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^{18}FDG-PET/CT for the early evaluation of response to neoadjuvant treatment in triple negative breast cancer: influence of the chemotherapy regimen

Running title: ^{18}FDG-PET/CT in TNBC

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ABSTRACT

Patients with triple negative breast cancer (TNBC) have poor outcome when pathological complete response (pCR) is not reached after neoadjuvant chemotherapy (NAC). Early prediction would be helpful. We evaluated the association between metabolic response after 2 cycles of NAC, 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 SIM (dose-intensified/dose-dense protocol of Epirubicin+Cyclophosphamide for 6 cycles). Positron emission tomography/computed tomography with ^{18}F-fluorodeoxyglucose (^{18}FDG) was performed at baseline and after two cycles of NAC. The associations between clinical factors, biological 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 maximum standardized uptake value (ΔSUV_{max}) after two cycles was more pronounced in patients who achieved pCR (-72% *vs.* -42%; P<0.0001). ΔSUV_{max} was more pronounced under SIM than with 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 months). pCR was associated with EFS (log-rank: P=0.001). ΔSUV_{max} was also significantly associated with EFS, in patients receiving SIM (P=0.028) as well as in those receiving EC-D (P=0.021). The optimal ΔSUV_{max} to predict pCR and EFS was, however, specific to the treatment regimen. EFS was not associated with tumor grade (P=0.98), histological subtype (P=0.17) or clinical stage (P=0.097).

Conclusions: Early metabolic change during NAC can predict pathological response and EFS in TNBC patients under different chemotherapy regimens. However, the metabolic response varies with the type of chemotherapy.

Keywords: ^{18}FDG-PET/CT, triple negative breast cancer, neoadjuvant chemotherapy, dose-dense chemotherapy, metabolic response, prognosis.

Pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) is a strong predictor of favorable outcome, especially in aggressive breast cancer (BC) subtypes such as triple negative breast cancer (TNBC; lacking estrogen and progesterone receptors and without HER2-overexpression) (*1*,*2*). Large or locally advanced BCs 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 two different dose-dense, dose-intensified regimen (*6*). Others approaches could be of interest in TNBC (eg. PARP inhibitors (*7*), inhibitors of immune checkpoints (*8*), or 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, it has not been demonstrated that an increase in pCR in studies translates into better patient outcome (*2*,*10*), although some associations were found in trials comparing intensified/dose-dense chemotherapy *vs.* standard-dose regimens (*10*).

The pathological response is known only at the end of NAC. An earlier prediction of residual disease would lead to treatment adaptation in an attempt to increase the pCR rate in non-responders and improve the clinical outcome (*11*). Positron emission tomography/computed tomography (PET/CT) with ^{18}F-fluorodeoxyglucose (^{18}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 morphological changes (*12*). The potential prognostic value of PET gains full power and clinical meaning when considering each breast cancer phenotype separately (*13*–*18*). Recently, in 142 HER2-positive BC patients, the pCR rate was increased when the neoadjuvant treatment was changed early according to PET information (*18*).

In TNBC patients, small series suggested that PET information could 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 previous studies. The main objective of our study was to determine if PET is useful to predict pCR and patients outcome early in 78 triple-negative breast cancer patients and to evaluate if the type of chemotherapy regimen influences metabolic response. The secondary objectives were to optimize PET criteria to be used to predict pathological response and to determine if assessing ^{18}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 non-interventional design of this retrospective analysis. Eligibility criteria were patients with stage II-III triple negative BC scheduled for neoadjuvant chemotherapy. Patients with distant metastases and patients with uncontrolled diabetes were not included.

All patients had a baseline PET (PET_1) and a second (PET_2) after two cycles of neoadjuvant chemotherapy. After completion of NAC, patients underwent breast-conserving surgery or mastectomy as well as axillary lymph node dissection. Two regimens were used: a conventional dose chemotherapy with an anthracycline-based sequence followed by a taxane-based sequence (EC-D), and a dose-dense dose-intense concomitant regimen (SIM). Preliminary findings with promising results encouraged continuation of the prospective study (*14*). The present study involves a larger number of patients so that the influence of the chemotherapy regimen on metabolic response could be analyzed.

Breast Cancer Diagnosis and Neoadjuvant Chemotherapy Regimen

Breast cancer was diagnosed on a core-needle biopsy. Histological grade was determined using the modified Scarff-Bloom-Richardson grading for invasive carcinoma. Tumors were defined as triple-negative when estrogen receptor (ER) and progesterone receptor (PR) were both negative and HER2 not over-expressed.

