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ORIGINAL ARTICLE

Diagnostic and prognostic correlates of preoperative FDG PET for breast cancer

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Abstract
Purpose To explore the preoperative utility of FDG PET for the diagnosis and prognosis in a retrospective breast cancer case series.
Methods In this retrospective study, 104 patients who had undergone a preoperative FDG PET scan for primary breast cancer at the UZ Brussel during the period 2002–2008 were identified. Selection criteria were: histological confirmation, FDG PET performed prior to therapy, and breast surgery integrated into the primary therapy plan. Patterns of increased metabolism were recorded according to the involved locations: breast, ipsilateral axillary region, internal mammary chain, or distant organs. The end-point for the survival analysis using Cox proportional hazards was disease-free survival. The contribution of prognostic factors was evaluated using the Akaike information criterion and the Nagelkerke index.
Results PET positivity was associated with age, gender, tumour location, tumour size >2 cm, lymphovascular invasion, oestrogen and progesterone receptor status. Among 63 patients with a negative axillary PET status, 56 (88.9 %) had three or fewer involved nodes, whereas among 41 patients with a positive axillary PET status, 25 (61.0 %) had more than three positive nodes ($P<0.0001$). In the survival analysis of preoperative characteristics, PET axillary node positivity was the foremost statistically significant factor associated with decreased disease-free survival (hazard ratio 2.81, 95% CI 1.17–6.74).
Conclusion Preoperative PET axillary node positivity identified patients with a higher burden of nodal involvement,

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which might be important for treatment decisions in breast cancer patients.

Keywords Breast cancer · Prognosis · Survival · Lymph nodes · Staging · Surgery

Introduction

The diagnostic value, i.e. the ability to detect disease, of FDG PET in breast cancer have been investigated in many studies. The consensus from several reviews is that due to its limited spatial resolution PET lacks sensitivity for the diagnostic assessment of the axilla in patients with early breast cancer [1–5]. Most guidelines tend to recommend PET for breast cancer only in particular circumstances (in advanced disease, for recurrences, for treatment monitoring and possibly to evaluate the efficacy of neoadjuvant therapy) [6–12]. The prognostic value of FDG PET in breast cancer has received considerably less attention [13–16].

At the UZ Brussel, starting informally at the end of 2002, patients with operable breast cancer referred for primary treatment have received a whole-body FDG PET scan preoperatively, depending on appointment availability. The rationale was to use the scan for staging, and to improve target delineation for subsequent postoperative radiation treatment [17]. In the present study, we evaluated the diagnostic utility of the preoperative PET scan with regard to lymph node involvement, and also evaluated its prognostic value with regard to survival.

Materials and methods

We retrospectively identified patients presenting with primary breast cancer who received a PET scan at the UZ Brussel between 2002 and 2008. The study was approved by the institution's review committee. We selected patients in whom the cancer was the first primary breast cancer and in whom surgery was part of planned primary therapy. Patients with sarcoma of the breast, surgery performed but not as part of primary therapy, no histopathological confirmation of cancer, noninvasive carcinoma, or clinical metastatic disease were excluded.

FDG PET image acquisition and reconstruction

The procedure at the UZ Brussel has been previously reported [17]. The patients fasted for at least 6 h. Prescanning glucose levels were systematically checked. Tracer activity administered ranged from 370 to 536 MBq (average 464±56 MBq). Imaging was performed with the patients in the supine position with the arms placed above the head. Whole-body images corrected for attenuation were acquired with an LSO PET camera (ECAT Accel; Siemens, Hoffman Estates, IL) 60 min after tracer administration according to an interleaved protocol. Emission data were obtained in three-dimensional mode over 3 min per bed position. For transmission, ^{68}Ge sources (3×74 MBq; decay-corrected) were used and data were acquired in two-dimensional mode over 2 min per bed position. Emission data were reconstructed iteratively (OSEM, two iterations, 16 subsets), corrected for scatter, and a postreconstruction filter (6 mm Gauss) was applied. Filtered back-projection was used for the transmission. The constructed attenuation map was subsequently segmented into regions with similar attenuation factors. This segmented image was then forward-projected to obtain attenuation correction factors for each line of response. Only PET scanning was used.

Data abstraction

Data were retrieved from the patients' medical records, which included the FDG PET diagnostic summary report and a single-page hard-copy print-out of images. Standardized uptake values (SUV) were not routinely recorded. Due to changes in the archiving system over time, full PET imaging and SUV could not be consistently retrieved. Patterns of PET positivity were abstracted from the diagnostic reports according to the absence or presence of increased metabolic uptake in the following sites: involved breast, ipsilateral axillary region, internal mammary chain, or distant organs. Diagnosis of increased uptake was based on visual inspection globally, right versus left comparison, and tracer distribution within areas of interest (breast right and left, axillary right and left, peristernal, and elsewhere) (Fig. 1). We used the first examination in patients who had received a repeat PET scan. In patients with bilateral synchronous breast tumours, we retained the side of the first histopathological confirmation if there were different histopathology dates, or the side which had more axillary lymph nodes removed.

