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18F-FDG PET/CT to predict response to neoadjuvant chemotherapy and prognosis in inflammatory breast cancer.

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ABSTRACT
The aim of this prospective study was to assess the predictive value of 18F-FDG PET/CT imaging for pathologic response to neoadjuvant chemotherapy (NACT) and outcome in Inflammatory Breast Cancer (IBC) patients.
Methods: Twenty-three consecutive patients (51 years±12.7) with newly diagnosed IBC, assessed by PET/CT scan at baseline (PET1), after the third course of NACT (PET2) and before surgery (PET3), were included. Patients were divided into 2 groups according to the pathologic response assessed by the Sataloff classification: pCR for complete responders (TA and NA or NB) and non-pCR for non-complete responders (not stage A for tumor and/or not NA or NB for lymph nodes). In addition to SUVmax measurements, a global breast Metabolic Tumor Volume (MTV) was delineated using a semi-automatic segmentation method. Changes of SUVmax and MTV between PET1 and PET2 (ΔSUV1-2; ΔMTV1-2) and PET1 and PET3 (ΔSUV1-3; ΔMTV1-3) were measured.
Results: Mean SUVmax on PET1, PET2 and PET3 were not statistically different between the 2 pathologic response groups. Using ROC analysis, a 72% cutoff of ΔSUV1-3 provided the best performance to predict residual disease with sensitivity, specificity and accuracy of 61%, 80%, and 65%, respectively. On univariate analysis, the 72% cutoff of ΔSUV1-3 was the best predictor of Distant Metastasis-Free Survival (p= 0.05). On multivariate analysis, the 72% cutoff ΔSUV1-3 was an independent predictor of DMFS (p=0.01). **Conclusion**: Our results emphasize the good predictive value of ΔSUVmax between baseline and before surgery to assess pathologic response and survival in IBC patients undergoing NACT.

Key words:
Inflammatory breast cancer, 18F-FDG PET/CT, neoadjuvant chemotherapy, Survival

INTRODUCTION

Inflammatory breast cancer (IBC), the rarest and most deadly form of primary breast adenocarcinoma, is associated with a 5-year survival rate of about 40% (*1*). Distant metastases are frequently present at the time of diagnosis and Positron Emission Tomography/Computed Tomography using [^{18}F]-2-fluorodeoxy-D-Glucose (18F-FDG PET/CT) has been shown to be sensitive for the detection of metastases (*2*). The current consensus treatment consists of neoadjuvant chemotherapy (NACT) with an anthracycline- and taxane-based regimen, associated with trastuzumab for HER2-positive tumors, followed by mastectomy and axillary lymph node dissection for clinical responders and non-metastatic patients, locoregional radiotherapy and, when appropriate, endocrine therapy (*3*). Chemosensitivity may be the best prognostic indicator in IBC (*4,5*). Assessment of clinical response by tumor palpation is often inaccurate in IBC patients due to the presence of breast swelling and edema, and a diffusely infiltrating behavior of the tumor without a measurable mass (*5*). Pathologic response is accurately assessed at final surgery. As in the case of non-IBC, IBC patients achieving a pathologic complete response (pCR) after NACT have longer DFS and OS compared to patients with residual disease (*6*). Pathologic response to NACT in stage II and non-inflammatory stage III breast cancer has been shown to be predicted by serial 18F-FDG PET/CT during treatment (*7-10*). In contrast with non-IBC, few data are available concerning the predictive value of 18F-FDG imaging for response to NACT in IBC in both metastatic and non-metastatic patients (*11*).
The aim of this study was to prospectively assess the predictive value of PET/CT imaging for non-pCR to NACT and prognosis in a homogeneous series of non-metastatic IBC patients. PET/CT criteria were quantitative parameters: maximum Standardized Uptake Value (SUVmax) on PET1 (Positron Emission Tomography at baseline) and changes (Δ) of SUVmax and Metabolic Tumor Volume (MTV) between PET1 and PET2 (Positron Emission Tomography after the third course of NACT) (ΔSUV1-2; ΔMTV1-2) and PET1 and PET3 (Positron Emission Tomography before surgery) (ΔSUV1-3; ΔMTV1-3).

PATIENTS AND METHODS

Patients

This study is part of a previous prospective study which assessed the value of 18F-FDG PET/CT in the initial staging of 59 consecutive women with unilateral IBC, staged T4d according to the AJCC (American Joint Committee on Cancer) classification (*2, 12*). From April 2003 to June 2007, twenty-three of these women with newly diagnosed unilateral non-metastatic IBC and treated by mastectomy with axillary lymph node dissection after NACT underwent 3 serial PET/CT scans. All patients received 6 to 8 courses of NACT with anthracycline (FEC100 fluorouracil, epirubicin and cyclophosphamide or AC60 doxorubicin and cyclophosphamide) +/- docetaxel 100 mg/m^2 every 21 days. Five patients had HER2-positive tumors, but only 2 patients diagnosed after April 2005 received neoadjuvant trastuzumab. IBC patients underwent clinical examination, mammography, breast ultrasound, and image-guided core needle biopsy, CT and/or MRI. Tumor size was established by clinical examination and imaging. Exclusion criteria were age less than 18 years, previous breast surgery, chemotherapy or radiation therapy, inability to undergo serial PET/CT scans, ineligibility for surgery, presence of distant metastases at

diagnosis.
The institutional review board approved this study and all subjects signed a written informed consent.

