Estrogen receptor-positive/human epidermal growth factor receptor 2-negative breast tumors: Early prediction of chemosensitivity with (18) F-fluorodeoxyglucose positron emission tomography/computed tomography during neoadjuvant chemotherapy.

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TITLE PAGE

Estrogen receptor-positive/HER2-negative breast tumors: Early prediction of chemosensitivity with ^{18}F-FDG PET/CT during neoadjuvant chemotherapy

Running title: FDG-PET/CT for luminal breast cancer

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Condensed abstract:

When they respond to neoadjuvant chemotherapy, the majority of estrogen receptor-positive/human epidermal growth factor receptor 2-negative breast tumors, exhibit partial tumor shrinkage, and PET parameters combining volume and activity measurement, such as total lesion glycolysis (TLG), seem to be more adapted to early prediction than SUV_{max} measurements. Progesterone receptor-negativity and luminal B status are also associated with response, but have a weaker predictive power than TLG.

Abstract:

Background: This prospective study aimed at evaluating the ability of ^{18}F-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (^{18}F-FDG PET/CT) to predict chemosensitivity in estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER+/HER2-) breast cancer.

Methods: 64 consecutive patients underwent ^{18}F-FDG PET/CT scans at baseline and after the second course of neoadjuvant chemotherapy (NAC). The evolution (Δ) between the two scans of image parameters (SUVmax, SUVmean, metabolic tumor volume, and total lesion glycolysis "TLG") was measured. Correlations between early changes of PET-derived parameters and pathological response found on surgical specimens at completion of 8 courses of NAC were estimated with Mann-Whitney-U tests. Response prediction on the basis of clinical data, histological type, or molecular markers was also assessed (Fisher's exact test). Receiver operating characteristic (ROC) analysis was used to compare area under the curves (AUC) of the various parameters.

Results: Best prediction of chemosensitivity was obtained with ΔTLG (-49±31% in Non-responders *vs.* -73±25% in Responders; p<0.0001). Among biological parameters, only progesterone receptor negativity (57% were responders *vs.* 31%, p=0.04) and luminal B subtype (63% were responders *vs.* 22%, p=0.02) were predictive of pathological response. ROC analysis resulted in AUCs of 0.81, 0.73, 0.71 and 0.63, respectively for ΔTLG, ΔSUV_{max}, luminal subtype, and progesterone receptor status.

Conclusions: When they respond to neoadjuvant chemotherapy, the majority of ER+/HER2- tumors exhibit partial tumor shrinkage and PET parameters that combine volume and activity measurement, such as TLG, offer better accuracy for early prediction than SUV_{max}. Progesterone receptor-negativity and luminal B status have weaker predictive power than PET-derived parameters.

Keywords: ^{18}F-FDG PET/CT, SUVmax, Total lesion glycolysis, ER+/HER2- breast cancer, luminal tumor, neoadjuvant chemotherapy, metabolic response, pathological response, chemosensitivity.

Neoadjuvant chemotherapy (NAC) is commonly offered to patients with locally advanced breast cancer and to women with primary operable but large breast cancer. This strategy allows more patients to undergo breast-conserving surgery (BCS) and provides information on the efficacy of chemotherapy. Breast carcinoma is a heterogeneous class of tumors and gene-expression profiling has led to the identification of five different subtypes with clinical implications (i.e., luminal A, luminal B, basal-like, HER2-like and normal-like subtypes) (1). To some degree, these molecular subtypes can be distinguished using immunohistochemistry (IHC) (2). Estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER+/HER2-) breast cancer regroups the majority of luminal A and B tumors. This important group is characterized by potential hormonosensitivity and relatively good prognosis, mainly for luminal A subtype (3). Chemosensitivity of ER+/HER2- tumors is variable and mostly limited (3-8). Therefore, factors which could help in predicting chemosensitivity are required.

Early change in ^{18}F-FDG (^{18}F-fluorodeoxyglucose) uptake, as measured on PET/CT (Positron Emission Tomography/Computed Tomography), is a potential predictive biomarker of response to NAC (8-12). However, at baseline, as demonstrated in recent studies, ER-positive tumors are usually characterized by rather low standardized uptake values (SUV) because of lower ^{18}F-FDG uptake compared to other breast cancer phenotypes (8,10,11,13). Because of this limitation, and because of incomplete regression when ER+/HER2- tumors are treated by NAC, PET parameters taking into account volume measurements could be of interest in this specific subgroup. The value of some PET-derived parameters as biomarkers, such as metabolically active tumor volume (MATV), and total lesion glycolysis (TLG), which takes into account MATV and tumor SUV_{mean}, is being actively investigated in several malignancies (14-16). Given the potential of these new biomarkers, their role in breast cancer deserves investigation.