Twenty-three patients received EC-D (4 cycles of Epirubicin 75 mg/m² d1 plus Cyclophosphamide 750 mg/m² d1 administered every 3 weeks, followed by 4 cycles of Docetaxel 100 mg/m² d1 qw3). Fifty-five patients (from the more recent period) received Epirubicin 75 mg/m² d1 plus Cyclophosphamide 1200 mg/m² d1 every 2 weeks (SIM) for 6 cycles. After surgery, patients who received SIM chemotherapy received 3 cycles of Docetaxel (75mg/m2 d1 plus cyclophosphamide 750mg/m2 d1) every 3 weeks. The shift towards the use of dose dense, dose intense cyclophosphamide-anthracyclins (SIM) in the treatment of TNBC patients at Saint-Louis hospital, aimed at increasing pCR rates based on our previous data (*20*).

^{18}FDG-PET/CT Imaging

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

A 3D region of interest (3D-ROI) was drawn around the primary tumor and around axillary lymph nodes when present. The change in SUV_{max} (maximum SUV value within the

ROI) after two cycles of chemotherapy was expressed as ΔSUV_{max} (%) = 100 × (2^{nd} cycle SUV_{max} - baseline SUV_{max})/baseline SUV_{max}.

Pathology Assessment and Event-free Survival

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

During neoadjuvant chemotherapy, patients underwent clinical examination every two cycles. After surgery, patients had follow-up visits every 4 months for two years, then twice yearly. Events included local, regional, or distant recurrences or death. Event-free survival was defined as the time period between the date of baseline PET acquisition (or the date of surgery if considering the impact of pathological response on EFS) and the date of the first event or of the last follow-up.

Statistical Analysis

Comparisons between variables were performed using Wilcoxon rank sum test for quantitative variables and Fisher's exact test for categorical variables.

The performance of PET parameters for prediction of non-pCR was evaluated using receiver operating characteristics (ROC) analyses. Areas under the curves (AUC) were estimated with their 95% confidence intervals (CI), and compared using DeLong and DeLong's test. The predictive performances of the values of SUV_{max} (measured at PET_1 and PET_2) and of the variation (ΔSUV_{max}) were evaluated, according to measurements in different localizations: in the primary tumor, in axillary lymph nodes, in the target (the site with the highest baseline SUV_{max} value, either the breast tumor or a lymph node), and combining SUV_{max} changes in the primary

tumor and axillary nodes using the linear predictor of a logistic regression model predicting pathological response (*19*). Predictive performances were examined at various cut-offs.

Event-free survival was estimated using the Kaplan-Meier method and compared using the log-rank test according to clinical factors, biological factors, pathological findings, PET parameters.

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

All tests were two-sided and *P* values ≤ 0.05 were considered statistically significant. Analyses were performed using R software (version 3.0.2).

RESULTS

Patient's and tumors characteristics

Seventy-eight M0-patients with large or locally-advanced TNBC were consecutively enrolled. Twenty-three patients were treated with EC-D while 55 received the SIM protocol. There were no differences in patients' characteristics between the 2 groups, except for tumor grade, grade-3 tumors being more frequent in patients treated with SIM (Table 1).

Metabolic PET parameters at baseline and association with tumors' characteristics

Median tumor SUV_{max} of the 78 primary breast tumors at baseline was 10.1 (range: 1.6-27.5). In 58 patients, there was ^{18}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 highest initial uptake was a lymph node.

Baseline breast tumor SUV_{max} was higher in grade-3 than in grade-2 tumors (P=0.004). There was no statistical difference in tumor SUV_{max} according to tumor size (≤5cm *vs.* >5cm;

P=0.72), lymph node status (cN0 *vs.* cN1-2-3; P=0.32) and AJCC stage (stage II *vs.* stage III; P=0.60). Baseline tumor ^{18}FDG uptake was also similar in the EC-D and SIM group (median SUV_{max} was 9.9 and 10.1, respectively; P=0.84).

Relation between pCR and clinical, biological, histological and PET parameters

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

Among the 78 TNBC, 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 ^{18}FDG 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 ^{18}FDG 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 higher AUC in predicting pathology response (AUC=0.86) than the absolute SUV_{max} values measured at PET_1 (AUC=0.70, P=0.016) or at PET_2 (AUC=0.67, P=0.0003) (Table 3).

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

In multivariate analysis, adjusted on AJCC stage, tumor ΔSUV_{max} remained associated with pCR (OR=2.33 for a 10% decrease in FDG uptake, 95%CI:1.51-3.60, *P*=0.0001).

Prediction of pCR according to the chemotherapy regimen

Preparation procedures and PET instrumental factors were similar in the EC-D and in the SIM group (Table 4). Some variability in the time between FDG injection and imaging was observed. However, differences were not significant between the two groups (Table 4). As expected, the time between PET_1 and PET_2 and between PET_1 and surgery were shorter in the SIM group than in the EC-D group (6 weeks *vs.* 8 weeks and 17 weeks *vs.* 28 weeks, respectively).

