^{18}F-FDG PET/CT for the Early Evaluation of Response to Neoadjuvant Treatment in Triple-Negative Breast Cancer: Influence of the Chemotherapy Regimen

David Groheux[1,2], Lucie Biard[3], Sylvie Giacchetti[4], Luis Teixeira[2,4], Elif Hindié[5], Caroline Cuvier[4], Laetitia Vercellino[1], Pascal Merlet[1], Anne de Roquancourt[6], Patricia de Cremoux[2,7], Matthieu Resche-Rigon[3], and Marc Espié[2,4]

[1]Department of Nuclear Medicine, APHP, Saint-Louis Hospital, Paris, France; [2]University Paris-Diderot, PRES Paris Cité, INSERM/CNRS UMR944/7212, Paris, France; [3]Department of Biostatistics and Information, APHP, Saint-Louis Hospital, Paris, France; [4]Department of Medical Oncology, Breast Diseases Center, APHP, Saint-Louis Hospital, Paris, France; [5]Department of Nuclear Medicine, CHU Bordeaux, University of Bordeaux, France; [6]Department of Pathology, APHP, Saint-Louis Hospital, Paris, France; and [7]Molecular Oncology Unit, APHP, Saint-Louis, Paris, France

Patients with triple-negative breast cancer (TNBC) have poor outcome when pathologic complete response (pCR) is not reached after neoadjuvant chemotherapy. Early prediction would be helpful. We evaluated the association between metabolic response after 2 cycles of neoadjuvant chemotherapy, pCR, and outcome in patients receiving 2 different anthracycline-based regimens (conventional and intensified). **Methods:** Of 77 consecutive TNBC patients, 23 received EC-D (4 cycles of epirubicin + cyclophosphamide followed by 4 cycles of docetaxel at conventional doses) and 55 received a dose-intensified, dose-dense concomitant regimen of epirubicin + cyclophosphamide (historically called SIM) for 6 cycles. PET/CT with ^{18}F-FDG was performed at baseline and after 2 cycles of neoadjuvant chemotherapy. The associations between clinical factors, biologic factors, early metabolic change, pCR, and event-free survival (EFS) were examined (log-rank test). **Results:** Of the 78 patients, 29 (37%) achieved pCR. The change in SUV$_{max}$ (ΔSUV$_{max}$) after 2 cycles was more pronounced in patients who achieved pCR (−72% vs. −42%; $P < 0.0001$). ΔSUV$_{max}$ was more pronounced under SIM than under EC-D (−68% vs. −35%, $P = 0.009$), and there was a trend for a higher pCR rate (44% vs. 22%, $P = 0.078$). Twenty-two patients relapsed and 10 of them died (median follow-up, 34 mo). pCR was associated with EFS (log-rank, $P = 0.001$). ΔSUV$_{max}$ was also significantly associated with EFS both in patients receiving SIM ($P = 0.028$) and in those receiving EC-D ($P = 0.021$). The optimal ΔSUV$_{max}$ for predicting pCR and EFS was, however, specific to the treatment regimen. EFS was not associated with tumor grade ($P = 0.98$), histologic subtype ($P = 0.17$), or clinical stage ($P = 0.097$). **Conclusion:** Early metabolic change during neoadjuvant chemotherapy can predict pathologic response and EFS in TNBC patients under different chemotherapy regimens. However, the metabolic response varies with the type of chemotherapy.

Pathologic complete response (pCR) after neoadjuvant chemotherapy is a strong predictor of favorable outcome, especially in aggressive breast cancer subtypes such as triple-negative breast cancer (TNBC; lacking estrogen and progesterone receptors and without HER2 overexpression) (1,2). Large or locally advanced breast cancers are currently treated with an anthracycline-based sequence followed by a taxane-based sequence at conventional doses (3). Dose-dense and dose-intensified chemotherapy has yielded encouraging results in TNBC (4,5). One phase III trial, "GeparOcto," is now comparing 2 different dose-dense, dose-intensified regimens (6). Other approaches could be of interest in TNBC (e.g., PARP inhibitors (7), inhibitors of immune checkpoints (8), and pan-EGF-R inhibitors (9)). When novel treatments are tested, the pCR rate is currently an important endpoint. However, although pCR is a strong predictor of outcome, studies have not shown that an increase in pCR translates into better patient outcome (2,10), although some associations have been found in trials comparing intensified, dose-dense chemotherapy with standard-dose regimens (10).

