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Detection of extra-axillary lymph node involvement with FDG PET/CT in patients with stage II–III breast cancer

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ABSTRACT

Purpose: The aim of this prospective study was to assess the incidence of extra-axillary lymph node involvement on baseline FDG PET/CT in patients with stage II–III breast cancer scheduled for neo-adjuvant chemotherapy.

Methods: Patients with invasive breast cancer of >3 cm and/or proven axillary lymph node metastasis were included for before neo-adjuvant chemotherapy. Baseline ultrasound of the infra- and supraclavicular regions was performed with fine-needle biopsy as needed. Subsequently FDG PET/CT was performed. All visually FDG-positive nodes were regarded as metastatic based on the previously reported high specificity of the technique.

Results: Sixty patients were included. In 17 patients (28%) extra-axillary lymph nodes were detected by FDG PET/CT, localised in an intra-mammary node (1 lymph node in 1 patient), mediastinal (2 lymph nodes in 2 patients), internal mammary chain (9 lymph nodes in 8 patients), intra- and interpectoral (6 lymph nodes in 4 patients), infraclavicular (5 lymph nodes in 4 patients) and in the contralateral axilla (3 lymph nodes in 2 patients). Ultrasound-guided cytology had detected extra-axillary lymph node involvement in seven of these patients, but was unable to detect extra-axillary nodes in the other 10 patients with positive extra-axillary lymph nodes on FDG PET/CT. Radiotherapy treatment was altered in 7 patients with extra-axillary involvement (12% of the total group).

Conclusions: FDG PET/CT detected extra-axillary lymph node involvement in almost one-third of the patients with stage II–III breast cancer, including regions not evaluable with ultrasound. FDG PET/CT may be useful as an additional imaging tool to assess extra-axillary lymph node metastasis, with an impact on the adjuvant radiotherapy management.

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1. Introduction

The predominant lymphatic drainage pathway from the breast is towards the axilla.[1] In routine clinical practice, lymph node metastases in the axilla are treated by an axillary lymph node dissection (ALND). However, nodal metastases outside the axilla may be present in up to 56% of breast cancer patients.[2,3] The sites of extra-axillary nodes include the internal mammary chain (IMC), the infraclavicular region, the supraclavicular fossa, the breast itself and the interpectoral (Rotter's) space. In general, these nodes are not harvested or treated by routine surgical procedures.

Depicting lymph node involvement in levels or basins other than those addressed by routine ALND may have an impact on staging and treatment strategies. Metastases to the infraclavicular lymph nodes are associated with a worse prognosis compared to metastases to level I or II of the axilla.[4] Metastases to the supraclavicular lymph nodes indicate advanced regional disease and are associated with a poor prognosis. Positive internal mammary lymph node metastases may upstage patients to N2b orN3b (depending on the presence or absence of positive axillary lymph nodes), indicating a need for additional regional radiotherapy.

Although positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose (FDG) is less sensitive than sentinel node biopsy for the detection of lymph node metastases, its specificity for the detection is high, ranging from 95% to 100%.[5–12] Several studies suggest that FDG PET performs better than conventional imaging in depicting the involvement in high-level axillary (Berg level III) as well as in supraclavicular and internal mammary lymph nodes.[13–15] Unfortunately the lack of anatomical information of FDG PET alone may affect its specificity. Integrated FDG PET/CT can provide both morphologic and metabolic information, by combining anatomical CT data and functional FDG PET data. Subsequently, integrated FDG PET/CT can provide the precise location of involved nodes.[6]

The aim of this prospective study was to assess the incidence of extra-axillary lymph node involvement on FDG PET/CT in patients with stage II–III breast cancer for whom neo-adjuvant chemotherapy was indicated.

2. Patients and methods

2.1. Patients

Women who presented invasive breast cancer larger than 3 cm in diameter and/or at least one tumour-positive axillary lymph node were scheduled to be treated with neo-adjuvant chemotherapy in our institute. Since September 2007 patients were asked to participate in a study to assess the value of FDG PET/CT in the neo-adjuvant setting. This study was approved by the institutional ethical committee and informed consent was obtained from all patients.

In this pilot study, we included 60 consecutive patients who had a FDG PET/CT scan before the administration of neo-adjuvant chemotherapy. All breast cancers were initially diagnosed by fine-needle aspiration, further core biopsies were taken to determine hormone receptors and HER2 status, and to obtain tumour tissue for expression microarray analysis.[16] The tumour size was assessed with ultrasound, mammography and MRI. Ultrasonography and fine-needle aspiration (FNA) of suspect lymph nodes were performed in the ipsilateral axilla, infra and supraclavicular region. If indicated, i.e. based on physical examination or MRI, additional regions were examined. In patients with negative lymph nodes (ultrasound and/or FNA-cytology negative), a sentinel node biopsy (SNB) procedure was performed prior to neo-adjuvant chemotherapy.

