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Original article

Different biological and prognostic breast cancer populations identified by FDG-PET in sentinel node-positive patients: Results and clinical implications after eight-years follow-up

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ABSTRACT

Background: Sentinel node (SN) biopsy is the standard method to evaluate axillary node involvement in breast cancer (BC). Positron emission tomography with 2-(fluorine-18)-fluoro-2-deoxy-D-glucose (FDG-PET) provides a non-invasive tool to evaluate regional nodes in BC in a metabolic-dependent, biomolecular-related way. In 1999, we initiated a prospective non-randomized study to compare these two methods and to test the hypothesis that FDG-PET results reflect biomolecular characteristics of the primary tumor, thereby yielding valuable prognostic information.

Patients and methods: A total of 145 cT1N0 BC patients, aged 24–70 years, underwent FDG-PET and lymphoscintigraphy before surgery. SN biopsy was followed in all cases by complete axillary dissection. Pathologic evaluation in tissue sections for involvement of the SN and other non-SN nodes served as the basis of the comparison between FDG-PET imaging and SN biopsy.

Results: FDG-PET and SN biopsy sensitivity was 72.6% and 88.7%, respectively, and negative predictive values were 80.5% and 92.2%, respectively. A subgroup of more aggressive tumors (ER-GIII, Her2+) was found mainly in the FDG-PET true-positive (FDG-PET+) patients, whereas LuminalA, Mib1 low-rate BCs were significantly undetected ($p = 0.009$) in FDG-PET false-negative (FDG-PET−) patients. Kaplan–Meier survival estimates after a median follow-up of more than 8 years showed significantly worse overall survival for FDG-PET+ patients in node-positive (N+) patients ($p = 0.035$) as compared to N+/FDG-PET− patients, which overlapped with survival curves of N− and FDG-PET+ or − patients.

Conclusions: Our findings suggest that FDG-PET results reflect intrinsic biologic features of primary BC tumors and have prognostic value with respect to nodal metastases. FDG-PET false negative cases appear to identify less aggressive indolent metastases. The possibility to identify a subgroup of N+ BC patients with an outcome comparable with N− BC patients could reduce the surgical and adjuvant therapeutic intervention.

Introduction

Although the need for information on nodal status in breast cancer (BC) management and for planning adjuvant treatment is now debatable [1–3], axillary node management remains a fundamental part of BC clinical practice. In the last 15 years, sentinel node (SN) biopsy, localized by lymphoscintigraphy, blue-dye, or both [4,5], has become the gold standard for the

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evaluation of regional nodal metastases and for decisions regarding complete axillary dissection [6–8]. Positron emission tomography with 2-(fluorine-18)-fluoro-2-deoxy-D-glucose (FDG-PET) is a non-invasive tool able to evaluate the regional nodes in breast cancer in a metabolic-dependent, biomolecular-related way [9]. Our initial evaluation of BC nodal involvement by FDG-PET revealed promising results as compared to those of histology after axillary dissection with respect to negative predictive value (NPV) and sensitivity [10], findings supported by subsequent studies in a larger series of patients [11,12]. However, further studies in order to replace SNB with the less-invasive FDG-PET compared FDG-PET and SN in the same patients in terms of sensitivity, accuracy and NPV, but showed that SN was superior in predicting nodal status [13,14]. In 1999, we also began the present study with the aim of verifying the possibility of FDG-PET to replace SNB in axillary staging, as well as the potential ability of FDG-PET to detect a subset of more aggressive nodal metastases reflective of the intrinsic clinical and biomolecular aggressiveness of the primary tumor, thereby providing prognostic information and then a selection criteria for therapeutic planning.

