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Original article

Is [^{18}F] fluorodeoxyglucose uptake by the primary tumor a prognostic factor in breast cancer?

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ABSTRACT

Background: We retrospectively investigated ^{18}F-FDG uptake by the primary breast tumor as a predictor for relapse and survival.
Patients and methods: We studied 203 patients with cT1-T3N0 breast cancer. Standardized uptake value (SUVmax), was measured on the primary tumor. After a median follow-up of 68 months (range 22–80), the relation between SUVmax and tumor factors, disease free-survival (DFS) and overall survival (OS) was investigated.
Results: In the PET-positive patients, the median FDG uptake by the tumor was 4.7. FDG uptake was significantly related to tumor size, number of involved axillary nodes, grade, negative ER, high Ki-67 and HER2 overexpression. No distant metastases or deaths occurred in the PET-negative group. Five-year DFS was 97% and 83%, respectively in the PET-negative and PET-positive groups ($P = 0.096$). At univariate analysis, DFS was significantly lower in patients with SUVmax >4.7 compared to the patients with negative PET ($P = 0.042$), but not to the patients with SUVmax ≤4.7 ($P = 0.106$). At multivariable analysis, among PET-positive patients, SUVmax was not an independent prognostic factor for DFS ($HR_{>4.7 \text{ vs } \leq 4.7}$: 1.02 (95% CI 0.45–2.31)). Five-year OS was 100% and 93%, respectively, in the PET-negative and PET-positive groups ($P = 0.126$).
Conclusion: FDG uptake by the primary lesion was significantly associated with several prognostic variables, but it was not an independent prognostic factor.

Introduction

Breast cancer is the commonest cancer in women and the second leading cause of cancer mortality in women in Western countries.[1] Our understanding of breast cancer at the molecular biology level has increased markedly in recent years, driving the development new and more effective treatments, and providing a plausible explanation for the decline in breast cancer mortality, notwithstanding increasing incidence.[2] Although numerous tumor and patient characteristics correlate with prognosis in breast cancer, it would be useful to have more reliable prognostic indicators in order to more precisely tailor treatment and follow-up to individual patients.

The TNM classification, which originally defined only the anatomical extent of the disease, provided the first useful guide to prognosis and treatment. With the advent of mammographic screening, most breast cancers in Western countries were diagnosed at stage T1N0M0. Hormone receptor status, HER2 overexpression and peritumoral vascular invasion are additional and important prognostic indicators for early disease and have been proposed for inclusion in a revised TNM.[3]

Tumor grade has also been validated as a prognostic factor for breast cancer[4] and, although not included in the latest edition of the breast cancer TNM, is incorporated into the Saint Gallen guidelines for choosing adjuvant chemotherapy in early breast cancer.[5] Unfortunately however G2 tumors, which account to 30–60% of all breast cancers, have an indeterminate risk for which therapeutic decision-making is often difficult. There are indications that ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-

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PET) may be able to refine breast cancer prognosis, and this would be particularly useful for G2 disease. Thus, FDG-PET has been reported to be more sensitive than conventional imaging for detecting metastatic or recurrent breast cancer[6] and also for monitoring the response to neoadjuvant treatment.[7–9] Moreover, several studies have investigated the ability of PET to predict clinical outcomes in patients with advanced breast cancer after neoadjuvant or adjuvant treatment[10–13] with encouraging results.

In the present retrospective study we assessed the prognostic value of FDG-PET in combination with CT (PET/CT) in patients presenting with T1-T3 primary breast carcinoma, without clinical evidence of axillary metastases. We were interested in determining whether FDG uptake by the primary breast lesion before surgery could predict patient outcomes.