The pathologic response is known only at the end of neoadjuvant chemotherapy. An earlier prediction of residual disease would lead to treatment adaptation in an attempt to increase the pCR rate in nonresponders and improve the clinical outcome (11). PET/CT with ^{18}F-FDG has shown potential to detect residual disease early and also to predict poor outcome. The main advantage of metabolic imaging over conventional imaging is its ability to assess response earlier because the tumor metabolic changes occur before the morphologic changes (12). The potential prognostic value of PET gains full power and clinical meaning when each breast cancer phenotype is considered separately (13–18). Recently, in 142 HER2-positive breast cancer patients,

TABLE 1
Patient and Tumor Characteristics in Whole Population and in EC-D and SIM Groups

Variable	Whole population	EC-D group	SIM group	P
Patients (n)	78 (100)	23 (29)	55 (71)	
Median age (y)	51 (27–78)	55 (38–78)	49 (27–71)	0.21
Median tumor size (mm)	50 (18–170)	50 (22–160)	45 (18–170)	0.46
Histology (n)				0.15
Invasive ductal carcinoma	73 (94)	20 (87)	53 (96)	
Metaplastic	5 (6)	3 (13)	2 (4)	
SBR grade (n)				0.039*
2	8 (10)	5 (23)	3 (5)	
3	69 (90)	17 (77)	52 (95)	
Tumor classification† (n)				0.93
T1	1 (1)	0 (0)	1 (2)	
T2	36 (46)	10 (43)	26 (47)	
T3	22 (28)	7 (30)	15 (27)	
T4	19 (24)	6 (26)	13 (24)	
Lymph node classification† (n)				0.57
N0	32 (41)	11 (48)	21 (38)	
N1	27 (35)	6 (26)	21 (38)	
N2	15 (19)	4 (17)	11 (20)	
N3	4 (5)	2 (9)	2 (4)	
AJCC stage† (n)				0.83
IIA	21 (27)	7 (30)	14 (25)	
IIB	18 (23)	4 (17)	14 (25)	
IIIA	18 (23)	5 (22)	13 (24)	
IIIB	17 (22)	5 (22)	12 (22)	
IIIC	4 (5)	2 (9)	2 (4)	
Type of surgery (n)				0.62
Breast-conserving surgery	34 (44)	9 (39)	25 (46)	
Mastectomy	43 (56)	14 (61)	29 (54)	
Pathologic response (n)				0.078
Non-pCR	49 (63)	18 (78)	31 (56)	
pCR	29 (37)	5 (22)	24 (44)	

*Statistically significant.
†Prescan classification according to *AJCC Cancer Staging Manual* (*24*).
Data in parentheses are percentage or range.

the pCR rate was increased when the neoadjuvant treatment was changed early according to PET information (*18*).

In TNBC patients, some small series have suggested that PET information can be used to predict pCR early (*14,16*), while others found that PET was not predictive (*15,17*). Mixed chemotherapy regimens were used in those studies. The main objective of our study was to determine whether PET is useful in predicting pCR and patient outcome early in TNBC patients and to evaluate whether the type of chemotherapy regimen influences metabolic response. The secondary objectives were to optimize the PET criteria for predicting pathologic response and to determine whether assessing ^{18}F-FDG changes in axillary nodes, in addition to the primary tumor, improves PET prediction as recently suggested (*19*).

MATERIALS AND METHODS

Patients

The Institutional Review Board approved the study and stated that no informed consent was needed, considering the noninterventional design of this retrospective analysis. The eligibility criteria were patients with stage II or III TNBC scheduled for neoadjuvant chemotherapy. Patients with distant metastases and patients with uncontrolled diabetes were not included.

All patients underwent PET at baseline (PET$_1$) and after 2 cycles of neoadjuvant chemotherapy (PET$_2$). After completion of the neoadjuvant chemotherapy, the patients underwent breast-conserving surgery or mastectomy, as well as axillary lymph node dissection. Two regimens were used: conventional-dose chemotherapy with an anthracycline-based sequence followed by a taxane-based sequence, EC-D (4 cycles

TABLE 2

Clinical, Histologic, and Immunohistochemical Factors and PET Parameters According to Pathologic Response

Variable	Non-pCR	pCR	P
Patients (n)	49 (63)	29 (37)	
Median age (y)	50 (27–78)	51 (33–70)	0.78
Median tumor size (mm)	50 (18–160)	40 (21–170)	0.16
Histology (n)			0.15
Invasive ductal carcinoma	44 (90)	29 (100)	
Metaplastic	5 (10)	0 (0)	
Grade (n)			0.022*
2	8 (17)	0 (0)	
3	40 (83)	29 (100)	
T-score (n)			0.003*
T1	1 (2)	0 (0)	
T2	17 (35)	19 (66)	
T3	20 (41)	2 (7)	
T4	11 (22)	8 (28)	
N-score (n)			0.019*
N0	19 (39)	13 (45)	
N1	13 (27)	14 (48)	
N2	14 (29)	1 (3)	
N3	3 (6)	1 (3)	
Stage (n)			0.031*
IIA	9 (18)	12 (41)	
IIB	12 (24)	6 (21)	
IIIA	16 (33)	2 (7)	
IIIB	9 (18)	8 (28)	
IIIC	3 (6)	1 (3)	
SUV_{max}			
At PET_1			
Tumor	9 (2–28)	13 (5–27)	0.004*
Axilla (n = 58)	6 (1–21)	5 (1–16)	0.22
Target	11 (2–28)	13 (5–27)	0.066*
At PET_2			
Tumor	5 (1–31)	3 (1–10)	0.013*
Axilla (n = 58)	2 (1–17)	1 (0.5–4)	0.001*
Target	5 (1–31)	3 (1–10)	0.001*
Difference (ΔSUV_{max} %)			
Tumor	−42 (−89 to 142)	−72 (−95 to −49)	<0.0001*
Axilla (n = 58)	−53 (−90 to 0)	−74 (−94 to 0)	0.21
Target	−48 (−90 to 17)	−74 (−95 to −49)	<0.0001*

*Statistically significant.