Patients and methods

Criteria for inclusion and treatments

At our Institute, patients with clinical and/or radiological evidence of cT1N0 BC and cytological confirmation of a malignant tumor were considered eligible and accrued in the prospective non-randomized clinical study. The accrual of the patients was done in a period of slightly more than 5 years. At the time of the study, around 150 cT1N0 BC patients per annum would be potentially eligible in our Institute. However, from 1998 to 2003 we enrolled 565 cT1N0 patients for our randomized trial 09/98. Around 20% of the 150 annually eligible cT1N0 patients refused to take part to the trial, whereas they accepted to take part to this protocol. Furthermore, it has to be considered that only one PET slot was available to this study by week.

Patients were generally in good state of health, with normal hepatic, renal, and cardio-respiratory function. In diabetic patients, the feasibility of PET examination was carefully evaluated, due to the interference of abnormal blood glucose levels with FDG biodistribution [15]. Exclusion criteria were: previously documented infiltrating BC or other malignancies, radiotherapy on the breast or chemotherapy, and clinical evidence of palpable regional nodes or distant metastases.

Written informed consent for all procedures was obtained from all patients. This study was approved by the Ethics Committee of our Institute.

All patients underwent quadrantectomy and postoperative radiotherapy on residual operated breast as previously described [16]. Surgical management of the axilla consisted in SN biopsy and complete axillary dissection for all patients. Adjuvant treatment [anthracycline-containing chemotherapy (CT) and/or hormonal treatment (OT)] was decided based on axillary nodal status and biopathologic characteristics of the primary tumor.

FDG-PET

FDG-PET scans were performed within a week before surgery in patients in 6-h fasting status and with normal blood glucose levels before administration of FDG, produced as described [17] in the PET Unit of Nuclear Medicine Division of our Institute. About 10 mCi of FDG was injected and after a 60-min uptake, PET images of the thorax were acquired using a dedicated stand-alone PET scanner (General Electric, Advance). Positioning of the breast and its nodal regions in the scanner field-of-view was checked by a built-in laser guide. Technical details have been previously reported [18].

FDG-PET images were evaluated by three experienced nuclear medicine physicians who concurred in the final evaluation. Images were considered positive when focal FDG uptake in one or more areas consistent with lymph nodes was detected in the axilla ipsilateral to the breast tumor. Due to the small size (<10 mm) of the vast majority of FDG foci and the consequent risk of underestimation of FDG uptake, no semi-quantitative analysis (SUV) was performed.

Evaluation of regional nodes with lymphoscintigraphy and radio-guided surgery of SN

On the day of surgery, patients underwent lymphoscintigraphy with Tc-99m nanocolloids (NANOCOLL, Nycomed Amersham Sorin, Saluggia VC, Italy). Injected activity was 30 MBq (0.8 mCi), administered in two 0.2-ml doses in subdermal and peritumoral regions respectively. Immediately after injections, the patient was seated in front of a digital gamma camera equipped with a low-energy high-resolution collimator in lateral position. A dynamic study (6 frames at 3 min/frame) was followed by a static planar image (5 min). A cutaneous mark was drawn to indicate the first visualized lymph node.

Within 6 h of lymphoscintigraphy, a radio-guided biopsy was performed to identify the SN. Intra-operative surgical probe C-Track (Care-Wise, USA) was used to locate the SN. Only the highest emitting node was considered the SN. Further nodes were considered as SN only if the emission rate was >10% of the first SN. All other nodes, independent of their emission rate, were classified as “remaining nodes”. The identified SN was sent for histologic examination.

Pathologic assessment of regional nodes

SN were examined grossly and measured. All formalin-fixed, paraffin-embedded lymph node pieces were sectioned into two or three parts, and one or more sections were prepared from each part for histologic examination and hematoxylin and eosin (H&E) staining. When H&E staining was negative, two sections were used for immunohistochemical analysis.

