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Comparison between ^{18}F -FDG PET image derived indices for early prediction of response to neoadjuvant chemotherapy in breast cancer

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short running foot line: sequential ^{18}F -FDG PET for breast cancer

ABSTRACT

The goal of this study was to determine the best predictive factor among image-derived parameters extracted from sequential ^{18}F -FDG Positron Emission Tomography (PET) scans for early tumor response prediction after two cycles of neoadjuvant chemotherapy (NAC) in breast cancer.

Methods: 51 breast cancer patients were included. Responders and non-responders status were determined in histopathology according to the tumor and nodes Sataloff scale. PET indices (SUV_{max} and SUV_{mean} , metabolically active tumor volume and total lesion glycolysis (TLG)), at baseline and their evolution (Δ) after two cycles of NAC were extracted from the PET images. Their predictive value was investigated using Mann-Whitney-U tests and ROC analysis. Sub-group analysis was also carried out by considering ER-positive/HER2-negative, triple-negative, and HER2-positive tumors separately. The impact of partial volume correction (PVC) was also investigated using an iterative deconvolution algorithm.

Results: There were 24 pathological non-responders and 27 responders. None of the baseline PET parameters was correlated with response. After two NAC cycles, the reduction of each parameter was significantly associated with response, the best prediction of response being obtained with ΔTLG (96% sensitivity, 92% specificity, 94% accuracy) with significantly higher AUC (0.91 vs. 0.82, $p=0.01$) than $\Delta\text{SUV}_{\text{max}}$ (63% sensitivity, 92% specificity, 77% accuracy). Sub-group analysis confirmed a significantly higher accuracy for ΔTLG than ΔSUV for ER-positive/HER-negative, but not for triple-negative and HER2-positive tumors. PVC had no impact on the predictive value of any of the PET image derived parameters despite significant changes of their absolute values.

Conclusion: Our results suggest that the reduction after two NAC cycles of the metabolically active volume of primary tumor measurements such as Δ TLG predicts histopathological tumor response with higher accuracy than Δ SUV measurements, especially for ER-positive/HER2-negative breast cancer. These results should be confirmed in a larger group of patients as they may potentially increase the clinical value and efficiency of ^{18}F -FDG PET for early prediction of response to NAC.

Keywords: Breast cancer, Neoadjuvant chemotherapy, ^{18}F -FDG, tumor delineation, pathological response

1 **Introduction**

2 Preoperative neoadjuvant chemotherapy (NAC) has been used as standard
3 treatment for inflammatory and non-operable locally advanced breast carcinoma
4 patients and it is now increasingly being used for patients with operable but large
5 breast tumors. This strategy allows patients to undergo breast-conserving surgery
6 (BCS) and provides information regarding the efficacy of chemotherapy (1). Early
7 response prediction after one or two cycles of NAC might enable the selection of
8 alternative treatment strategies (2). Breast carcinoma is composite and
9 immunohistochemistry allows defining three main subgroups with different
10 therapeutic response and different outcome (triple negative, HER2+ and luminal
11 tumors). Pathological Complete Response (pCR) is associated with a better outcome
12 in the HER2-overexpressed and triple negative breast cancer patients. On the other
13 hand, recent studies showed than in luminal tumors, especially for luminal A, the
14 impact of pCR on patient's survival remains less established (3, 4). Thus an
15 intermediate response with tumor shrinkage allowing BCS might be considered as a
16 reasonable clinical objective for this group.

17 Within this context, ¹⁸F-FDG PET imaging has been demonstrated as a potent
18 predictive tool (5-8). Indeed, correlations between the pathological tumor response
19 after completion of NAC and the decrease of tumor standardized uptake values
20 (SUV) after one or two courses of chemotherapy have been demonstrated in several
21 studies. A recent meta-analysis (8) conducted on 19 studies including 920 patients
22 for the early prediction of primary tumor response to NAC reported a pooled
23 sensitivity of 84% and specificity of 66% in identifying responders. The authors
24 emphasized that the low pooled specificity (66%) still calls for caution.

1 Most studies have considered SUV measurements only; mostly SUV_{max} , or SUV_{peak}
2 averaging the SUV_{max} voxel with its neighboring voxels (9). On the other hand, it has
3 been demonstrated in several recent studies and for various malignancies that other
4 ^{18}F -FDG PET image derived parameters can have statistically significant higher
5 predictive value than SUV in determining tumor response (10, 11). These
6 parameters, which allow for a more comprehensive tumor functional level evaluation,
7 include metabolically active tumor volume (MATV) (11) and total lesion glycolysis
8 (TLG), defined as the product of MATV and its associated mean SUV (SUV_{mean}) (12).
9 One recent study compared SUV_{max} and TLG derived using manual delineation and
10 threshold, showing that SUV_{max} had better predictive value than TLG in identifying
11 pCR (13).

12 To the best of our knowledge, no study has investigated the predictive value,
13 regarding response to NAC for breast cancer, for all of the previously described ^{18}F -
14 FDG PET image derived parameters (SUV_{max} , SUV_{mean} , SUV_{peak} , TLG, MATV) within
15 the same study, at both the baseline and during treatment time points.

16 The current study was therefore conducted with the objective of determining the
17 predictive value of several ^{18}F -FDG PET derived parameters both at baseline and
18 after two NAC cycles.

19

20 **MATERIALS AND METHODS**

21 **Patient Population**

22 The current study consists of a retrospective analysis of a prospective cohort of 55
23 consecutive patients diagnosed with breast cancer included in a previous clinical trial
24 (14), performed in agreement with guidelines of the institutional ethical committee
25 with patients' informed consent. PET/CT image datasets of 3 patients could not be

1 retrieved from the database due to a corrupt archive file, and one was excluded from
2 the analysis due to insufficient initial uptake ($SUV_{max}=1.5$) in the primary tumor.
3 Therefore 51 patients were included in the retrospective analysis presented in this
4 work (table 1).

5 All patients underwent NAC with four cycles of epirubicin + cyclophosphamide,
6 followed by four cycles of docetaxel (+Herceptin in case of HER2+++). Patients
7 underwent ^{18}F -FDG PET/CT scans at baseline and after the second cycle of NAC.
8 From here onwards, these scans will be denoted as PET_1 and PET_2 respectively. At
9 completion of chemotherapy, all patients underwent surgery (mastectomy or
10 lumpectomy).

11

12 **^{18}F -FDG PET/CT acquisitions**

13 All ^{18}F -FDG PET/CT scans were performed at Saint Louis Hospital in Paris between
14 July 2007 and May 2009. A rigorous imaging protocol was designed to ensure robust
15 SUV measurements across both time points. Blood glucose level had to be ≤ 7
16 mmol/L. For both acquisitions, patients received an intravenous injection (in the arm
17 opposite to the breast tumor using a venous line) of ^{18}F -FDG (5 MBq/kg) after a
18 fasting period of 6 hours. Following an uptake period of 60 minutes, all acquisitions
19 were carried out from mid-thigh level to the base of the skull with the arms raised, on
20 a Philips Gemini XI PET/CT that combines a germanium oxyorthosilicate-based PET
21 scanner and a 16-slice Brilliance CT scanner. CT data were acquired first (120 kV,
22 100 mAs, no contrast enhancement). PET emission list mode data were acquired in
23 3D mode, with 2 min per bed position, and reconstructed using a 3D row-action
24 maximum-likelihood (RAMLA) algorithm with voxel size of $4 \times 4 \times 4 \text{mm}^3$. The

1 attenuation corrected images were normalized for injected dose and body weight and
2 converted into standardized uptake values (SUVs) defined as:

3 $\text{tracer concentration [kBq/mL]} / (\text{injected activity [kBq]} / \text{patient body weight [g]})$

4

5 **Tumor Histology and Immunohistochemistry Analysis**

6 Tumor type was determined on the core needle biopsy performed before
7 neoadjuvant chemotherapy. Immunohistochemical tests were performed on formalin-
8 fixed, paraffin embedded tissues, using specific antibodies and an automated
9 immunostainer (XT Immunostainer; Ventana). Tumors were considered to
10 overexpress HER2 (HER2+++) if more than 30% of invasive tumor cells showed
11 definite membrane staining resulting in a so-called fishnet appearance; control by
12 FISH (fluorescence in situ hybridization) or SISH (silver enhanced in situ
13 hybridization) was done for ambiguous cases. Tumors were considered estrogen
14 receptor (ER)–negative or progesterone receptor (PR)–negative if there was less
15 than 10% staining.