Data in parentheses are percentage or range.

of epirubicin, 75 mg/m^2 d^1, plus cyclophosphamide, 750 mg/m^2 d^1, every 3 wk, followed by 4 cycles of docetaxel, 100 mg/m^2 d^1, every 3 wk), and a dose-dense, dose-intense concomitant regimen historically called SIM (epirubicin, 75 mg/m^2 d^1, plus cyclophosphamide, 1,200 mg/m^2 d^1, every 2 wk for 6 cycles). Promising preliminary results encouraged continuation of the prospective study (*14*). The present study involved a larger number of patients so that the influ-

ence of the chemotherapy regimen on metabolic response could be analyzed.

Breast Cancer Diagnosis and Neoadjuvant Chemotherapy Regimen

Breast cancer was diagnosed by core-needle biopsy. Histologic grade was determined using the modified Scarff-Bloom-Richardson
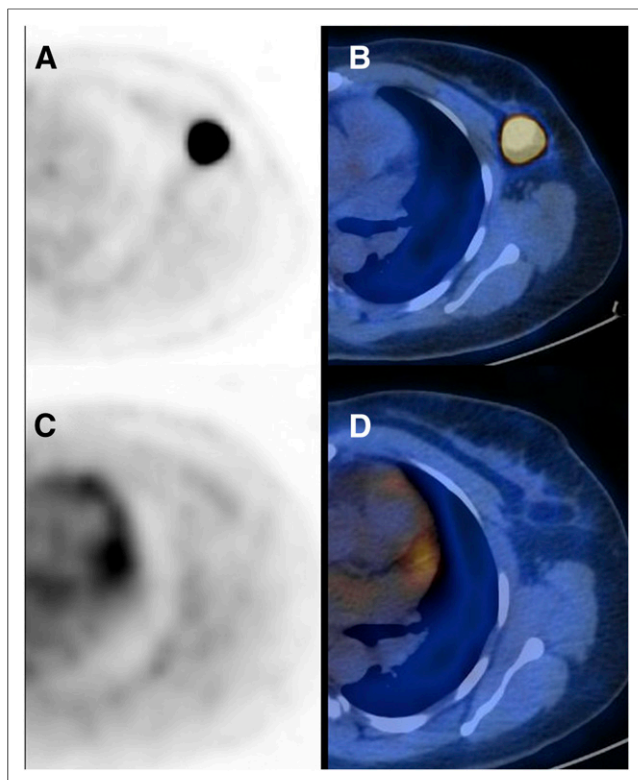
FIGURE 1. In 44-y-old patient with TNBC of left breast, transaxial PET (A) and PET/CT (B) images of primary tumor at baseline (SUV_{max}, 27.3) and after 2 cycles of SIM (C and D; SUV_{max}, 1.4). ΔSUV_{max} is −95%. No residual tumor was detected at surgery after 4 additional cycles of chemotherapy. Patient had no local or distant recurrence more than 1 y after surgery.

(SBR) system for invasive carcinoma. Tumors were defined as triple-negative when they were negative for both estrogen receptor (ER) and progesterone receptor (PR) and did not overexpress HER2.

Twenty-three patients received EC-D. Fifty-five patients (from the more recent period) received SIM. After surgery, patients who received SIM received 3 cycles of docetaxel, 75 mg/m^2 d^1, plus cyclophosphamide, 600 mg/m^2 d^1, every 3 wk. The shift toward the use of SIM in TNBC patients at Saint-Louis Hospital was based on our previous data (20), with the aim of increasing pCR rates.

^{18}F-FDG PET/CT Imaging

Patients fasted for 6 h, and blood glucose level had to be less than 7 mmol/L. ^{18}F-FDG (5 MBq/kg) was administered, and imaging started almost 60 min later. A Gemini XL PET/CT scanner (Philips) was used. CT data were acquired first (120 kV; 100 mAs; no contrast enhancement). PET emission data were acquired for 2 min per bed position. SUV was defined as [tracer concentration (kBq/mL)]/[injected activity (kBq)/patient body weight (g)].

A 3-dimensional region of interest was drawn around the primary tumor and, when present, around axillary lymph nodes. The percentage ΔSUV_{max} within the region of interest after 2 cycles of chemotherapy was calculated as $100 \times$ (second-cycle SUV_{max} − baseline SUV_{max})/baseline SUV_{max}.

Pathology Assessment and Event-Free Survival

pCR was defined as no evidence of residual invasive cancer in breast tissues or lymph nodes (2). Absence of carcinoma in situ was not mandatory.

During neoadjuvant chemotherapy, the patients underwent clinical examination every 2 cycles. After surgery, the patients made follow-up visits every 4 mo for 2 y and then twice yearly. Events included local, regional, or distant recurrence or death. Event-free survival (EFS) was defined as the time between PET_1 (or the date of surgery if considering the impact of pathologic response on EFS) and the date of the first event or of the last follow-up.