Biologic characterization of the primary tumor and regional nodes

Paraffin sections of primary tumors were analyzed for grade as previously described [19]. In addition, biological parameters (estrogen (ER) and progesterone (PgR) receptors and c-erbB-2/Her2) were analyzed by immunohistochemistry using a sensitive peroxidase-streptavidin method on formalin-fixed, paraffin-embedded material after antigen retrieval by heating slides for 6 min at 96 °C in 0.01 mol/L citrate buffer, pH 6. Expression of ER and PgR was assessed with mouse monoclonal antibody clone 1D5 and clone PgR636, respectively (Dako, Glostrup, Denmark). Tumors were considered positive for ER or PgR if more than 10% of tumor cell nuclei were immunostained. c-erbB2/Her2 was analyzed using rabbit polyclonal anti-human c-erbB2 oncoprotein (code number A0485; Dako) at the same dilution of anti-c-erbB2 antibody provided in the HercepTest kit (Dako). c-erbB-2 overexpression was interpreted according to Dako’s instructions for HercepTest results, and tumors with more than 10% of cells with complete membrane moderate (2+) or strong (3+) staining were scored positive.

Patients were then classified as: 1) luminalA-like (ER+/PgR+/Her2−, labeling index <14%); 2) luminalB-like (ER+/PgR+or−/Her2−, labeling index >14%); 3) luminal Her2-enriched (ER+/PgR+

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or−/Her2+); 4) basal-like (ER−/PgR−/Her2−) (triple-negative, TN); and 5) Her2-like (ER−/PgR−/Her2+).

Follow-up

Patients were followed at 6-month intervals for the first 5 years and annually thereafter. A chest X-ray, bilateral mammography, liver ultrasound examination and total body bone scan were requested annually. Patients taking Tamoxifen also underwent annual pelvic ultrasound examination and gynecologic evaluation.

Statistical analyses

Overall survival (OS) was calculated from date of diagnosis to death (any cause) or last follow-up. Disease-free survival (DFS) was calculated from date of randomization to date of first evidence of distant disease or latest follow-up. OS and DFS curves were estimated according to the Kaplan–Meier method and compared using the two-sided exact log-rank test [20].

The two-sided Fisher exact test was used to assess the association between two categorical variables, and the two-sided Wilcoxon rank-sum test was used to test for differences between two patients' groups on the basis of a continuous covariate.

The predictive performance of SN biopsy and FDG-PET to detect lymph node metastases was evaluated in terms of overall accuracy, sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratio, using post-surgery histology results as reference.

In addition, FDG-PET and SNB were combined according to the triage and add-on tests [21] and their predictive power was investigated. In triage, FDG-PET was used before SNB and combined using a conjunctive positivity criterion; only patients with a positive result on the FDG-PET test performed SNB and the outcome of the composite test was positive if both component tests were positive and negative in all other cases. In add-on test, FDG-PET was used after SNB and combined using a disjunctive positivity criterion; only patients with a negative result on the SNB test performed FGD-PET and the outcome of the composite test was negative if both FDG-PET and SNB tests were negative and positive in all other cases.

Differences were considered significant at $p < 0.05$. Statistical analyses were carried out using Stata11 [22] and R ver. 2.15.2 [23].

Results

Descriptive comparison between FDG-PET and SN biopsy

A total of 145 cT1N0 BC patients, mean age 54.0 (±11.5; range 24–78) years, was progressively accrued from 1999 to 2005. Of these patients, 92 (63.5%) had lesions in external quadrants. Except for 26 patients (17.9%) who had pT2 (<25 mm) BC, all others had pT1 breast carcinoma. The mean histological tumor size was 15.8 (±6.7) mm. Infiltrating ductal carcinoma was found in 118 (81.4%) of the 145 patients. Forty-two patients (29.0%) had high-grade tumors and 11 (7.6%) had low-grade tumors; 118 patients (81.4%) were ER-positive. The patient series was further grouped as: luminalA, 53 patients (36.6%); luminalB, 38 (26.2%); luminalB-Her2, 30 (20.7%); Her2-like, 6 (4.1%); and basal-like, 18 (12.4%) (Table 1).

All lymph nodes detected by lymphoscintigraphy were in the axilla, and the detection rate was 100%. Lymphoscintigraphy revealed only a single node in 129 patients (89.0%).