The main objective of this prospective study was to investigate the value of several PET parameters (SUV_{mean}, SUV_{max}, MATV and TLG) for early tumor response prediction after two cycles of NAC in ER+/HER2- breast cancer. The second objective was to compare PET performances to several previously established molecular markers such as histological type, tumor grade, progesterone receptor (PR) expression and luminal subtype (3,17).

MATERIALS AND METHODS

Patients' inclusion and treatment

This prospective study was designed to evaluate the ability of ^{18}F-FDG PET/CT to predict chemosensitivity in ER+/HER2- breast cancer. From July 2007 to October 2011 (52 months), 64 consecutive patients with a large or locally advanced breast carcinoma and an ER+/HER2- phenotype underwent an ^{18}F-FDG PET/CT scan before treatment (PET_1) and just before the third course of chemotherapy (PET_2). NAC is routinely used in our institution for large/locally advanced breast carcinoma, even for luminal A tumors. Patients received 4 cycles of epirubicin 75mg/m² plus cyclophosphamide 750mg/m² (EC) administered every 3 weeks, followed by 4 courses of docetaxel 100mg/m² (D). After completion of NAC, all patients underwent BCS or mastectomy and axillary dissection. The study followed the guidelines of the institutional ethical committee.

Histology, immunohistochemistry and molecular biology

Tumor histology and biological parameters were evaluated on the core needle biopsy before NAC. Histological grade was determined using the modified Scarff-Bloom-Richardson (SBR) system (18).

IHC was performed on formalin fixed, paraffin-embedded tissues. All immunostainings were performed on an automated immunostainer (Ventana XT; Tucson, AZ, USA). Tumors

showing at least 10% of positive cells using estrogen receptor (ER) antibody were considered ER+ (19). Tumors showing at least 10% of positive cells using progesterone receptor (PR) antibody were considered PR+ (19). Tumors were considered to overexpress c-erbB-2 oncoprotein (HER2+) if more than 30% of invasive tumor cells showed definite membrane staining resulting in a so-called fishnet appearance (20); control by FISH or SISH was performed for ambiguous cases. Ki67 was quantified by IHC with MIB-1. Ki67 < 14% was considered as low and associated with luminal A subtype (21).

Luminal A & B subclassification is a molecular classification based on transcriptome analysis. To some extent, however, ER-positive tumors, can be segregated into "luminal A" and "luminal B" on the basis of PR expression, Ki67 expression, and tumor grade (21,22). This is convenient for the prediction of responsiveness to hormone therapy (Luminal A > Luminal B) and to chemotherapy (Luminal B > Luminal A). We considered as Luminal A, tumors with ER+ and PR+ expression, and low Ki67 and/or low grade; all other tumors were classified as Luminal B. Note that the molecular definition of luminal B also extends to some patients with ER+ and HER2-overexpressing tumors (23) that were not included in the present study.

^{18}F-FDG PET/CT Imaging

Patients fasted for 6 hours. Blood glucose level had to be <7mmol/L. ^{18}F-FDG (5MBq/kg) was administered into the arm opposite to the breast tumor using a venous line to prevent extravasations. Imaging started 60 minutes after injection on a Philips Gemini XL PET/CT scanner. CT data was acquired first (120kV; 100mAs; no contrast-enhancement). PET 3D data was acquired with 2min per bed position, and reconstructed using a 3D row-action maximum likelihood algorithm (RAMLA). SUV was defined as: [tracer concentration (kBq/mL)] / [injected activity (kBq)/patient body weight (g)].

Image analysis

Pathological response was unknown by the team who measured PET parameters. For each image, the tumor was identified by a nuclear physician with more than 10 years experience and semi-automatically isolated in a volume of interest (VOI) containing the tumor and its surrounding background. Tumors were subsequently delineated using the Fuzzy Locally Adaptive Bayesian (FLAB) algorithm (24) applied to the previously defined VOI.

Metabolically active tumor volume (MATV) is the functional tumor volume that can be seen and delineated on the PET image and is different from morphological tumor volume measured by anatomical/morphological imaging (US, CT, or MRI) (25). It is determined by the number of voxels with ^{18}F-FDG uptake (reflecting viable tumor cells) significantly higher than that of background healthy tissues. In order to decide which voxels were included to this MATV, we used an automatic image segmentation algorithm (FLAB) that is not based on the use of thresholding but takes into account through iterative estimation the following parameters: statistical noise distributions in the image, partial volume effects specific to PET imaging and spatial correlation between voxels. This method has been previously validated against both simulated and clinical images for accuracy and robustness (24,26).