16 Three specific tumor subgroups as described previously were considered, namely
17 triple-negative, ER-positive/HER2-negative (luminal) and HER2-positive.

18

19 **Pathological Tumor Response**

20 Histopathological response was assessed on surgical specimens at completion of
21 NAC. Response was graded according to the Sataloff scale in primary tumor (T) and
22 nodes (N) (15), that was used in the frequently cited study by Rousseau et al (6) :
23 TA: total or nearly-total therapeutic effect, TB: >50% therapeutic effect but less than
24 total or nearly-total effect, TC: <50% therapeutic effect but visible effect, TD: no
25 therapeutic effect, NA: evidence of therapeutic effect and no residual disease, NB: no

1 node metastases or therapeutic effect, NC: evidence of a therapeutic effect but
2 metastasis still present, ND: metastasis still present and viable, no therapeutic effect.
3 Complete and partial responders [T(A-B) with N(A-B-C)] were considered as
4 histopathological responders, whereas patients with no response or progression
5 [T(C-D), N(D)] were considered as non-responders.

6 The pCR rate, defined as absence of invasive cancer cells in the primary tumor and
7 in lymph nodes (16) was also evaluated and the predictive power of PET parameters
8 to predict pCR was measured.

9

10 **Investigated Parameters and Analysis**

11 All PET image-derived parameters were extracted from the PET₁ and PET₂ images.
12 For each patient, the primary tumor was identified on the PET image by a nuclear
13 medicine physician with more than 10 years experience and subsequently semi-
14 automatically isolated in a 3D region of interest (ROI) containing the tumor and its
15 surrounding background. Tumors were subsequently automatically delineated using
16 the Fuzzy Locally Adaptive Bayesian (FLAB) algorithm (17) applied to the previously
17 defined ROI. The FLAB approach allows automatic tumor delineation by computing a
18 probability of belonging to a given “class” (e.g. tumor or background) for each voxel
19 within the 3D ROI. This probability is calculated by taking into account the voxel’s
20 intensity with respect to the statistical distributions (characterized by their mean and
21 variance) of the voxels in the various regions of the image, as well as its spatial
22 correlation with neighboring voxels in 3D. This approach has been previously
23 validated on simulated and clinical datasets for accuracy, robustness and
24 reproducibility, on both homogeneous and heterogeneous MATVs (17-19).

1 Potential impact of partial volume effects (PVE) was also investigated by correcting
2 the image before analysis using a state-of-the-art iterative deconvolution previously
3 validated for oncology PET imaging applications (20). The analysis was subsequently
4 carried out on both the original and PVE corrected (PVC) images.

5 SUV_{max} , SUV_{peak} and SUV_{mean} as well as the MATV and the TLG were then
6 automatically calculated from the tumor delineations. SUV_{peak} was defined as the
7 mean of voxels intensities in a 1.7 cm^3 spheric ROI (27 voxels) centered on SUV_{max}
8 (9). MATV was defined as the sum of all voxels contained in the FLAB delineated
9 volumes multiplied by the volume of a voxel (64 mm^3). SUV_{mean} was defined as the
10 mean of voxel intensities in the MATV delineated by FLAB. Subsequently, TLG was
11 determined by multiplying the MATV and its associated SUV_{mean} . The percentage
12 evolution of each parameter between baseline and after the second NAC cycle
13 ($\Delta\text{param, \%}$) was calculated as :

$$14 \Delta\text{param} = (\text{param_PET}_2 - \text{param_PET}_1) / \text{param_PET}_1 \times 100.$$

15

16 **Statistical Analysis**

17 Statistical analyses were performed using MedCalc™ (MedCalc Software, Belgium).
18 All parameters' distributions were expressed as median (or mean depending on
19 normality) \pm standard deviations (SD) and range (minimum, maximum). Normality
20 was tested using D'Agostino-Pearson test (21). For each parameter, its correlation
21 with patient response was carried out by testing the statistical difference between
22 responders' and non-responders' distributions using a Mann-Whitney U test. For
23 each parameter, their absolute values at PET_1 and PET_2 , as well as their evolution
24 $\Delta(PET_1, PET_2)$ were investigated. The predictive performance regarding the
25 identification of responders was evaluated using receiver operating characteristic

1 (ROC) analysis. Area under the curve (AUC), sensitivity, specificity, and accuracy
2 were reported. Absolute and associated predictive parameters values extracted from
3 the PVC PET images were compared to original ones. Sub-group analysis was also
4 carried out by considering triple-negative, HER2-positive, and ER-positive/HER2-
5 negative tumors separately. All tests were two-sided and p values ≤ 0.05 were
6 considered statistically significant.

7 **RESULTS**

8 ER, PR and HER2 receptors status are provided in table 1. 13 patients had triple
9 negative tumors, 12 had HER2-positive tumors, and 26 had ER-positive/HER2-
10 negative tumors, which is representative (22). Considering the pathological tumor
11 response established at surgery (after completion of chemotherapy), there were 27
12 pathological responders (53%) and 24 non-responders (47%). pCR was found in 7
13 patients (13.7%), among which, 3 had triple negative, and 4 had HER2-
14 overexpressing tumors, and 0 were ER-positive/HER2-negative. Figure 1 illustrates
15 for a pathological non-responder and a responder the two scans, including the
16 delineation of the primary tumor.

17

18 **Predictive Value of Parameters' Absolute Values**

19 According to the D'Agostino-Pearson test, considering the entire patient cohort
20 ($n=51$), none of the parameters' absolute values at baseline and after the second
21 cycle or associated variation (Δ) were normally distributed (table 2). Similarly, the
22 distribution of responders and non-responders groups were not normally distributed
23 (figure 2), except for the variation (Δ) values (figure 3).

24 According to Mann-Whitney-U tests, no significant correlation ($p>0.1$) was observed
25 between the baseline values and histopathological response (table 2), distributions of

1 the parameters among responders and non-responders being largely overlapped
2 (figure 2A), leading to low AUC of 0.52-0.63 (table 3).

3 Primary tumors of non-responders were characterized by higher PET₂ SUV_{max}
4 (5.3±6.2 vs. 2.8±2.9, $p=0.04$) and TLG (30±160 vs. 14±13, $p=0.05$). However, no
5 correlation ($p\geq 0.07$) was found for all of the other parameters considered (table 2).

6 For all parameters, the distributions were largely overlapped (figure 2A-C), as the
7 results of ROC analysis demonstrate, with low AUC of 0.62-0.67 (table 3). For SUV,
8 sensitivity (57-69%) and specificity (71-75%) were limited. On the other hand, for
9 volume-based measurements, sensitivity was higher (89% and 78% for MATV and
10 TLG respectively) but specificity was lower (42% and 63% for MATV and TLG
11 respectively).

12

13 **Evolution of Parameters and Associated Predictive Value**

14 There was a global trend of decreasing MATV and associated tumors' uptake after
15 the first two NAC cycles, although for some patients PET image derived parameters
16 were also found to be increasing (table 2). The lowest and largest decrease were
17 observed for $\Delta\text{SUV}_{\text{max}}$ (-34%±32%) and ΔTLG (-59%±34%) respectively.