Pathologic response
At surgery, fresh surgical specimens were cut in 5 mm thick slices and examined for the presence or absence of macroscopic tumor. All pathology specimens were reviewed in a blinded fashion by 2 pathologists. Pathologic response was assessed using the Sataloff classification (*13*). pCR was defined as the absence of invasive disease in breast and axilla: stage TA and NA or NB. All other pathologic responses were classified as non-pCR.
Two groups of patients were then defined: pCR group and non-pCR group.

Clinical response
Clinical response was assessed by palpation at each cycle and before surgery, according to the Response Evaluation Criteria In Solid Tumors criteria (RECIST 1.0) (*14*). Complete Response (CR) was defined as tumor disappearance and partial response (PR) as reduction of the tumor lesion by at least 30%.

PET/CT imaging
Patients underwent PET/CT scans at baseline (PET1), after the third course of NACT, generally corresponding to midcourse (PET2) and before surgery (PET3), using the same scanner (Discovery LS, GEMS, Waukesha, WI, USA). After fasting for at least 6 hours, blood glucose levels were determined on capillary blood samples before 18F-FDG injection and were less than 7 mmol/L for all but 3 patients, who had blood glucose levels of 13.6, 12.7 and 10.6 mmol/L, respectively. Only one of these 3 patients was a known diabetic.
Intravenous injection of 4-5 MBq/kg of 18F-FDG was performed in the arm opposite to the breast cancer or via a dorsal pedal vein. Images were acquired approximately 60 min (73±21 min) after injection on 2D mode, from the skull to the mid-thigh, with 5 to 7 bed positions of 4 minutes each. Patients were placed in the supine position with the arms alongside the body and were allowed to breathe normally (shallow breathing) during PET and non-contrast-enhanced CT acquisitions. CT images were used for attenuation correction and fusion. Both attenuation-corrected and non-corrected PET images, together with coregistered CT data, were reviewed.

PET/CT analysis
PET/CT images were interpreted by 2 experienced nuclear medicine physicians, blinded to the patients' record.

SUVmax measurements
A 3D region of interest was placed manually over the area of maximum activity on slices with the clearest definition of the entire breast tumor mass, skin and locoregional lymph nodes. The highest initial SUVmax was measured on each PET/CT scan.

Relative change in SUVmax (normalized to 100% for PET1)
ΔSUV1-2 and ΔSUV1-3 were measured.

Global MTV

The MTV (cm^3), including breast mass, skin abnormalities, and regional lymph node 18F-FDG uptakes was obtained by semi-automatic segmentation software, using volume delineation on the MIP image. The corresponding extracted "volume" was obtained on the basis of a SUVmax cutoff of 2.5.

Relative changes of MTV between PET1 and PET2 (ΔMTV1-2) and PET1 and PET3 (ΔMTV1-3) were measured.

Statistical analysis

The primary endpoint was residual disease.

Nonparametric tests (Kruskal-Wallis, t-test) were used for between-group comparisons.

The predictive performance of PET/CT for identification of responders and non-responders was evaluated using ROC (Receiver Operating Characteristic) analysis (MEDCALC statistical software). Correlation between PET/CT and survival parameters was analyzed using the Kaplan-Meier method by univariate analysis. Overall Survival (OS) and Distant Metastasis-Free Survival (DMFS) were calculated from the date of the baseline PET/CT scan.

The multivariate Cox proportional hazards model was used to assess the effects of multiple factors on OS and DMFS. The following factors were analyzed: decrease in tumor SUVmax, age, grade, hormone receptor (HR) status, and HER2 status.

All tests were two-sided and P values of 0.05 or less were considered statistically significant.

Analysis by Hormone Receptor and HER2 status

The 3 main molecular subgroups of breast cancer (Triple Negative n=7; HR-positive/HER2-negative n=11; HR-negative/HER2-positive n=5) were analyzed separately for SUVmax, ΔSUVmax and survival parameters.

RESULTS

Patient characteristics and clinical and pathologic response

Patient, clinical and pathologic characteristics and outcome are listed in Table 1. Mean age was 51±12 years and median follow-up was 76±27 months.

Overall pCR rate was 22% (4 TA NA and 1 TA NB). The pCR rate differed according to subtype, as 4 of the 5 pCR were achieved in HR-negative tumors (Table 1). Only one pCR was observed among the 14 patients treated with an anthracycline alone compared to 4 pCR among the 9 patients who received anthracycline and docetaxel, associated with neoadjuvant trastuzumab in 2 patients (p= 0.018). No significant difference in pCR rate was observed between patients who received 6 or 8 courses of NACT.

A complete clinical response was noted in 5 patients (22%), associated with pCR in 3 patients (Table 2). No case of progressive disease was observed.