Materials and methods

Patients

In this retrospective study, we studied cT1-T3 cN0 breast cancer patients enrolled between September 2003 and April 2005 in prospective study to compare sentinel node biopsy and PET/CT, in patients who received both, for their ability to detect occult axillary metastases.[14] We considered 203 of the 236 patients enrolled in the study, excluding those who received breast surgery, radiotherapy or chemo-endocrine therapy before PET/CT (21 patients), those previously treated for another primary cancer (4 patients), and those unavailable for follow-up (8 patients). Patient characteristics (age, type of surgery, number of positive lymph nodes, tumor histotype, tumor size, oestrogen (ER), progesterone (PgR) and HER2 status, grade and Ki-67) are shown in Table 1.

PET/CT

PET/CT was performed using a standard technique. Briefly, [^{18}F]-FDG (5.3 MBq/kg) was administered i.v. in the arm opposite that of the primary breast tumor. Whole-body images, from head base to pelvis, were obtained starting 45 min after injection, with the patient in the supine position, and arms extended behind the head. The raw tomographic data were corrected for attenuation using transmission data from the CT scans carried out before emission imaging. Attenuation-corrected images were reconstructed in transaxial, coronal and sagittal planes. CT images were also available for evaluation.

Quantitative imaging analysis

The images were reassessed visually by two experienced nuclear medicine physicians to identify the area of the primary breast tumor. Physicians assessing the FDG-PET results were blinded to outcomes. FDG uptake in the area was measured. When uptake in the involved breast quadrant did not allow visual identification of the lesion because it was equal to or less than background, quantitative measurement was not performed and the lesions were considered PET-negative. To quantitate uptake, the slice with highest uptake was selected on axial images and for multicentric lesions the entire involved area was considered. The region of interest (ROI) was defined manually around the lesion. The single-pixel maximum standardized uptake value normalized to body weight (SUVmax) was determined. The maximum standardized uptake normalized to lean body mass (SULmax) and average SUL (SULav) in a small circular (12 mm diameter) ROI centered on the pixel corresponding to SULmax, were also

Table 1
General and tumour characteristics of 203 breast cancer patients stratified according to PET findings on the primary tumour.

		All patients $N = 203$	PET negative $N = 32$	PET positive SUVmax $\leq$4.7 $N = 86$	PET positive SUVmax >4.7 $N = 85$	P value[b]
Age	<40	21 (10.3)	1 (4.8)	9 (42.9)	11 (52.4)	0.089
	40–49	74 (36.5)	10 (13.5)	35 (47.3)	29 (39.2)	
	50–64	70 (34.5)	12 (17.1)	25 (35.7)	33 (47.1)	
	≥65	38 (18.7)	9 (23.7)	17 (44.7)	12 (31.6)	
Type of surgery	Quadrantectomy	153 (75.4)	25 (16.3)	68 (44.4)	60 (39.2)	0.260
	Mastectomy	50 (24.6)	7 (14.0)	18 (36.0)	25 (50.0)	
Histotype	Ductal	154 (75.9)	20 (13.0)	61 (39.6)	73 (47.4)	0.030
	Lobular	25 (12.3)	7 (28.0)	15 (60.0)	3 (12.0)	
	Other	24 (11.8)	5 (20.8)	10 (41.7)	9 (37.5)	
Tumour size (cm)	≤1	30 (14.8)	17 (56.7)	12 (40.0)	1 (3.3)	<0.001[c]
	1.1–2	80 (39.4)	10 (31.3)	40 (50.0)	30 (37.5)	
	2.1–5	81 (39.9)	4 (4.9)	29 (35.8)	48 (59.3)	
	>5	12 (5.9)	1 (8.3)	5 (41.7)	6 (50.0)	
Lymphnodal status at FDG-PET	Negative	162 (79.8)	32 (19.8)	73 (45.1)	57 (35.2)	<0.001[c]
	Positive	41 (20.2)	0	13 (31.7)	28 (68.3)	
Number of positive lymph nodes	0	110 (54.2)	25 (22.7)	44 (40.0)	41 (37.3)	0.006
	1–3	67 (33.0)	5 (7.5)	34 (50.8)	28 (41.8)	
	≥4	26 (12.8)	2 (7.7)	8 (30.8)	16 (61.5)	
Estrogen receptors	Positive	174 (85.7)	31 (17.8)	79 (45.4)	64 (36.8)	<0.001[c]
	Negative	29 (14.3)	1 (3.4)	7 (24.1)	21 (72.4)	
Progesterone receptors	Positive	151 (74.4)	25 (16.6)	71 (47.0)	55 (36.4)	0.597
	Negative	52 (25.6)	7 (13.5)	15 (28.9)	30 (57.7)	
Grade[a]	1	28 (14.1)	13 (46.4)	9 (32.1)	6 (21.4)	<0.001[c]
	2	102 (51.0)	18 (17.7)	56 (65.9)	28 (27.5)	
	3	69 (34.9)	1 (1.5)	20 (28.9)	48 (69.6)	
Ki-67	<20	91 (44.8)	26 (28.6)	48 (52.8)	17 (18.7)	<0.001[c]
	≥20	112 (55.2)	6 (5.4)	38 (33.9)	68 (60.7)	
HER2	Overexpressed	34 (16.7)	1 (2.9)	9 (26.5)	24 (70.6)	<0.001[c]
	Not overexpressed	169 (83.3)	31(18.3)	77 (45.6)	61 (36.1)	