Survival times were computed from the date of first pathological diagnosis to the date of last known follow-up status. Events for evaluating disease-free survival (DFS) were defined as local-regional or distant recurrence, secondary tumour, or death from any cause. Recurrence and metastatic disease status were based on assessment of the physicians in charge of the patient as recorded in the medical files.

Statistical data analysis

Missing data The diagnostic procedure for first histopathology was missing in one patient, HER2-neu score in one patient, oestrogen receptor (ER) and progesterone receptor

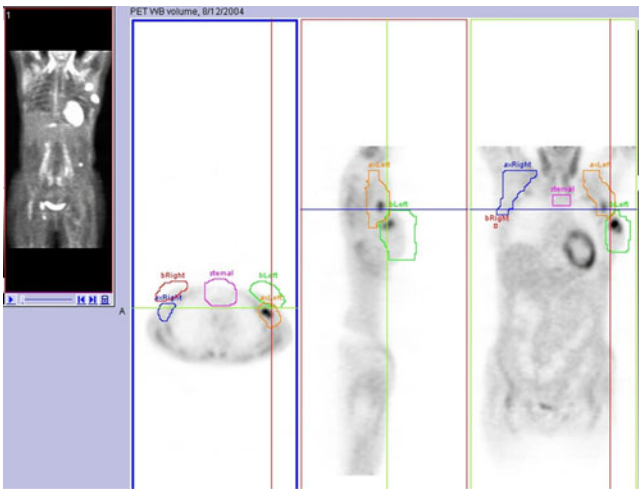

Fig. 1 PET imaging hard-copy of screen. Patient scored as PetT+ and PetN+

(PR) status in one patient, grade in four patients, tumour size in one patient, and number of examined and positive nodes in five patients (Table 1). These were imputed using the method of multivariate imputation by chained equations [18]. Assessment of presence or absence of lymphovascular invasion was missing in 20 patients. We did not impute the missing lymphovascular invasion, but classified it as yes, no or unknown. HER2 fluorescence in situ hybridization (FISH) data were missing in 51 patients, and we did not use data from this test in the analyses.

Analysis procedures For descriptive purposes, we used a contingency table to summarize the patient characteristics, complemented by step-wise logistic regression to identify the more significant relationships between PET positivity and patient age at diagnosis, gender, source of first pathology, histology, grade, neu status, lymphovascular invasion, hormone receptor status, T4 stage, laterality, tumour location, and tumour size. Nodal involvement assessed postoperatively was separately detailed according to PET positivity. For survival analyses, the end-point was DFS, where an event was defined as any local-regional or distant recurrence, new primary tumour, or death from any cause. The Kaplan-Meier method was used for univariate analysis of survival [19]. Cox proportional hazards models were used for multivariate analysis of survival [20]. The variables considered for inclusion in the Cox models by step-wise regression were patient age at diagnosis, gender, source of first pathology, histology, grade, neu status, lymphovascular invasion, hormone receptor status, T4 stage, laterality, tumour location, tumour size, PET characteristics, nodal variables, number of positive nodes, number of examined nodes, and lymph node ratio (LNR, number of positive/number of examined nodes) [21], neoadjuvant therapy, type of surgery, adjuvant chemotherapy, adjuvant hormone therapy, and adjuvant radiation therapy. The Akaike information criterion (AIC) was used for the step-wise selection of variables. The AIC does not rely on *P* values. The AIC penalizes a model's log likelihood against the number of parameters brought into the models by a variable. A variable is considered informative if it reduces the AIC. Nagelkerke's index (R2N) was used to evaluate the relative importance of the variables selected. The Nagelkerke R2N index represents the proportion of variation explained by covariates in a regression model. R2N ranges from 0 to 1; it is close to 1 for a perfectly predictive model, and close to 0 for a model that has no predictive value.

R version 2.10.1 was used for all statistical computations. The package MICE was used for imputation of missing data [18]. The generalized linear model from the Stats package was used for logistic regression. The stepAIC function from the MASS package was used for step-wise selection of variables for the logistic regression and the Cox models [22].

Results

Out of 157 consecutive records, there were 104 patients matching the selection criteria, who constituted the study population. Causes of exclusion were: PET after surgery (17 patients), breast surgery was not first intention (12 patients), previous primary cancer (8 patients), duplicated records (5 records), no cancer (2 patients), no axillary exploration (2 patients), missing histological data (2 patients), sarcoma (2 patients), unknown primary therapy (2 patients), ductal carcinoma in situ (1 patient). Of the 104 patients, 85 (81.7%) received immediate surgery, and 19 (18.3%) received surgery after neoadjuvant therapy. Surgical nodal exploration was limited to the axilla; internal mammary chain nodes were not dissected. The median overall follow-up time in the 104 patients was 59 months (interquartile range 39–64 months). Other patient characteristics are summarized in Table 1.