No significant correlation was observed between pathologic and clinical response (p= 0.14).

PET/CT parameters and pathologic response

The median interval between PET1 and PET2 was 81±18 days and the median interval between PET2 and PET3 was 69±21 days. The mean interval between PET3 and surgery was 20.5 days (median: 10 days; range: 1-114; surgery was delayed in 1 patient because of sepsis during chemotherapy).

Baseline PET (PET1)

Baseline PET/CT showed increased 18F-FDG uptake in all primary tumors. Mean SUVmax on PET1 tended to be higher in the pCR group than in the non-pCR, although this difference was not statistically significant (13.7±5.7 vs 9.5±5.8 p= 0.18).

PET2 and PET3

Mean SUVmax was not significantly different between pCR and non-pCR groups on PET2 (4.3±3 vs 4.2±3.2, p= 0.9) or PET3 (1.7±0.5 vs 2.5±1.7, p= 0.14).

Mean changes of SUVmax

PET1 and PET2

ΔSUV1-2 was not significantly different between pCR and non-pCR groups (72%±16 and 54%±25, p= 0.13).

PET1 and PET3

ΔSUV1-3 was not significantly different between the 2 pathologic response groups, but was higher in the pCR group (80.9%±6.4) than in the non-pCR group (67.9%±19, p= 0.08).

The choice of ΔSUVmax threshold to predict pathologic response: ROC curves (Figures 1 to 3)

ΔSUV1-2 failed to predict residual disease, as no discriminant cutoff was identified.

A 72% cutoff for the decrease in SUV1-3 provided the best performance to predict pCR. The sensitivity for identification of residual disease (non-pCR) was 61% and the specificity was 80%. Positive predictive value, negative predictive value and accuracy were 92%, 36% and 65%, respectively. According to this 72% cutoff, there were 11 good metabolic responders (>72%) (Fig. 1) and 12 poor metabolic responders (≤72%) (Fig. 2).

Metabolic Tumor Volume (MTV)

Mean MTV on PET1 and PET2 were not significantly different between pCR and non-pCR groups (t-test).

Mean MTV on PET3 was lower in the pCR group compared to the non-pCR group, but the difference was not statistically significant (0.2 cm^3 vs 6.9 cm^3; p= 0.13).

PET analysis by Breast Cancer subtypes

SUVmax on PET1, ΔSUV1-2 and ΔSUV1-3 were not significantly different between the 3 molecular subgroups. However, the lowest ΔSUV1-2 and ΔSUV1-3 were observed in the HR-positive/HER2-negative subgroup (48.4% and 69% versus 67.1 % and 85% for Triple-Negative, p= 0.13 and 0.19, 63.1% and 94% for HER2-positive tumors, p= 0.4 and 0.09, respectively).

PET/CT parameters and survival

ΔSUV1-2

An early change in SUVmax (ΔSUV1-2) was not associated with survival on univariate or multivariate analysis.

ΔSUV1-3

On univariate analysis, the 72% cutoff of ΔSUV1-3 was the best predictor of DMFS (p= 0.05). A trend was observed for prediction of OS (p= 0.17).

On multivariate analysis (Table 3), the 72% cutoff of ΔSUV1-3 was an independent predictor of DMFS (p= 0.01). Clinical response (p= 0.03) and tumor grade (p= 0.04) were also significantly associated with DMFS. None of the other possible confounders (pathologic response, age, HR and HER2 status) was significantly associated with survival after adjusting for the factors in the final survival model.

A trend was observed with ΔSUV1-3 for prediction of OS (p= 0.17) (data not shown).

Survival by Breast Cancer Subtypes

DMFS and OS were higher in HR-positive/HER2-negative subgroup (70.2 and 94.3 months) than in Triple-Negative (36.7 and 63.7 months, p= 0.08 and 0.09) and HR-negative/HER2-positive (45.8 and 78.7 months, p= 0.7 and 0.4) subgroups (Table 4).

DISCUSSION

IBC accounts for about 2% of all invasive breast carcinomas with a metastasis rate at presentation of up to 30%. The present study included a small, but well-defined population of 23 non-metastatic IBC patients, who all underwent serial PET/CT scans and radical mastectomy. As about one-third of IBC patients are disease-free at 10 years, identification of the other two-thirds of patients with poorer prognosis remains a crucial goal in this aggressive disease.

Prediction of response to NACT for IBC patients would be of considerable value, allowing the possibility of switching to another more effective regimen or targeted therapies in non-responders. Response to chemotherapy in IBC patients is mainly based on clinical examination and has been correlated with survival (*4*). In non-IBC, conventional imaging to assess response to NACT has shown discordant results (*15*), probably due to the inability to differentiate fibrosis and granulomatous tissue from viable tumor cells. Volumetric MRI appears to be a more reliable tool to monitor response to NACT (*16*), but no published data on IBC are available. In the present study, comparison of PET/CT to morphological imaging results was not performed, because patients had either CT and/or MRI at initial evaluation workup.