SUV_{max}, SUV_{mean}, MATV and TLG were automatically calculated from the tumor delineations. SUV_{max} was defined as maximum SUV value within the MATV. MATV was defined as the sum of all voxels (64mm^3 each) included in the delineation. TLG was determined by multiplying the MATV and its associated SUV_{mean}. The percentage evolution of each parameter between baseline and after the second NAC cycle (Δ_{param}) was calculated as: $\Delta_{param} = (param\_PET_2 - param\_PET_1)/param\_PET1 \times 100$.

Response assessment with PET is known to be difficult when the baseline ^{18}F-FDG tumor uptake is low (10). We therefore performed the analysis on the entire group of 64 patients and on those with initial SUV_{max} >3 (59 patients).

Pathological response

Histopathological response was assessed on surgical specimens at completion of NAC. Response was graded according to the Sataloff scale in primary tumor (T) and nodes (N) (27): TA: total or near-total therapeutic effect, TB: >50% therapeutic effect but less than total or near-total effect, TC: <50% therapeutic effect, TD: no therapeutic effect, NA : evidence of therapeutic effect and no residual disease, NB : no node metastases or therapeutic effect, NC : evidence of a therapeutic effect but metastasis still present, ND : metastasis still present and viable, no therapeutic effect. For the purpose of the present study, patients with TA-B and NA-B-C were considered as Responders (complete or partial response) and patients with TC-D and/or ND as Non-responders (27).

The percentage of pCR was also measured; pCR was defined as no residual invasive cancer, both in breast tissues and lymph nodes (28).

Statistical analysis

Statistical analyses were performed using Medcalc^{TM} (MedCalc Software, Belgium). Sample size was calculated for assessing the efficacy of PET derived parameters to predict response with an AUC of about 0.85 being significantly different from the null hypothesis value of 0.5 (meaning no discriminating power), with type-I and II errors levels of 0.05, leading to a required size of 31 patients per group (29), assuming a rate of pathological response (total+partial) of 50% based on previously published data (9).

For each PET parameter, the correlation between the response and the absolute values at baseline, after the second cycle, as well as the evolution (Δ) between baseline and second cycle, was carried out with a Mann-Whitney U test. The predictive performance regarding the identification of Non-responders was evaluated using receiver operating characteristic (ROC) analysis. Optimal cut-off values were determined based on the highest Youden index (30).

Some molecular markers are known to be somewhat predictive of response to chemotherapy in ER+/HER2- tumors. It has been suggested that progesterone receptor positivity (3), luminal A status (3), and lobular histology type (17) would be associated with a poor response to neoadjuvant chemotherapy. Performances of clinical data, histological type and molecular markers to predict pathological Responders were assessed by univariate analysis with the Fisher's exact test.

ROC analysis was used to compare the areas under the curve (AUCs) of PET parameters and clinical and molecular markers that were significant in the univariate analysis.

All tests were two-sided and p values ≤ 0.05 were considered statistically significant.

RESULTS

Patient Characteristics

According to the protocol design, only ER+/HER2- patients were included. Main characteristics of the 64 included patients are shown in Table-1. Thirty-six tumors (56%) were progesterone receptors positive. Thirty-two tumors (50%) were luminal A. At inclusion, all patients were clinically M0. Suspicion of metastases on PET/CT was not an exclusion criterion, as far as the initially planned surgery was maintained. Although 5 patients had a weak ^{18}F-FDG uptake in the primary tumor (PET-1, $SUV_{max}<3$), no patient was excluded due to PET findings. No patient showed clinical progression during chemotherapy.

At completion of NAC, BCS was performed in 23 patients and mastectomy in 41 patients. There were 27 pathological Responders (42%) and 37 Non-responders (58%). Only 4 women (6%) had pCR (Table-1).

Predictive value of PET parameters

Table 2 shows ^{18}F-FDG PET parameters values at baseline (PET_1), after two cycles (PET_2) and the variation $\Delta(PET_1, PET_2)$. SUV_{max} values ranged between 2.1 and 15.8 (median=6.4) at PET_1 and between 1.1 and 13.6 (median=3.8) at PET_2. SUV_{max} decreased after 2 cycles in 59/64 patients, was unchanged in two patients, and showed a slight non-meaningful increase (+2.0% to +6.2%) in three patients.

No correlation was found between histopathological response and SUV_{max} values at baseline (p=0.8); a weak correlation was observed with SUV_{max} values after the second cycle of chemotherapy (p=0.05). Variation of SUV_{max} between PET_1 and PET_2 was more predictive (Table 2): the median ΔSUV_{max} was -31±20% in Non-responders *vs.* -48±18% in pathological Responders (p=0.002). Optimal ΔSUV_{max} cut-off value was -38% (Fig. 1a), with sensitivity of 62.2% and specificity of 77.8% in identifying Non-responders. The ability of ΔSUV_{max} to predict response was assessed with an AUC of 0.73 whereas a lower predictive value (0.67) was observed for ΔSUV_{mean}.