The median number of dissected SN was 1 (interquartile range, IQR = 1–2), and, specifically, the number of axillary lymph nodes identified as SN in each patients was: SN = 1 (68.3%), SN = 2 (24.1%), SN = 3 (4.8%), SN > 3 (2.8%). The median number of globally dissected axillary nodes was 20 (IQR = 16–25). The median number of involved nodes was 2 (IQR = 1–3). Nodal metastases were detected in 62 (42.8%) patients, 29 (46.8%) of whom had only one positive axillary node [8 of these 29 (27.6%) had only micrometastatic involvement]. When more than one positive lymph node was detected, the type of axillary nodal involvement is reported for the larger node.

Table 1
Patient characteristics.

Characteristic	Patients	
	%	# of cases (*n*/*N*)
Age (yrs)		
<50	36.6	53/145
50–70	58.6	85/145
>70	4.8	7/145
Menopausal status		
Pre-menopausal	53.8	78/145
Post-menopausal	46.2	67/145
Site		
External quadrants	64.1	93/145
Internal quadrants	35.9	52/145
Gene expression profile		
Luminal A	36.6	53/145
Luminal B	26.2	38/145
Luminal B-Her2+	20.7	30/145
Her2-like	4.1	6/145
Triple-negative	12.4	18/145
Estrogen receptor status		
ER+ PgR+	69.0	100/145
ER+ PgR−	14.5	21/145
ER− PgR−	16.5	24/145
Her2 status		
Her2-positive	24.1	35/145
Proliferative index (Mib-1)		
<12	42.7	50/117
≥12	57.3	67/117
Tumor size (cm)		
T1a (<0.5)	4.2	6/145
T1b (0.6–1.0)	17.2	25/145
T1c (1.1–2.0)	60.7	88/145
T2 (2.0–5.0)	17.9	26/145
Nodal status		
N−	57.2	83/145
N+	42.8	62/145
Histologic type		
IDC	81.4	118/145
ILC	13.8	20/145
IDC + ILC	2.1	3/145
Other	2.7	4/145
Grading		
I	7.6	11/145
II	63.4	92/145
III	29.0	42/145

+, positive; −, negative; ER, estrogen receptor; PgR, progesterone receptor; Her2, human epidermal growth factor receptor 2; N, axillary lymph node; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

Table 2 summarizes the predictive power of FDG-PET and SN biopsy. FDG-PET showed 45 true-positives and 17 false-negatives, whereas SN biopsy showed 55 true-positives and 7 false-negatives. The sensitivity of FDG-PET and SN was 72.6% and 88.7%, respectively, the negative predictive value was 80.5% and 92.2%, respectively.

All patients underwent breast conservative surgery, SN biopsy and axillary dissection. After surgery, 60 of the 62 (96.8%) N+ patients received CT with or without OT as adjuvant treatment, whereas 2 patients (3.2%) received OT only. In N− patients, 41 of 83 (49.4%) received CT with or without OT chemotherapy, 33 patients (39.8%) OT only, and 9 patients (10.8%) received no adjuvant treatment. Evaluation of the axillary FDG-PET results as an indicator for adjuvant treatment revealed a clear concordance between

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Table 2
Lymph node metastases identified by sentinel node (SN) biopsy and by FDG-PET.

	SN biopsy	FDG-PET
Detection rate	100% (145/145)	
Overall accuracy	95.2% (138/145)	79.3% (115/145)
Sensitivity	88.7% (55/62)	72.6% (45/62)
Specificity	100% (83/83)	84.3% (70/83)
Positive predictive value	100% (55/55)	77.6% (45/58)
Negative predictive value	92.2% (83/90)	80.5% (70/87)
Positive likelihood ratio	∞	4.6
Negative likelihood ratio	0.11	0.33