18 According to Mann-Whitney-U tests, the variation (Δ) of all parameters was
19 statistically different between responders and non-responders, especially for ΔMATV
20 and ΔTLG ($p<0.0001$), as well as $\Delta\text{SUV}_{\text{max}}$ ($p=0.0001$) (table 2).

21 According to ROC analysis, the best prediction was achieved using the ΔTLG , with a
22 sensitivity of 96% and specificity of 92% resulting in an accuracy of 94% (table 3).

23 The ΔMATV was also an accurate predictive factor (sensitivity 93%, specificity 88%,
24 accuracy 91%). On the other hand, ΔSUV measurements led to significantly lower
25 AUCs (0.68 for $\Delta\text{SUV}_{\text{mean}}$ to 0.82 for $\Delta\text{SUV}_{\text{max}}$ vs. 0.91 and 0.92 for ΔMATV and

1 Δ TLG, $p \leq 0.01$) (figure 4A), with significantly lower sensitivity (63-74%), specificity
2 (67-92%) and resulting accuracy (71-77%) (table 3). The least overlapped
3 distributions were those associated with Δ MATV and Δ TLG (figure 3). The optimal
4 cut-off values maximizing sensitivity and specificity were -48%, -42%, -30%, -42%
5 and -56% for Δ SUV_{max}, Δ SUV_{peak}, Δ SUV_{mean}, Δ MATV and Δ TLG respectively (table
6 3, figure 3).

7

8 **Tumor Subgroup Analysis**

9 When considering ER-positive/HER2-negative patients ($n=26$), all AUCs were slightly
10 higher but with the same hierarchy as for the entire cohort: Δ TLG and Δ MATV
11 resulted in AUC of 0.96 and 0.98 respectively, whereas Δ SUV measurements led to
12 AUC of 0.69, 0.84 and 0.88 for Δ SUV_{mean}, Δ SUV_{peak} and Δ SUV_{max} respectively.

13 The ROC analysis performed on the 12 HER2-positive and 13 triple-negative patients
14 resulted in non-statistically significant different AUCs for volume-based and SUVs
15 ($p > 0.05$) in both cases.

16

17 **Prediction of pCR**

18 The pCR predictive value of all parameters was reduced with respect of the
19 prediction of partial response. The hierarchy was however similar with AUCs of 0.76,
20 0.79, 0.67, 0.63 and 0.59 for Δ TLG, Δ MATV, Δ SUV_{max}, Δ SUV_{peak}, and Δ SUV_{mean}
21 respectively (figure 5A).

22

23 **Impact of Partial Volume Effects Correction**

24 The correction of partial volume effects had no significant impact on the resulting
25 variation (Δ) of neither SUV nor volume-based parameters, despite the significant

1 impact on their PET_1 and PET_2 absolute values. There were therefore no statistically
2 significant differences between the AUCs of ROC curves generated using $\Delta(\%)$
3 calculated using the original and PVC PET image derived parameters (figure 4B, 5B).
4

5 **DISCUSSION**

6 The current study is the first investigation into the predictive value of ^{18}F -FDG
7 PET derived parameters on a breast cancer cohort, including baseline three different
8 SUV measurements, MATV and TLG and their evolution (Δ). Our results are in
9 contradiction with the ones of the only other study to date comparing the
10 performance of ΔSUV_{max} and ΔTLG , that reported a higher predictive value for
11 ΔSUV_{max} (13). In this study, ΔSUV_{mean} , ΔSUV_{peak} or $\Delta MATV$ predictive values were
12 not considered. In addition, ΔTLG values were derived from tumor volumes
13 delineated through manual contouring using a fixed threshold. Such a delineation
14 approach has been previously shown to be inaccurate for PET imaging (23, 24). In
15 our study a previously validated robust and reproducible MATV segmentation
16 algorithm was used. Another difference is that results in the previously reported study
17 were reported for the prediction of pCR only, corresponding to 17% of the 142
18 patients, with a resulting cut-off ΔSUV_{max} value of 83-88%, which led to high
19 specificity (96%) but low sensitivity (67%). In our study, we considered as
20 pathological responders patients with complete or partial response in the primary
21 breast cancer and lymph nodes. According to this criterion we found that MATV and
22 TLG were more predictive than SUV. We refined a subsequent analysis considering
23 pCR only for responders and we observed also that volume parameters were
24 superior (AUC 0.76-0.79) to SUV (0.59-0.67).

1 In contrast to results in several malignancies such as locally advanced
2 esophageal cancer (11) or non-Hodgkin lymphoma (10), none of the absolute
3 baseline values (with or without PVC) was significantly associated with response.
4 The absolute values of some parameters (SUV_{max} and TLG) after the second cycle
5 (PET_2) were significantly correlated with response but had limited predictive value.
6 The most powerful predictive factors were the evolution between the baseline and
7 the second scan (Δ).

8
9 Pathological responders were associated with a significantly higher decrease
10 of the ^{18}F -FDG PET derived indices considered. Among these, the Δ TLG and
11 Δ MATV were the best predictive factors compared to Δ SUV measurements, with
12 significantly higher accuracy (91% and 94% for MATV and TLG vs. 71%, 76% and
13 77% for Δ SUV_{mean}, Δ SUV_{peak} and Δ SUV_{max} respectively). With respect to the recent
14 meta-analysis that reported an overall 84% sensitivity and 66% specificity based on
15 Δ SUV_{max} (8), our Δ SUV_{max} results demonstrated lower sensitivity (63%) but higher
16 specificity (92%), whereas Δ TLG resulted in both higher sensitivity (96%) and
17 specificity (92%). The meta-analysis also demonstrated large differences in
18 sensitivities and specificities among the various considered studies due to
19 combinations of different patient populations, response criteria (pCR and/or partial
20 response) and cut-off values. Our study is in line with previous findings that the
21 reduction (Δ) of PET indices after two cycles are good predictors of response to NAC
22 in breast cancer (8). We further demonstrated the added value of considering more
23 complete tumor characterization in ^{18}F -FDG PET images through the delineation of
24 the MATV over SUV measurements only. On the one hand, these results were
25 mostly unchanged when performing the analysis on the subgroup of ER+/HER2-

1 patients. On the other hand, the respective predictive values of ΔSUV , ΔMATV and
2 ΔTLG parameters were similar for the triple-negative and HER2-positive patients.
3 However, since this subgroup analysis included a small number of patients (13 triple-
4 negative and 12 HER2-positive), it needs to be further validated in a larger patient
5 population. Future validation studies on larger groups of patients will be focused on
6 ER-positive/HER2-negative patients since it is for this sub-group that the added value
7 of ΔMATV and ΔTLG over ΔSUV seems to be the most significant. This can be
8 explained by the fact that ER-positive/HER2-negative tumors are known to exhibit
9 lower initial FDG uptake and have therefore lower decrease margins (7, 25, 26).
10 These tumors are also known to only partially respond to NAC, requiring finer
11 characterization of their response (27, 28). Therefore, the addition of functional tumor
12 volume-based metrics logically provides improved predictive accuracy for these
13 tumors. For triple-negative and HER2-positive tumors that exhibit higher FDG uptake
14 and associated decrease margins, as well as better pCR rates, the addition of
15 volume-based metrics might not translate into significantly improved predictive value
16 over ΔSUV measurements.

