Revista Española de Medicina Nuclear e Imagen Molecular 41 (2022) 171–178

Predictive value of ^{18}F-FDG PET/CT indices on extensive residual cancer burden in breast cancer patients treated with neoadjuvant chemotherapy[☆,☆☆]

Tuğba Başoğlu[a,∗,1], Salih Özgüven[b,1], Hülya Şahin Özkan[c], Merve Çınar[d], Osman Köstek[e], Nazım Can Demircan[a], Rukiye Arıkan[a], Tuğba Akın Telli[a], Özlem Ercelep[a], Handan Kaya[c], Tunç Öneş[b], Tanju Yusuf Erdil[b], Mustafa Ümit Uğurlu[f], Faysal Dane[a], Perran Fulden Yumuk[a]

[a] Marmara University School of Medicine, Division of Medical Oncology, Istanbul, Turkey
[b] Marmara University School of Medicine, Department of Nuclear Medicine, Istanbul, Turkey
[c] Marmara University School of Medicine, Department of Pathology, Istanbul, Turkey
[d] Marmara University School of Medicine, Department of Internal Medicine, Istanbul, Turkey
[e] Edirne State Hospital, Division of Medical Oncology, Edirne, Turkey
[f] Marmara University School of Medicine, Department of General Surgery, Istanbul, Turkey

ARTICLE INFO

Article history:
Received 14 February 2021
Accepted 29 April 2021
Available online 26 May 2021

Keywords:
Breast neoplasms
Drug therapy
Residual cancer burden
Metabolic tumor volume
Total lesion glycolysis
Positron emission tomography computed tomography

ABSTRACT

Aim: We investigated the correlation between ^{18}F-FDG PET/CT indices and pathological response in breast cancer treated with neoadjuvant chemotherapy (NACT) which was scored with Residual Cancer Burden (RCB) system after surgery. Our aim is to detect extensive residual cancer burden earlier by using PET/CT indices.
Methods: Characteristics of patients were retrieved retrospectively. Baseline maximum Standart Uptake Value (SUVmax), Metabolic Tumor Volume (MTV) and Total Lesion Glycolysis (TLG) indices and reduction rate (RR) between baseline and interim evaluation were calculated with FDG PET/CT scan. All patients were evaluated according to RCB scores after surgery. Pathological responses and PET/CT measurement results were analyzed with demographic and clinical parameters.
Results: A total of 95 patients were included in the study. According to pathological responses, the distribution of RCB -0, -1, -2, -3 were 13 (13.7%), 11 (11.6%), 30 (31.6%), 41 (43.2%), respectively. Disease-free survival was significantly lower in the RCB3 group compared to the pathological responder group ($p = 0.01$). According to multivariate analysis, RR of SUVmax was determined as an independent variable predicting extensive residual cancer burden with an optimal cut-off value of 86% ($p < 0.05$).
Conclusions: We determined RR of SUVmax as an independent factor for predicting extensive residual tumor burden. We believe that RR of SUVmax is sufficient to predict pathological response in daily practice. In addition, MTV and TLG measurements do not contribute additionally to SUVmax alone and can cause unnecessary labor loss.

Valor predictivo de los índices 18F-FDG PET/CT sobre la carga tumoral residual en en pacientes con cáncer de mama extenso tratadas con quimioterapia neoadyuvante

RESUMEN

Objetivo: Investigamos la correlación entre los índices de PET/TC con ^{18}F-FDG y la respuesta patológica en el cáncer de mama tratado con quimioterapia neoadyuvante (NACT), que se puntuó con el sistema de carga de cáncer residual (RCB) después de la cirugía. Nuestro objetivo es detectar antes una carga extensa de cáncer residual mediante el uso de los índices de PET/TC.