those results and nodal involvement in FDG-PET true-negative and true-positive patients, whereas in FDG-PET false-negative patients, the indication for CT vs. OT depended exclusively on the biologic and pathologic characteristics of primary tumor, lacking the information of axillary nodal involvement. In this series, 5 of 17 (29.4%) FDG-PET false-negative patients had biologically aggressive tumors (TN, Her2-enriched tumors), for whom CT had to be prescribed independently by axillary nodal involvement, whereas 12 patients (70.6%) had biologically less aggressive luminalA tumors. All of these N+ patients received adjuvant chemotherapy, consistent with the guidelines for adjuvant treatment of 10 years ago. However, considering the present guidelines, only one of these luminalA patients had more than 3 axillary nodal metastases to possibly indicate the need for a shift from adjuvant hormonal therapy to chemotherapy, representing 5.8% of false-negative FDG-PET, 1.6% of the N+ BC patients of this series, and about 1% of the entire series. Conversely, the 13 axillary false-positive FDG-PET patients would not have had any change in adjuvant treatment, since 10 of these patients (76.9%) had biologically aggressive primary tumors (TN, Her2-enriched, and highly-proliferative luminalB), and only 3 patients (23.1%) had luminalA tumors.

Axillary nodal involvement and FDG-PET results

The ability of FDG-PET to detect the type of metastatic involvement depended significantly on size of nodal metastases ($p = 0.011$), but in N+/FDG-PET+ patients, 12 of 45 (26.7%) had minimal nodal involvement (micrometastasis or embolic involvement) far under the spatial limit of resolution of FDG-PET (defined as 5 mm), whereas 6 of 17 N+/FDG-PET− patients (35.3%) showed a nodal involvement over this theoretical spatial limit of resolution. In particular, FDG-PET detected 4 of 10 (40%) micrometastatic axillary nodes and 8 of 13 (61.3%) embolic or pluriembolic axillary nodes (Table 3).

Patients with 3 or fewer involved nodes represented 77.8% and 94.1% of N+/FDG-PET+ and in N+/FDG-PET− groups, respectively ($p = 0.262$), with no significant differences in tumor size or median number of involved nodes (Table 3). On the other hand, pathological and biomolecular analysis of the primary tumor seemed to identify two different populations within the N+ patients evaluated by FDG-PET. Any single unfavorable prognostic factor characterizing more aggressive tumors (ER−, GIII, Her2+) is mainly in the FDG-PET true-positive patients, and this higher rate is confirmed as well when a subgroup of two or more of these unfavorable prognostic factors were evaluated (Table 3).

Follow-up and PET results

The median follow-up was approximately 8 years (98.3 months, IQR = 79.5–121.5). Of 145 patients, 24 (16.5%) had distant metastases (6 N−/FDG-PET− patients, 25.0%; 2 N−/FDG-PET+ patients, 8.3%; 2 N+/FDG-PET− patients and 14 N+/FDG-PET+ patients, 58.3%), while 18 (12.4%) died after breast cancer progression (5 N−/FDG-PET− patients, 27.8%; 1 N−/FDG-PET+ patients, 5.6%; 1 N+/FDG-PET− patients; and 11 N+/FDG-PET+ patients, 61.1%).

Table 3
Clinical and pathobiologic features identified by FDG-PET in lymph node-positive (N+) patients.

Parameter	N+/FDG-PET+	N+/FDG-PET−	*P*
No. of patients	45	17	
Type of axillary metastases[a]			
Micrometastasis	4 (40.0%)	6 (60.0%)	0.011
Embolic/pluriembolic	8 (61.5%)	5 (38.5%)	
Partial	11 (73.3%)	4 (26.7%)	
Massive	22 (91.7%)	2 (8.3%)	
Age (yrs)	51 (44–60)	55 (46–57)	0.624
No. of positive lymph nodes	2 (1–3)	1 (1–2)	0.177
N+ ≤ 3	35 (77.8)	16 (94.2)	0.262
Tumor diameter (cm)	17 (13–20)	15 (12–18)	0.307
IDC	37 (82.2)	14 (82.4)	1.000
Grade III	18 (40.0)	4 (23.5)	0.372
ER−	8 (17.8)	1 (5.9)	0.423
HER2+	12 (26.7)	3 (17.7)	0.528
Luminal A	14 (31.1)	12 (70.6)	0.009
Mib1 < 12%	15 (33.3)	14 (82.4)	0.001

+, positive; −, negative; N, axillary lymph node; IDC, invasive ductal carcinoma; ER, estrogen receptor; Her2, human epidermal growth factor receptor 2; Mib1, proliferation index.