On the one hand, no correlation was found between pathological response and TLG values measured at PET_1 (p=0.9), and PET_2 (p=0.07) (Table 2). On the other hand, we observed a strong correlation between ΔTLG and pathological response. Median ΔTLG was -49±31% in Non-responders *vs.* -73±25% in Responders (p<0.0001). The optimal ΔTLG cut-off was -71% (Fig. 1b), with sensitivity of 89.2% and specificity of 74.1% in identifying Non-responders. The AUC of TLG for predicting pathology outcome was 0.81 as compared to 0.73 for ΔSUV_{max} (p=0.097) (Fig. 2a).

When excluding the 5 patients with initial SUV_{max}<3 (n=59), performances of ΔTLG and ΔSUV_{max} both improved, with a superiority of ΔTLG (AUC for ΔTLG=0.84 *vs*. ΔSUV_{max} 0.77; p=0.038) (Fig. 2b).

Predictive value of clinical, pathological and molecular parameters

We found no association between clinical findings (patient age, menopausal status, T-stage, N-stage) and response (Table 3). Pathological response was more frequent in grade 3 tumors than in lower grade tumors (62.5% *vs.* 34.8%), and in invasive ductal carcinoma than in invasive lobular carcinoma (47.3% *vs.* 20%), without reaching statistical significance, but the number of women with ILC was limited (n=5). Only progesterone receptor status and molecular subtypes were found to significantly predict response. The overall pathological response rate (total + partial) was significantly higher in luminal B (62.5%; 20/32) than in luminal A subgroup (21.9%; 7/32) (p=0.02). Response was also more frequent in PR-negative tumors than in PR-positive tumors (p=0.04).

Comparison of predictive value of PET parameters and molecular markers

In the 64 patients, ROC analysis led to AUCs of 0.81, 0.73, 0.71 and 0.63 for TLG, SUV_{max}, luminal subtype and progesterone receptor status (Fig. 3a). ΔTLG was significantly more predictive than the progesterone receptor status (p=0.02), and the difference was not significant between ΔTLG, ΔSUV_{max} and the luminal subtype.

Interestingly, subgroup analysis showed that ΔTLG was still of value when considering the more responsive subtypes (progesterone-negative and luminal B). ΔTLG, ΔSUV_{max} and luminal B status provided AUCs of 0.90, 0.82 and 0.58 in distinguishing the 16 responding from the 12 Non-responders progesterone-negative patients (Fig. 3b); ΔTLG was significantly more predictive than the luminal B status (p=0.0001). For the 32 patients with a luminal B

tumor (Fig. 3c), ΔTLG was significantly more predictive than the progesterone receptor status (AUC=0.85 *vs.* 0.52, p=0.0064). ΔSUV_{max} had an intermediate predictive power (AUC=0.75). The PET parameters were less predictive in the lower response rate subgroups: progesterone-positive (AUCs of 0.69 and 0.64, respectively for ΔTLG and ΔSUV_{max}) and luminal A (AUCs of 0.76 and 0.74, respectively for ΔTLG and ΔSUV_{max}).

DISCUSSION

Chemosensitivity of ER+/HER2- tumors is variable and mostly limited; pCR is rarely achieved (3–8). In a study about the role of ^{18}F-FDG PET to predict complete response to NAC, that involved different breast cancer subtypes, only one patient out of 53 with ER+/HER2- cancer achieved pCR (8). Thus, the authors could not evaluate the role of ^{18}F-FDG PET in this subgroup (8). In our study, 4 women (6%) achieved pCR after 8 courses of NAC. In ER+/HER2- tumor, especially for luminal A, the impact of pCR on patient's survival remains less established than in triple-negative (ER-/PR-/No HER2-overexpression) and in HER2+ tumor groups (6,31); an intermediate response with tumor shrinkage allowing BCS might be considered as a reasonable clinical objective (11).

We investigated performances of two different PET parameters to predict response after two NAC cycles: SUV_{max}, which is a simple parameter often used to evaluate response to chemotherapy, and TLG, which corresponds to the metabolically active tumor volume multiplied by its associated SUV_{mean} (15). All patients underwent an ^{18}F-FDG PET/CT scan before treatment, then after two cycles of chemotherapy. At surgery, 27 patients (42%) showed complete or partial pathological response (Sataloff A+B), while the others were non-responders. In line with previous findings (10,12,32), relative variation of parameters between PET_1 and PET_2 was significantly more accurate in predicting response than absolute values at any time point. Best prediction was observed with ΔTLG. Although a recent study found

ΔSUV_{max} to be superior to ΔTLG (32), tumor volumes were contoured with fixed thresholding, which has been previously shown to be inappropriate (33). In addition, all cancer subtypes were mixed (ER+/HER2-, triple-negative and HER2+) and the endpoint was to predict pCR (32).