2.2. FDG PET/CT

The FDG PET/CT scan was performed after conventional imaging of the breast and the axilla. Patients were prepared with a fasting period of 6 h, and 10 mg valium per os 10 min before FDG administration to avoid brown fat activation. Blood glucose levels were required to be <10 mmol/l. Patients received 180–240 MBq FDG intravenously. The interval between FDG administrations and scanning was 60 ± 10 min. A whole body FDG PET/CT scanner (Gemini TF, Philips, Eindhoven, The Netherlands) was used. FDG PET image acquisition was managed via standardised acquisition procedures. For regional staging, a high resolution FDG PET/CT was performed of the thorax (including breasts and axillae) with the patient in prone position with hanging breasts, 3:00 min acquisition per bed position, reconstructed to 2 mm voxel size, with low-dose CT images (40 mAs, 2 mm slices) for anatomical reference and attenuation correction. The administered activity, time of FDG administration and body weight on the day of scanning were recorded for calculation of the maximum standardised uptake value in the tumour (SUV_{max}).

2.3. Image interpretation

All FDG PET/CT scans were read in consensus by three experienced readers. Visual assessments of locations, extent and intensity of FDG-uptake patterns were made. The FDG uptake in the primary tumour and lymph node metastases was analysed semi-quantitatively using the SUV_{max}. For diagnostic evaluation, tumour FDG uptake was evaluated using a four-degree system: 0 = similar to other surrounding lymph nodes, 1 = slightly more than other lymph nodes, 2 = moderate intense and 3 = very intense. Lymph nodes with degrees 2 and 3 FDG uptake were considered suspects for malignancy. A SUV_{max} cut-off value of 2.5 was used to discriminate between malignant and benign lymph nodes in lymph nodes with a degree 1 uptake. {Duch, 2009 112/id; Okada, 2009 113/id; Torizuka, 1998 110/id and Zytoon, 2009 111/id}. All visually FDG-positive nodes were considered as metastatic, based on the previous reported high specificity of the technique.[5–12]

2.4. Radiotherapy

Radiotherapy was administered to the breasts of all patients receiving breast-conserving surgery, and to the chest wall in selected patients who underwent mastectomy. At the time of the study, elective irradiation of the IMC and peri-clavicular nodal area was the standard protocol at the NKI-AVL for all patients with pre- or post-chemotherapy positive axillary nodes. Some patients were referred to radiotherapy centres

elsewhere however, this was not a standard practice. The lateral axilla was irradiated in patients with stage N2 or N3 disease.

3. Results

A total of 60 patients were included in this study. Patient and tumour characteristics are outlined in Table 1. The mean age of the patients was 49 (range 29–68) years.

3.1. Ultrasound of the extra-axillary region

Baseline ultrasound, before FDG PET/CT, revealed extra-axillary lymph node metastases in 7 patients (12%). Lymph nodes outside the axilla were localised infraclavicular (4 patients), IMC (2 patients) and in the contralateral axilla (1 patient). All lesions were histopathologically confirmed with FNA. Ultrasound showed suspected supraclavicular lymph nodes in 2 patients and an intra-mammary lymph node in 1 patient. These suspicious nodes were tumour negative by histopathological evaluation with FNA cytology.

3.2. FDG PET/CT

In 17 patients (28%), extra-axillary lymph nodes were detected by FDG PET/CT. Two patients showed multiple anatomical localisations of lymph node involvement (Fig. 1). Lymph nodes outside the axilla on FDG PET/CT were localised in an intra-mammary node (1 lymph node), mediastinal (2 lymph nodes), IMC (9 lymph nodes), intra- and interpectoral (6 lymph nodes), infraclavicular (5 lymph nodes) and in the contralateral axilla (3 lymph nodes). The mean SUV_{max} of the involved lymph nodes was 5.5 (range 2.6–9.9).

Table 1 – Patients and tumour characteristics (total *n* = 60).

		Number	%
Patient age	Mean (range)	49 (29–68) years	
cT classification	cT 0	1	2
	cT 1	8	13
	cT 2	31	52
	cT 3	15	25
	cT 4	5	8
cN classification	cN0	15	25
	cN1	38	63
	cN2b/cN3	7	12
Histology	Ductal	52	87
	Lobular	5	8
	Mixed	1	2
	NS	2	3
Receptor status	ER-positive (HER2-negative)	34	56
	Triple negative (ER/PR/HER2: negative)	10	17
	HER2-positive	16	27

Abbreviations: NS (not specified), ER (oestrogen receptor), PR (progesterone receptor) and HER2 (human epidermal growth factor receptor 2).