18F-FDG PET/CT has been used to assess response to NACT in non-IBC patients (*7, 17-23*). Published data show a higher baseline 18F-FDG uptake in patients with pCR than in patients with a poorer response (*7, 17*). Very few data are available on this topic in IBC, although the value of 18F-FDG PET/CT in initial staging of IBC has been validated (*2, 12*). In our series of IBC patients, baseline SUVmax was not predictive of residual disease, but it must be noted that pCR was defined as complete or almost complete absence of invasive disease in the breast and lymph nodes.

Most studies performed in the neoadjuvant setting in non-IBC patients, have assessed the absolute value of SUVmax after 1 to 3 cycles of NACT (*7, 18-20*) and have suggested that 18F-FDG PET may accurately predict pCR. However, in our study, neither SUVmax on PET2 nor ΔSUV1-2 were predictive of residual disease, which could be partially explained by the presence of fibrosis, mucin pools and foamy histiocytes during chemotherapy, perhaps more important in IBC, resulting in dilution of the 18F-FDG "signal" (*21*).

Several studies have also evaluated the performance of 18F-FDG PET/CT after completion of NACT to predict pCR (*22-23*) and found that 18F-FDG PET did not provide an accurate assessment of residual tumor. Similar results were observed in the present study, as mean SUVmax on PET3 was not significantly different between the pCR and non-pCR groups. In contrast, we found that the decrease in 18F-FDG uptake with a 72% cutoff of ΔSUV1-3 allowed identification of residual disease with high specificity.

Only a trend towards a correlation between MTV on PET3 and pathologic response was observed. As it is often difficult to measure tumor volume, we tried to assess tumor volume by means of a global MTV, including breast, skin and regional lymph node activity, delineated by semi-automatic segmentation based on a fixed SUVmax cutoff of 2.5. This global volume reflects the real tumor burden, including skin uptake, as, by definition, skin is involved in IBC and participates in breast 18F-FDG uptake. This MTV, based on a fixed SUVmax cutoff (*24-25*), has been shown to be highly reproducible (*26*). The use of this MTV remains controversial, but, in the absence of a consensus, we decided to use this method.

Pathologic complete response to NACT is predictive of better survival, especially in HR-negative patients (*6, 27*). pCR did not predict survival in this IBC series. However the sample size was small, patients received various chemotherapy regimens and the definition of pCR was stringent although the overall 22% pCR rate is in accordance with previous IBC series (*6*). Recent studies have suggested that the clinical objectives of 18F-FDG PET/CT and the criteria used to predict efficacy of NACT should be established for separate molecular subgroups: estrogen receptor-positive and HER2-negative breast cancer, HER2-positive breast cancer, and triple-negative breast cancer (*27, 28, 29*). Eventually pCR to NACT seems to be a predictor of better survival specially in HR negative tumors and response to NACT should be established for separate subgroups (*6, 27*). Indeed studies on IBC have demonstrated the presence of molecular subtypes similar to those of non-IBC but with overrepresentation of Triple Negative and HER2 positive tumors (*5, 6, 11*). We analysed separately these subtypes but the limited size of each subgroup precludes definite conclusions. Nevertheless, according to published data, we observed that patients with HR positive tumors had better DMFS and OS than other subgroups despite a lower ΔSUV1-3 reflecting the poorer response to NACT (*6, 11*).

The most significant finding of the present study is that contrary to pCR, ΔSUV1-3 with a 72% cutoff was an independent predictor of DMFS. This finding is consistent with a retrospective study in mostly metastatic IBC patients undergoing primary chemotherapy (*11*). This is a very useful finding, as there is an urgent need for specific prognostic features in IBC. Although it does not modify neoadjuvant management, the prognostic value of ΔSUV1-3 may be clinically useful. Several clinical trials are currently underway to develop treatment strategies for these patients with an unfavorable prognosis after NACT.

CONCLUSION

18F-FDG PET/CT appears to be useful to predict residual disease after NACT and survival in IBC. However, due to the small sample size, these results deserve further investigation in larger studies.

Conflicts of interest: none.

REFERENCES

1. Lerebours F, Bieche I, Lidereau R. Update on inflammatory breast cancer. *Breast cancer Res*. 2005;7:52-58.

2. Alberini JL, Lerebours F, Wartski M, et al. 18F-Fluorodeoxyglucose positron emission tomography/ computed tomography (FDG-PET/CT) imaging in the staging and prognosis of inflammatory breast cancer. *Cancer*. 2009;115:5038–5047.

3. Dawood S, Merajver SD, Viens P, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. *Ann Oncol*. 2011;22:515-523.

4. Fleming RY, Asmar L, Buzdar AU, et al. Effectiveness of mastectomy by response to induction chemotherapy for control in inflammatory breast carcinoma. *Ann Surg Oncol*. 1997;4:452-461.

5. Robertson FM, Bondy M, Yang W, et al. Inflammatory breast cancer: the disease, the biology, the treatment. *CA Cancer J Clin*. 2010;60:351-375.