Figures in parentheses refer to percentages by column (all patients) and by row (PET subgroups).
[a] Grade and HER2 information missing for some patients.
[b] Mantel–Haenszel chi-square for trend.
[c] Differences were statistically significant after the Bonferroni correction was applied (significance level = 0.05/10 = 0.005).

determined, as recommended by Wahl et al.[15] SUVmax was defined as: [tracer concentration (Bq/ml)]/[injected activity (Bq)/patient body weight (g)]. SULmax was defined as [tracer concentration (Bq/ml)]/[injected activity (Bq)/lean body mass (g)]. LBM for females was calculated from the formula: 1.07*weight − 148 × (weight/height).[2]

Follow-up and data collection

Median follow-up was 68 months (range 22–80). The end date of the follow-up period was 31st December 2010. Patients living distant from our Institute were followed locally. Patients followed at our Institute were seen every 6 months for the first 5 years and then annually, when physical examination, breast ultrasound and mammography were performed, and tumor markers assessed. If recurrent disease was suspected, further conventional imaging such as liver ultrasound, CT scan, bone scan were performed. The status of these patients at most recent follow-up was obtained from our prospective database. Patients not attending for follow-up or followed elsewhere were contacted by telephone.

Statistical methods

The Mantel–Haenszel chi-square for trend was used to assess the relation of FDG uptake (negative, positive SUVmax ≤4.7, positive SUVmax >4.7) to the categorical variables age, surgery, histotype, tumor size, number of involved lymph nodes, estrogen status, progesterone status and HER2 status. The Bonferroni correction was applied to address the problem of multiple comparisons. The standard significance level of 0.05 was changed to 0.05/n, n being the number of comparisons.

Disease free survival (DFS) was time from surgery to any cancer recurrence or death from any cause, whichever occurred first. Overall survival (OS) was of time from surgery to death for any cause. In the absence of events, data for DFS and OS were censored at date of latest follow-up. Survival curves were estimated by the Kaplan–Meier method and the log-rank test used to test the significance differences in DFS and OS between patient subgroups. We did not show the results from the univariate analysis for all the variables in order to keep the paper focused on the main aim, i.e. the prognostic value of SUVmax.

To investigate the shape of the relationship between SUVmax and hazard of events, we used univariate Cox proportional hazard modeling with restricted cubic splines. Cubic splines are smoothly joined piecewise third-order polynomials.[16] Each polynomial function was fitted into intervals delimited by knots; restrictions were placed on the resulting curve to ensure it was smooth at the knot points. We set knots at the 25th, 50th, and 75th percentiles of the SUVmax distribution. The result was presented as a curve showing the relation between SUVmax and DFS. Because of the skewness of the distribution of SUVmax, values were log-transformed.

Correlations of SULav and SUVmax with SUVmax were assessed by Spearman's rank coefficient (rho).