17

18 Another interesting result of our study was that $\Delta\text{SUV}_{\text{mean}}$ had significantly
19 lower predictive value than $\Delta\text{SUV}_{\text{peak}}$ and $\Delta\text{SUV}_{\text{max}}$ (AUC of 0.68 vs. 0.79 and 0.82,
20 $p<0.02$). Considering the use of $\Delta\text{SUV}_{\text{peak}}$ relative to $\Delta\text{SUV}_{\text{max}}$, as proposed by the
21 PERCIST recommendations (9), in this study there were no statistically significant
22 differences between the two (AUC 0.82 vs. 0.79, $p=0.2$), despite $\Delta\text{SUV}_{\text{max}}$ leading to
23 slightly better results than $\Delta\text{SUV}_{\text{peak}}$. Both these parameters describe the highest
24 activity region of the tumor, whereas the mean value is a better representative
25 measurement of the entire tumor. A potential explanation for the lower predictive

1 value of $\Delta\text{SUV}_{\text{mean}}$ is its higher dependency on partial volume effects compared to
2 SUV_{max} and SUV_{peak} . It has however been recently shown in a group of 15 breast
3 cancer patients that PVC had limited impact on the SUV reduction (29), without
4 reporting however on the actual impact of this reduction on the overall response
5 predictive value. Another study investigated the impact of PVC on the prediction of
6 response to NAC for breast cancer using dynamic ^{18}F -FDG PET. They found that
7 PVC eliminated significant differences in % FDG uptake measurement changes for
8 non-responders (NR) versus partial responders (PR), but not for pCR versus other
9 response categories (30). In the aforementioned work PVC was performed using
10 simplistic recovery coefficients, applied only to tumors with size <3cm based on MR
11 imaging. In our study, PVC was systematically applied to all images using a
12 voxelwise iterative image deconvolution algorithm previously validated for PET
13 images (20). In this work, the use of PVC did not change either the predictive value
14 of the parameters or their evolution (Δ) or the statistical differences between groups
15 of response, despite a significant change of their absolute values. Finally, PVC did
16 not improve the predictive value of SUV_{mean} or the hierarchy of performance between
17 the three different SUV measurements, for neither the partial or pCR response
18 criteria. This lack of PVC impact is consistent with our previous findings (31, 32).

19

20 The delineation of breast cancer MATVs is challenging as they often exhibit
21 heterogeneous uptake distributions and complex shapes and/or low tumor-to-
22 background ratios, particularly in the mid-treatment scan. Therefore the use of a
23 robust algorithm is recommended. Within this context, the results presented here
24 using FLAB may be replicated using alternative approaches, such as gradient-based
25 (33) or improved fuzzy C-means (34) methods. Using less robust approaches might

1 lead to significant differences in the results concerning the value of volume derived
2 parameters (11, 13). In addition, this effect may be more important when considering
3 the temporal evolution of such parameters, as measurements have to be considered
4 with respect to the known physiological reproducibility ranges. Difference values
5 have to be larger than $\pm 30\%$ to characterize response, because of the upper and
6 lower physiological reproducibility limits associated with PET derived measurements
7 (19). Considering MATV and TLG values, these reproducibility limits were obtained
8 using the FLAB method, whereas less robust approaches (fixed and adaptive
9 threshold) lead to larger values ($\pm 50-90\%$) (19). The FLAB method also allows for
10 more repeatable measurements, with low inter- and intra-observer variability (18, 19).
11 Finally, the imaging protocol in this study was specifically designed to ensure robust
12 and reproducible tumor characterization between both time points. For most patients,
13 measured evolutions were outside the reproducibility limits. Optimal cut-off values
14 were also larger; -48% for SUV_{max} , which is in accordance to previous findings (8), $-$
15 42% and -56% for MATV and TLG respectively.

16

17 One potential limitation of this study is its retrospective nature and the
18 resulting potential bias, and the lack of reliable outcome information due to the short
19 delay between surgery and last follow-up. Another limitation is the relatively small
20 number of patients due to the previous prospective study that was limited to 55
21 patients (14), 4 of which could not be exploited in the present study. This small
22 sample is especially restrictive regarding the subgroup analyses of triple negative
23 and HER2-positive patients. The findings of this study need therefore to be validated
24 in larger patient cohorts. Another limitation is that although nodal status was
25 considered to define pathological response, only primary tumors were characterized

1 in the images to simplify the analysis. Finally, some of the patients were
2 characterized by Δ TLG and Δ MATV decreases that were close to the optimal cut-off
3 values but sufficient to avoid misclassification, whereas it was the opposite for
4 SUV_{max} (figures 3). The statistical difference between AUCs of Δ SUV_{max} and Δ TLG
5 might therefore be lower in larger prospective studies. However, it has to be
6 emphasized that values of Δ MATV and Δ TLG present a higher spread than Δ SUV
7 measurements as demonstrated in figure 3, showing their higher discriminative
8 power demonstrated by Mann-Whitney-U tests (table 2).

9 **CONCLUSION**

10 The reduction of metabolically active primary tumor volumes and associated activity
11 measurements such as Total Lesion Glycolysis after two neo-adjuvant chemotherapy
12 cycles predicts histopathological tumor response with statistically significant higher
13 accuracy (94%) than SUV_{max} (77%). The advantage of TLG over SUV_{max} was
14 particularly evident for the 26 patients in the ER-positive/HER2-negative sub-group
15 and therefore we will focus on confirming these results in a larger group of ER-
16 positive/HER2-negative patients as they may potentially increase the clinical value
17 and efficiency of ^{18}F -FDG PET for early prediction of response to NAC.

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Figure captions

Figure 1: Illustration of PET₁ (left) and PET₂ (right) for (A) a responder ($\Delta\text{SUV}_{\text{max}}$ -46%, ΔTLG -89%) and (B) a non-responder (both $\Delta\text{SUV}_{\text{max}}$ and ΔTLG -43%). The green contours represent the FLAB delineation.

Figure 2: Box-and-whisker distributions plots of (A) SUV_{max} , SUV_{peak} , SUV_{mean} , (B) MATV and (C) TLG absolute values at PET₁ and PET₂. One patient with extremely high MATV and TLG values does not appear for readability purposes.

The central box represents values from the 25 to 75 percentile. The middle line represents the median. A line extends from minimum to maximum, excluding "outliers" which are displayed as separate points.

Figure 3: Box-and-whisker distributions plots of $\Delta\text{SUV}_{\text{max}}$, $\Delta\text{SUV}_{\text{peak}}$, $\Delta\text{SUV}_{\text{mean}}$, ΔMATV and ΔTLG . Optimal cut-off values providing best accuracy in predicting response are displayed.

The central box represents values from the 25 to 75 percentile. The middle line represents the median. A line extends from minimum to maximum, excluding "outliers" which are displayed as separate points.

Figure 4: ROC curves related to the prediction of responders, for $\Delta\text{SUV}_{\text{max}}$, $\Delta\text{SUV}_{\text{peak}}$, $\Delta\text{SUV}_{\text{mean}}$, ΔMATV and ΔTLG , (A) without or (B) with partial volume effects correction.

Figure 5: ROC curves related to the prediction of pCR, for $\Delta\text{SUV}_{\text{max}}$, $\Delta\text{SUV}_{\text{peak}}$, $\Delta\text{SUV}_{\text{mean}}$, ΔMATV and ΔTLG , (A) without or (B) with partial volume effects correction.

Table 1 - Patients characteristics

	Number of Patients (%)
AJCC clinical stage*	
IIA	11 (21.5)
IIB	13 (25.5)
IIIA	12 (23.5)
IIIB	14 (27.5)
IIIC	1 (2)
Tumor Type	
Invasive ductal, no special type	45 (88)
Metaplastic	3 (6)
Lobular	3 (6)
Grade	
grade-1	4 (8)
grade-2	28 (55)
grade-3	17 (33)
Grade unknown	2 (4)
Estrogen receptor status**	
Positive	30 (59)
Negative	21 (41)
HER2 status†	
Positive	12 (23.5)
Negative	39 (76.5)
Triple negative Status	
Triple negative	13 (25.5)
Not Triple negative	38 (74.5)
Surgery	
Breast-conserving surgery	25 (49)
Mastectomy	26 (51)
Pathological Response	
Responders	27 (53)
Non-responder	24 (47)

* AJCC version 7 (16) according to clinical examination and conventional imaging findings. ** Tumors were considered positive for ER or for PR if more than 10% of cells showed staining by IHC. † Tumors were considered to overexpress c-erbB-2 oncoprotein (HER2-positive) if more than 30% of invasive tumor cells showed definite membrane staining resulting in a so-called fishnet appearance.