[a] In patients with more than 1 positive lymph node, the type of axillary nodal metastases is given for the largest involved node.

Kaplan–Meier curves for OS estimated on the entire patient population (Fig. 1) showed a significantly worse survival in N+/FDG-PET+ patients as compared to all others groups ($p = 0.007$), while N+/FDG-PET−, N−/FDG-PET+ and N−/FDG-PET− curves overlapped and did not differ significantly ($p = 0.777$). Kaplan–Meier curves for DFS showed a similar pattern (Fig. 2), with N+/FDG-PET+ patients showing significantly worse survival ($p = 0.008$).

Prognosis for OS and DFS was significantly worse in N+/FDG-PET+ patients compared to the N+/FDG-PET− group ($p = 0.035$ and $p = 0.073$, respectively, although the latter was borderline).

Triage test and add-on test

Combining FDG-PET with SNB test according to the conjunctive positivity rule showed in Fig. 3(a) yields the so-called “triage test”. Comparing the outcome of this test with node positivity, 22 false negative and no false positive cases were found. Overall accuracy, sensitivity and negative predictive value of the test were 84.8%, 64.5% and 79.0%, respectively (Fig. 3(a)). The investigation of overall

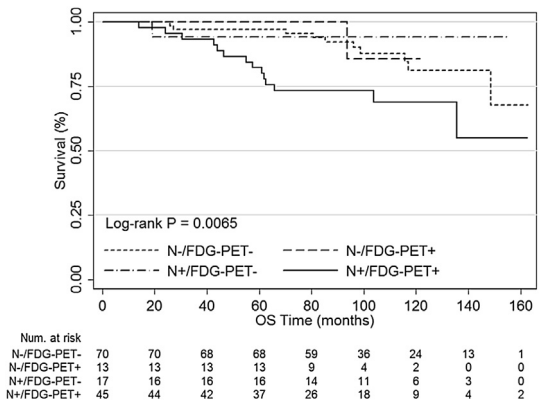

Fig. 1. Kaplan–Meier overall survival curves and *p*-value of the log-rank test in the N−/FDGPET−, N−/FDGPET+, N+/FDGPET− and N+/FDGPET+ groups.

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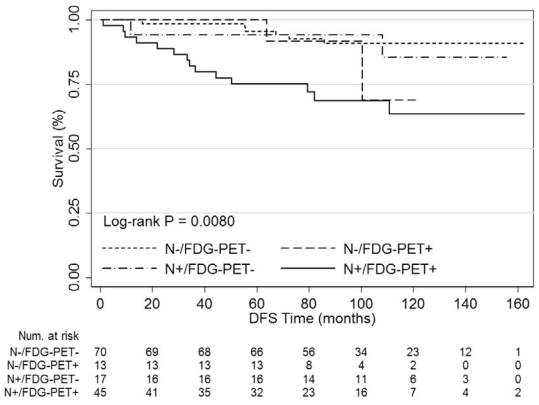

Fig. 2. Kaplan–Meier disease-free survival curves and *p*-value of the log-rank test in the N–/FDGPET–, N–/FDGPET+, N+/FDGPET– and N+/FDGPET+ groups.

survival in the 40 triage-positive cases (SNB+ and FDG-PET+) showed statistically significant differences ($p = 0.003$, Fig. 4(a)). Ten-year OS for SNB+ and FDG-PET+ was 0.67 (95% CI = 0.48–0.81) and 0.84 (95% CI = 0.72–0.91) for the other cases (SNB– or FDG-PET–).

