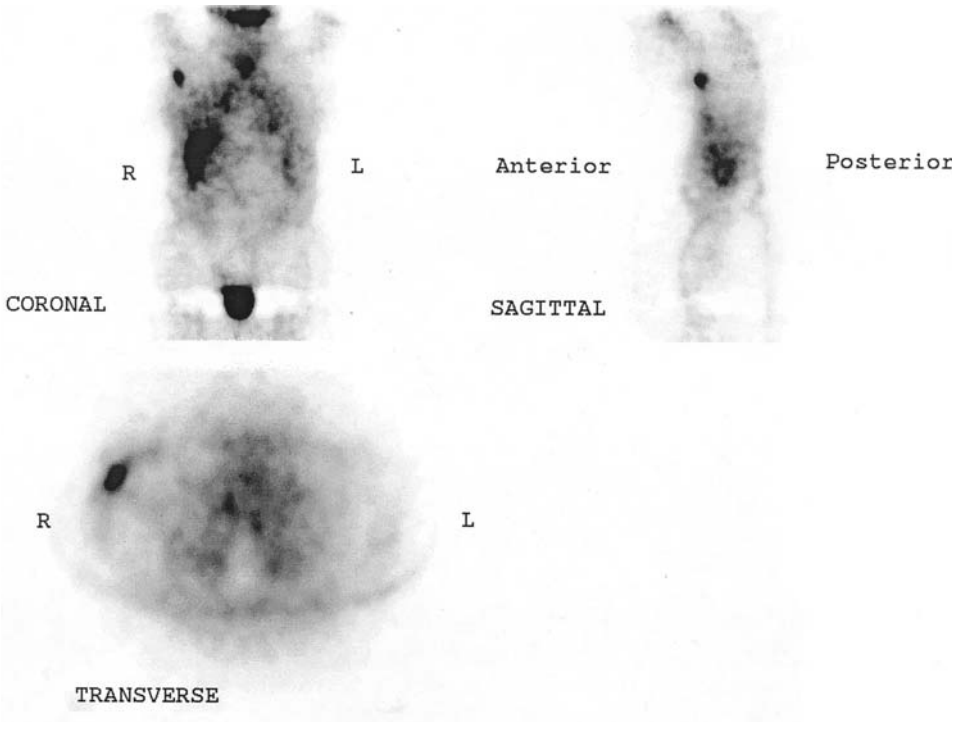

Figure 1. Typical gamma camera PET scanning showing primary tumour and involved axilla.

Table III. Results of PET scans in demonstrating axillary nodal metastases.

	Positive by GCPET	Negative by GCPET
Positive by histology/cytology	10	2
Negative by histology/cytology	0	15

assessed to be larger than 2 cm (the majority were grade II) and/or had palpable axillary nodes, 12 of 27 of these patients (44%) were confirmed to have nodal metastases by histology or cytology. This is within the published range of 40-60% of patients with tumours 2-5 cm in size (9-11). In the 12 patients with nodal disease, GCPET was positive in 10 cases. No false positive results were found, resulting in a sensitivity of 83% and specificity of 100%. In the 2 patients with false negative results, histopathological examination demonstrated solitary involved nodes, the tumour deposits measuring 5 and 4 mm, respectively. Such small lesions are below the resolution of GCPET, which is limited by partial volume effects (29). The results also highlighted the efficacy of GCPET, sited in a district general hospital, to detect axillary lymph node metastases with high specificity in women with large and LABCs.

In a series of 50 patients, Smith *et al* (21) reported an overall sensitivity of 90% and a specificity of 97%. In 24 patients with LABCs (T3, T4, N2) PET had a sensitivity of 93% and a specificity of 100% (21). Greco *et al* (30) reported a sensitivity of 94.4% and a specificity of 86.3%, respectively in a series of 167 consecutive patients (30). However, Avril *et al* (31) reported a sensitivity of only 33%, in patients with small primary breast cancers (stage pT1) with micro-metastases, indicating that the resolution of current dedicated PET scanners is also limited (31). The sensitivity of GCPET is lower than some of the published values for dedicated PET scanners, which are known to have better resolution than GCPET. However, these data were from patient with early disease. In terms of predicting or evaluation of response in LABCs, GCPET is sensitive and more cost-effective than dedicated PET (23).

Non-invasive techniques of assessing the axilla prior to surgery, besides PET imaging, include ^{99m}Tc Sestamibi imaging and MRI. The sensitivity of Sestamibi imaging ranges from 67 to 75%, with a specificity of 80% (32,33). The lower sensitivity is probably related to the higher background in the neighbourhood of the axilla compared with the breast, thus, reducing the signal to noise ratio and detection of cancer cells. PET imaging with ^{18}F-FDG, has a higher signal to noise ratio than Sestamibi imaging, resulting in fewer false negative results. MRI has been shown to have high sensitivity (100%) but has low specificity (56%), leading to a large number of false positive results (34).

Knowledge of the status of the axilla prior to surgery, however, could obviate the need for any axillary surgery in many patients. Those with proven axillary nodal disease can be treated by axillary radiotherapy following breast surgery, with good locoregional control and long-term survival (35). Some patients may undergo neo-adjuvant chemotherapy, prior to subsequent breast surgery (wide local excision/mastectomy) and axillary irradiation.

However, even in large or LABCs, only 40-60% had axillary node metastases (9-11). Therefore, up to 50% of breast cancer patients had undergone axillary dissection without any lymph node metastases and this represents an unnecessary invasive surgical procedure (9,12). Thus, the recent rapid growing interest in developing less invasive surgical procedures, such as sentinel lymph node biopsy (SLNB) or ultrasound guided FNAC or core cut of the axillary lymph nodes, for staging the axilla. The SLNB approach in the best series, reliably predicts axillary lymph node status in up to 98% of patients (36). However, the procedure requires an individual expertise and is rather invasive compared with the imaging scan. The results from this study document the benefits of a pre-operative GCPET scan, supporting the surgeons' decision to carry out either a therapeutic axillary dissection (clearance or sample with irradiation) or no surgery with irradiation of the axilla only, for PET positive axillary nodes.

The question remains about the best approach for those patients with negative assessment (clinical, ultrasonography and GCPET) of the axilla. No diagnostic test will be 100% sensitive and 100% specific and a small percentage of patients will have micro-metastases (<5 mm) that will go undetected, but may never become clinically overt (9,37,38). It could be argued that surgery of the axilla be postponed until there is evidence of local recurrence as this will not affect overall survival (37,38). In addition, many of these patients may receive adjuvant therapy, for example, anti-hormonal therapy, if the cancer is oestrogen receptor positive, that may control or deal with small axillary deposits. Perhaps patients should be given the choice, having had the risks explained to them clearly and in detail. However, in the mean time, we recommend performing SLNB in the absence of enhancing spots from the GCPET of the axilla.

The role of PET scanning in the management of breast cancer is very encouraging. It has shown its potential in assessing the primary lesion, detecting residual disease, monitoring the response to chemotherapy and in staging of the axilla (23,26). The results of this study, using a GCPET scanner, fully support this view.

In conclusion this study shows that in the group of patients with large and LABCs, GCPET is effective in demonstrating axillary nodal disease with a sensitivity of 83% and a specificity of 100%. In high-risk surgical patients, or those likely to develop post-operative morbidity, it could be a useful alternative staging technique that may obviate the need for axillary surgery in patients with positive PET results.

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