Statistical Analysis

Variables were compared using the Wilcoxon rank sum test for quantitative variables and the Fisher exact test for categoric variables.

The performance of PET parameters for prediction of non-pCR was evaluated using receiver-operating-characteristic analyses. Areas under the curve (AUCs) were estimated, along with their 95% confidence intervals, and compared using DeLong and DeLong's test. The predictive performance of SUV_{max} at PET_1 and PET_2 and of ΔSUV_{max} was evaluated according to measurements in different locations (primary tumor, axillary lymph nodes, and target, i.e., the site with the highest baseline SUV_{max}, either the breast tumor or a lymph node) and combining ΔSUV_{max} in the primary tumor and axillary nodes using the linear predictor of a logistic regression model predicting pathologic response (19). Predictive performance was examined at various cutoffs.

EFS was estimated using the Kaplan–Meier method and compared using the log-rank test according to clinical factors, biologic factors, pathologic findings, and PET parameters.

The predictive value of ΔSUV_{max} as a continuous variable was also estimated in multivariate analysis for pathologic response (logistic regression) and for EFS (Cox regression).

All tests were 2-sided, and P values equal to or less than 0.05 were considered statistically significant. Analyses were performed using R software (version 3.0.2).

TABLE 3
Performance of PET Parameters in Predicting pCR Early in All 78 TNBC Patients

SUV_{max}	AUC	95% confidence interval
At PET_1		
Tumor	0.70	0.57–0.81
Axilla ($n = 58$)	0.60	0.45–0.74
Target*	0.62	0.49–0.74
Tumor + axilla†	0.71	0.59–0.82
At PET_2		
Tumor	0.67	0.55–0.79
Axilla ($n = 58$)	0.76	0.62–0.88
Target	0.72	0.6–0.83
Tumor + axilla	0.76	0.65–0.87
Difference (ΔSUV_{max} %)		
Tumor	0.86	0.77–0.93
Axilla ($n = 58$)	0.69	0.54–0.84
Target	0.82	0.72–0.9
Tumor + axilla	0.86	0.77–0.93

*Site with highest baseline SUV_{max} (either breast tumor or axillary lymph node).

†Logistic regression analysis combining tumor and axilla measurements.

TABLE 4
Comparison of Preparation Procedures, Some Patient Characteristics, and Instrumental Factors Between EC-D and SIM Groups

Variable	EC-D group ($n = 23$)	SIM group ($n = 55$)	P
Weeks between PET_1 and PET_2	8 (6–14)	6 (4–12)	<0.0001
Weeks between PET_1 and surgery	28 (10–37)	17 (14–37)	<0.0001
Uptake time (min)			
PET_1	69 (51–93)	70 (57–95)	0.49
PET_2	64 (55–95)	67 (55–109)	0.25
Injected ^{18}F-FDG dose (MBq)			
PET_1	317 (249–486)	359 (248–476)	0.22
PET_2	335 (272–503)	359 (210–494)	0.50
Patient weight (kg)			
PET_1	65 (55–99)	70 (49–100)	0.22
PET_2	66 (55–103)	68 (48–110)	0.68
Patient glycemia (mmol/L)			
PET_1	5.8 (4.4–8.3)	5.3 (3.6–10.9)	0.082
PET_2	5.4 (4.0–7.5)	5.5 (3.7–9.8)	0.71

Data in parentheses are range.

RESULTS

Patient and Tumor Characteristics

Seventy-eight M0 patients with large or locally advanced TNBC were consecutively enrolled. Twenty-three patients were treated with EC-D, and 55 with SIM. Except for tumor grade, characteristics did not differ between the groups. Grade 3 tumors were more frequent in the SIM group (Table 1).

Metabolic PET Parameters at Baseline and Association with Tumor Characteristics

The median SUV_{max} of the 78 primary breast tumors at baseline was 10.1 (range, 1.6–27.5). In 58 patients, there was ^{18}F-FDG uptake in the axilla suggesting lymph node invasion (median SUV_{max}, 5.1; range, 0.8–21.2). In 20 patients, the site with the highest initial uptake was a lymph node.

Baseline SUV_{max} was higher in grade 3 than grade 2 tumors ($P = 0.004$). There was no statistical difference in SUV_{max} according to tumor size (≤5 vs. > 5 cm; $P = 0.72$), lymph node status (cN0 vs. cN1-2-3; $P = 0.32$), or American Joint Committee on Cancer (AJCC) stage (II vs. III; $P = 0.60$). Baseline tumor uptake was also similar between the EC-D and SIM groups (median SUV_{max}, 9.9 and 10.1, respectively; $P = 0.84$).

Relation Between pCR and Clinical, Biologic, Histologic, and PET Parameters

Of the 78 patients, 29 (37%) achieved pCR and 49 (63%) had residual disease. pCR was more frequent in patients with high-grade tumors ($P = 0.022$), with smaller tumors ($P = 0.003$), without (or with limited) clinical lymph nodes ($P = 0.019$), and with a low AJCC stage ($P = 0.031$) (Table 2). The pCR rate was higher in patients treated with SIM, but the difference from EC-D was not significant (44% vs. 22%, $P = 0.078$).