SNB and FDG-PET tests can also be combined using the disjunctive positivity rule of Fig. 3(b) (add-on test). In this case, 2 false negative and 13 false positive cases were identified. Overall accuracy, sensitivity and specificity of the test were 89.7%, 96.8% and 84.3%, respectively. Negative and positive predictive values were 84.3% and 97.2%, respectively. The overall survival for the positive cases (SNB+ or FDG-PET+) did not show statistically significant differences ($p = 0.120$, Fig. 4(b)). Ten-year OS for add-on positive cases was 0.77 (95% CI = 0.64–0.86) and 0.82 (95% CI = 0.67–0.91) for the other cases (SNB+ or FDG-PET+).

Discussion

This study shows that FDG-PET for axillary staging can distinguish two different patient populations in terms of biological and clinical implications in N+ early BC.

Our study related FDG-PET results on a series of early BC with long-term outcome of these patients. In this series, N+ BC patients undetected by FDG-PET had survival curves overlapping with curves of N– BC patients, suggesting that FDG-PET results reflect intrinsic biologic features of the primary tumor with respect to the clinical and prognostic implications of nodal metastases. This predictive ability of PET, to distinguish two different prognostic groups of involved node patients has been shown in term of DFS also in a series of BC patients treated with neo-adjuvant chemotherapy [24].

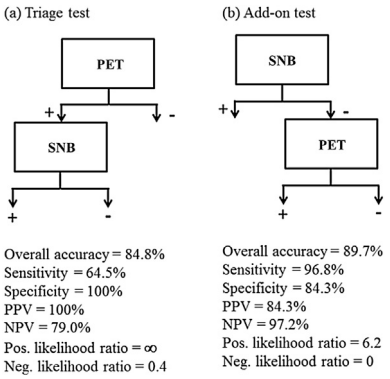

Fig. 3. Combining SNB and PET diagnostic tests; predictive measures of (a) triage and (b) add-on tests.

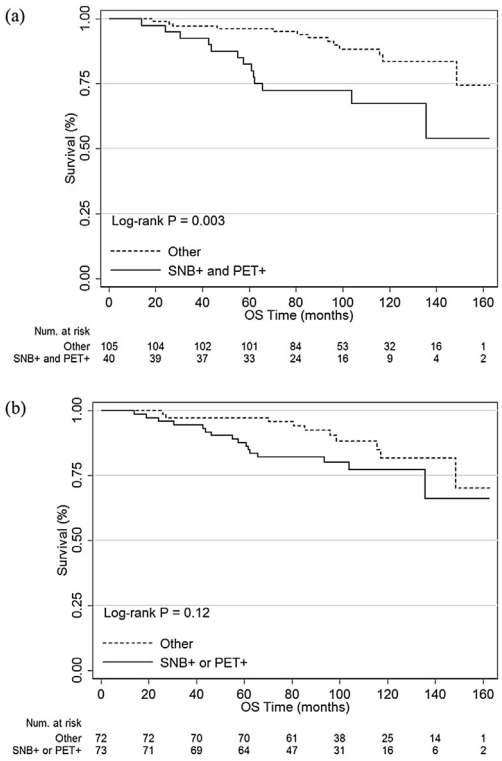

Fig. 4. Combining SNB and PET diagnostic tests; (a) Kaplan–Meier overall survival curves for triage test and (b) Kaplan–Meier overall survival curves for add-on test.

In our pioneering study on FDG-PET in the largest single-institution series, we found a high sensitivity and NPV of FDG-PET as compared with histopathologic results of axillary dissection [10]. However, later data reported controversial sensitivity of this method [25], in particular when FDG-PET was compared to SN directly on the same patients [13,14]. The differences have been variously attributed to patient selection criteria and/or to protocols for histologic assessment of axillary nodes, and a recent meta-analysis concluded that a high false-negative rate precludes FDG-PET from being recommended in clinical practice for node-negative early BC patients [26]. Although the lower sensitivity and NPV of FDG-PET has generally been attributed to its intrinsic limit of spatial resolution, other factors are clearly at play since FDG-PET can detect very small lesions inside axillary nodes.