The more significant patient characteristics associated with different PET positivity according to models selected by AIC are summarized in Table 2. An increased odds ratio for PET positivity in the primary breast tumour was associated with male gender, ductal histology, and larger tumour size. An increased odds ratio for nodal positivity was associated with young age, presence of lymphovascular invasion, and negative oestrogen and/or negative progesterone receptor. Large tumour size was not significant (odds ratio 1.14, 95% CI 0.96–1.36), but it was retained by the AIC selection as a risk factor for nodal positivity. Increased risk of PET positivity in the internal mammary chain or in distant sites was associated with bilateral tumours, clinical

Table 1 Patient characteristics according to PET pattern. Characteristics significantly associated with PET positivity are highlighted in bold type (compare Table 2)

Characteristic	All patients (n =104)	PET positivity							
		Breast (n =87)		Axillary/supraclavicular region (n =41)		Internal mammary chain (n =6)		Distant organs (n =18)	
		No. of patients	Unadjusted relative risk	No. of patients	Unadjusted relative risk	No. of patients	Unadjusted relative risk	No. of patients	Unadjusted relative risk
Age at diagnosis (years)									
<40	6	6	1.20	**6**	**2.54**	0	0.00	0	0.00
40-59	49	42	1.02	15	0.78	1	0.35	7	0.83
≥60	49	**39**	**0.95**	20	1.04	5	1.77	11	1.30
Male gender	2	**2**	**1.20**	0	0.00	0	0.00	0	0.00
Source of first pathology									
Fine needle aspiration	52	46	1.06	21	1.02	5	1.67	9	1.00
Trucut/Mammotome biopsy	34	27	0.95	10	0.75	0	0.00	6	1.02
Surgical procedure	12	9	0.90	5	1.06	1	1.44	2	0.96
Non-breast site	5	4	0.96	4	2.03	0	0.00	1	1.16
Unknown	1	1	1.20	1	2.54	0	0.00	0	0.00
Clinical T4 stage	8	7	1.05	4	1.27	**2**	**4.33**	3	2.17
Tumour laterality									
Bilateral	5	5	1.2	**4**	**2.03**	**2**	**6.93**	**3**	**3.47**
Left	46	38	0.99	17	0.94	4	1.51	11	1.38
Right	53	44	0.99	20	0.96	0	0	4	0.44
Tumour quadrant									
Inner	17	14	0.98	5	0.75	1	1.02	**5**	**1.70**
Central	14	13	1.11	4	0.72	0	0.00	**2**	**0.83**
Outer	68	55	0.97	29	1.08	3	0.76	**9**	**0.76**
Other	4	4	1.20	2	1.27	2	8.67	**1**	**1.44**
Unknown	1	1	1.20	1	2.54	0	0.00	**1**	**5.78**
Primary systemic therapy	19	15	0.94	11	1.47	2	1.82	4	1.22
Surgery									
Mastectomy	77	71	1.10	35	1.15	6	1.35	17	1.28
Tumorectomy[a]	27	16	0.71	6	0.56	0	0.00	1	0.21
Radiation therapy									
None	9	8	1.06	4	1.13	0	0.00	2	1.28
Postoperative	92	76	0.99	36	0.99	6	1.13	15	0.94
Preoperative	2	2	1.20	1	1.27	0	0.00	0	0.00
Radiosurgery	1	1	1.20	0	0.00	0	0.00	1	5.78
Postop chemotherapy	53	48	1.08	30	1.44	2	0.65	7	0.76
Anthracycline	36	32	1.06	21	1.48	1	0.48	5	0.80
Taxane	11	9	0.98	7	1.61	0	0.00	1	0.53
Postoperative hormone therapy[b]	88	75	1.02	32	0.92	5	0.98	16	1.05
Grade									
1	29	26	1.07	8	0.70	1	0.60	4	0.80
2	42	34	0.97	15	0.91	2	0.83	10	1.38
3	29	25	1.03	17	1.49	2	1.20	4	0.80
Unknown	4	2	0.60	1	0.63	1	4.33	0	0.00
Lymphovascular invasion									
Yes	39	37	1.13	**27**	**1.76**	3	1.33	8	1.19
No	45	35	0.93	8	0.45	2	0.77	6	0.77
Unknown	20	15	0.90	6	0.76	1	0.87	4	1.16
Histology									
Invasive ductal carcinoma	84	**75**	**1.07**	36	1.09	4	0.83	16	1.10
Lobular carcinoma	14	**8**	**0.68**	3	0.54	2	2.48	1	0.41

Table 1 (continued)