The decrease of 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} cut-off value to predict non-pCR would be dependent upon the type of chemotherapy regimen. For example, the optimal cut-off to predict residual disease while maintaining a specificity higher than 90% (less than 10% of pCR in metabolic non-responders) is observed with a cut-off value of ΔSUV_{max} close to -65% in the SIM group and close to -50% in the EC-D group (Table 5).

Relation between EFS and clinical, biological, histopathological and PET parameters

Median follow-up was 34 months (range: 3-85) in the whole population, 61 months in the patients treated with EC-D and 26 months in those treated with SIM. 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). Tumor ΔSUV_{max} was also associated with EFS (HR for a 10% decrease = 0.86, 95%CI 0.78-0.94, P=0.001). EFS was not associated with tumor SBR-grade (log-rank: P=0.98), histological 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 date of surgery when adjusted on pathological response (P=0.29). However, ΔSUV_{max} was associated with EFS from date of diagnosis when adjusted on AJCC stage (P=0.004).

Tumor ΔSUV_{max} was predictive of EFS whatever the chemotherapy used (Fig. 5). As observed in the prediction of pCR, the cut-off value to predict EFS was also higher in the SIM group. The cut-off ΔSUV_{max} -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, the cut-off ΔSUV_{max} -50% was close to significance in predicting EFS (log rank: P=0.049). The value of -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 meta-analysis (*2*). If pathologic response could be predicted earlier, treatment might then be adapted to increase the pCR rate and potentially improve patients' outcomes (*11*). This has been recently demonstrated for HER2-positive BC patients (*18*).

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

Results of our study are important as they show that the decrease in tumor ^{18}FDG uptake is dependent on the chemotherapy regimen. The change of breast tumor metabolism as assessed

by FDG imaging after two cycles was less pronounced with EC-D than with SIM (-35% *vs.* -68%, P=0.009). Thus, an optimal ΔSUV_{max} cut-off value to predict non-pCR appears to be dependent upon specific regimens (Table 5). Novel therapy strategies are limited in TNBC patients and treatment should be modified only in the case of low probability of achieving pCR with initial chemotherapy. If considering specificity superior to 90% (pCR rate < 10% in non-responders) and good sensitivity to predict residual disease, optimal ΔSUV_{max} cut-offs were close to -65% in patients treated with SIM and close to -50% in those treated with EC-D (Table 5). Best prediction was obtained with ΔSUV_{max} measured in the primary tumor. Combining changes in the tumor and axillary nodes, was not of added-value.

Interestingly, the metabolic response was also predictive of patient's outcome whatever the chemotherapy used (Fig. 5).

Our single institution study has some limitations. Although interim PET was always performed after the second cycle, median time between baseline PET and interim PET was lower in the SIM group (6 weeks *vs.* 8 weeks). However, despite a shorter time since the beginning of treatment, ΔSUV_{max} was larger in the SIM group (-35% *vs.* -68%, P=0.009), which suggests that the ^{18}FDG decrease was dependent on the chemotherapy regimen. The two chemotherapy regimens were given without randomization. Indeed, in 2009, there has been a shift toward the use of SIM in TNBC patients in our institution (*20*). The two 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). The median follow-up was also shorter in the SIM group.

CONCLUSION

In summary, our study confirms that the change in ^{18}FDG tumor uptake after 2 cycles of neoadjuvant chemotherapy allows detecting pCR early and predicting outcomes in TNBC patients. However, the decrease in tumor SUV_{max} is dependent upon the NAC regimen, the level of decrease being more important with a dose-dense, dose-intense chemotherapy than with a standard dose schedule. The optimal SUV_{max} cut-off to apply to early predict pCR and patients survival varies therefore with the type of chemotherapy.