6. Masuda H, Brewer TM, Liu DD, et al. Long-term treatment efficacy in primary inflammatory breast cancer by hormonal receptor- and HER2-defined subtypes. *Ann Oncol*. 2014;25:384-391.

7. Rousseau C, Devillers A, Sagan C, et al. Monitoring of early response to neoadjuvant chemotherapy in stage II and III breast cancer by [18F] fluorodeoxyglucose positron emission tomography. *J Clin Oncol*. 2006 1;24:5366-5372.

8. Duch J, Fuster D, Muñoz M, et al. 18F-FDG PET/CT for early prediction of response to neoadjuvant chemotherapy in breast cancer. *Eur J Nucl Med Mol Imaging*. 2009;36:1551-1557.

9. Andrade WP, Lima EN, Osório CA, et al. Can FDG-PET/CT predict early response to neoadjuvant chemotherapy in breast cancer? *Eur J Surg Oncol*. 2013;39:1358-1363.

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

11. Carkaci S, Sherman CT, Ozkan E, Adrada BE, Wei W, Rohren EM, et al. (18)F-FDG PET/CT predicts survival in patients with inflammatory breast cancer undergoing neoadjuvant chemotherapy. *Eur J Nucl Med Mol Imaging*. 2013;40:1809-1816.

12. Champion L, Lerebours F, Cherel P, et al. F-FDG PET/CT imaging versus dynamic contrast-enhanced CT for staging and prognosis of inflammatory breast cancer. Eur J Nucl Med Mol Imaging. 2013;40:1206-1213.

13. Sataloff DM, Mason BA, Prestipino AJ, Seinige UL, Lieber CP, Baloch Z. Pathologic response to induction chemotherapy in locally advanced carcinoma of the breast: a determinant of outcome. *J Am Coll Surg*. 1995;180:297–306.

14 Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92:205-16.

15. Kanazawa T, Akashi-Tanaka S, Iwamoto E, et al. Diagnosis of complete response to neoadjuvant chemotherapy using diagnostic imaging in primary breast cancer patients. *Breast J*. 2005;11:311-6

16. Lorenzon M, Zuiani C, Londero V, Linda A, Furlan A, Bazzocchi M. Assessment of breast cancer response to neoadjuvant chemotherapy: Is volumetric MRI a reliable tool? *Eur J Radiol*. 2008;71:82-88.

17. Smith IC, Welch AE, Hutcheon AW, et al. Positron emission tomography using [(18)F]-fluorodeoxy-D-glucose to predict the pathologic response of breast cancer to primary chemotherapy. *J Clin Oncol*. 2000;18:1676-1688.

18. McDermott GM, Welch A, Staff RT, et al. Monitoring primary breast cancer throughout chemotherapy using FDG-PET. *Breast Cancer Res Treat*. 2007;102:75-84.

19. Berriolo-Riedinger A, Touzery C, Riedinger JM, et al. [18F]FDG-PET predicts complete pathological response of breast cancer to neoadjuvant chemotherapy. *Eur J Nucl Med Mol Imaging*. 2007;34:1915-1924.

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

21. Newman LA, Pernick NL, Adsay V, et al. Histopathologic evidence of tumor regression in the axillary lymph nodes of patients treated with preoperative chemotherapy correlates with breast cancer outcome. *Ann Surg Oncol*. 2003;10:734-739.

22. Kim SJ, Kim SK, Lee ES, Ro J, Kang Sh. Predictive value of [18F]FDG PET for pathological response of breast cancer to neo-adjuvant chemotherapy. *Ann Oncol*. 2004;15:1352-1357.

23. Dose-Schwarz J, Tiling R, Avril-Sassen S, et al. Br J Cancer Assessment of residual tumour by FDG-PET: conventional imaging and clinical examination following primary chemotherapy of large and locally advanced breast cancer. *Br J Cancer*. 2010;102:35-41.

24. Costelloe CM, Macapinlac HA, Madewell JE, et al. 18F-FDG PET/CT as an indicator of progression-free and overall survival in osteosarcoma. *J Nucl Med*. 2009;50:340–347.

25. Biehl KJ, Kong FM, Dehdashti F, Jin JY, et al. 18F-FDG PET definition of gross tumor volume for radiotherapy of non-small cell lung cancer: is a single standardized uptake value threshold approach appropriate? *J Nucl Med*. 2006;47:1808-1812.

26. Tylski P, Stute S, Grotus N, Doyeux K, Hapdey S, Gardin I, Vanderlinden B, Buvat I. Comparative assessment of methods for estimating tumor volume and standardized uptake value in 18F-FDG PET. *J Nucl Med*. 2010;51:268-276.

27. Groheux D. Predicting pathological complete response in breast cancer early. *Lancet Oncol.* 2014;15:1415-16.

28. Groheux D, Giacchetti S, Espié M, Rubello D, Moretti JL, Hindié E. Early monitoring of response to neoadjuvant chemotherapy in breast cancer with 18F-FDG PET/CT: defining a clinical aim. *Eur J Nucl Med Mol Imaging*. 2011;38:419–25

29. Humbert O, Berriolo-Riedinger A, Riedinger JM, et al. Changes in 18F-FDG tumor metabolism after a first course of neoadjuvant chemotherapy in breast cancer: influence of tumor subtypes. *Ann Oncol*. 2012;23:2572–77.