Table 2 – PET parameters values and correlation with response

Parameter*	PET ₁	ρ^\dagger	PET ₂	ρ^\dagger	$\Delta(\text{PET}_1, \text{PET}_2)$ (%)	ρ^\dagger
SUV _{max}	6.8 (2.3, 27.5)	0.8	3.9 (1.4, 30.7)	0.04	-34 (-90, +104)	0.0001
SUV _{peak}	4.8 (1.9, 22.0)	0.8	2.9 (1.0, 24.5)	0.07	-39 (-90, +73)	0.0004
SUV _{mean}	3.7 (1.3, 18.7)	0.7	2.5 (1.0, 17.9)	0.2	-36 (-87, +69)	0.026
MATV (cm ³)	14 (2, 227)	0.1	7 (1, 154)	0.09	-45 (-89, +74)	<0.0001
TLG	51 (9, 668)	0.4	16 (1, 758)	0.05	-59 (-98, +51)	<0.0001

* median (min, max)

[†] ρ value of Mann-Whitney-U test (responders vs. non-responders). **Bold** indicates significant value.

Table 3 - Predictive value according to ROC analysis

Parameter		AUC [95% CI]	Cut-off value	Sensitivity [95% CI] (%)	Specificity [95% CI] (%)	Accuracy [95% CI] (%)
SUV _{max}	PET ₁	0.52 [0.37-0.66]	>11.6	30 [14-50]	83 [63-95]	55 [38-68]
	PET ₂	0.67 [0.52-0.79]	<=3.7	67 [46-84]	75 [53-90]	71 [49-87]
	Δ (%)	0.82 [0.68-0.91]	<=-48	63 [42-81]	92 [73-99]	77 [57-90]
SUV _{peak}	PET ₁	0.52 [0.37-0.66]	>11.7	22 [9-42]	88 [68-97]	53 [34-69]
	PET ₂	0.65 [0.50-0.78]	<=2.8	63 [42-81]	71 [49-87]	67 [46-85]
	Δ (%)	0.79 [0.65-0.89]	<=-42	70 [50-86]	83 [63-95]	76 [54-91]

SUV _{mean}	PET ₁	0.53 [0.38-0.67]	<=2.2	19 [6-38]	92 [73-99]	53 [34-69]
	PET ₂	0.62 [0.47-0.75]	<=2	59 [39-78]	75 [53-90]	67 [46-85]
	Δ (%)	0.68 [0.54-0.81]	<=-30	74 [54-89]	67 [45-84]	71 [49-88]
MATV (cm ³)	PET ₁	0.63 [0.48-0.76]	>7	85 [66-96]	42 [22-63]	65 [48-79]
	PET ₂	0.64 [0.49-0.77]	<=11.3	89 [71-98]	42 [22-63]	67 [45-84]
	Δ (%)	0.92 [0.82-0.98]	<=-42	93 [76-99]	88 [68-97]	91 [72-98]
TLG	PET ₁	0.57 [0.43-0.71]	>16	93 [76-99]	29 [13-51]	63 [42-81]
	PET ₂	0.66 [0.51-0.79]	<=23.3	78 [58-91]	63 [41-82]	71 [49-88]
	Δ (%)	0.91 [0.79-0.97]	<=-56	96 [81-100]	92 [73-99]	94 [79-99]

Figure 1

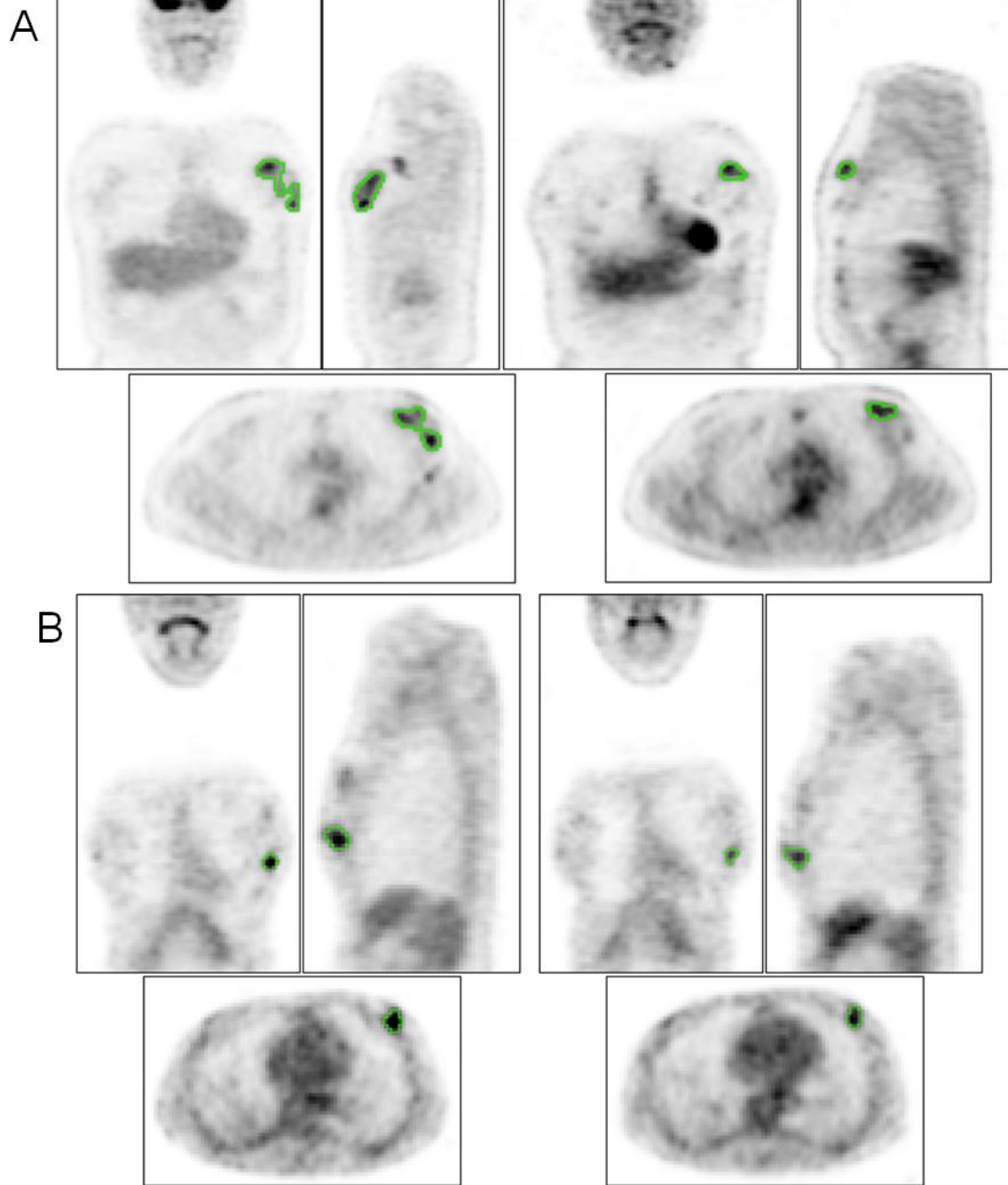
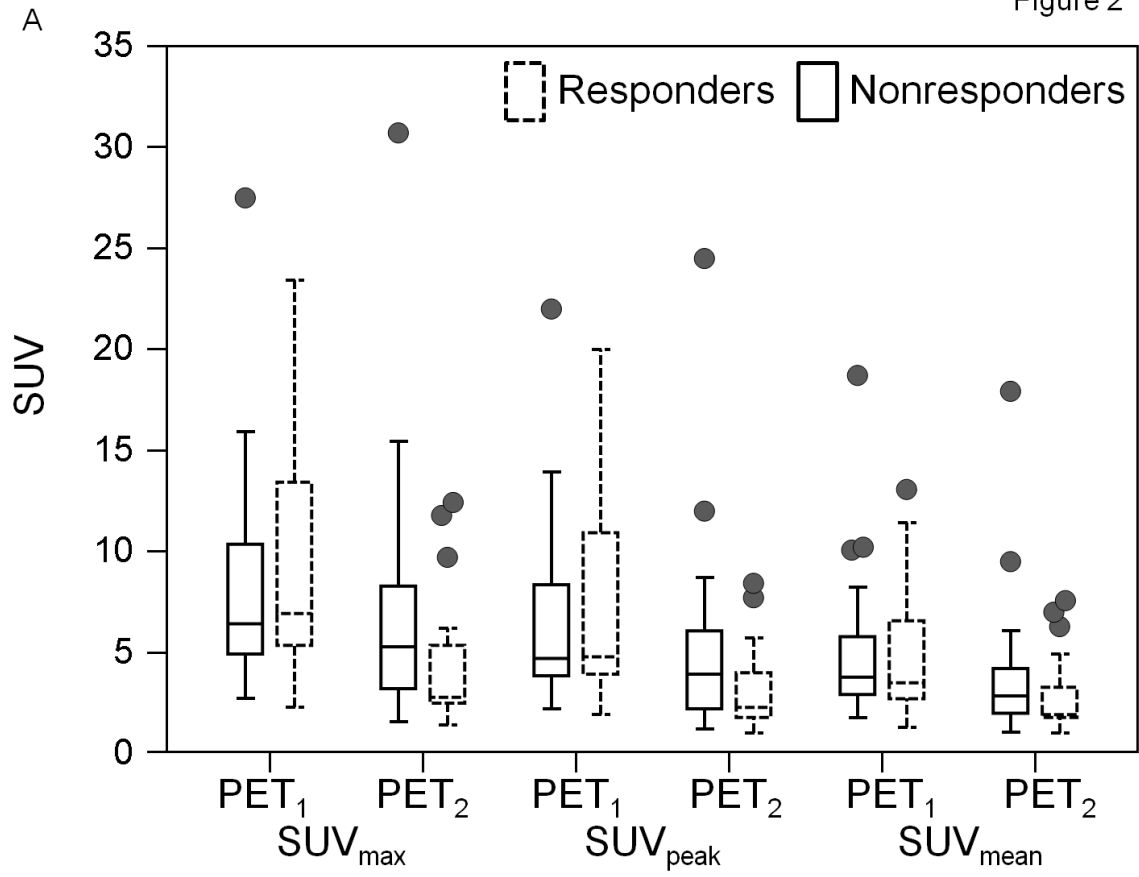