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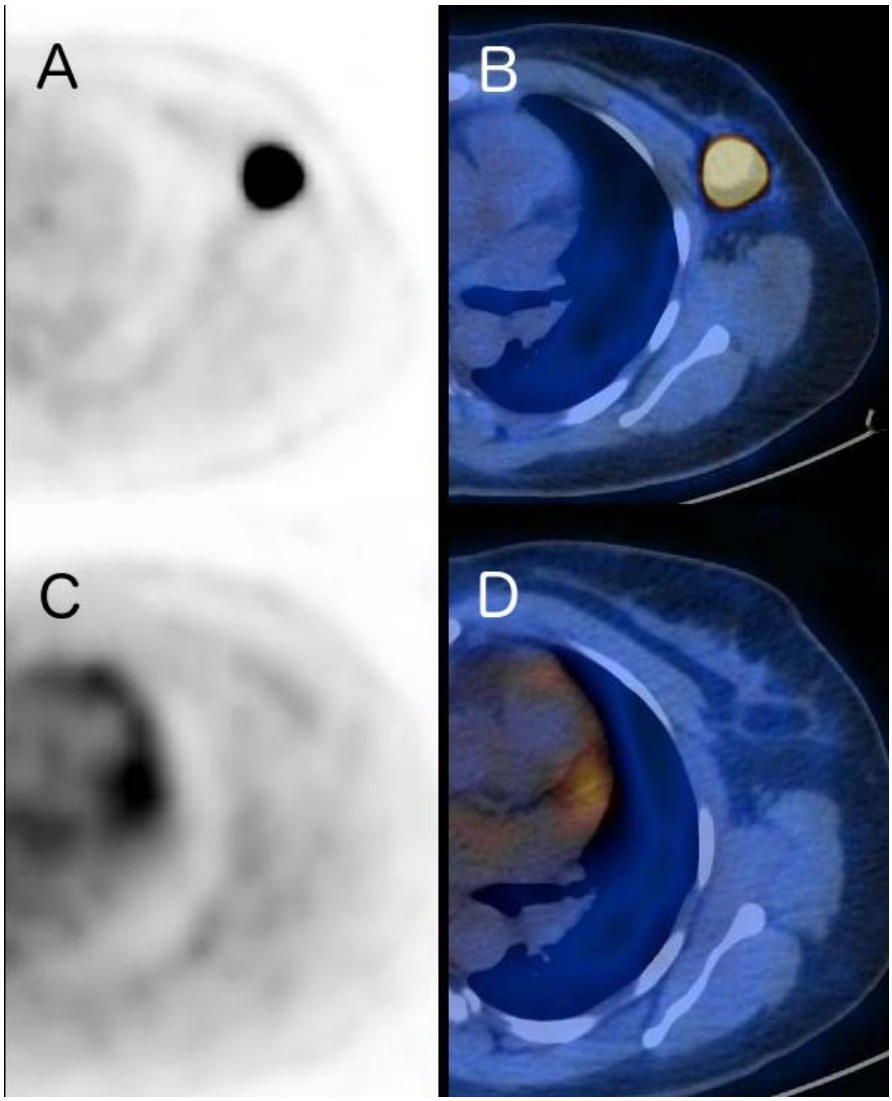

Fig.1. A 44-y-old patient with TNBC of the left breast. (A and B) Transaxial PET and PET/CT fused images of primary tumor at baseline; SUV_{max} = 27.3. (C and D) Corresponding images after two cycles of SIM; tumor SUV_{max} is 1.4 (ΔSUV_{max}= -95%). At surgery (after 4 additional cycles of chemotherapy), no residual tumor was detected. No recurrence was observed more than 1 year after surgery.