☆ Please cite this article as: Başoğlu T, Özgüven S, Özkan HS, Çınar M, Köstek O, Demircan NC, et al. Valor predictivo de los índices 18F-FDG PET/CT sobre la carga tumoral residual en en pacientes con cáncer de mama extenso tratadas con quimioterapia neoadyuvante. Rev Esp Med Nucl Imagen Mol. 2022;41:171–178.
☆☆ This manuscript has not been published or presented elsewhere in part or in entirety, and is not under consideration by another journal.
∗ Corresponding author.
E-mail addresses: basoglutugba@gmail.com (T. Başoğlu), drsozg@gmail.com (S. Özgüven), drshulyasahin@gmail.com (H.Ş. Özkan), cinar.merve48@gmail.com (M. Çınar), osmankostek@hotmail.com (O. Köstek), ncdemircan@gmail.com (N.C. Demircan), dr_rukiyearikan@hotmail.com (R. Arıkan), tugbaakintelli@gmail.com (T.A. Telli), ozlembalvan@yahoo.com (Ö. Ercelep), hkaya@marmara.edu.tr (H. Kaya), tones@marmara.edu.tr (T. Öneş), yerdil@marmara.edu.tr (T.Y. Erdil), umit.ugurlu@marmara.edu.tr (M.Ü. Uğurlu), faysaldane@yahoo.com (F. Dane), fuldenyumuk@yahoo.com (P.F. Yumuk).
[1] Equal contributor.

Métodos: Se registraron las características de las pacientes de forma retrospectiva. Se calculó el valor máximo de captación estándar (SUVmáx), el volumen metabólico del tumor (MTV) y los índices de glucólisis total de la lesión (TLG), así como la tasa de reducción (RR) entre la línea de base y la evaluación intermedia, con la exploración FDG PET/TC. Todos los pacientes fueron evaluados según las puntuaciones RCB después de la cirugía. Las respuestas patológicas y los resultados de las mediciones de PET/TC se analizaron con parámetros demográficos y clínicos.

Resultados: Un total de 95 pacientes fueron incluidos en el estudio. Según las respuestas patológicas, la distribución de RCB -0, -1, -2, -3 fue de 13 (13,7%), 11 (11,6%), 30 (31,6%), 41 (43,2%), respectivamente. La supervivencia libre de enfermedad fue significativamente menor en el grupo RCB3 en comparación con el grupo de respuesta patológica ($p = 0,01$). Según el análisis multivariante, se determinó que el RR del SUVmax era una variable independiente que predecía la carga de cáncer residual extensa con un valor de corte óptimo del 86% ($p < 0,05$).

Conclusiones: Determinamos el RR de SUVmax como un factor independiente para predecir la carga tumoral residual extensa. Creemos que el RR de SUVmax es suficiente para predecir la respuesta patológica en la práctica diaria. Además, las mediciones de MTV y TLG no contribuyen adicionalmente al SUVmax por sí solas y pueden causar una pérdida de trabajo innecesaria.

Introduction

Breast cancer is the most frequently observed cancer in women, accounting for 25% of all cancers and the most common cause of cancer-related deaths worldwide.[1] Locally advanced stage is seen in 10–20%, and these patients have a poor prognosis.[2] Most patients with locally advanced, inflammatory, or high-risk early-stage breast cancer are lately treated with neo-adjuvant chemotherapy (NACT).

The goals of NACT are to assess response to treatment which also gives us hints of the biology of disease, eliminate micrometastases, down-staging primary tumor aiming for breast-conserving surgery, and prolonging survival.

Besides achieving pathological complete response (pCR) after NACT, it is also very important to identify non-responder patients. Because clinical trials and additional treatment options can be considered in non-responder groups. Several systems, such as Residual Cancer Burden (RCB),[3] Miller-Payne,[4] American Joint Committee on Cancer (AJCC),[5] Pinder[6] and National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18,[7] have been proposed to classify pathologic response after neo-adjuvant treatment.

Miller-Payne system was well known and widely used until the RCB system becomes more common in the past few years. According to Miller-Payne system pathological response is divided into five categories; grade 1 being no pathological response and no reduction in tumor cellularity, to grade 5 which is pCR, with no invasive carcinoma seen.[4] The presence of carcinoma in situ does not exclude pCR, and metastatic lymph nodes are not evaluated in this system. Recently, RCB has been the most commonly used system due to its quantitative nature, it is easier to compute, and World Health Organization encourages using this system.

Metabolic and volumetric parameters measured with ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computer tomography (PET/CT) had been studied before, as altered glucose metabolism which is the main subject of PET principles, occurs earlier than tumor shrinkage, and it might help to predict response to NACT before surgery.[8] A significant association between maximum standardized uptake value (SUVmax) and pCR has been reported after NACT.[9] The idea of combining volumetric and metabolic parameters might better reflect tumor response via reflect whole tumor activity and has become the interest of the latest studies.