Figure 2



B

Figure 2

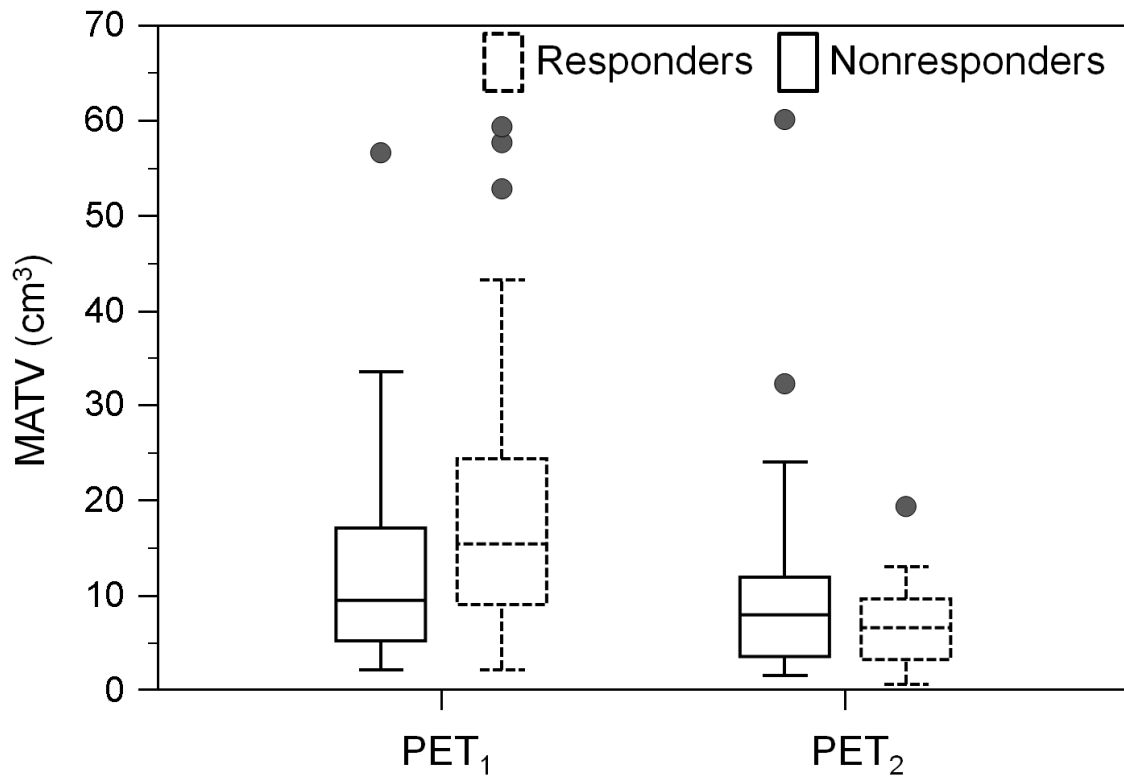


Figure 2

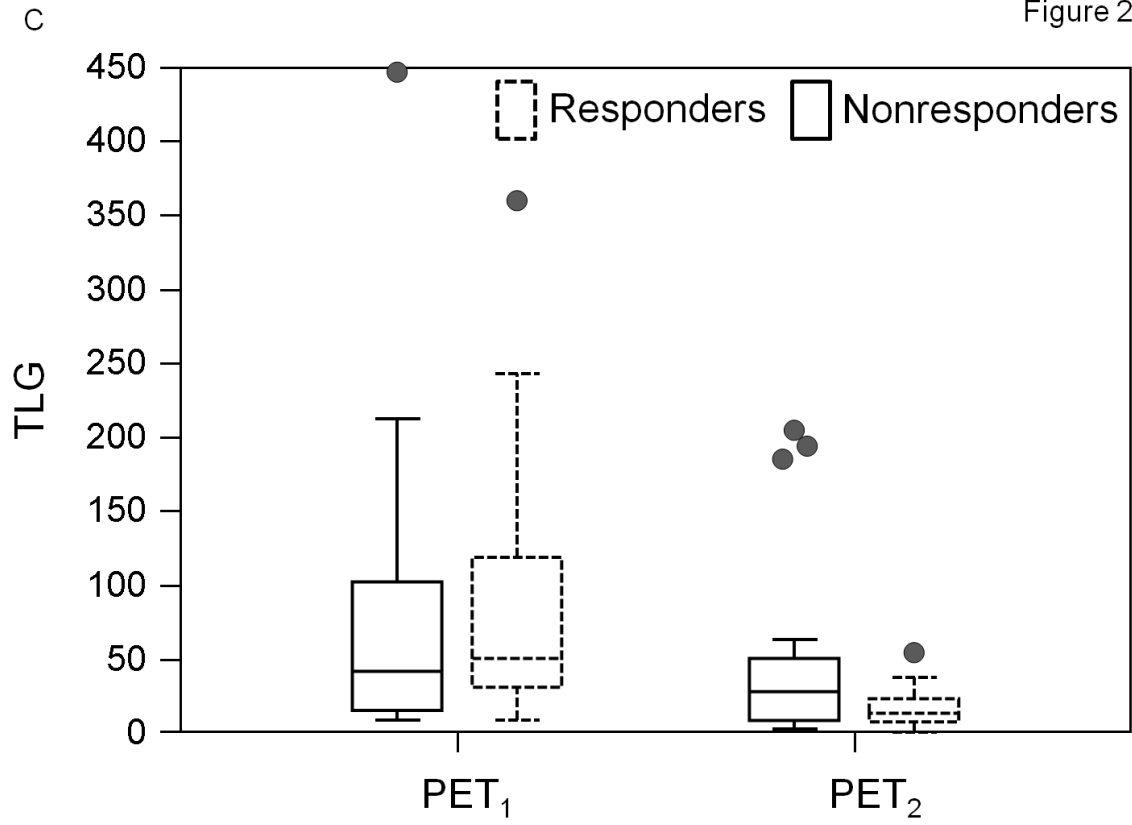