Characteristic	All patients (n =104)	PET positivity							
		Breast (n =87)		Axillary/supraclavicular region (n =41)		Internal mammary chain (n =6)		Distant organs (n =18)	
		No. of patients	Unadjusted relative risk	No. of patients	Unadjusted relative risk	No. of patients	Unadjusted relative risk	No. of patients	Unadjusted relative risk
Other[c]	6	**4**	**0.80**	2	0.85	0	0.00	1	0.96
Hormone receptor status									
ER+/PR+	67	54	0.96	**16**	**0.61**	2	0.52	10	0.86
ER−/PR–	20	17	1.02	**14**	**1.78**	2	1.73	5	1.44
Other	17	16	1.13	**11**	**1.64**	2	2.04	3	1.02
Neu status									
0/1	56	45	0.96	19	0.86	5	1.55	10	1.03
2/3	47	41	1.04	21	1.13	1	0.37	8	0.98
Unknown	1	1	1.20	1	2.54	0	0.00	0	0.00
HER-2 FISH ratio									
<2	42	35	1.00	17	1.03	2	0.83	9	1.24
≥2	11	11	1.20	6	1.38	0	0.00	1	0.53
Unknown	51	41	0.96	18	0.90	4	1.36	8	0.91
Tumour size (mm)									
0–20	37	**25**	**0.81**	8	0.55	2	0.94	5	0.78
>20	66	**61**	**1.10**	32	1.23	4	1.05	13	1.14
Unknown	1	1	1.20	1	2.54	0	0.00	0	0.00
Number of positive nodes									
0	39	29	0.89	5	0.33	2	0.89	4	0.59
1–3	30	28	1.12	11	0.93	0	0.00	7	1.35
4–9	20	18	1.08	14	1.78	1	0.87	2	0.58
≥10	10	9	1.08	10	2.54	2	3.47	4	2.31
Unknown	5	3	0.72	1	0.51	1	3.47	1	1.16
Number of examined nodes									
0	5	3	0.72	1	0.51	1	3.47	1	1.16
1–9	25	17	0.81	1	0.10	2	1.39	4	0.92
≥10	74	67	1.08	39	1.34	3	0.70	13	1.02
Lymph node ratio									
0	39	29	0.89	5	0.33	2	0.89	4	0.59
0.01–0.20	30	28	1.12	12	1.01	0	0.00	7	1.35
0.21–0.65	18	16	1.06	12	1.69	1	0.96	1	0.32
0.66–1.00	12	11	1.10	11	2.33	2	2.89	5	2.41
Unknown	5	3	0.72	1	0.51	1	3.47	1	1.16
Events									
Local-regional recurrence	1	1	1.20	0	0.00	0	0.00	0	0.00
Distant metastases	20	17	1.02	13	1.65	3	2.60	5	1.44
Death from any cause	10	7	0.84	6	1.52	1	1.73	3	1.73

[a] One case of radiosurgery assimilated with tumorectomy.

[b] Includes one unknown.

[c] One mixed ductal lobular, one invasive papillary, one medullary, one tubular, one unspecified, one undifferentiated.

T4 stage, and inner, medial or overlapping quadrants. Age 60 years or older was also associated with a significantly increased risk of PET positivity in the internal mammary chain or at distant sites, with relative risks of, respectively, 1.77 and 1.30 (Table 1). Although age 60 years or more is not retained in Table 2, when the analyses were run pooling the combined risk of internal mammary chain and distant site positivity, age 60 years or more was retained by the AIC, giving an odds ratio of 1.14 (95% CI 0.99–1.32, P=0.07).

Regarding the postoperative nodal information, among the PET node-positive patients, 35 were histopathological node-positive (Table 1; 1–3 positive nodes in 11 patients, 4–

Table 2 Preoperative variables associated with PET positivity selected by step-wise logistic regression. The values are odds ratio (95% CI)

Variable	PET positivity			
	Breast	Axillary/supraclavicular region	Internal mammary chain	Distant organs
Age <40 vs. ≥40 years	–	1.46 (1.04–2.05)	–	–
Age ≥60 vs. <60	0.88 (0.77–1.00)	–	–	–
Male vs. female	1.46 (0.91–2.36)	–	–	–
Bilateral breast tumours vs. unilateral	–	–	1.40 (1.15–1.70)	1.60 (1.15–2.22)
Quadrant inner, central, overlapping vs. outer	–	–	–	1.14 (0.98–1.32)
Tumour size >2 cm vs. ≤2 cm	1.35 (1.17–1.55)	1.14 (0.96–1.36)	–	–
T4 stage vs. not T4 stage	–	–	1.20 (1.02–1.40)	–
Ductal histology vs. nonductal or mixed ductal	1.38 (1.17–1.62)	–	–	–
Lymphovascular invasion vs. no	–	1.40 (1.18–1.66)	–	–
ER–/PR– vs. ER+/PR+	–	1.44 (1.18–1.76)	–	–
ER+/PR– or ER–/PR+ vs. ER+/PR+	–	1.26 (1.01–1.58)	–	–

9 in 14, and 10+ in 10), and in 34 of these patients the pathological record mentioned coloration. Node positivity was based on haematoxylin-eosin (HE) staining of >2 mm in all these 34 patients (100%). Among the PET node-negative patients, 25 were histopathological node-positive, and in 24 of these patients the record mentioned coloration: node positivity in 15 patients was based on HE staining of >2 mm, in 4 HE >0.2 and ≤2 mm, in 1 small HE clusters, and in 4 immunohistochemical only, that is minimal involvement in 37.5%. Extracapsular extension was noted in 9 of 30 PET node-positive patients (30%) for whom extracapsular information was available, as compared with 3 of 21 PET node-negative patients (14%).