Among the 78 TNBCs, all PET parameters measured in the primary tumor (PET_1 SUV_{max}, PET_2 SUV_{max}, and ΔSUV_{max}) were predictive of pCR (Table 2). Baseline tumor uptake was higher in patients who achieved pCR (median SUV_{max}, 13 vs. 9; $P = 0.004$). At PET_2, residual tumor uptake was lower in patients who achieved pCR (median SUV_{max}, 3 vs. 5; $P = 0.013$). The decrease in tumor uptake between PET_1 and PET_2 was more pronounced in patients who achieved pCR (-72% vs. -42%; $P < 0.0001$) (Fig. 1). ΔSUV_{max} offered a higher AUC in predicting pathologic response (0.86) than did absolute SUV_{max} measured at PET_1 (0.70; $P = 0.016$) or at PET_2 (0.67; $P = 0.0003$) (Table 3).

PET prediction was not further improved when axillary node uptake was considered in addition to breast tumor analysis (Table 3).
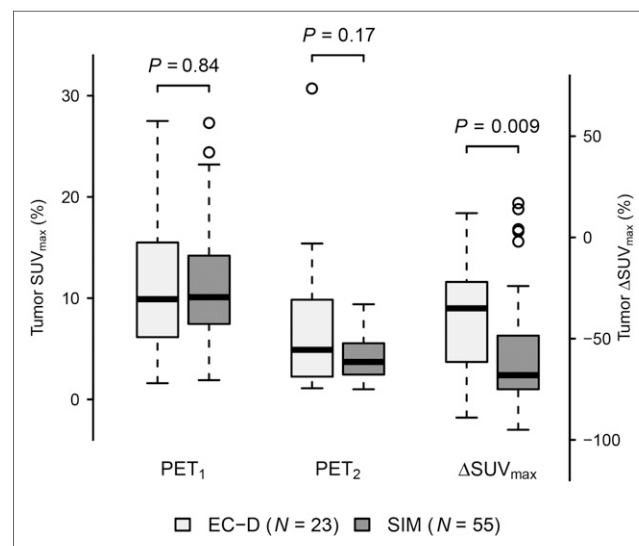

FIGURE 2. SUV_{max} of primary tumor at PET_1 and PET_2 and ΔSUV_{max} in EC-D and SIM groups.

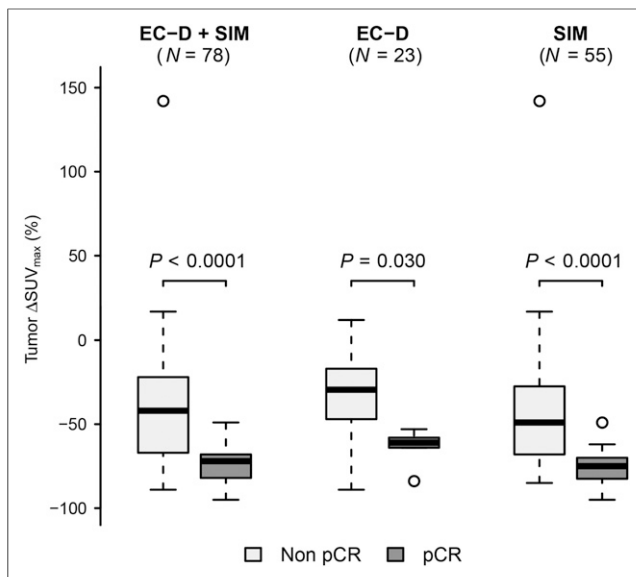**FIGURE 3.** ΔSUV$_{max}$ according to pathologic response after neoadjuvant chemotherapy (pCR vs. non-pCR) in whole population and in EC-D and SIM groups.

In multivariate analysis, adjusted for AJCC stage, ΔSUV$_{max}$ remained associated with pCR (odds ratio, 2.33 for a 10% decrease in ^{18}F-FDG uptake; 95% confidence interval,1.51–3.60; $P = 0.0001$).

Prediction of pCR According to Chemotherapy Regimen

Preparation procedures and PET instrumentation factors were similar in the EC-D and SIM groups (Table 4). Some variability in the time between ^{18}F-FDG injection and imaging was observed but was not significantly different between groups (Table 4). As expected, the time between PET$_1$ and PET$_2$ and between PET$_1$ and surgery was shorter in the SIM group than in the EC-D group (6 vs. 8 wk and 17 vs. 28 wk, respectively).

The decrease in tumor SUV$_{max}$ was less pronounced in the EC-D group than in the SIM group (-35% vs. -68%, $P = 0.009$) (Figs. 2 and 3). Table 5 shows that the optimal ΔSUV$_{max}$ cutoff for predicting

non-pCR would be dependent on the type of chemotherapy regimen. For example, the optimal cutoff to predict residual disease while maintaining a specificity higher than 90% ($<10\%$ of pCR in metabolic nonresponders) was observed with a ΔSUV$_{max}$ cutoff close to -65% in the SIM group and close to -50% in the EC-D group (Table 5).