The higher predictive value of ΔTLG over ΔSUV_{max} that we observed in these ER+/HER2- tumors could have several explanations. Baseline ^{18}F-FDG uptake is weaker and the decrease in SUV during NAC is lower than for other phenotypes (8,10,13) as it was shown in one study: -45±25% and -57±30% respectively in the TN and the HER2+ subtypes vs. -19±35% in the ER+/HER2- subtype ($p<0.0001$) (8). In the present series, when taking into account modifications in volume, in addition to activity, discrimination increased. Values of ΔTLG exhibited a greater dispersion range than ΔSUV_{max} measurements (Fig. 1), which might also contribute in explaining its higher discriminative power.

We found no correlation between patient age, menopausal status, T-stage, N-stage, and response. Only two biological markers were significantly associated with response: progesterone receptor status and luminal subtype. These findings are in agreement with a report from Lips and colleagues (3). However, these markers had only weak accuracy, and the authors stated "*decision to refrain from neoadjuvant chemotherapy to ER+/HER2- breast tumors should not be based on predictive markers, but exclusively on estimates of prognosis*" (3). In the present study, biological markers were less predictive than ΔTLG (Fig. 3).

Our study has some limitations. Although we found TLG superior to SUV_{max} in this patient population, the use of TLG requires robust and accurate MATV delineation. Therefore, results from this study remain hypothesis generating, and need confirmation by larger studies. It would also be interesting to compare the predictive values of PET performed at two cycles with PET performed at an earlier time point (one cycle) (8).

Because pCR is rare in ER+/HER2- breast cancer, we chose to consider pCR as well as partial response (>50% therapeutic effect according to Sataloff scale), as also used by Rousseau and colleagues (9). We acknowledge that this definition of response is somewhat arbitrary and less meaningful than assessment of clinical outcome. However, correlation of changes in PET parameters with outcomes would have been challenging, requiring long-term follow-up, as recurrences in ER+/HER2- would often occur late, several years after surgery (34).

Our study population included both subtypes of luminal breast cancer. However, the response rate (total+partial) was higher for luminal B than for luminal A subtype (62.5% *vs.* 21.9%, p=0.02). Because patients with luminal A tumor are less likely to respond, neoadjuvant endocrine therapy could be an alternative to chemotherapy (4). Importantly, response prediction based on TLG was also more effective in the luminal B subtype (AUC= 0.85 *vs.* 0.76 for luminal A). Therefore, if chemotherapy is used only in luminal B patients, prediction based on PET may be expected to yield excellent results.

Future studies should also focus on neoadjuvant endocrine therapy, especially for luminal A breast cancer. If our study is replicated in this setting, the use of the PEPI score, which has been shown to be correlated to patient's outcome (35), should be preferred to the Sataloff scale. It will also be helpful in future studies to compare PET parameters to other factors, such as gene expression signatures (Oncotype DX) (36).

CONCLUSION

Our results suggest that PET parameters could help in predicting chemosensitivity of ER+/HER2- breast cancer early during treatment. When they respond to neoadjuvant treatment, most of these tumors exhibit partial tumor shrinkage and parameters such as TLG provide higher predictive accuracy than SUV_{max} measurements.

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	Number of Patients (%)
Mean age (range)	52 years (30-83)
Menopausal status	
Postmenopausal	22 (34)
Premenopausal	41 (64)
Perimenopausal	1 (2)
Tumor classification*	
T1	1 (2)
T2	21 (33)
T3	25 (39)
T4	17 (26)
Lymph node classification*	
N0	24 (37.5)
N1	29 (45)
N2	8 (12.5)
N3	3 (5)
Tumor Type	
Invasive ductal carcinoma	55 (86)
Invasive lobular carcinoma	5 (8)
Invasive ductal and lobular carcinoma	2 (3)
Others	2 (3)
Grade	
1	4 (6)
2	42 (66)
3	16 (25)
Unknown	2 (3)
Progesterone receptor status	
Positive	36 (56)
Negative	28 (44)
Luminal Status	
A	32 (50)
B	32 (50)
Surgery	
Breast-conserving surgery	23 (36)
Mastectomy	41 (64)
Pathological Response**	
Responders (TA-B with NA-B-C)	27 (42)
Non-responders (TC-D, ND)	37 (58)
Pathological Complete Response (pCR)	
Yes	4 (6)
No	60 (94)

Table 1. Patients' characteristics***

*UICC/AJCC version 7, and based on clinical examination and findings at breast and axilla ultrasound, and breast MRI. **According to Sataloff scale. ***All tumors are ER+/HER2-