Quantitative nodal information is summarized in Table 1, while more detailed information including imputed cases is provided in Table 3, with the corresponding graphical display in Fig. 2. Among 63 PET node-negative patients, 26 (41.3%) were histopathological node-positive. Among 41 PET node-positive patients, 36 (87.8%) were histopathological node-positive (Table 3). Taking into consideration the TNM classification of lymph node involvement in which three or fewer involved nodes is stage pN0/1 and more than three involved nodes is stage pN2/3 [23], among the PET node-negative patients, 56 (88.9%) were pN0/1 and 7 (11.1%) were pN2/3, whereas among the PET node-positive patients, 16 (39.0%) were pN0/1 and 25 (61.0%) were pN2/3 ($P<0.0001$, chi-squared test). Taking into consideration the Geneva classification in which LNR ≤0.20 is low risk and LNR >0.20 is intermediate/high risk [24], among the PET node-negative patients, 55 (87.3%) were low risk LNR and 12.7% were intermediate/high risk LNR, whereas among PET node-positive patients, 17 (41.5%) were low risk LNR and 24 (58.5%) were intermediate/high risk LNR ($P<0.0001$).

Analysis of unadjusted survival showed significantly different DFS according to PET axillary nodal status ($P=0.017$) with a 3-year DFS of 89% (95% CI 81–97%) in PET node-negative patients and 68% (95% CI 55–85%) in PET node-positive patients (Fig. 3). The difference was more significant when PET axillary status was combined with internal mammary status ($P=0.013$; not shown). No significant survival differences were found analysing PET breast, internal mammary, or distant status separately.

We ran two separate multivariate survival analyses, one including all variables except number of positive nodes, number of examined nodes, and LNR, and the other including number of positive nodes, number of examined nodes, and LNR. In the first run, step-wise regression with AIC retained only three variables: PET axillary status, age, and adjuvant hormone therapy. The corresponding hazard ratios are shown in Table 4. In the second run, the regression retained only the LNR, adjuvant hormone therapy, and adjuvant chemotherapy, the corresponding hazard ratios are shown in Table 4. As shown in Table 4. PET nodal status was considerably superseded by LNR, i.e. LNR gave a larger AIC reduction and increased R2N. However, in the absence of LNR information, PET nodal status was the foremost prognostic factor with a hazard ratio for DFS of 2.81 (95% CI 1.17–6.74) (Table 4). Note that adjuvant chemotherapy alone did not improve model information (negative AIC), but was nevertheless retained when the model included LNR.

Discussion

PET axillary nodal status was found to be the foremost preoperative prognostic factor for DFS in our patients. This is in line with the relationship between PET positivity and adverse prognostic factors such as tumour size, axillary lymph node status, histological type, histological grade,

Table 3 Relationship between histopathological nodal involvement and PET nodal positivity in the axillary-supraclavicular region. Figures are number of patients, using imputation for five missing patients

Number of positive lymph nodes	PET nodal status		Lymph node ratio	Histopathological nodal status	
	Negative (n=63)	Positive (n=41)		Negative (n=63)	Positive (n=41)
0	37	5	0	37	5
1	11	4	0.01–0.10	11	7
2	5	5	0.11–0.20	7	5
3	3	2	0.21–0.30	2	7
4	1	4	0.31–0.40	3	4
5	3	3	0.41–0.50	0	2
6	1	2	0.51–0.60	1	0
7	2	1	0.61–0.70	1	3
8	0	1	0.71–0.80	0	3
9	0	4	0.81–0.90	0	3
10+	0	10	0.91–1.00	1	2

and hormone receptor status [25–31]. Oshida et al. reported overall and relapse-free survival in 70 patients according to differential absorption ratio [13]. Mankoff et al. found in a series of 37 patients a poorer DFS among those who presented with a high tumour metabolic rate as shown by high FDG uptake [14]. Inoue et al. in a case series of 81 patients with preoperative PET found that patients with a high SUV (SUVmax) and positive PET nodal status showed a significantly poorer prognosis than the other patients with 5-year DFS of 44.4% vs. 96.8% [15]. Jung et al. reported the prognostic impact of PET response after neoadjuvant therapy, but did not assess the relationship between baseline PET status and survival [32]. Ueda et al. reported higher relapse and mortality rate associated with high SUV, but they did not report survival data [26].

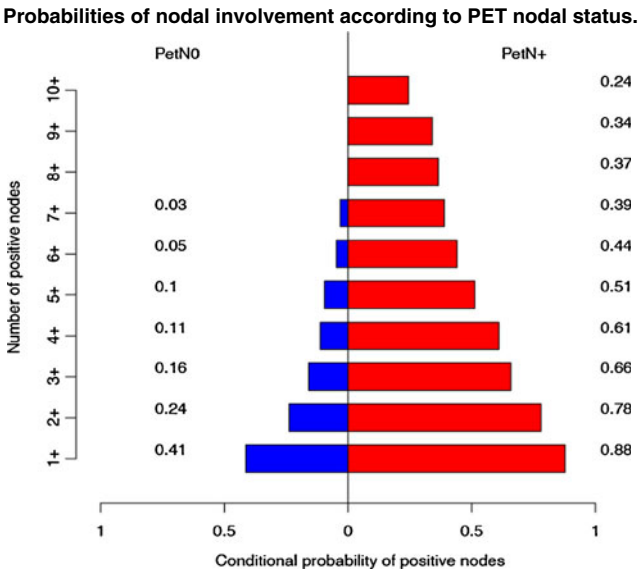

Fig. 2 Probabilities of nodal involvement according to PET nodal status

Regarding the study's objective of evaluating the diagnostic utility of preoperative PET, it might be noted that among 63 PET node-negative patients, 26 had lymph node involvement, i.e. missed by PET (sensitivity). This confirms the low sensitivity of PET for detecting nodal involvement, as already reported in the literature. Positive PET axillary nodal status was associated with the extent of nodal involvement. In PET node-negative patients, the risk of major nodal involvement decreased considerably (Fig. 2), whereas in patients PET node-positive patients, the risk was particularly high (Fig. 2). The probability estimates suggest that in sentinel node-positive but preoperative PET node-negative patients, the risk of additional positive nodes is small, and there would be no