Finally we used multivariable Cox proportional hazard models to investigate the prognostic effect of SUVmax on disease-free survival in the entire population and various sub-groups. Each multivariable model was adjusted for the variables that showed some evidence of association with the disease-free survival ($P < 0.10$) in the univariate analysis. The analyses were carried out with SAS software (SAS Institute, Cary, NC) and R software with (http://cran.r-project.org/) Harrell's Design and Hmisc libraries. All reported P values are two-sided.

Results

In 32 patients, FDG uptake by the primary was equal to or less than background (PET-negative). In the remaining 171 cases, median SUVmax was 4.7 (range 1.5–35.8). SUVmax correlated strongly with SULmax (Spearman's rho = 0.987) and SULav (rho = 0.952). Results with SULmax and SULav were closely similar to those obtained with SUVmax (data not shown); therefore we only present results for SUVmax.

There was some evidence of an association between SUVmax and the number of involved lymph nodes and between SUVmax and histology (unadjusted $P = 0.006$ and $P = 0.030$, respectively), with lobular carcinoma more often PET-negative (7/25 cases; 28%) than ductal carcinoma (20/154; 13%; see Table 1). Moreover, high SUVmax was strongly and significantly related to large tumor size, high tumor grade, high Ki-67, negative ER, and HER2 overexpression.

Table 2 shows first unfavorable events and deaths according to the PET findings. Eleven patients died of breast cancer, one of a second (non breast) primary cancer. Eleven (5.4%) patients developed a local recurrence as first event, and 21 (10.3%) had distant metastasis as first event. Neither metastases, deaths, nor contralateral breast cancers occurred in the PET-negative group.

Fig. 1 shows the relation between SUVmax and risk of adverse events in PET-positive patients. The risk of adverse events increased steeply with increasing SUVmax up to about SUVmax 5 and remained flat thereafter. Therefore the median SUVmax of 4.7 was chosen to divide PET-positive patients into lower and higher uptake groups.

Five-year Kaplan–Meier DFS was 97% in the PET-negative group, 88% in the PET-positive SUVmax ≤4.7 group and 79% in the PET-positive SUVmax >4.7 group ($P = 0.057$). DFS was significantly higher ($P = 0.042$) in the PET-negative than SUVmax >4.7 group (Fig. 2). Five-year OS was 100% in the PET-negative and 93% in the PET-positive group ($P = 0.126$).

At multivariable analysis, SUVmax did not emerge as an independent prognostic factor for DFS ($HR_{>4.7 \text{ vs } \leq 4.7}$: 1.02 (95% CI 0.45–2.31)), either in entire whole population or the various subgroups (Table 3). Patients with G1 and triple-negative tumors were not included in the subgroup analyses as numbers of both patients and events were too small. Multivariable analysis for OS was not performed as the number of deaths was too small.

Discussion

Breast cancer is an inhomogeneous disease: diverse subtypes (defined by various and evolving means[17]) are characterized by differing biological behavior, therapeutic responses and prognoses. It is essential, therefore, to be able to tailor the aggressiveness of the treatment to the aggressiveness of the disease.

Table 2
First unfavorable events and deaths according to PET findings on primary breast cancer.

	All patients $N = 203$	PET-negative $N = 32$	PET-positive SUVmax ≤4.7 $N = 86$	PET-positive SUVmax >4.7 $N = 85$
First events	**43 (21.2)**	**5 (15.6)**	**16 (18.6)**	**22 (25.9)**
Locoregional	11 (5.4)	2 (6.3)	4 (4.7)	5 (5.9)
Distant	21 (10.3)	0 (0.0)	8 (9.3)	13 (15.3)
Contralateral breast tumour	4 (2.0)	0 (0.0)	1 (1.2)	3 (3.5)
Other primary tumour	6 (3.0)	3 (9.4)	3 (3.5)	0 (0.0)
Death	1 (0.5)	0 (0.0)	0 (0.0)	1 (1.2)
Deaths (total)	12 (5.9)	0 (0.0)	5 (5.8)	7 (8.2)

Figures in parentheses refer to percentages by column.