Relation Between EFS and Clinical, Biologic, Histopathologic, and PET Parameters

Median follow-up was 34 mo (range, 3–85 mo) in the whole population, 61 mo in the EC-D group, and 26 mo in the SIM group. Twenty-two patients relapsed (15 with distant metastases), and 10 of them died.

In the whole population, pCR was significantly associated with EFS (log-rank, $P = 0.001$) (Fig. 4). ΔSUV$_{max}$ was also associated with EFS (hazard ratio for a 10% decrease, 0.86; 95% confidence interval, 0.78–0.94; $P = 0.001$). EFS was not associated with tumor SBR grade (log-rank, $P = 0.98$), histologic subtype (log-rank, $P = 0.17$), or AJCC stage (log-rank, $P = 0.097$) (Fig. 4).

In multivariate analysis, ΔSUV$_{max}$ was not significantly associated with EFS after the date of surgery when adjusted for pathologic response ($P = 0.29$). However, ΔSUV$_{max}$ was associated with EFS from the date of diagnosis when adjusted for AJCC stage ($P = 0.004$).

ΔSUV$_{max}$ was predictive of EFS regardless of the chemotherapy type (Fig. 5). As observed in the prediction of pCR, the cutoff to predict EFS was also higher in the SIM group. A cutoff ΔSUV$_{max}$ of -65% was able to predict EFS in this group (log rank, $P = 0.028$) but not in the EC-D group (log rank, $P = 0.14$) (Fig. 5). In the 23 patients treated with EC-D, a cutoff ΔSUV$_{max}$ of -50% was close to significance in predicting EFS (log rank, $P = 0.049$). The value -42% was strongly associated with EFS ($P = 0.021$), confirming our previous finding (15) with a longer follow-up.

DISCUSSION

In 78 TNBC patients, we observed a strong association between pCR and EFS ($P = 0.001$). These results are in line with a recent metaanalysis (2). If pathologic response could be predicted earlier,

TABLE 5
Performance of Various ΔSUV$_{max}$ Cut-Offs in Predicting Non-pCR in EC-D and SIM Groups

| | EC-D | | | | | | | SIM | | | | | | |
Cutoff	R	NR	Acc	Se	Sp	PPV	NPV	R	NR	Acc	Se	Sp	PPV	NPV
−75	13	87	74	89	20	80	33	29	71	75	90	54	72	81
−70	17	83	70	83	20	79	25	47	53	82	81	83	86	77
−65	17	83	70	83	20	79	25	58	42	78	68	92	91	69
−60	30	70	74	78	60	88	43	62	38	78	65	96	95	68
−55	35	65	78	78	80	93	50	64	36	76	61	96	95	66
−50	39	61	83	78	100	100	56	69	31	71	52	96	94	61
−45	44	57	78	72	100	100	50	76	24	67	42	100	100	57
−40	48	52	74	67	100	100	46	82	18	62	32	100	100	53

R = metabolic responders (percentage of patients with ΔSUV$_{max} \geq$ cutoff); NR = metabolic nonresponders; Acc = accuracy; Se = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value.
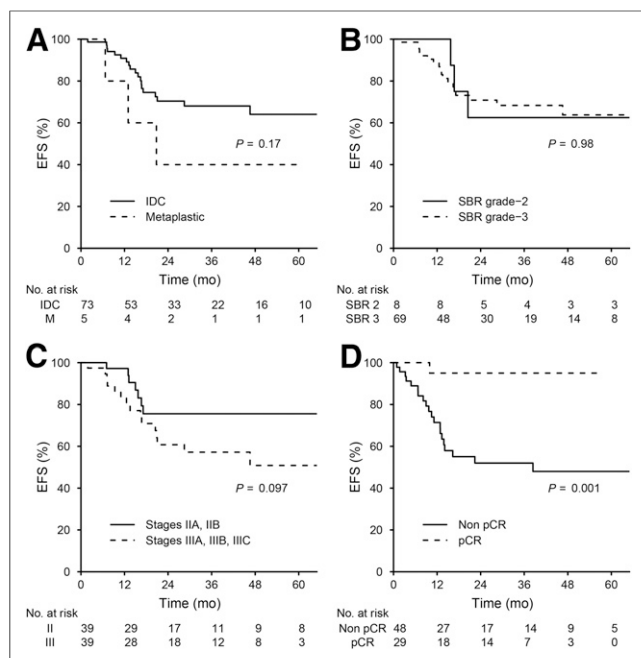Data are percentages ($n = 23$ for EC-D group and 55 for SIM group).

FIGURE 4. Kaplan–Meier curves for EFS in 78 patients according to tumor histology (A), SBR grade (B), AJCC stage (C), and pathology findings after neoadjuvant chemotherapy (D).