Parameter		All patients (n=64)*	Non-responders (n=37)†	Responders (n=27)†	*P*
SUV_{max}	PET_1	6.4±3.4 (7.0, 2.1, 15.8)	6.6±3.5	5.9±3.3	0.8
	PET_2	3.8±2.6 (4.4, 1.1, 13.6)	4.1±2.9	2.8±1.9	**0.05**
	$\Delta(PET_1, PET_2)$ (%)	-40±20 (-37, -83, +6)	-31±20	-48±18	**0.002**
SUV_{mean}	PET_1	3.8±1.9 (4.1, 1.4, 10.0)	3.8±2.0	3.4±1.7	0.8
	PET_2	2.5±1.3 (2.7, 1.0, 7.9)	2.6±1.5	2.4±0.9	0.1
	$\Delta(PET_1, PET_2)$ (%)	-34±17 (-33, -78, +5)	-29±16	-38±17	**0.02**
MATV	PET_1	10.7±49.0 (21.0, 1.4, 383.4)	10.6±62.1	10.7±20.7	1.0
	PET_2	5.8±33.3 (13.9, 0.0, 254.4)	7.4±42.0	4.1±14.0	0.07
	$\Delta(PET_1, PET_2)$ (%)	-35±37 (-33, -100, +77)	-21±31	-57±37	**0.0002**
TLG	PET_1	37±399 (117, 4, 3168)	34±515	40±126	0.9
	PET_2	13±251 (60, 0, 2007)	23±327	11±35	0.07
	$\Delta(PET_1, PET_2)$ (%)	-58±32 (-54, -100, +51)	-49±31	-73±25	**<0.0001**

Table 2. ^{18}F-FDG PET Parameters values at baseline (PET_1), after two cycles (PET_2) and the variation $\Delta(PET_1, PET_2)$ (%) for all patients, as well as their correlations with pathological response groups (Mann-Whitney U tests).

* median ± standard deviation (mean, min, max). † median ± standard deviation.

	Non-responders (n=37) %	Responders (n=27) %	*P* *
Patients Age			
<50 years	50.0	50.0	0.31
>50 years	65.6	34.4	
Menopausal status			
Menopaused	63.6	36.4	0.6
Non-menopaused	56.1	43.9	
T-stage			
T1-T2	59.1	40.9	1.0
T3-T4	57.1	42.9	
N-stage			
N0	58.3	41.7	1.0
N+	57.5	42.5	
Histology type			
Ductal	52.7	47.3	0.37
Lobular	80.0	20.0	
Tumor grade			
1-2	65.2	34.8	0.078
3	37.5	62.5	
Progesterone receptor status			
Negative	42.9	57.1	**0.04**
Positive	69.4	30.6	
Molecular subtypes			
Luminal A	78.1	21.9	**0.02**
Luminal B	37.5	62.5	

Table 3. Associations between clinical, histological, molecular variables and response at completion of chemotherapy

* Fisher exact test

Figures legends

FIGURE 1. Distributions of ΔSUV_{max} values (a) and ΔTLG values (b) for Responders and Non-responders. Cut-off values providing optimal accuracy in predicting response are displayed.

FIGURE 2. ROC curves for ΔTLG and ΔSUV_{max} for early prediction of responders, (a) for all 64 patients and (b) for the 59 patients with PET_1 $SUV_{max} \geq 3$.

FIGURE 3. ROC curves for ΔTLG, ΔSUV_{max}, luminal subtype and PR expression for prediction of responders, (a) for all 64 patients, (b) for 28 patients with PR negative tumor and (c) for 32 patients with luminal B tumor.