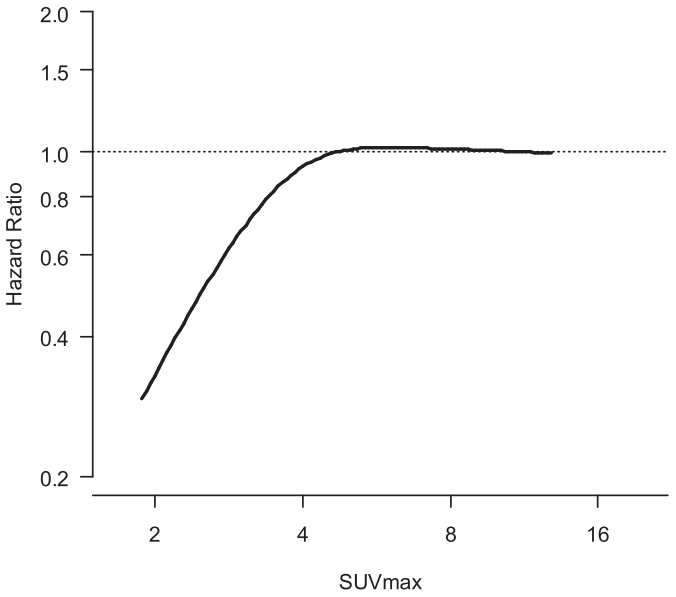

Fig. 1. Curve showing the relation between SUVmax and DFS in patients with PET-positive tumors at univariate analysis. Analysis limited to PET-positive patients only. Events for disease free survival were local, regional, and distant events, and death as first event. The curve shows the relation between SUVmax and DFS as a continuous curve based on the univariate spline Cox regression model. The median SUVmax value 4.7 was selected as reference (HR = 1). HR is plotted on a log scale.

In this study we investigated whether FDG uptake by the primary breast lesion using a dedicated PET/CT scanner, was able to predict outcomes in patients with breast cancer (cT1-T3N0). Scans were taken preoperatively and follow-up was close to six years (median 68 months). FDG uptake was assessed with the widely-used SUVmax (normalized to body weight) and also SULmax and SULav, in agreement with PERCIST recommendations.[15] We found, however, that results obtained using the three measures were closely similar and correlated strongly; therefore we only present SUVmax.

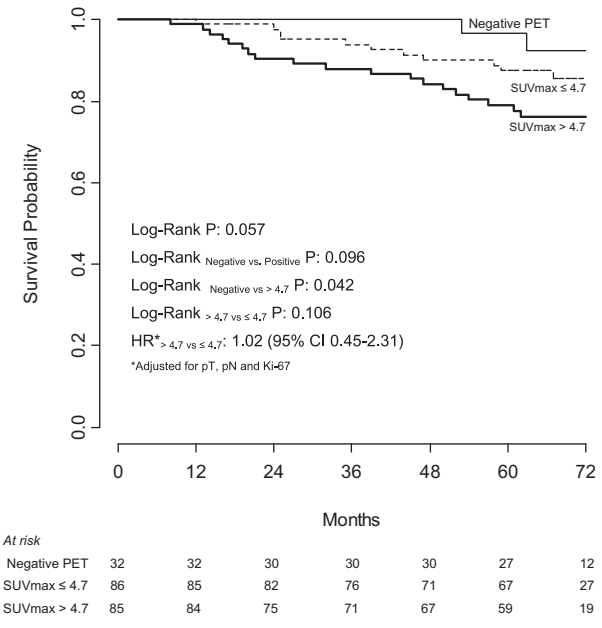

Fig. 2. Disease free survival according to SUVmax.

Table 3
Prognostic effect of SUVmax on disease-free survival in entire population and various risk groups.