The relationship between biological characteristics of the primary tumor and FDG uptake has been widely evaluated. We previously reported that FDG uptake was associated with p53 expression and high tumor grade [27]. The latter association was confirmed by Shimoda et al. [28], who found a significant relationship between FDG uptake and Ki67-positive cell percentage. Other authors have reported a positive relationship between FDG uptake and tumor grade, estrogen receptor status and Ki67 expression [29,30]. Interestingly, Groheux et al. [31], who found higher FDG uptake by high-grade, estrogen receptor-negative tumors, showed that uptake in triple-negative BC was almost twice than other BC subtypes, as recently confirmed by others [32,33]. Mavi et al. [34] confirmed an association between predictive and prognostic factors (estrogen, progesterone, and C-erbB-2 receptor status) and FDG uptake in primary breast cancer lesions, suggesting that such an association may be of importance to treatment planning.

All of these studies sought information on the degree of malignancy of BC subgroups with respect to a preoperative FDG-PET exam but without considering the possibility that the involved

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nodes might have different clinical and biological implications. In fact, all previous studies analyzing the usefulness of FDG-PET were focused on staging the early BC and the axilla [35], or on its ability to predict response to chemotherapy [36,37]. For staging evaluation, the usefulness of preoperative FDG-PET in early BC has been limited as a tool in indicating directly the need for axillary dissection and avoiding SN biopsy. Instead, SN biopsy has become the gold standard in the last 15 years for the evaluation of regional nodal metastases and for the decision regarding complete axillary dissection [6,7,38], although SN biopsy is an invasive procedure, with a relative low risk of false-negative results [4,7,39], and until very recently, axillary dissection was performed even for minimal metastatic tissue.

Here, we focused on the prognostic meaning of N+ BC patients who did or did not show FDG uptake at the axillary nodal level. Interestingly, we found that these two groups of patients differed in terms of biology, i.e., the subgroup of N+/FDG-PET− patients with luminalA-like, low-proliferation primary tumors are significantly more numerous than among N+/FDG-PET+ patients, and in term of prognosis, i.e., OS in N+/FDG-PET+ patients was significantly worse than that of N+/FDG-PET− patients. Overall, our study shows that the usefulness of FDG-PET rests mainly in its ability to identify nodal metastases with different prognostic implications rather than in detecting nodal metastases based on size, and that nodal metastases cannot be considered independent of the biologic characteristics of the primary tumor. A further investigation using combination of FDG-PET and SNB tests (triage and add-on combined tests) confirmed this result. In fact, according to the hypothesis that all nodal metastases would have the same prognostic meaning, the add-on test, in which the disjunctive combination of SNB and FDG-PET allowed the selection of almost all N+ patients (except for 2 patients resulting false-negative with both methods), should identify the worst prognostic group if compared with the subgroup of positive patients according to triage test (in which the conjunctive combination of FDG-PET and SNB allows to select only the subgroup of true-positive FDG-PET patients). Conversely, the results showed that in triage test OS curves were significantly worse for the subgroup of FDG-PET+ and SNB+ patients vs. all the others, whereas in add-on test the OS curves of positive patients lacked to show significant differences.

While our conclusions await confirmation in studies of a larger patient series, we hypothesize that the ability of SN to identify true-negative axillary nodes and the ability of FDG-PET to identify true-positive axillary nodes will allow identification by FDG-PET of patients with worse prognosis among N+ BC patients, supporting the paradigm of Cady [40] that lymph node metastases are “indicators, but not governors” of survival. In that case, FDG-PET may identify less aggressive, indolent metastasis, of which the removal may be facultative without the risk of understaging or undertreatment of the disease.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

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