3.3. Comparison of FDG PET/CT and conventional imaging

In 7/17 patients with extra-axillary lymph involvement on FDG PET/CT, nodes were also detected by baseline ultrasound and were histopathologically confirmed. In 10 patients (17%), FDG PET/CT showed suspicious uptake in extra-axillary lymph nodes that were not detected by conventional imaging. In two of these patients, SNB was performed which showed no drainage to extra-axillary lymph nodes. Suspected extra-axillary lymph nodes on FDG PET/CT were not verified by histopathological examination because surgery did not include the resection of these lymph node regions.

3.4. Change of treatment

FDG PET/CT upgraded the TNM stage in 17% (10/60) of the patients. In 7 patients (12%) the initial radiotherapy plan was changed based on the extra-axillary lymph node involvement

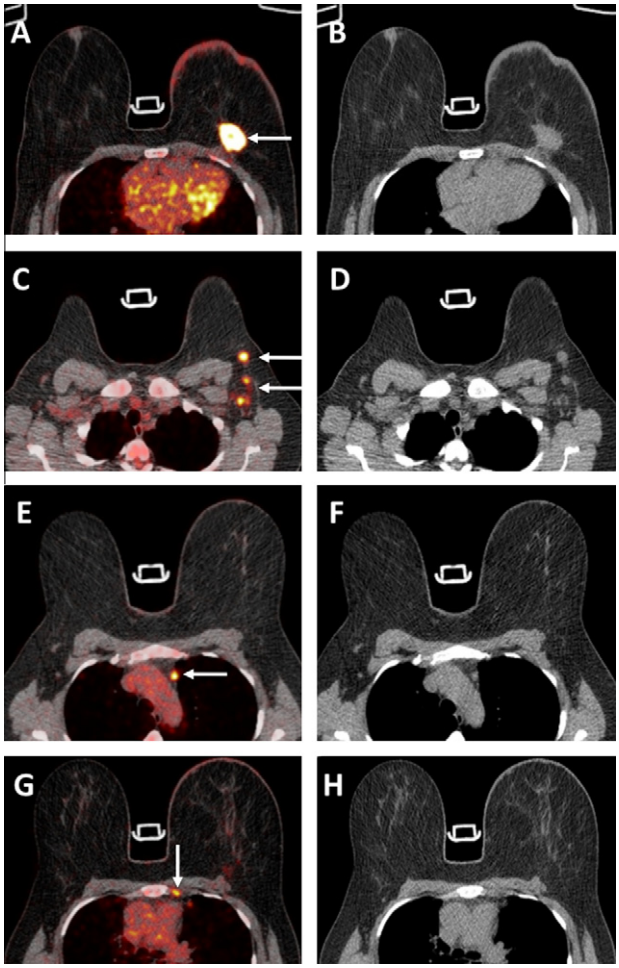

Fig. 1 – Patient with a FDG-avid carcinoma of the left breast seen on FDG PET/CT fusion (arrow on A) and corresponding CT (B) transversal images. FDG PET/CT (C) shows three hot spots in the left axilla (arrows) corresponding with some enlarged lymph nodes on CT (D). In this patient PET-CT detected also lymph node metastases (arrows) in the mediastinal area (E and F) and in one of the intercostal spaces (G, H).

Table 2 – The patients within the study cohort with hypermetabolic extra-axillary nodes on FDG PET/CT (17/60). Additional information of ultrasound, localisation, initial staging, upstaging as a result of FDG PET/CT and adjustment of radiotherapy treatment.

Axillary metastasis	Extra-axillary ultrasound	Localisation	N status[a]	Extra- axillary PET/CT	Localisation	N status[b]	Upstaging	Adjustment radiotherapy
Yes	Negative	–	1	Positive	IMC	3b	Yes	Yes
Yes	Positive	Infraclavicular	3a	Positive	Infraclavicular	3a	No	No
Yes	Negative	–	1	Positive	IMC	3b	Yes	Yes
Yes	Positive	Infraclavicular	3a	Positive	Infraclavicular	3a	No	No
Yes	Negative	–	1	Positive	Contralateral axilla	3/M1	Yes	Yes
No	Positive	IMC	2b	Positive	IMC	2b	No	No
Yes	Negative	–	1	Positive	Retropectoral	3b	Yes	No
No	Negative	–	0	Positive	Intrapectoral	3b	Yes	No
Yes	Negative	–	1	Positive	Subpectoral	3b	Yes	No
Yes	Positive	Infraclavicular	3a	Positive	Infraclavicular	3a	No	No
Yes	Negative	–	1	Positive	IMC	3b	Yes	No
Yes	Positive	Contralateral axilla	3/M1	Positive	Contralateral axilla	3/M1	No	Yes
Yes	Positive	IMC	3b	Positive	IMC and intrapectoral	3b	No	Yes
Yes	Positive	Infraclavicular	3a	Positive	Infraclavicular and IMC	3	No	No
Yes	Negative	–	1	Positive	Mediastinal	3	Yes	Yes
Yes	Negative	–	1	Positive	Mediastinal and IMC	3	Yes	Yes
Yes	Negative	–	1	Positive	IMC	3b	Yes	No