In this study, we investigated the impact of SUVmax, MTV, and TLG on predicting pathological no response, which was scored by the RCB system, in breast cancer patients treated with NACT.

Patients and methods

Study design and patients selection

Clinical files of 245 locally advanced breast cancer patients who were treated with NACT, and followed in Medical Oncology Clinic between November 2012–December 2019, were retrospectively evaluated. Of these 245 patients, 95 had their baseline and interim ^{18}F-FDG PET/CT scans were performed in the Department of Nuclear Medicine of our institution, and postoperative pathological specimens were evaluated by the Department of Pathology at our institution. These 95 patients were included in our study, and demographic and clinical features were recorded. All patients were evaluated with ^{18}F-FDG PET/CT prior to and an average of 3 months after NACT (median four cycles of chemotherapy). PET/CT scans were used to measure metabolic and volumetric indices. Baseline indices and reduction rate (RR) between baseline and interim scans were obtained for primary lesion and metastatic lymph nodes. Pathological responses and PET/CT measurement results were analyzed with demographic and clinical parameters.

TNM classification of AJCC Cancer Staging Manual, Eight Edition (2017) was used for disease staging.[5] Diagnostic biopsy materials were evaluated for hormone (estrogen and progesterone) receptors (ER and PR) and human epidermal growth factor receptor 2 (HER2) status. ER and PR were considered as positive if immune-reactive cell nuclei were more than 1%. HER2 positivity was defined as 3+ by immunohistochemistry (IHC) or 1+, 2+ with IHC plus positive fluorescence observed in situ hybridization results.

Pathological evaluation

A web-based calculator for the RCB system was used to determine pathological response to NACT in this study. Data of largest two dimensions of post-treatment tumor bed, average tumor cellularity of residual invasive and in-situ carcinoma, number of metastatic lymph nodes, and the largest diameter of nodal metastasis are used to classify pathologic response into four categories in the RCB system: RCB-0 (pCR; absence of residual invasive and/or in situ carcinoma and nodal metastasis), RCB-1 (minimal residual disease), RCB-2 (moderate residual disease) and RCB-3 (extensive residual disease).[3] We reviewed post-operative pathology reports for the largest two dimensions of post-treatment tumor bed area, cellularity of residual invasive and in situ carcinoma, number of metastatic lymph nodes, and the largest diameter of nodal metastasis.

Slides of cases were re-evaluated. The size of the tumor bed area was calculated with extensive tissue sampling due to tumor heterogeneity and problematic gross assessment of post-therapy specimens. When macroscopic and microscopic calculations were discordant, the latter was used. Since tumor cellularity was heterogeneous in the majority of cases, the average cellularity of different slides was calculated. Cellularity of carcinoma in situ was separately noted. RCB scores were estimated by using the online MD Anderson Residual Cancer Burden Calculator. This web-based Residual Cancer Burden Calculator is free and can be reached on http://www.mdanderson.org/breastcancer_RCB. Graphical illustrations, which were provided at the above-mentioned link, were used to achieve a clearer estimation.

F-FDG PET/CT imaging and interpretation

All ^{18}F-FDG PET/CT scans were performed using a Discovery ST PET/CT scanner (GE Healthcare, Milwaukee, WI). All patients fasted for 6 h prior to the PET/CT scan, only oral hydration with glucose-free water and medications was allowed. All patients required to have <150 mg/dL blood glucose level prior to ^{18}F-FDG injection. ^{18}F-FDG (5 M Bq/kg) was injected intravenously. Approximately 1 h later, a low-dose multi-slice CT scan was done using a 16-slice multi-detector scanner (parameters: 80 mA, 140 kV, table speed 27 mm/rotation, and slice thickness 5.0 mm) of areas from the upper thigh to the skull base with the patient in shallow breathing. A standard whole-body PET scan was performed in 3D mode with an acquisition time of 3 min per bed position (six to eight-bed positions) covering the same field as the CT scan. Acquired data were reconstructed using an iterative algorithm, and CT images without contrast enhancement were acquired for attenuation correction. PET images were reconstructed with and without correction for attenuation using an iterative algorithm, then displayed for reading as sagittal, axial, and coronal views on Advantage Windows Workstation 4.5 using PET Volume Computerized Assisted Reporting (PET VCAR) software. CT, PET, and co-registered PET/CT images were reviewed in transaxial, coronal and sagittal views, and evaluated by two experienced nuclear medicine physicians.