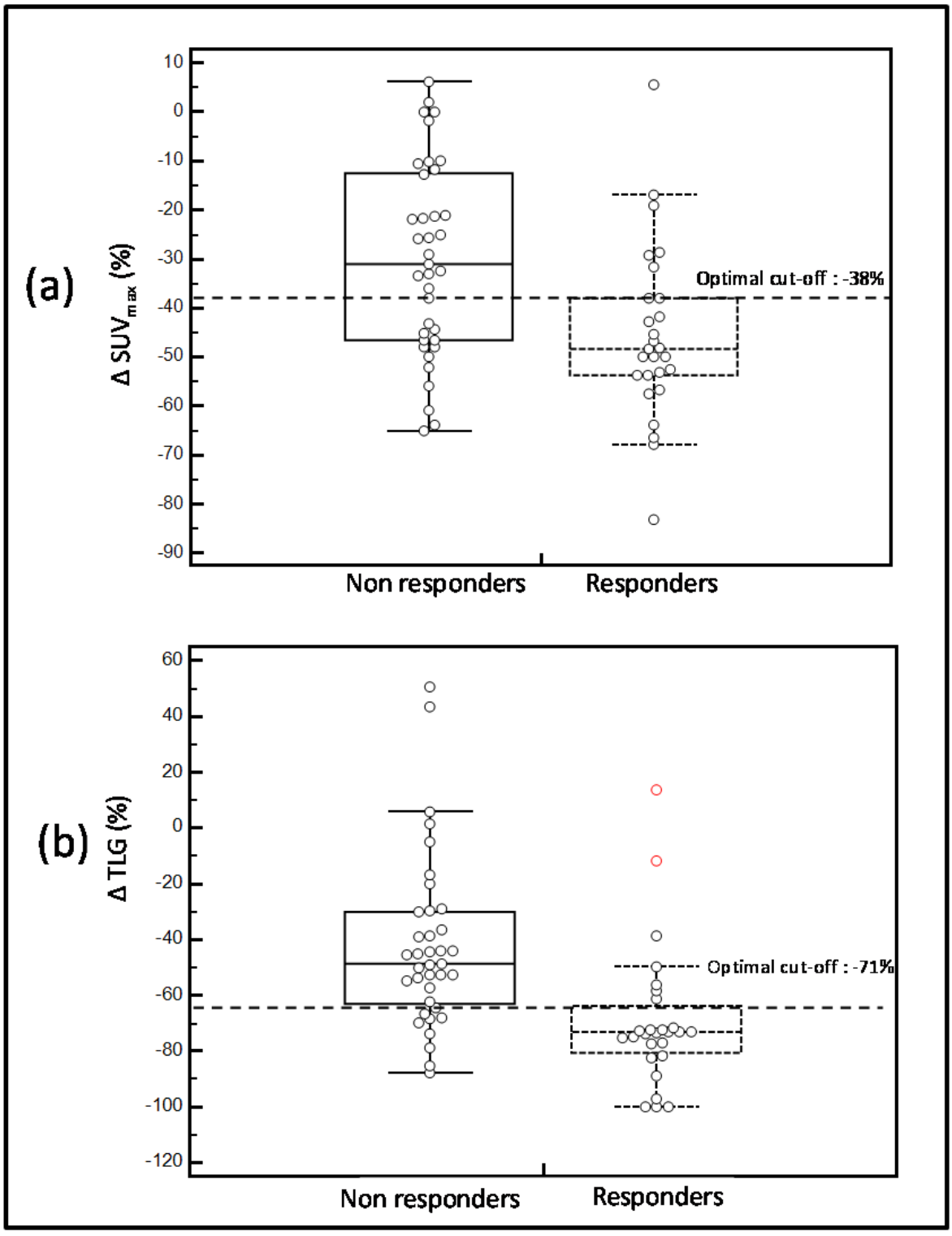
(a)
Δ SUVmax (%)
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
Optimal cut-off : -38%
Non responders
Responders
(b)
Δ TLG (%)
60
40
20
0
-20
-40
-60
-80
-100
-120
Optimal cut-off : -71%
Non responders
Responders