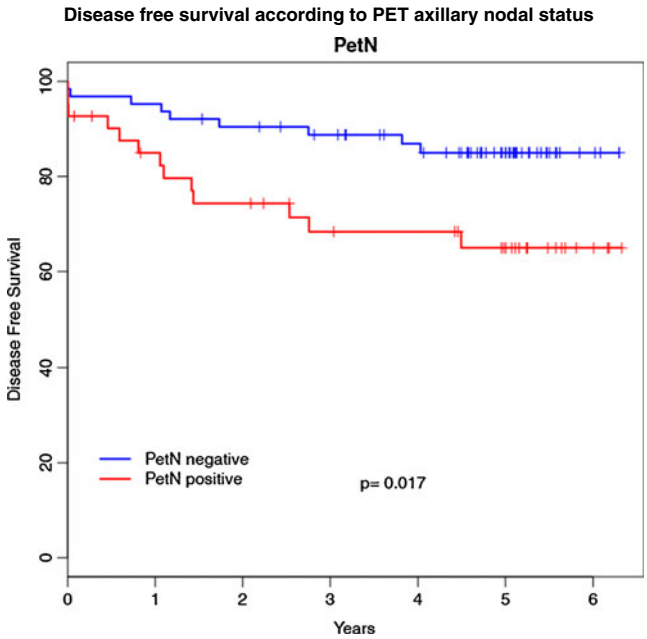

Fig. 3 Disease-free survival according to PET axillary nodal status

Table 4 Multivariate analysis of DFS based on step-wise selection. A hazard ratio for DFS of <1 indicates improved DFS, and >1 indicates poorer DFS. AIC and R2N were computed relative to a model without variables

Variable	Model with PET nodal status		Model with LNR		Model scoring	
	Hazard ratios	95% CI	Hazard ratios	95% CI	AIC reduction	R2N contribution
Axillary PET-positivity (vs. axillary PET-negative)	2.81	1.17–6.74	–	–	3.35	0.059
Age (continuous, years)	1.05	1.01–1.09	–	–	2.15	0.046
Adjuvant hormone therapy (vs. no adjuvant hormone therapy)	0.43	0.16–1.13	0.28	0.10–0.77	0.70	0.030
Adjuvant chemotherapy (vs. no adjuvant chemotherapy)	–	–	0.46	0.19–1.12	−1.93	0.000
Lymph node ratio	–	–	24.82	7.14–86.3	19.16	0.217

need to proceed to complete axillary lymph node dissection. In sentinel node-positive and preoperative PET node-positive patients, the risk of additional positive nodes is high, which could justify complete axillary dissection or radiation therapy of the regional lymph node. From a diagnostic perspective, if the purpose is to classify lymph node involved versus not involved, then preoperative PET is not efficient. However, if the purpose is to classify low versus high burden of lymph node involvement, then preoperative PET may represent a powerful tool for stratification. Prospective studies might be warranted to evaluate how PET information can be combined with nomograms for the prediction of non-sentinel node involvement.

Other noteworthy observations were the association of age <40 years with PET node positivity, whereas age >60 years was marginally associated with PET-positive internal mammary chain and distant organs. Bilateral breast cancer was associated with PET-positive internal mammary chain and distant organs. Lymphovascular invasion was found significantly associated with PET axillary node positivity, in keeping with the findings of Mankoff et al. who reported the predictive ability of metabolic FDG uptake and blood flow in patients with locally advanced breast cancer [14], and Groves et al. who reported that FDG uptake was highly significantly associated with angiogenesis [28]. Tumour size, ER/PR status and ductal histology were also in keeping with the findings of other correlation studies [25, 27]. We have previously reported the poorer prognosis associated with breast inner quadrant location [33]. The present study found a trend for a higher risk of PET-positive distant organs associated with medial/central tumour location. Male gender appeared to be associated with increased risk of breast PET positivity. We are not aware of previous reports of this finding. However, although we had only two male patients with breast cancer, the odds ratio of 1.48 retained by AIC selection was nevertheless not significant (95% CI 0.93–2.36; Table 2).