Imaging analysis

A cuboid volume of interest (VOI) marking a breast cancer lesion and metastatic lymph nodes was set and VOI was automatically drawn along the margin of tumor uptake according to a specific SUV threshold by using PET VCAR software. SUVmax was defined as the maximum SUV in the VOI. The highest SUVmax value was used (tumor or metastatic lymph nodes) in patients with locoregional disease.[10] MTV refers to the volume of tumor greater than or equal to 40% of the SUVmax in VOI.[11,12] SUVmean was taken as average SUV concentration in VOI. TLG was calculated as MTV multiplied by the SUVmean.

Changes in SUVmax, MTV, and TLG values between pre-treatment (first ^{18}F-FDG PET/CT) and post-NACT (second ^{18}F-FDG PET/CT) were measured, and a RR of these parameters were calculated (Fig. 1). If the primary lesion and metastatic lymph nodes were indistinguishable from the surrounding glandular tissue on post-NACT ^{18}F-FDG PET/CT, the RR was noted as 100% (Fig. 2).

RR of SUVmax : [(SUVmax1-SUVmax2)/SUVmax1]x100(%)

RR of MTV: [(MTV1-MTV2)/MTV1]x100(%)

RR of TLG: [(TLG1-TLG2)/TLG1]x100(%)

Statistical analysis

SPSS 20.0 for Windows was used. Descriptive statistics were given as numbers and percentages for categorical variables, averages, standard deviations, minimums, and maximums for numeric variables. Two independent group comparisons of numerical variables were performed with Mann–Whitney U Test when normal distribution conditions were not achieved. More than two independent group comparisons were done with Kruskal–Wallis Test. Relationships between numerical variables were performed using Spearman's correlation analysis. Logistic regression analysis was used to determine independent factors for predicting RCB3. Confidence interval (CI) was selected as 95% and a two-sided *p*-value less than 0.05 was accepted as statistically significant. Disease-free survival (DFS) and overall survival (OS) were estimated with Kaplan–Meier method and log-rank test.

Results

A total of 95 female patients were included in the study. The median age was 47 (range: 39−57) years and median follow-up time was 35.1 (range: 10.8–84.3) months. Fifty-eight (61.1%) patients were premenopausal at the time of diagnosis, and invasive ductal carcinoma was the pathological diagnosis in 80%. According to molecular subtypes, 42.1% of patients as hormone receptor positive-HER2 negative, 26.3% of patients as hormone receptor positive- HER2 enriched, 22.1% of patients were reported as triple-negative breast cancer (TNBC), and 9.5% of patients as hormone negative-HER2 enriched breast cancer.

While 71.6% of patients had clinical stage 3 disease, others had clinical stage 2. Lymph node metastases were seen in 85.3% at the time of diagnosis.

Most of the patients (73.7%) received a combination of anthracyclines [doxorubicin (A) or epirubicin (E)], cyclophosphamide (C), and then taxane [paclitaxel (T) or docetaxel (D)] chemotherapy regimen. Eighteen (18.9%) patients received anthracycline, C and fluorouracil combination chemotherapy.

Sixty-six (69.5%) patients underwent modified total mastectomy, while the rest had breast-conserving surgeries.

Patient demographics, tissue biopsy characteristics, and treatment details are given in Table 1.

Evaluation results according to pathological response

When patients were classified according to RCB scoring system, the distribution of RCB -0, -1, -2, -3 were 13 (13.7%), 11 (11.6%), 30 (31.6%), 41 (43.2%), respectively. pCR (pCR = RCB 0) group was akin to non-pCR groups regarding to demographic and baseline clinical characteristics as seen in Table 2. Fourty-one pathological non-responder (RCB3) and 54 (56.8%) responder (RCB-0-1-2) patient groups also had similar characteristics, including histological subtypes.

F-FDG PET/CT results analysis

Response evaluation was done with PET/CT after a median of 4 cycles of chemotherapy, mostly AC/EC. Response to the chemotherapy regimens was not statistically different as given in Table 3 (***p* > 0.05**). RR (%) between baseline and interim measurements of SUVmax, TLG, MTV were calculated. As seen in Table 4 that pathological non-responders had lower median RR values. Optimal cut-off values to predict tumor response were calculated with ROC analysis (Table 5).