Figure 1

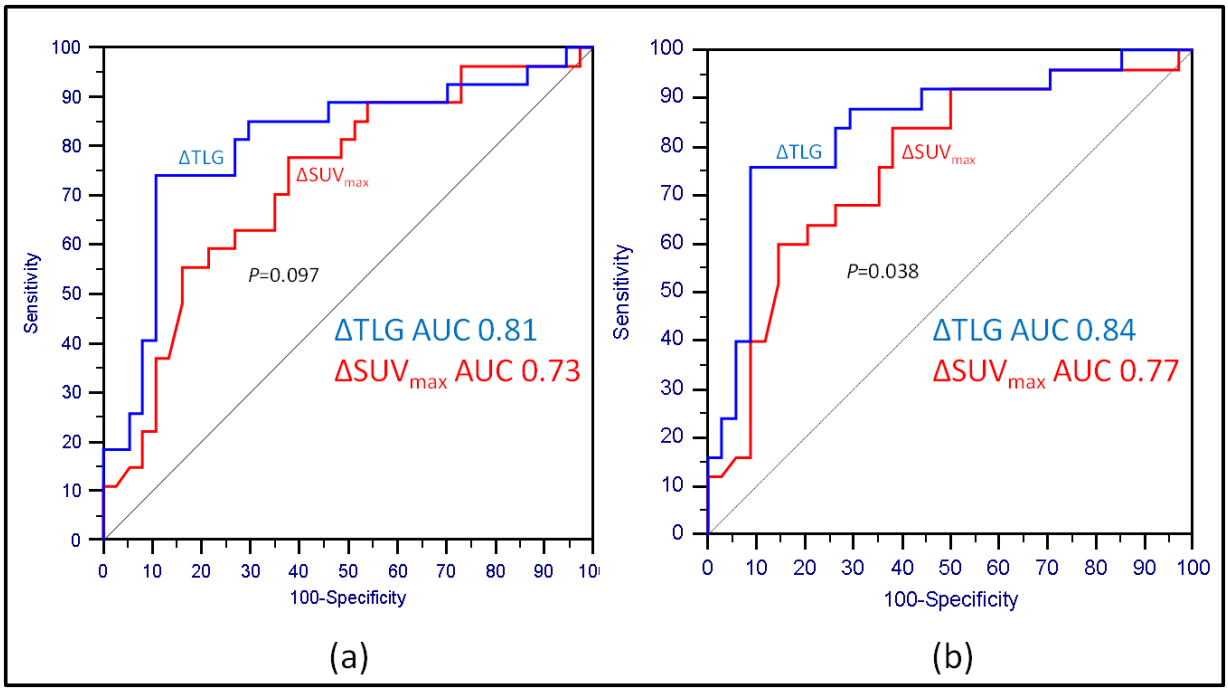

Figure 2

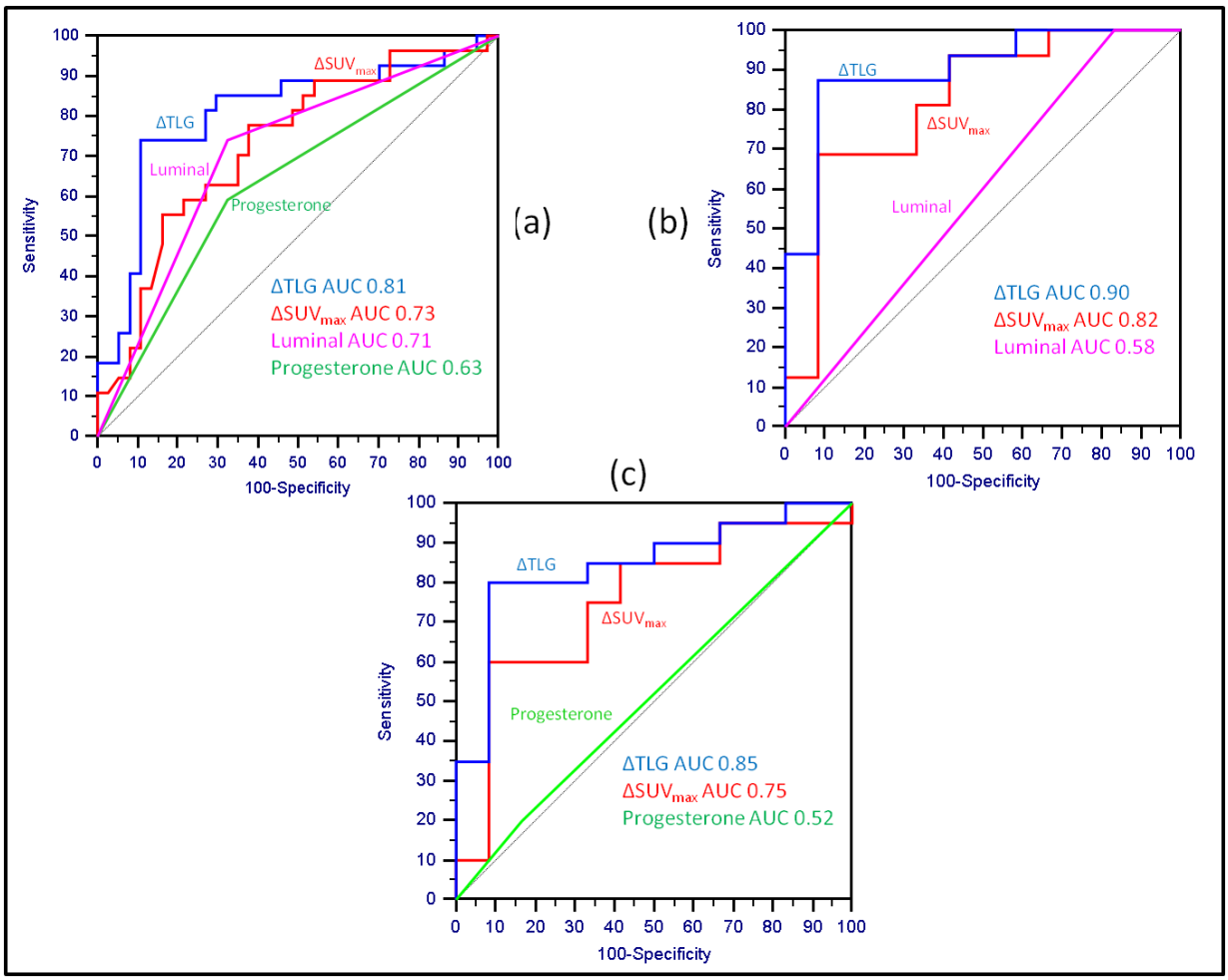

Figure 3