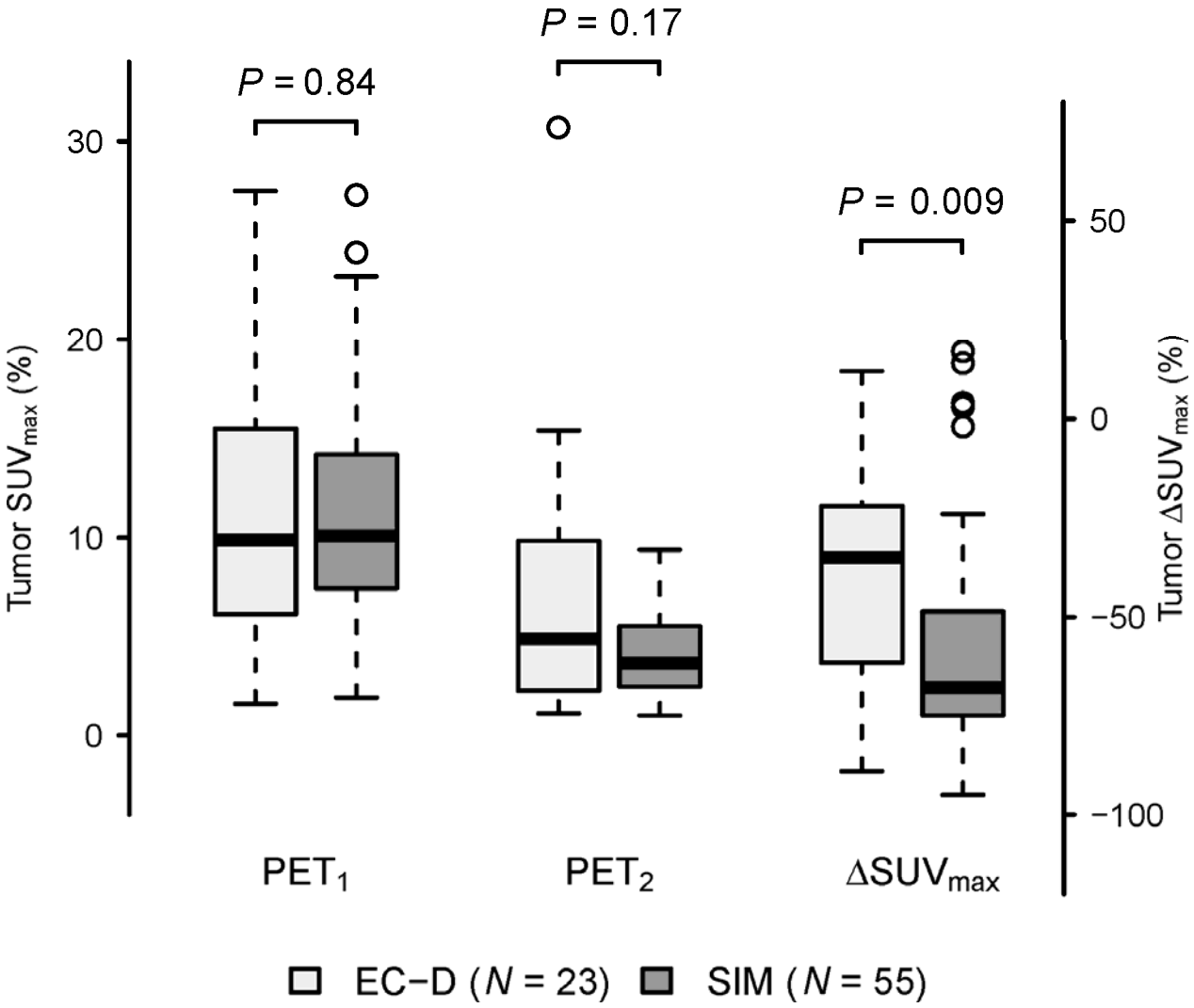

Fig.2. SUV_{max} measured in the primary tumor at baseline (PET_1), after 2 courses of chemotherapy (PET_2) and the change between the 2 PET/CT scans (ΔSUV_{max}) in two groups with different chemotherapy regimen.