TLG–MTV, SUVmax–TLG, and SUVmax–MTV reduction rates had a significant positive correlation among themselves ($r = 0.76$ and $p < 0.001$; $r = 0.79$ and $p < 0.001$; $r = 0.72$ and $p < 0.001$, respectively).

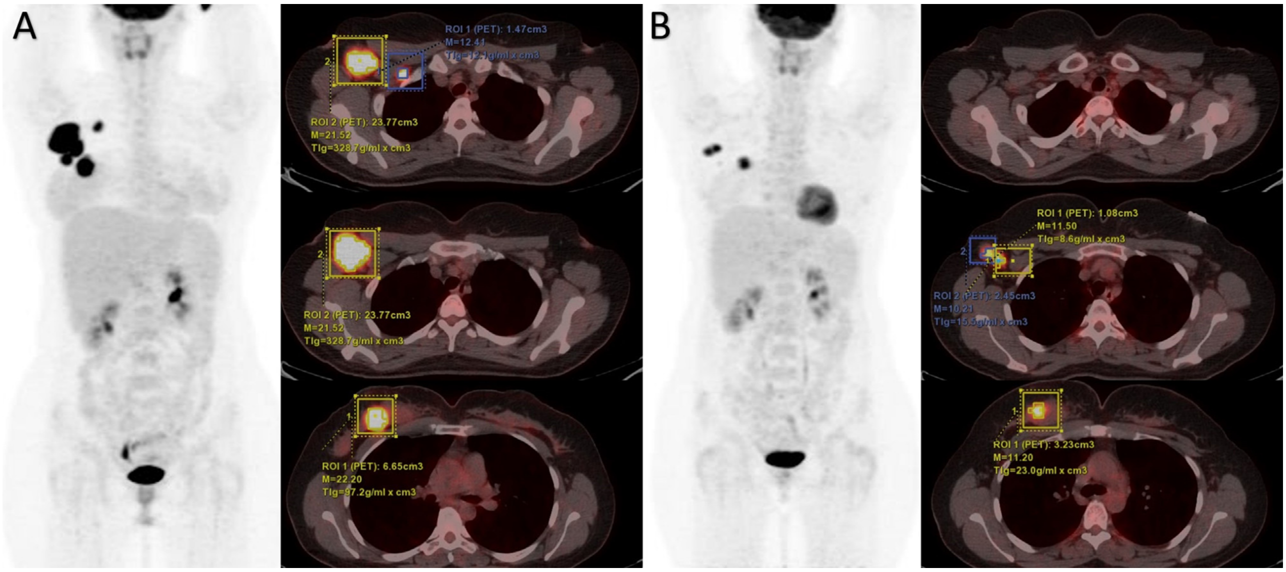

Fig. 1. A representative case of breast cancer showing no pCR. Maximum intensity projection and axial PET/CT images at baseline (A) and after chemotherapy (B) in a 47-year-old woman with invasive ductal carcinoma of the right breast. The reduction rate of SUVmax, TLG, and MTV observed after chemotherapy were 48.1%, 89.2%, 78.8% respectively. After surgery, the patient was classified as RCB-II according to the RCB classification.

Table 1
Patients' characteristics.

Age, years	
Median (range)	47 (39–57)
Body mass index, n (%)	
Normal and underweight	31 (32.6)
Obese and overweight	64 (67.4)
Smoking, n (%)	25 (26.3)
Menopausal status, n (%)	
Premenopausal	58 (61.1)
Postmenopausal	37 (38.9)
Tumor size (cm)	
≤2.5	46 (48.4)
>2.5	49 (51.6)
Lymph node metastasis, n (%)	
Negative	14 (14.7)
Positive	81 (85.3)
Nuclear grade, n (%)	
Grade 1 and 2	53 (55.8)
Grade 3	42 (44.2)
Ki67 expression levels, n (%)	
<15	23 (24.2)
15–30	38 (40.0)
≥30	33 (34.7)
Subtypes	
Triple negative	21 (22.1)
Luminal - HER2 (-)	40 (42.1)
HER2 (+)	34 (35.8)
Histopathology	
Invasive ductal	76 (80.0)
Invasive lobular	2 (2.1)
Others	17 (17.9)
Clinical Stage	
2	27(28.4)
3	68(71.6)
Type of surgery	
Breast conserving surgery	29 (30.5)
Mastectomy	66 (69.5)