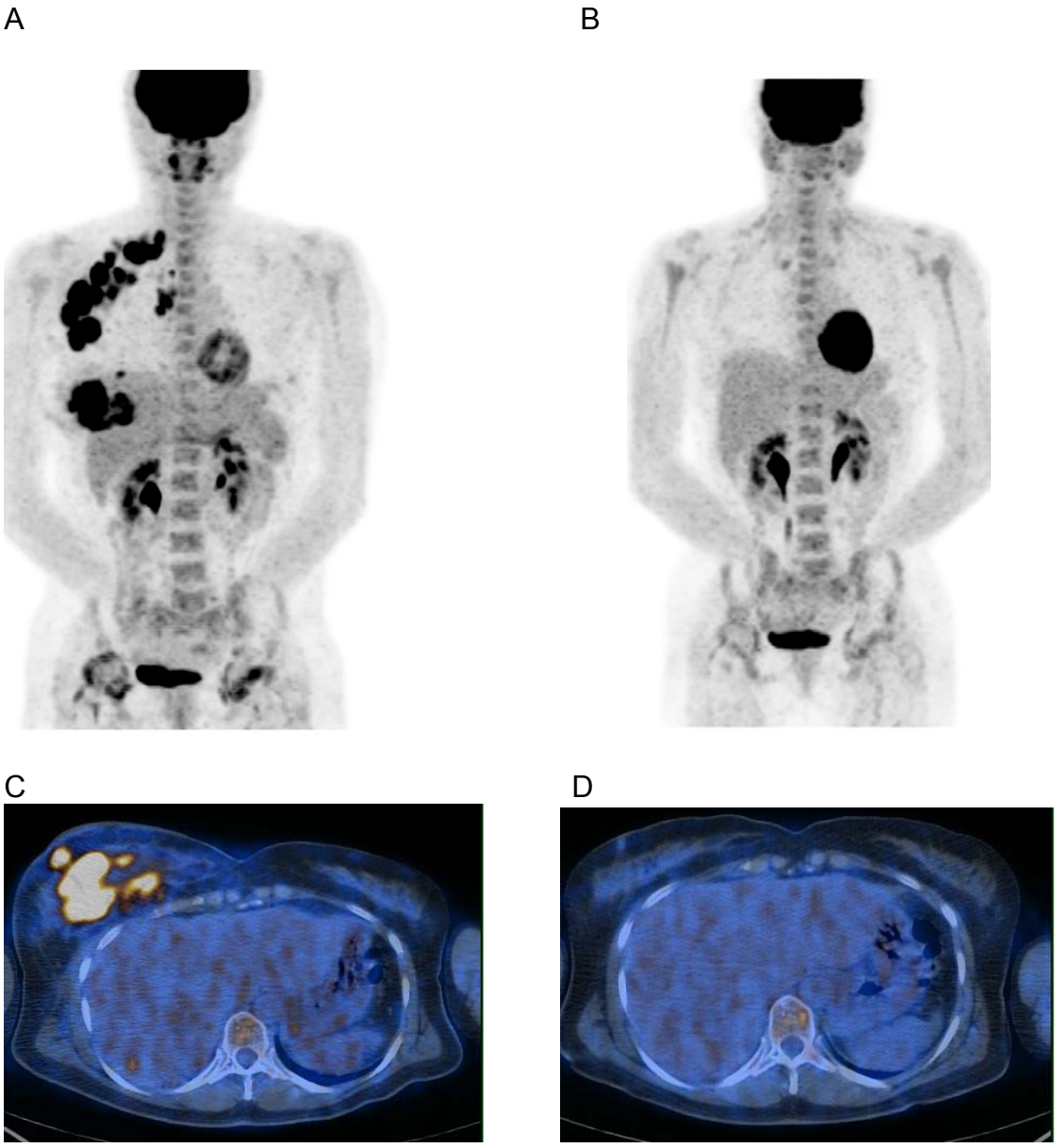
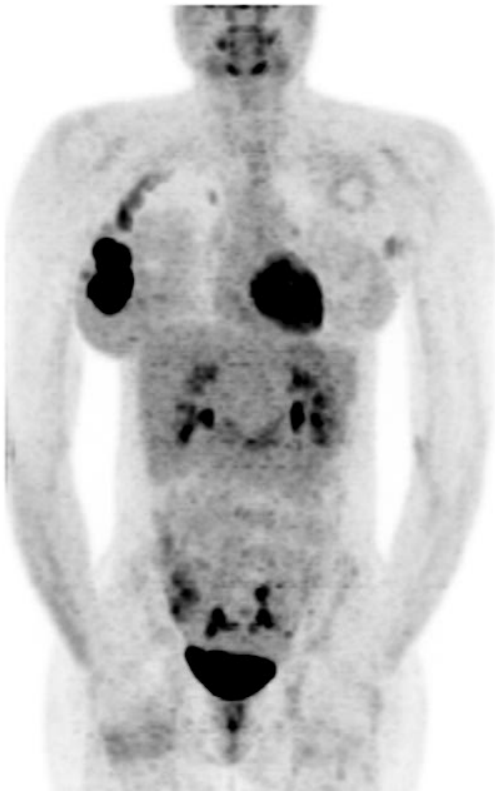