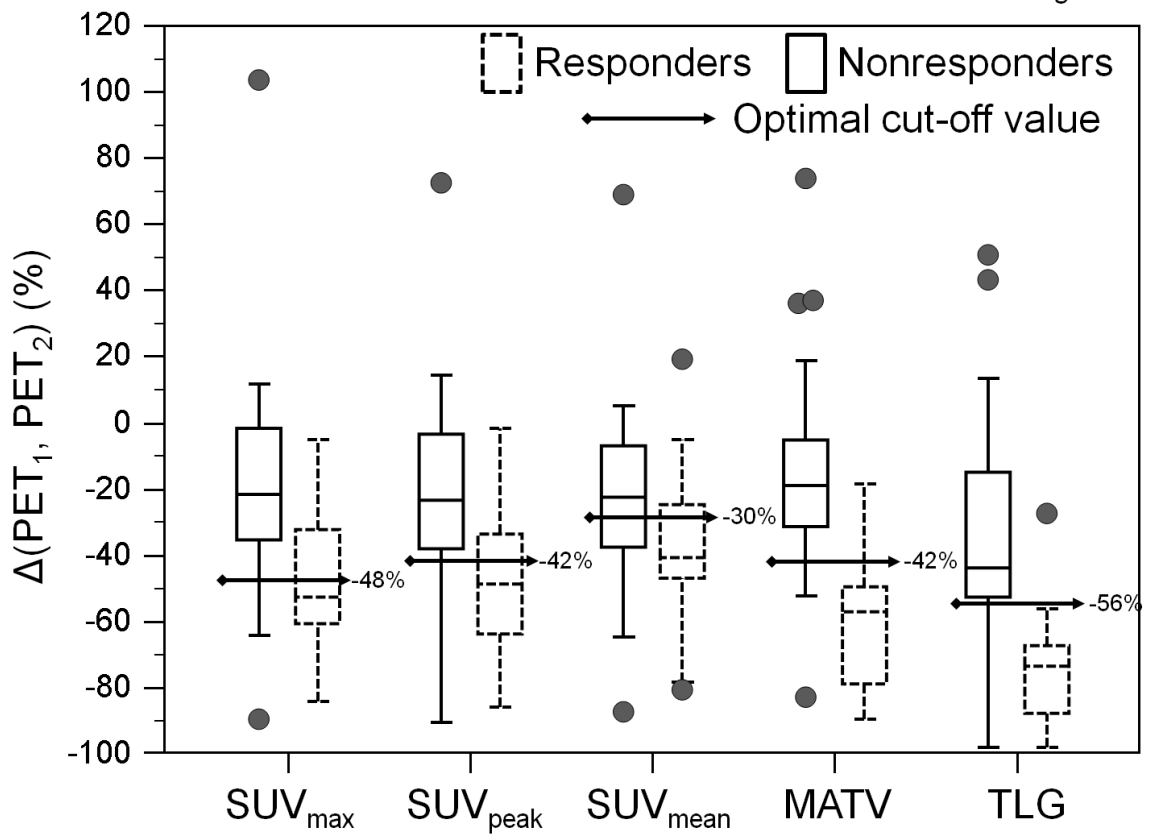
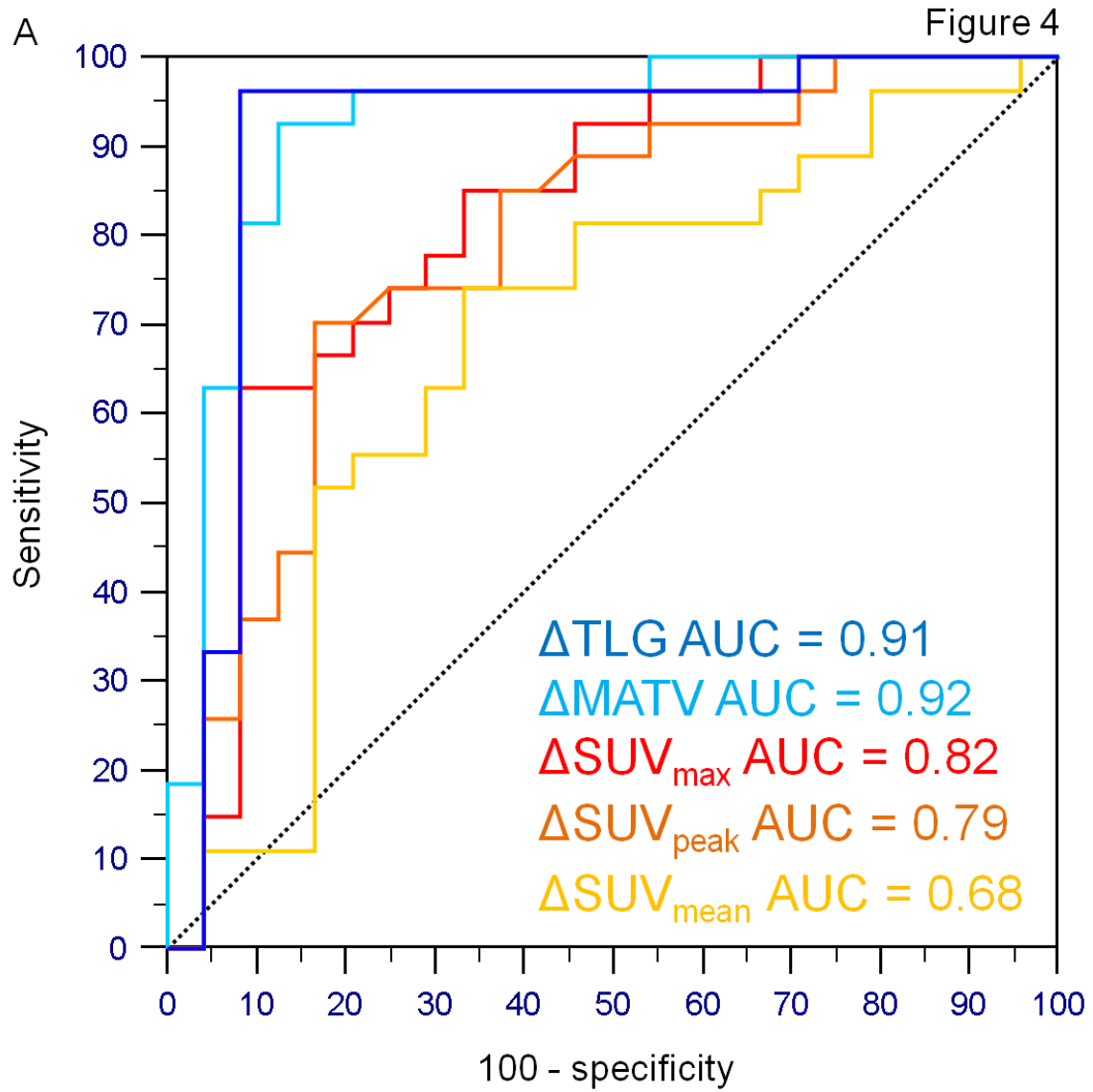