IMC: internal mammary chain.
[a] N staging according to ultrasound.
[b] N staging according to FDG PET/CT.

on FDG PET/CT (Table 2). In four patients with a positive IMC or mediastinal lymph nodes on FDG PET/CT, the radiotherapy target volume (clinical target volume, CTV) was adjusted to the individual situation and position of the affected nodes, two patients received radiotherapy to the contralateral axilla based on the FDG PET/CT results and one patient referred elsewhere received IMC irradiation based on the FDG PET/CT results in a radiotherapy centre where this was not the standard protocol.

4. Discussion

This study shows that FDG PET/CT appears to be a valuable modality for the detection of extra-axillary lymph nodes in patients with stage II–III breast cancer. FDG PET/CT detected extra-axillary lymph nodes in 28% of the patients. In 17% of the patients, FDG PET/CT showed suspicious uptake in extra-axillary lymph nodes that were not detected by conventional imaging (ultrasound examination and sentinel node biopsy). Consequently, FDG PET/CT can have a considerable impact on the TNM staging of these patients.

Patients with IMC node involvement, regardless of axillary node status, have a highly significant decrease in 20-year disease-free survival.[17] FDG PET/CT detected unexpected IMC node involvement in 6 patients who were subsequently reclassified as having N3b stage disease, as is recommended by the American Joint Committee on Cancer (AJCC) staging system.[4] Furthermore, infraclavicular and supraclavicular lymph node metastases are associated with a poor prognosis.[18,19] All these findings may have implications for treatment: more extensive radiotherapy fields, possible indication for chemotherapy with more intensive schedules and potential extended long-term endocrine treatments if tumours are endocrine responsive.[20–24] All this may benefit the patients since the prognosis of patients with N3 disease has improved over the years.[19]

The value of IMC irradiation in breast cancer patients in terms of efficacy and toxicity remains controversial. In patients with high-risk stage II–III breast cancer, the inclusion of the IMC in the radiotherapy field was associated with a significant increase in disease-free survival and a borderline increase in overall survival in a study reported by Stemmer and colleagues.[25] However, recently Romestaing and colleagues[26] demonstrated in a multicentric randomised phase III trial for patients with positive axillary nodes or internal/central tumour location that IMC irradiation does not improve overall survival, neither in any subgroup. During the course of this study, IMC irradiation was administrated to patients with positive axillary nodes and/or PET or sentinel node positive internal mammary nodes.

Another possible patient-tailored approach to reduce toxicity is giving irradiation to the part of the IMC in which the PET-positive node is localised instead of the whole IMC.

Several studies demonstrated that FDG PET is superior to conventional diagnostic techniques in the detection of extra-axillary nodal metastases, particularly to the internal mammary lymph nodes.[14,27,28] Eubank and colleagues demonstrated that mediastinal and internal mammary lymph node metastases were seen twice as often with FDG PET as with CT in patients with recurrent or metastatic disease.[28] In stages III and IV breast cancer patients, Danforth and colleagues showed that FDG PET was positive in the internal mammary nodal region in 25% of the patients.[14] Cermik and colleagues detected extra-axillary metastatic lymph nodes on FDG PET in 5% of the stage I–IV breast cancer patients.[13] However, these studies are hampered by a lack of anatomical

localisation since they used FDG PET alone. Fuster and colleagues reported that integrated FDG PET/CT is a valuable tool to exclude unsuspected extra-axillary lymph node and distant metastases in patients with large breast cancer.[6] In a previous pilot study,[29] we reported 36 patients of whom 16% had suspicious uptake on FDG PET/CT in extra-axillary lymph nodes that were not detected by conventional imaging. Our current results are in line with the pilot experience.

A limitation of this study was that we were unable to secure histopathological confirmation in all suspected lymph node metastases detected by FDG PET/CT imaging. Due to the anatomical localisation of the lymph nodes (e.g. intra-interpectoral), in some patients histopathological confirmation would require surgical interventions, which are not routinely employed in this population. Nonetheless, we feel that our results are reliable enough due to the high specificity of FDG PET/CT for the detection of lymph node involvement, ranging from 95% to 100% as demonstrated in various studies.[5–12]

In conclusion, FDG PET/CT may detect extra-axillary lymph node involvement in almost one-third of the patients with stage II–III breast cancer. These suspicious lymph nodes are as well located in several regions not evaluable with ultrasound. FDG PET/CT may be useful as an additional imaging tool to assess extra-axillary lymph node metastasis, with impact on management; particularly in patients who are candidates for neo-adjuvant chemotherapy.

Conflict of interest statement

None declared.

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