We acknowledge several limitations. The study was retrospective, implying selection bias, most patients receiving preoperative PET were more likely to have more advanced disease than a population of screened patients. Only 39 (37.5%) of the 104 patients were node-negative. Our data also included eight patients with T4 stage. We used pathological tumour size, which can be affected by neoadjuvant therapy. The number of events was small, which limits the number of variables that could be found significant, and did not allow detailed subgroup analyses. We did not formally investigate how different cut-offs of tumour size could affect PET positivity. We used multiple outcomes and multiple testings in our analyses. Metastatic status was attributed with knowledge of the PET findings, and furthermore surgery included patients with metastatic disease, which could have biased the results. There were missing data that required imputation, which can limit the reliability of results. SUVmax has been shown to be a prognostic factor for survival of those with operable breast cancer [15], as well as of those with metastatic breast cancer [34]. Our scoring of PET positivity was based on visual inspection, making it liable to observer variability. SUV measurements were not used. Due to changes in image archiving systems, we were only able to retrieve the records of 51 patients in whom SUVmax could be estimated (Appendix). This number of patients was too small to efficiently evaluate the contribution of SUVmax in our patient's population.

Despite these limitations, we believe that the study provides data that warrants further investigations. The data directly reflect the daily practice and the clinical status of the patients. PET-positive distant organs could have affected the staging; however, all our selected patients received surgery as planned by first intent. The number of patients (104) was insufficient for subgroup analyses, yet that number is a non-negligible contribution to evaluate the role of preoperative PET. In version 1.2011 of the clinical practice guidelines in oncology for breast cancer of the National Comprehensive Cancer Network, the recommendations discourage the use of PET or PET/CT in the staging of clinical stage I, stage II, or operable stage III breast cancer [12]. Our results present a counterpoint. Postoperatively, lymph node involvement was confirmed as the most important prognostic factor. Based on values of the R2N index, the histopathological lymph node

ratio provided prognostic information that was a 3.7 times stronger predictor of survival than the PET status (0.217/0.059, Table 4). However, preoperatively—which matters when treatment options are under consideration in newly diagnosed patients—out of 12 conventional preoperative prognostic factors (as listed in Materials and methods), PET was the only unequivocal preoperative predictor of DFS, overriding all other factors (Table 4). Recently there has been a growing trend for not dissecting the axillary lymph nodes even in patients with a positive sentinel node [35]. Even though this might be considered safe, the trend implies that prognostic information becomes poorer. Considering that preoperative PET provided prognostic information second only to postoperative lymph node extent of involvement, outright rejection of preoperative PET at a time when axillary dissection is no longer performed further deprives patients of the next most important prognostic tool. This is an issue that may become critically important in view of a recent randomized trial showing a poorer survival in women who did not undergo axillary clearance [36].

We are currently conducting a prospective trial of preoperative FDG PET/CT recruiting patients with T1/2 node-negative breast cancer (ClinicalTrials.gov, NCT01432002) [37]. We hope that the trial will provide further data to evaluate the hypothesis that preoperative PET might stratify patients into different risk groups.

Conclusion

Positive axillary PET in the preoperative assessment of breast cancer patients was significantly associated with a poorer DFS, and was predictive of a high metastatic lymph node involvement. We argue that the role of preoperative PET as a surrogate indicator of lymph node involvement and as a marker of survival should be taken into consideration as a potential tool for treatment decision.

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Conflicts of interest None.