FIGURE 5. Kaplan–Meier curves for EFS according to metabolic response after 2 courses of neoadjuvant chemotherapy. Analysis was performed with 3 different ΔSUV_{max} cutoffs.

treatment might then be adapted to increase the pCR rate and potentially improve patient outcomes (*11*), as recently demonstrated for HER2-positive breast cancer patients (*18*).

Discordant results have been observed in TNBC patients (*14–17,19,21*). Two teams found that PET information was helpful in predicting pCR early (*14,16*), whereas in one other report PET was not predictive (*17*). Unlike their preliminary findings (*15*), Humbert et al. recently reported that PET has high accuracy in predicting pCR (*22*). In a multicenter study (mixing TNBC and hormone-positive/HER2-negative breast cancer), PET was also predictive (*23*).

The results of our study are important because they show that the decrease in ^{18}F-FDG uptake is dependent on the chemotherapy regimen. The change in breast tumor metabolism as assessed by ^{18}F-FDG imaging after 2 cycles was less pronounced with EC-D than with SIM (−35% vs. −68%, $P = 0.009$). Thus, the optimal ΔSUV_{max} cutoff for predicting non-pCR appears to depend on specific regimens (Table 5). Novel therapy strategies are limited in TNBC patients, and treatment should be modified only when there is a low probability of achieving pCR with initial chemotherapy. When considering specificity superior to 90% (pCR rate < 10% in nonresponders) and good sensitivity to predict residual disease, optimal ΔSUV_{max} cutoffs were close to −65% in the SIM group and close to −50% in the EC-D group (Table 5). The best prediction was obtained with ΔSUV_{max} measured in the primary tumor. Combining changes in the tumor and axillary nodes had no added value.

Interestingly, metabolic response was also predictive of patient outcome regardless of the type of chemotherapy (Fig. 5).

Our single-institution study had some limitations. Although interim PET was always performed after the second cycle, the median time between baseline PET and interim PET was lower in the SIM group (6 vs. 8 wk). However, despite a shorter time
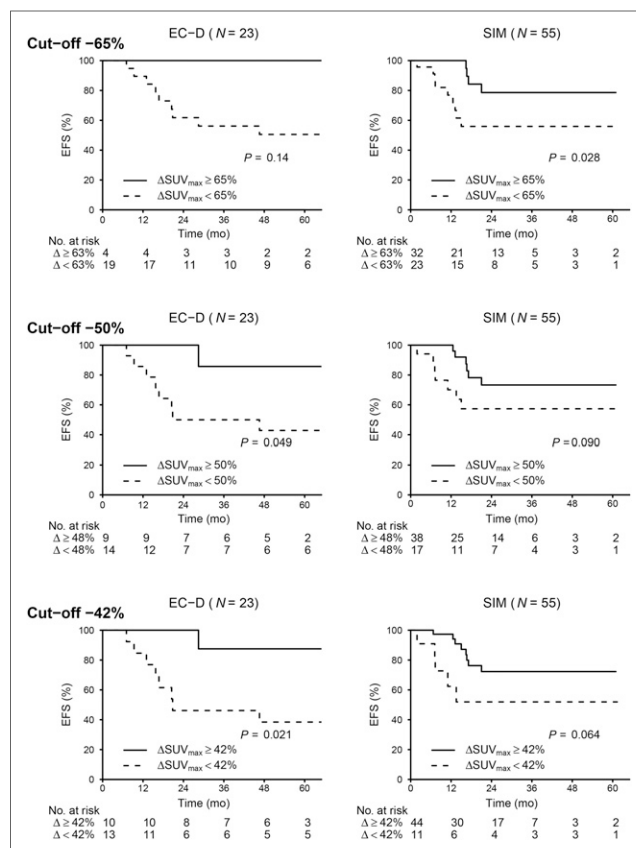
since the beginning of treatment, the fact that ΔSUV_{max} was larger in the SIM group than in the EC-D group (−68% vs. −35%, $P = 0.009$) suggests that the ^{18}F-FDG decrease was dependent on the chemotherapy regimen. The chemotherapy regimen was chosen without randomization. Indeed, in 2009 our institution shifted toward use of SIM in TNBC patients (*20*). The groups did not have the same number of patients (23 patients in the EC-D group and 55 in the SIM group). SBR grade 3 tumors were more frequent in patients treated with SIM ($P = 0.039$). Median follow-up was also shorter in the SIM group.

CONCLUSION

Our study confirmed that the change in ^{18}F-FDG tumor uptake after 2 cycles of neoadjuvant chemotherapy in TNBC patients allowed early detection of pCR and early prediction of outcome. However, the decrease in tumor SUV_{max} was dependent on the neoadjuvant chemotherapy regimen, with the level of decrease being more important in dose-dense, dose-intense chemotherapy than in a standard-dose schedule. The optimal SUV_{max} cutoff for early prediction of pCR and patient survival therefore varies with the type of chemotherapy.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance

REFERENCES

1. Carey LA, Dees EC, Sawyer L, et al. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. *Clin Cancer Res.* 2007;13:2329–2334.

2. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet.* 2014;384:164–172.

3. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27. *J Clin Oncol.* 2008;26:778–785.