Risk group	$HR_{>4.7 \text{ vs. } \leq 4.7}$ (95% CI)
Entire population	1.02 (0.45–2.31)
Ki-67 < 20	0.72 (0.12–4.36)
Ki-67 ≥ 20	1.18 (0.48–2.88)
G2	1.35 (0.48–3.78)
G3	1.61 (0.42–6.08)
ER-positive	1.09 (0.45–2.61)
ER-negative	2.86 (0.13–64.4)
HER2 overexpressed	2.53 (0.44–14.5)

The HR for the entire population was adjusted for pT, pN and Ki-67. HRs of other categories were adjusted for pT and pN. HRs for ER groups were also adjusted for Ki-67. HER2 overexpression was determined by immunohistochemistry or FISH as appropriate.

We found that SUVmax correlated strongly with several established prognostic variables, but was not an independent predictor of outcomes. This was true for the whole population and also for all subgroups (Table 3) including G2 cancers where it is particularly important to separate cancers with worse prognoses.[18–20] It must be said that analyses of subgroups had intrinsic limitations in relation to statistical power and were conducted for exploratory aims only.

To our knowledge the present study is one of the few aimed at assessing the predictive value of PET/CT in a large series of patients with breast cancer. We found, as other authors did[21–23] that FDG uptake was strongly related to tumor size. We also found a significant relation between tumor histotype and FDG uptake, in that although 18 (72%) lobular carcinomas were PET-positive, only 3 (12%) had SUVmax >4.7. In agreement with previous findings[24–26] this suggests that lobular carcinomas generally have lower glucose consumption than ductal carcinomas.

While there is general agreement in the literature that high SUVmax correlates with high proliferation index,[21,24,27–29] no clear relation between SUVmax and ER status, tumor grade, HER2 overexpression, and number of involved lymph nodes has emerged.[24,27,28,30,31] By univariate analyses (Mantel–Haenszel chi-square tests for trend) we found that high FDG uptake was strongly and significantly associated with large tumor size, high Ki-67, ER-negative disease, high tumor grade, HER2 overexpression, and high number of involved lymph nodes. These findings suggest that FDG uptake has the same prognostic value as these established markers of tumor aggressiveness, but, because it was not an independent indicator of tumor aggression, does not provide more or more reliable information.

It is interesting that the incidence of adverse events was low in the 32 patients with PET-negative lesions (locoregional relapse 6.3%, distant metastases 0%); while 10.6% of PET-positive patients had locoregional relapse and 24.6% developed distant metastases. These findings suggest that a negative PET is a favorable prognostic factor, particularly since PET-negative patients had significantly higher DFS ($P = 0.042$) than SUVmax >4.7 patients (Fig. 2). However, probably because of the small numbers in the PET-negative group, the DFS difference was not significant comparing PET-negative and PET-positive groups ($p = 0.096$; Fig. 2).

The shape of the relationship between SUVmax and the hazard of events showed that, above SUVmax of about 5, further increase in uptake did not result in increased risk of adverse events (Fig. 1). This provided a justification for adopting the median SUVmax (4.7) as cut-off between supposedly high risk and low risk PET-positive patients. Even if there is not a standard cutpoint reported in the literature, our data seem in agreement with those of the two most numerous series, in which a SUV greater than 4 was found to correlate with a major aggressiveness of the disease.[30,32] Nevertheless, in spite of the initial increase in risk of adverse events with increasing SUVmax this variable was not an independent predictor

of outcomes. This disappointing finding suggests that FDG-PET/CT should not be routinely employed in the preoperative work-up of patients with early breast cancer, and that established indicators of prognosis (TNM stage, hormone receptor status, HER2 over-expression, tumor grade, Ki-67 proliferation index, peritumoral vascular invasion, and number of involved lymph nodes) collectively provide the same indication of prognosis than FDG uptake by the primary tumor.

In our opinion the results obtained confirm that FDG PET will have a more appropriate role in local advanced breast cancer disease in which the scan may represent an effective staging procedure, besides providing additional prognostic information.

Conflict of interest statement

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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