Fig 1. 51-year-old woman with primary right IBC, axillary lymph node involvement and pulmonary infection. Grade 3 HR-negative/ HER2-positive inflammatory breast cancer. Ki 67 8%.
Baseline 18F-FDG PET/CT: Maximum Intensity Projection MIP (A) and axial fusion slice on breast (C).
18F-FDG PET/CT 2 realised after 3 cycles of anthracycline-based chemotherapy: MIP (B) and axial fusion slice on breast (D). ΔSUV1-2 and ΔSUV1-3 were -95%.
The patient received 4 courses of anthracycline-based chemotherapy and 4 courses of taxane and trastuzumab. Pathologic complete response at surgery.

A



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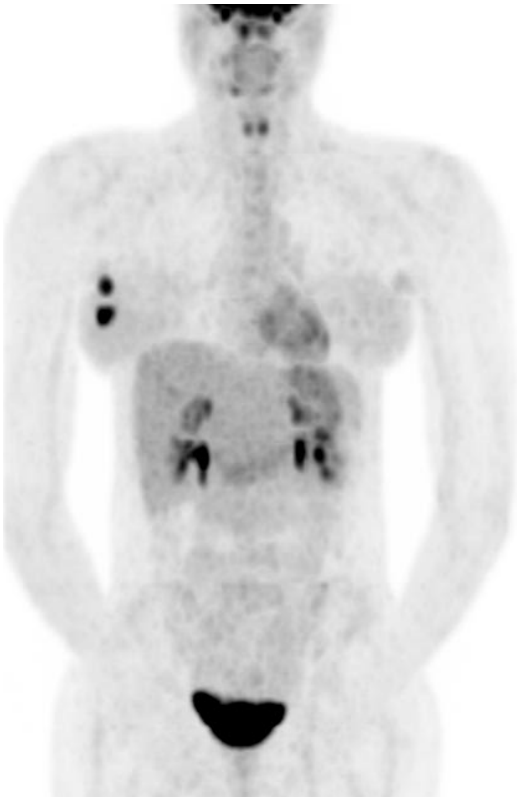

Fig 2. 35-year-old woman with primary right IBC, and axillary lymph node. Grade 3 triple-negative breasr cancer. Ki 67 30%.
A: Baseline 18F-FDG PET/CT (Maximum Intensity Projection MIP).
B: 18F-FDG PET/CT 3 (MIP) ΔSUV1-3 was -16.7%.
The patient received 6 courses of anthracycline-based chemotherapy. Non-pathologic complete response at surgery.

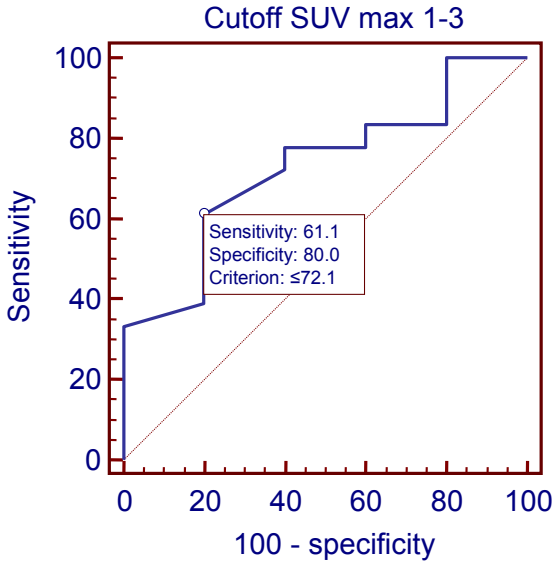

Fig.3 Capacity of ΔSUV 1-3 to predict residual tumor at surgery after completion of NACT, derived by the area under the receiver-operating-characteristic curve (AUC). AUC = 0.75

	Overall population		pCR group		non-pCR group	
Number of patients	n= 23		n= 5	22%	n= 18	78%
Age(y) mean± SD (range	51± 12.7 (34 -78)		50.6± 9.9 (37-60)		52.2± 13.3 (34-78)	
Histology						
Invasive ductal carcinoma	22	95%	4	80%	18	100%
Metaplastic carcinoma	1	5%	1	20%		
Elston-Ellis grade						
I	2	9%			2	11%
II	7	30%			7	39%
III	14	61%	5	100%	9	50%
Hormone receptor status						
Positive	11	43%	1	20%	10	55%
Negative	12	57%	4	80%	8	45%
HER2 receptor status						
Positive	5	22%	2	40%	3	17%
Negative	18	78%	3	60%	15	83%
Triple-negative cancer	7	30%	2	40%	5	28%
Ki67						
<25%	7	30%	1	20%	6	33%
≥25%	14	61%	4	80%	10	55%
unknown	2	9%			2	12%
Neoadjuvant chemotherapy						
Anthracycline alone	14	61%	4	80%	10	55%
Anthracycline and docetaxel	9	39%	1	20%	8	45%
Clinical response						
CR (complete response)	5	22%	3	60%	2	11%
PR (partial response)	15	65%	2	40%	13	72%
SD (stable disease)	3	13%			3	17%
Survival parameters (months)						
DMFS (distant metastasis-free survival)	52.6		46		54	
OS (overall survival)	73.9		79.5		72.4	