Univariate and multivariate analysis of extensive residual cancer burden (RCB3)

Univariate analysis with clinical parameters and PET/CT indices was performed to predict extensive residual cancer burden. In addition to three groups which were below cut-off values, the fourth group where RR of SUVmax was below 86%, and RR of TLG was below 95%, or RR of MTV was below 80%, was also included in univariate analysis. As presented in Table 6, RR of all indices had a statistically significant impact on extensive residual cancer burden ($p < 0.05$). According to multivariate analysis, RR of SUVmax was determined as an independent variable predicting extensive residual cancer burden ($p < 0.05$).

Survival analysis

At the end of the final analysis, sixteen (16.8%) of our 95 patients had relapsed and eleven (11.6%) patients had died. Median OS and DFS of the whole patient population and also RCB3 patients could not be reached. Estimated three-year survival rates of RCB3 groups and others were 91% vs. 97%, and five-year survival rates were 85% vs. 88% respectively. DFS was significantly lower in the RCB3 group compared to the pathological responder group ($p = 0.01$), as shown in Fig. 3.

Discussion

Pathological response after NACT correlates with survival and it has been determined in the literature before.[13] It is also very important to identify non-responder patients after NACT. Additional treatment options for the pathological non-pCR group after NACT, as in Katherine trial[14] and CreateX trial,[15] constitute desired approach recently. In addition, tumor progression is seen approximately 3% of patients as surgery is delayed during NACT period.[16,17] This is also a sign of primary resistance to the NACT regimen and reflects tumors aggressive biology. Therefore, it is very crucial to improve a marker that can determine treatment-resistant group earlier and can easily be used in routine patient care.

We still do not have a good marker that shows us non-responders before surgery. In this study, we aimed to identify patients who are not responsive to NACT prior to surgery by using data of baseline and post-NACT PET/CT scans.

In our study, RR of SUVmax, TLG and MTV were determined as significant variables that predict residual cancer in univariate analysis while RR of SUVmax was determined as the best predictor of RCB in multivariate analysis. It was found that the baseline PET/CT indices were not effective in predicting RCB.

Table 2
Patients' characteristics according to residual cancer burden scores.

	RCB 0 (n = 13)	RCB 1 (n = 11)	RCB 2 (n = 30)	RCB 3 (n = 41)	*p*
Age, years					
Median (range)	47 (41–53)	46 (33–51)	48 (42–56)	46 (39–58)	0.66
Body mass index, n (%)					
Overweight and obese	10(76.9)	5(45.5)	19(63.3)	30(73.2)	0.41
Smoking, n (%)	2 (15.4)	2 (18.2)	9 (30.0)	12 (29.3)	0.66
Menopausal status, n (%)					
Premenopausal	9 (69.2)	10 (90.9)	16 (53.3)	23 (56.1)	0.12
Postmenopausal	4 (30.8)	1 (9.1)	14 (46.7)	18 (43.9)	
Tumor size (cm)					
≤2.5	6 (46.2)	6(54.5)	17 (56.7)	17 (41.5)	0.61
>2.5	7 (53.8)	5 (45.5)	13 (43.3)	24 (48.5)	
Lymph node metastasis, n (%)					
Negative	2 (15.4)	3 (27.3)	6 (20.0)	3 (7.3)	0.28
Positive	11 (84.6)	8 (72.7)	24 (80.0)	38 (92.7)	
Nuclear grade, n (%)					
Grade 1 and 2	5 (38.5)	7 (63.6)	18 (60.0)	23 (56.1)	0.55
Grade 3	8 (61.5)	4 (36.4)	12 (40.0)	18 (43.9)	
Ki67 expression levels, n (%)					0.49
<15	4 (33.3)	1 (9.1)	8 (26.7)	10 (24.4)	0.49
15–30	2 (16.7)	6 (54.5)	11 (36.7)	19 (46.3)	
≥30	6 (50.0)	4 (36.4)	11 (36.7)	12 (29.3)	
Subtypes					0.24
Triple negative	4 (30.8)	2 (18.2)	6 (20.0)	9 (22.0)	0.24
Luminal - HER2 (-)	2 (15.4)	6 (54.5)	14 (46.7)	18 (43.9)	
HER2 (+)	7 (53.9)	3 (27.3)	10 (33.3)	14 (34.1)	
Histopathology					
Invasive ductal	11 (84.6)	10 (90.9)	21 (70.0)	34 (82.9)	0.42
Others	2 (15.4)	1 (9.1)	9 (30.0)	7 (17.1)	
Type of surgery					
Breast conserving surgery	2 (15.4)	7 (63.6)	9 (30.0)	11 (26.8)	0.06
Mastectomy	11 (84.6)	4 (36.4)	21 (70.0)	30 (73.2)	