Figure 3





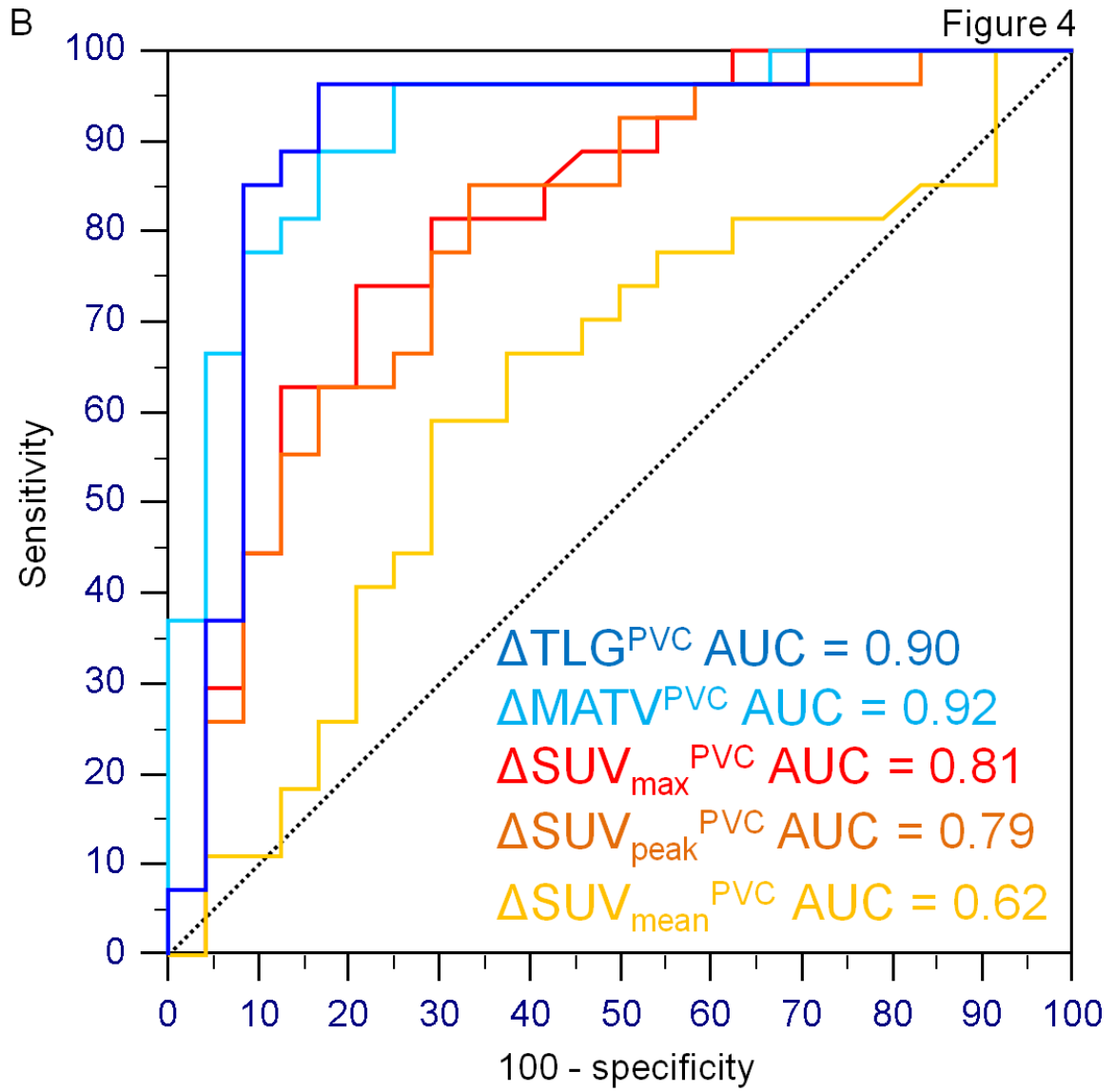


Figure 5

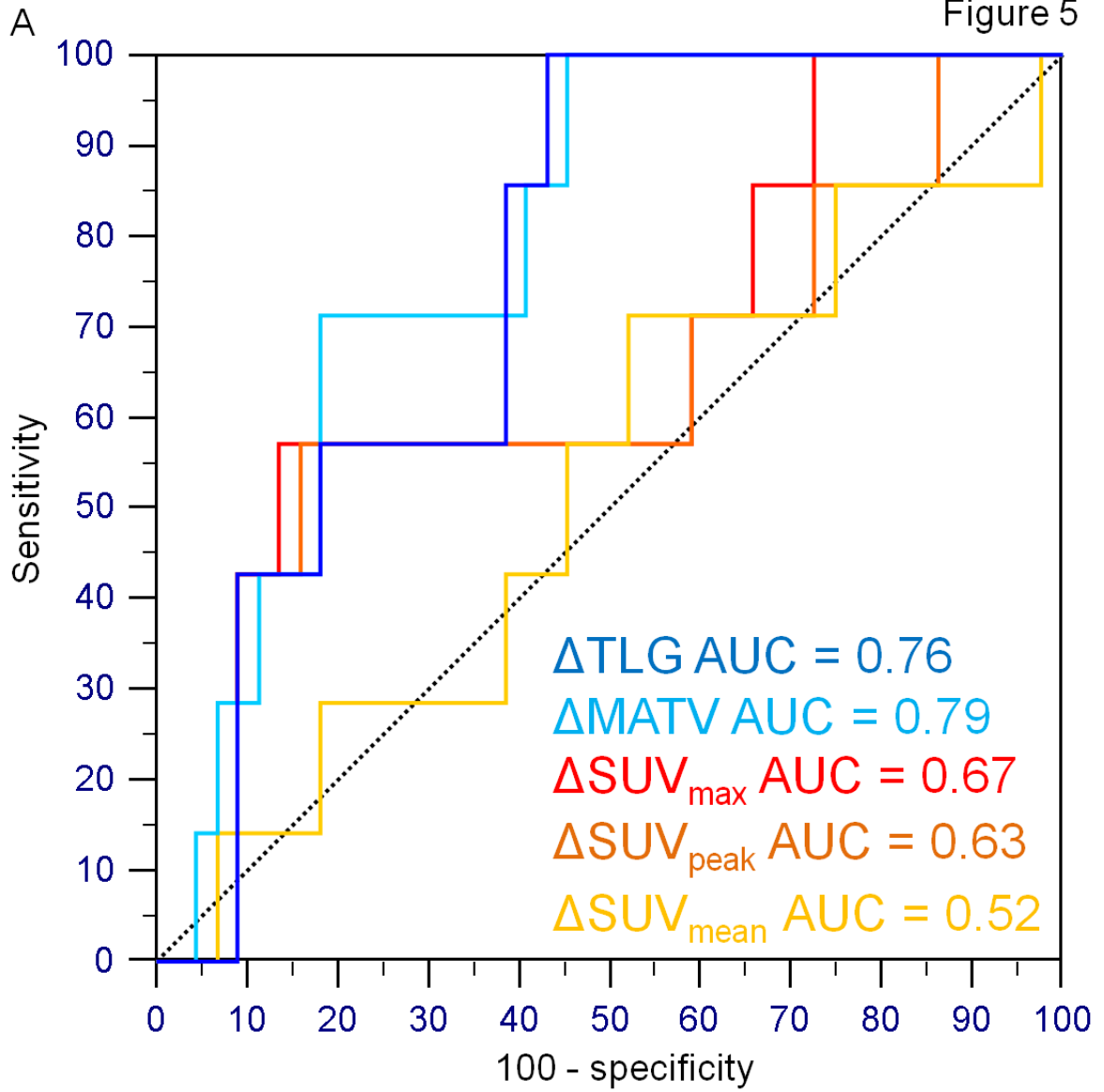


Figure 5