Table 1. Clinical and pathologic characteristics and outcome of 23 patients with IBC

Patient No.	Grade	HR status	HER2 status	Treatment	SUV max1	ΔSUV max1-2	ΔSUV max1-3	Clinical response	Pathologic response
1	3	neg	neg	anthracycline-based X 6	25	- 62.8%	- 70%	PR	non-pCR
2	3	neg	neg	anthracycline-based X 4 docetaxel X 4	3.9	- 43.6%	- 41%	PR	non-pCR
3	1	pos	neg	anthracycline-based X 6	4.3	- 72%	- 72%	PR	non-pCR
4	2	pos	neg	anthracycline-based X 6	14	- 50%	- 64.3%	PR	non-pCR
5	1	pos	neg	anthracycline-based X 6	14	- 2.1%	- 88.6%	PR	non-pCR
6	2	neg	pos	anthracycline-based X 6	4.9	- 81.6%	- 89.8%	CR	non-pCR
7	3	neg	pos	anthracycline-based X 6	16	- 84.4%	- 93.8%	PR	non-pCR
8	2	pos	neg	anthracycline-based X 6	8	- 50%	- 68.8%	PR	non-pCR
9	2	neg	pos	anthracycline-based X 4 docetaxel X 4	3.4	- 61.5%	- 61.8%	PR	non-pCR
10	3	neg	neg	anthracycline-based X 6	6	- 16.7%	- 16.7%	SD	non-pCR
11	3	pos	neg	anthracycline-based X 6	10	- 40%	- 70%	PR	non-pCR
12	2	pos	neg	anthracycline-based X 6	5.4	- 61.1%	- 64.8%	PR	non-pCR
13	3	pos	neg	anthracycline-based X 6	10.9	- 72.5%	- 86.2%	CR	non-pCR
14	2	pos	neg	anthracycline -based X 3 docetaxel X 3	11.9	- 65.5%	- 71%	PR	non-pCR
15	3	pos	neg	anthracycline -based X 6	3.2	0%	- 43.8%	SD	non-pCR
16	2	neg	neg	anthracycline -based X 4 docetaxel X 4	13.2	- 63.6%	- 78.8%	SD	non-pCR
17	3	neg	neg	anthracycline-based X 3 docetaxel X 3	12	- 79.2%	- 90.8%	PR	non-pCR
18	3	pos	neg	anthracycline-based X 4 docetaxel X 4	4.1	- 78%	- 87.8%	PR	non-pCR
19	3	pos	neg	anthracycline-based X 6	12.1	- 71.1%	- 91.7%	PR	pCR
20	3	neg	pos	anthracycline-based X 3 docetaxel -Trastuzumab X 4	22	- 95.5%	- 95.5%	CR	pCR
21	3	neg	neg	anthracycline-based X 6	16	- 70%	- 87.5%	CR	pCR
22	3	neg	pos	anthracycline-based X 3 docetaxel -Trastuzumab X 3	6.6	- 50%	- 66.7%	PR	pCR
23	3	neg	neg	anthracyclines-based X 4 docetaxel X 4	12	- 25%	- 81%	CR	pCR

Table 2. Individual characteristics of 23 IBC patients

CR= complete response
PR= partial response
SD= stable disease
pCR= pathologic complete response
non-pCR= absence of pathologic complete response
HR= hormone receptor
neg= negative
pos=positive
SUV= Standardized Uptake Value

Variable	p value
Δ SUV (Standardized Uptake Value) max 1-3	**0.0128**
Clinical response	**0.0280**
Histologic grade	**0.0384**
Age	0.1078
Pathologic response	0.1321
Hormone Receptor status	0.2270
HER2 status	0.6391

Table 3. Multivariate analysis for Distant Metastasis-Free Survival.

Molecular subtypes	n	Pathologic response		SUV max PET1	ΔSUV max1-3	Survival (months)	
		pCR	non-pCR			DMFS	OS
HR positive/HER2 negative	11	1	10	9.5±3.8	- 69%±18	70.2	94.3
HR negative/HER2 positive	5	2	3	16.7±5.3	- 94%±17	45.8	78.7
Triple-negative	7	2	5	12.5±7	- 85%±27	36.7	63.7

Table 4. Molecular Breast Cancer subtype analysis.

HR= hormone receptor
pCR= pathologic complete response
non-pCR= absence of pathologic complete response
SUV= Standardized Uptake Value
DMFS= Distant Metastasis-Free-Survival
OS= Overall Survival