4. Mehta RS. Dose-dense and/or metronomic schedules of specific chemotherapies consolidate the chemosensitivity of triple-negative breast cancer: a step toward reversing triple-negative paradox. *J Clin Oncol.* 2008;26:3286–3288.

5. von Minckwitz G, Untch M, Nüesch E, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. *Breast Cancer Res Treat.* 2011;125:145–156.

6. Home page. ClinicalTrials.gov website. http://clinicaltrials.gov. Accessed January 25, 2016.

7. Telli ML, Jensen KC, Vinayak S, et al. Phase II study of gemcitabine, carboplatin, and iniparib as neoadjuvant therapy for triple-negative and BRCA1/2 mutation-associated breast cancer with assessment of a tumor-based measure of genomic instability: PrECOG 0105. *J Clin Oncol.* 2015;33:1895–1901.

8. Denkert C, von Minckwitz G, Brase JC, et al. Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. *J Clin Oncol.* 2015;33:983–991.

9. Nabholtz JM, Abrial C, Mouret-Reynier MA, et al. Multicentric neoadjuvant phase II study of panitumumab combined with an anthracycline/taxane-based chemotherapy in operable triple-negative breast cancer: identification of biologically defined signatures predicting treatment impact. *Ann Oncol.* 2014;25:1570–1577.

10. Berruti A, Amoroso V, Gallo F, et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: a meta-regression of 29 randomized prospective studies. *J Clin Oncol.* 2014;32:3883–3891.

11. Groheux D. Predicting pathological complete response in breast cancer early. *Lancet Oncol.* 2014;15:1415–1416.

12. Groheux D, Espié M, Giacchetti S, Hindié E. Performance of FDG PET/CT in the clinical management of breast cancer. *Radiology.* 2013;266:388–405.

13. Groheux D, Giacchetti S, Espié M, Rubello D, Moretti J-L, Hindié E. Early monitoring of response to neoadjuvant chemotherapy in breast cancer with ^{18}F-FDG PET/CT: defining a clinical aim. *Eur J Nucl Med Mol Imaging.* 2011;38:419–425.

14. Groheux D, Hindié E, Giacchetti S, et al. Triple-negative breast cancer: early assessment with ^{18}F-FDG PET/CT during neoadjuvant chemotherapy identifies patients who are unlikely to achieve a pathologic complete response and are at a high risk of early relapse. *J Nucl Med.* 2012;53:249–254.

15. Humbert O, Berriolo-Riedinger A, Riedinger JM, et al. Changes in ^{18}F-FDG tumor metabolism after a first course of neoadjuvant chemotherapy in breast cancer: influence of tumor subtypes. *Ann Oncol.* 2012;23:2572–2577.

16. Koolen BB, Pengel KE, Wesseling J, et al. FDG PET/CT during neoadjuvant chemotherapy may predict response in ER-positive/HER2-negative and triple negative, but not in HER2-positive breast cancer. *Breast.* 2013;22:691–697.

17. Zucchini G, Quercia S, Zamagni C, et al. Potential utility of early metabolic response by ^{18}F-2-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography in a selected group of breast cancer patients receiving preoperative chemotherapy. *Eur J Cancer.* 2013;49:1539–1545.

18. Coudert B, Pierga J-Y, Mouret-Reynier M-A, et al. Use of [^{18}F]-FDG PET to predict response to neoadjuvant trastuzumab and docetaxel in patients with HER2-positive breast cancer, and addition of bevacizumab to neoadjuvant trastuzumab and docetaxel in [^{18}F]-FDG PET-predicted non-responders (AVATAXHER): an open-label, randomised phase 2 trial. *Lancet Oncol.* 2014;15:1493–1502.

19. Koolen BB, Pengel KE, Wesseling J, et al. Sequential ^{18}F-FDG PET/CT for early prediction of complete pathological response in breast and axilla during neoadjuvant chemotherapy. *Eur J Nucl Med Mol Imaging.* 2014;41:32–40.

20. Giacchetti S, Porcher R, Lehmann-Che J, et al. Long-term survival of advanced triple-negative breast cancers with a dose-intense cyclophosphamide/anthracycline neoadjuvant regimen. *Br J Cancer.* 2014;110:1413–1419.

21. Groheux D, Hindié E, Giacchetti S, et al. Early assessment with ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography can help predict the outcome of neoadjuvant chemotherapy in triple negative breast cancer. *Eur J Cancer.* 2014;50:1864–1871.

22. Humbert O, Riedinger JM, Charon-Barra C, et al. Identification of biomarkers including [18]FDG-PET/CT for early prediction of response to neoadjuvant chemotherapy in triple-negative breast cancer. *Clin Cancer Res.* 2015;21:5460–5468.

23. Connolly RM, Leal JP, Goetz MP, et al. TBCRC 008: early change in ^{18}F-FDG uptake on PET predicts response to preoperative systemic therapy in human epidermal growth factor receptor 2-negative primary operable breast cancer. *J Nucl Med.* 2015;56:31–37.

24. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A KKK. *AJCC Cancer Staging Manual.* 7th ed. New York, NY: Springer; 2010.