References

1. Facey K, Bradbury I, Laking G, Payne E. Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers. Health Technol Assess. 2007;11:iii–267.
2. Sloka JS, Hollett PD, Mathews M. A quantitative review of the use of FDG-PET in the axillary staging of breast cancer. Med Sci Monit. 2007;13:RA37–46.
3. Podoloff DA, Ball DW, Ben-Josef E, et al. NCCN task force: clinical utility of PET in a variety of tumor types. J Natl Compr Cancer Netw. 2009;7 Suppl 2:S1–26.
4. Escalona S, Blasco JA, Reza MM, Andradas E, Gomez N. A systematic review of FDG-PET in breast cancer. Med Oncol. 2010;27:114–29.
5. Peare R, Staff RT, Heys SD. The use of FDG-PET in assessing axillary lymph node status in breast cancer: a systematic review and meta-analysis of the literature. Breast Cancer Res Treat. 2010;123:281–90.
6. Avril N, Adler LP. F-18 fluorodeoxyglucose-positron emission tomography imaging for primary breast cancer and loco-regional staging. Radiol Clin North Am. 2007;45:645–57. vi.
7. Groheux D, Hindie E, Espie M, et al. Interests and perspectives of PET-CT for breast cancer: review of the literature. Bull Cancer. 2007;94:658–68.
8. Lim HS, Yoon W, Chung TW, et al. FDG PET/CT for the detection and evaluation of breast diseases: usefulness and limitations. Radiographics. 2007;27 Suppl 1:S197–213.
9. Rosen EL, Eubank WB, Mankoff DA. FDG PET, PET/CT, and breast cancer imaging. Radiographics. 2007;27 Suppl 1:S215–29.
10. Pons F, Duch J, Fuster D. Breast cancer therapy: the role of PET-CT in decision making. Q J Nucl Med Mol Imaging. 2009;53:210–23.
11. Almubarak M, Osman S, Marano G, Abraham J. Role of positron-emission tomography scan in the diagnosis and management of breast cancer. Oncology (Williston Park). 2009;23:255–61.
12. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, version 1.2011. 2010; Available via: http://www.nccn.org. Accessed 30 Nov 2010.
13. Oshida M, Uno K, Suzuki M, et al. Predicting the prognoses of breast carcinoma patients with positron emission tomography using 2-deoxy-2-fluoro[18F]-D-glucose. Cancer. 1998;82:2227–34.
14. Mankoff DA, Dunnwald LK, Gralow JR, et al. Blood flow and metabolism in locally advanced breast cancer: relationship to response to therapy. J Nucl Med. 2002;43:500–9.
15. Inoue T, Yutani K, Taguchi T, Tamaki Y, Shiba E, Noguchi S. Preoperative evaluation of prognosis in breast cancer patients by [(18)F]2-Deoxy-2-fluoro-D-glucose-positron emission tomography. J Cancer Res Clin Oncol. 2004;130:273–8.
16. Mercier-Vogel L, Couson F, Kohlik M, Bodmer A. Impact of breast MRI and PET-CT in breast cancer staging. Rev Med Suisse. 2010;6:1076–8. 1080.
17. Bral S, Vinh-Hung V, Everaert H, De CP, Storme G. The use of molecular imaging to evaluate radiation fields in the adjuvant setting of breast cancer: a feasibility study. Strahlenther Onkol. 2008;184:100–4.
18. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res. 2007;16:219–42.
19. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457–81.
20. Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model, vol. 87. New York: Springer-Verlag; 2000.
21. Woodward WA, Vinh-Hung V, Ueno NT, et al. Prognostic value of nodal ratios in node-positive breast cancer. J Clin Oncol. 2006;24:2910–6.
22. Venables WN, Ripley BD. Modern applied statistics with S, vol. 172. 4th ed. New York: Springer-Verlag; 2002.
23. Sobin LH, Gospodarowicz M, Wittekind C. TNM classification of malignant tumours, vol. 181. 7th ed. Oxford: Wiley-Blackwell; 2009.
24. Vinh-Hung V, Verkooijen HM, Fioretta G, et al. Lymph node ratio as an alternative to pN staging in node-positive breast cancer. J Clin Oncol. 2009;27:1062–8.
25. Gil-Rendo A, Martinez-Regueira F, Zornoza G, Garcia-Velloso MJ, Beorlegui C, Rodriguez-Spiteri N. Association between [18F]fluorodeoxyglucose uptake and prognostic parameters in breast cancer. Br J Surg. 2009;96:166–70.

26. Ueda S, Tsuda H, Asakawa H, et al. Clinicopathological and prognostic relevance of uptake level using 18F-fluorodeoxyglucose positron emission tomography/computed tomography fusion imaging (18F-FDG PET/CT) in primary breast cancer. Jpn J Clin Oncol. 2008;38:250–8.
27. Heudel P, Cimarelli S, Montella A, Bouteille C, Mognetti T. Value of PET-FDG in primary breast cancer based on histopathological and immunohistochemical prognostic factors. Int J Clin Oncol. 2010;15:588–93.
28. Groves AM, Shastry M, Rodriguez-Justo M, et al. (18)F-FDG PET and biomarkers for tumour angiogenesis in early breast cancer. Eur J Nucl Med Mol Imaging. 2011;38:46–52.
29. Nakajo M, Kajiya Y, Kaneko T, et al. FDG PET/CT and diffusion-weighted imaging for breast cancer: prognostic value of maximum standardized uptake values and apparent diffusion coefficient values of the primary lesion. Eur J Nucl Med Mol Imaging. 2010;37:2011–20.
30. Tozaki M, Hoshi K. 1H MR spectroscopy of invasive ductal carcinoma: correlations with FDG PET and histologic prognostic factors. AJR Am J Roentgenol. 2010;194:1384–90.
31. Osborne JR, Port E, Gonen M, et al. 18F-FDG PET of locally invasive breast cancer and association of estrogen receptor status with standardized uptake value: microarray and immunohistochemical analysis. J Nucl Med. 2010;51:543–50.
32. Jung SY, Kim SK, Nam BH, et al. Prognostic impact of [18F] FDG-PET in operable breast cancer treated with neoadjuvant chemotherapy. Ann Surg Oncol. 2010;17:247–53.
33. Vinh-Hung V, Truong PT, Janni W, et al. The effect of adjuvant radiotherapy on mortality differs according to primary tumor location in women with node-positive breast cancer. Strahlenther Onkol. 2009;185:161–8.
34. Morris PG, Ulaner GA, Eaton A, et al. Standardized uptake value by positron emission tomography/computed tomography as a prognostic variable in metastatic breast cancer. Cancer 2012. doi:10.1002/cncr.27579.
35. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA. 2011;305:569–75.
36. Avril A, Le BG, Lorimier G, et al. Phase III randomized equivalence trial of early breast cancer treatments with or without axillary clearance in post-menopausal patients results after 5 years of follow-up. Eur J Surg Oncol. 2011;37:563–70.
37. Vinh-Hung V, Vees H. FDG-PET/CT for Simulation and Radiation Treatment Planning of Early Breast Cancer. ClinicalTrials gov 2011; Available via: http://clinicaltrials.gov/ct2/show/NCT01432002. Accessed 8 Sep 2011.