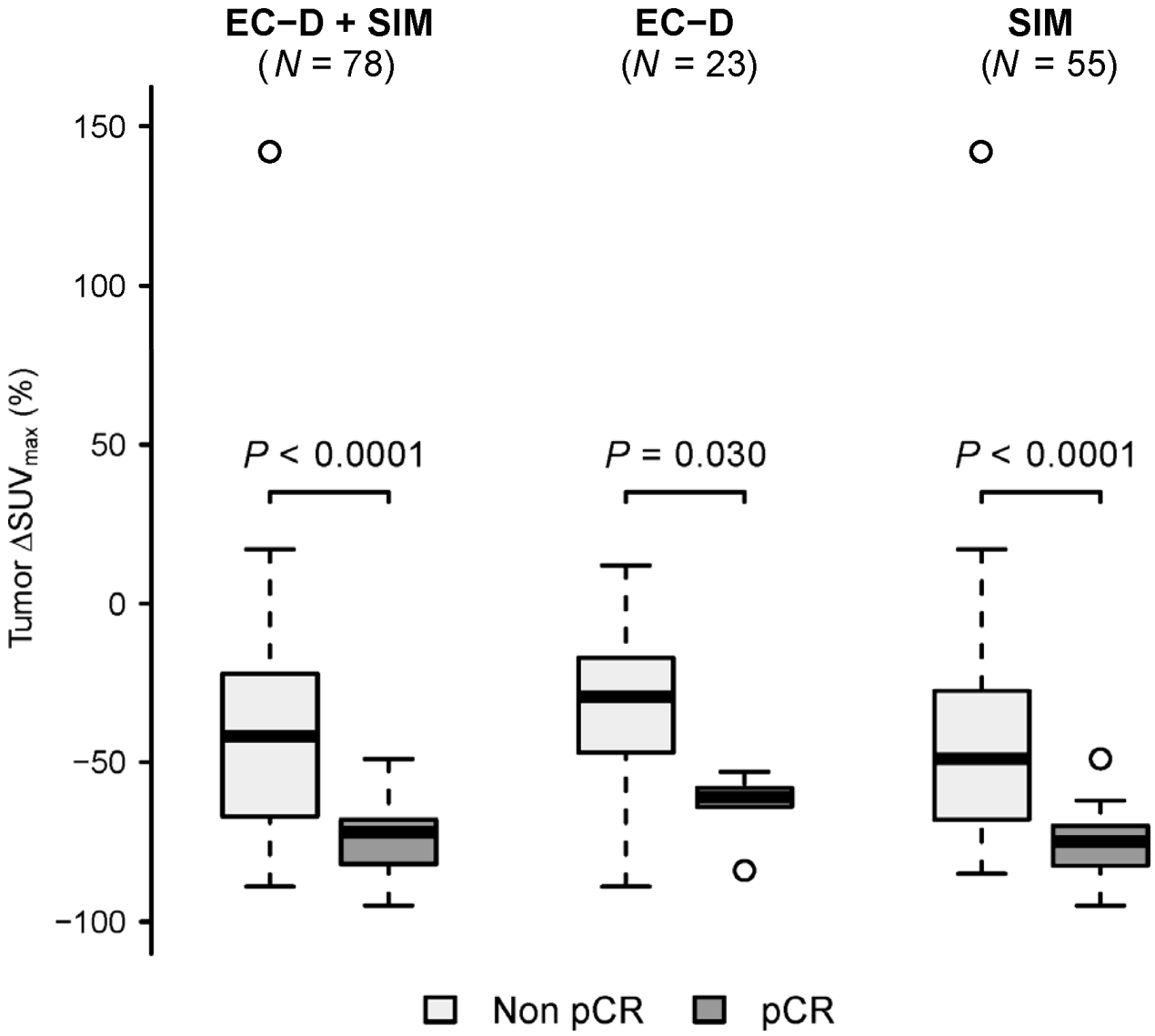

Fig.3. Tumor ΔSUV_{max} according to pathological response after neoadjuvant chemotherapy (pCR *vs.* non-pCR), in the whole population, in the group treated with conventional dose chemotherapy (EC-D) and in the group treated with dose-dense and dose-intensified chemotherapy (SIM).

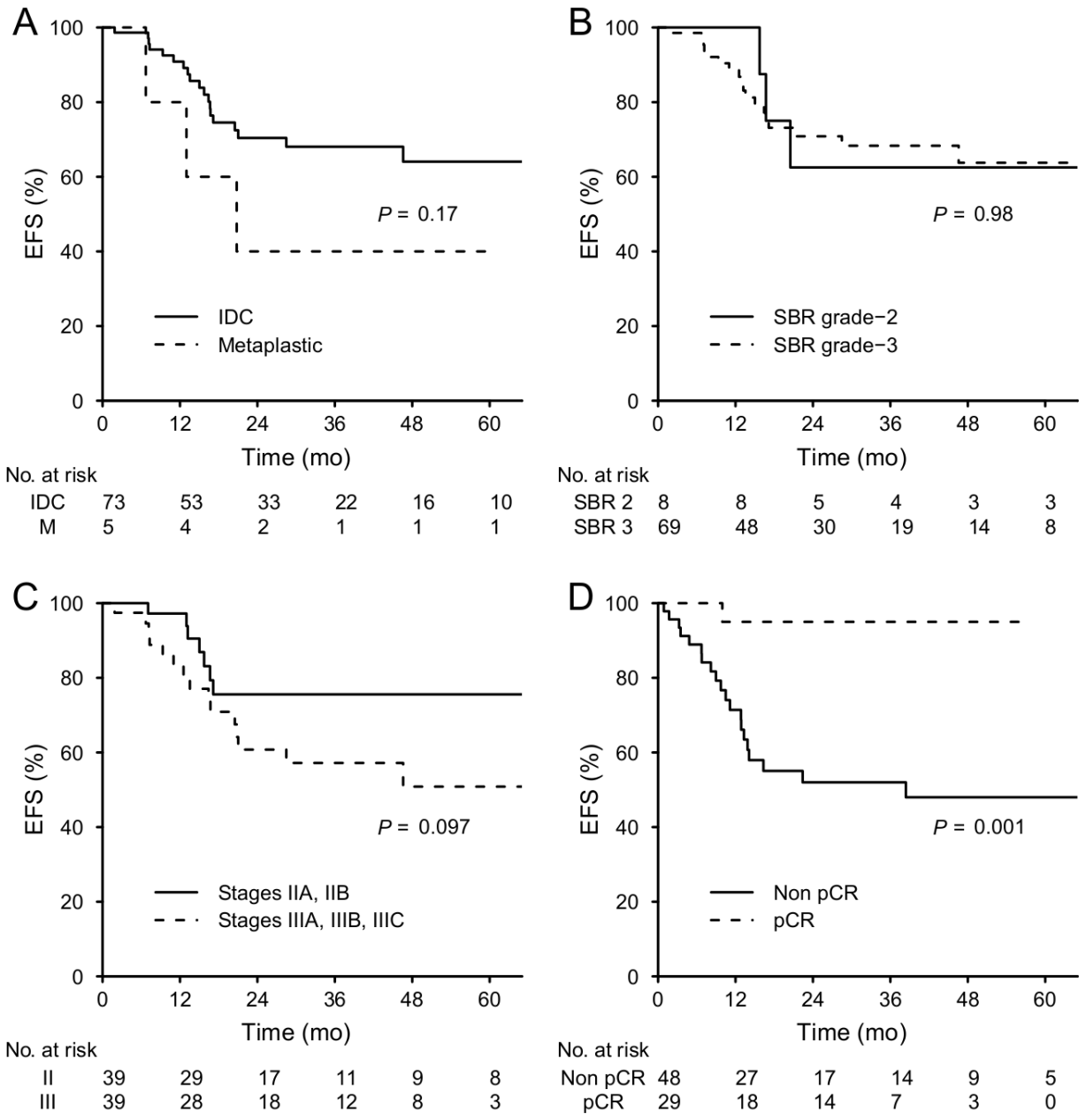

Fig.4. Kaplan-Meier curves of event-free survival (EFS) in 78 patients according to tumor histology (A), SBR-grade (B), AJCC stage (C) and pathology findings after neoadjuvant chemotherapy (D).

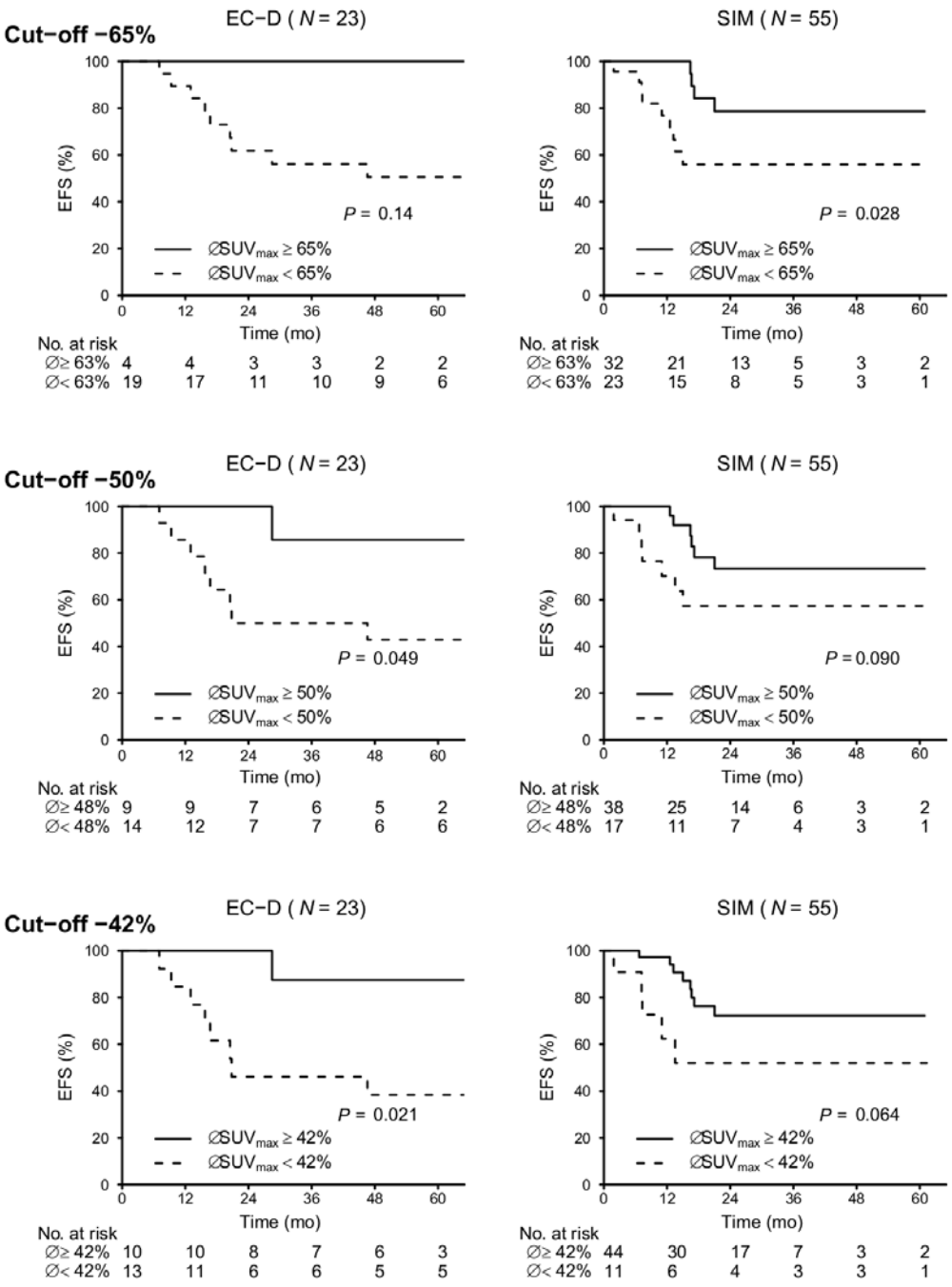

Fig.5. Kaplan-Meier curves of event-free survival (EFS) according to the metabolic response after 2 courses of neoadjuvant chemotherapy. Analysis performed with 3 different cut-off values of tumor ΔSUV_{max} in patients treated with EC-D and in those treated with SIM.

Variables	Whole population N (%)	EC-D group N (%)	SIM group N (%)	*P*
N Patients	78 (100)	23 (29)	55 (71)	
Age (years) median [min; max]	51 [27; 78]	55 [38; 78]	49 [27; 71]	0.21
Tumor Size(mm) median [min; max]	50 [18; 170]	50 [22; 160]	45 [18; 170]	0.46
Histology				0.15
IDC	73 (94)	20 (87)	53 (96)	
Metaplastic	5 (6)	3 (13)	2 (4)	
SBR Grade				**0.039**
2	8 (10)	5 (23)	3 (5)	
3	69 (90)	17 (77)	52 (95)	
Tumor Classification ∗				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 nodes Classification ∗				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 ∗				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				0.62
BCS	34 (44)	9 (39)	25 (46)	
Mastectomy	43 (56)	14 (61)	29 (54)	
Pathological Response				0.078
Non-pCR	49 (63)	18 (78)	31 (56)	
pCR	29 (37)	5 (22)	24 (44)	

Table 1. Patients and Tumor characteristics in the whole population and in patients treated with EC-D and in those treated with SIM

* Clinical classification before ^{18}FDG-PET/CT scan according to the seventh edition of the AJCC Staging Manual.
BCS: Breast Conserving surgery
Bold numerals correspond to statistically significant *P* values

Variables		Non-pCR (%)	pCR (%)	*P* value
N patients (%)		49 (63)	29 (37)	
Age (years) median [min; max]		50 [27 ; 78]	51 [33 ; 70]	0.78
Tumor Size (mm) median [min; max]		50 [18-160]	40 [21; 170]	0.16
Histology				0.15
CCI		44 (90)	29 (100)	
Metaplastic		5 (10)	0 (0)	
Grade				**0.022**
2		8 (17)	0 (0)	
3		40 (83)	29 (100)	
T-score				**0.003**
T1		1 (2)	0 (0)	
T2		17 (35)	19 (66)	
T3		20 (41)	2 (7)	
T4		11 (22)	8 (28)	
N-score				**0.019**
N0		19 (39)	13 (45)	
N1		13 (27)	14 (48)	
N2		14 (29)	1 (3)	
N3		3 (6)	1 (3)	
Stage				**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)	
PET parameters median [min; max]				
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**
SUV_{max} 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**
ΔSUV_{max}	Tumor	-42 [-89 ; 142]	-72 [-95 ; -49]	**<0.0001**
	Axilla (n=58)	-53[-90 ; 0]	-74 [-94 ; 0]	0.21
	Target	-48 [-90 ; 17]	-74 [-95 ; -49]	**<0.0001**

Table 2. Clinical, histological, immunohistochemical factors and PET parameters according to pathological response (pCR *vs* non-pCR)

Numbers in brackets are ranges

PET Parameters		AUC	CI (95%)
SUV_{max} 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)
SUV_{max} 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)
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)

Table 3. Performances of PET parameters to predict pCR early in the whole population of 78 TNBC patients

AUC: Area under the curve of ROC analysis

CI: Confidence interval

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

**Logistic regression analysis combining tumor and axilla measurements

Variables		EC-D group (N = 23)	SIM group (N = 55)	P
Time between PET_1 and PET_2 (weeks)		8 [6 ; 14]	6 [4 ; 12]	<0.0001
Time between PET_1 and surgery (weeks)		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
^{18}FDG injected 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
Patients glycaemia (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

Table 4. Comparison of Preparation procedures, some patient's characteristics and instrumental factors between the 23 patients treated with EC-D and the 55 treated with SIM

Numbers in brackets are ranges

cut-off (%)	EC-D (n=23)							SIM (n=55)						
	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

Table 5. Performance of tumor ΔSUV_{max} with various cut-offs to predict residual disease (non-pCR): analysis in patients treated with EC-D and in patients treated with SIM

R = Metabolic Responders (percentage of patients with ΔSUVmax ≥ cut-off value); NR = Metabolic Non-Responders; Acc = Accuracy; Se= Sensitivity; Sp=Specificity; PPV=Positive Predictive Value; NPV=Negative Predictive Value