Table 3
Response to chemotherapy regimens.

	pCR, n(%)	*p* value	RR of SUVmax > 86%	*p* value	RR of TLG > 95%	*p* value	RR of MTV > 80%	*p* value
Group A	11(14.3)	0.72	42(54.5)	0.44	46(59.7)	0.74	45(58.4)	0.28
Group B	2(11.1)		8(44.4)		10(55.6)		8(44.4)	

Group A: [Doxorubicin (A) or Epirubicin (E)], Cyclophosphamide (C), and then Taxane [paclitaxel (T) or docetaxel (D)].
Group B: [Fluorouracil (F), Anthracycline (E)] and Cyclophosphamide (C).
pCR: pathological complete response, RR: reduction rate, SUVmax: maximum standardized uptake value, TLG: total lesion glycolysis, MTV: metabolic tumor volume.

Table 4
Median of PET/CT indices according to residual cancer burden scores.

	RCB 0 (n = 13)	RCB 1 (n = 11)	RCB 2 (n = 30)	RCB 3 (n = 41)
RR of SUVmax %	100	95	88	68
RR of TLG %	100	97	93	88
RR of MTV %	100	100	74	60

RR: reduction rate, SUVmax: maximum standardized uptake value, TLG: total lesion glycolysis, MTV: metabolic tumor volume, RCB: residual cancer burden.

Table 5
Reduction rates to predict RCB3-extensive cancer burden patients.

Reduction rate	Sensitivity	Specificity	PPV	NPV
SUVmax, Low (<86%)	70	70	64	76
TLG, Low (<95%)	60	70	64	71
MTV, Low (<80%)	58	53	57	67
Low TLG and/or MTV with Low SUVmax[a]	58	74	63	70

RR: reduction rate, SUVmax: maximum standardized uptake value, TLG: total lesion glycolysis, MTV: metabolic tumor volume, RCB: residual cancer burden, PPV: positive predictive value, NPV: negative predictive value.
[a] RR of SUVmax, TLG and MTV best cut-off values for RCB3 is 86%, 95%, 80%.

In the literature, the first studies focusing on the correlation of PET/CT parameters with the pathological response after NACT used baseline SUVmax measurements. In 2011, data of 920 patients from 19 studies were pooled in a meta-analysis,[18] and sensitivity and specificity of ^{18}F-FDG PET/CT in predicting histopathological response were reported as 84% (95% CI 78–88%) and 66% (95% CI 62–70%), respectively. Another study showed higher ^{18}F-FDG uptake (SUVmax) was independently associated with pCR.[19] In our study, there was a significant concordance between higher baseline SUVmax and pCR, which is consistent with the literature (median baseline SUVmax 11.5 in patients with pCR, 8.2 with non-pCR).

Subsequent studies were designed to predict pathological response according to different molecular subtypes of breast cancer using PET/CT parameters. In previous studies, it was stated that baseline measurements of PET/CT are higher in aggressive subtypes such as TNBC and HER2 enriched groups, and there was a correlation with pCR. Similarly, there was a positive correlation between RR of SUVmax and pCR in these groups. However, the same result could not be confirmed in ER positive-HER2 negative subtype.[20–22] As FDG uptake reflects tumor metabolism indirectly, higher FDG uptake at baseline and increased RR after NACT is expected to have a higher pCR in aggressive subtypes. In our patient population, the median baseline measurements and RR of SUVmax, TLG, MTV values of ER positive HER2-negative subtypes were lower than TNBC and HER2 enriched subtypes, similar to the literature data (median baseline SUVmax, TLG, MTV values were 7.5, 33.3, 9.8 vs. 10.5, 69.2, 12.7, respectively; median RR of SUVmax, TLG, MTV values were 85%, 96%, 84% vs. 90%, 97%, and 88%, respectively).

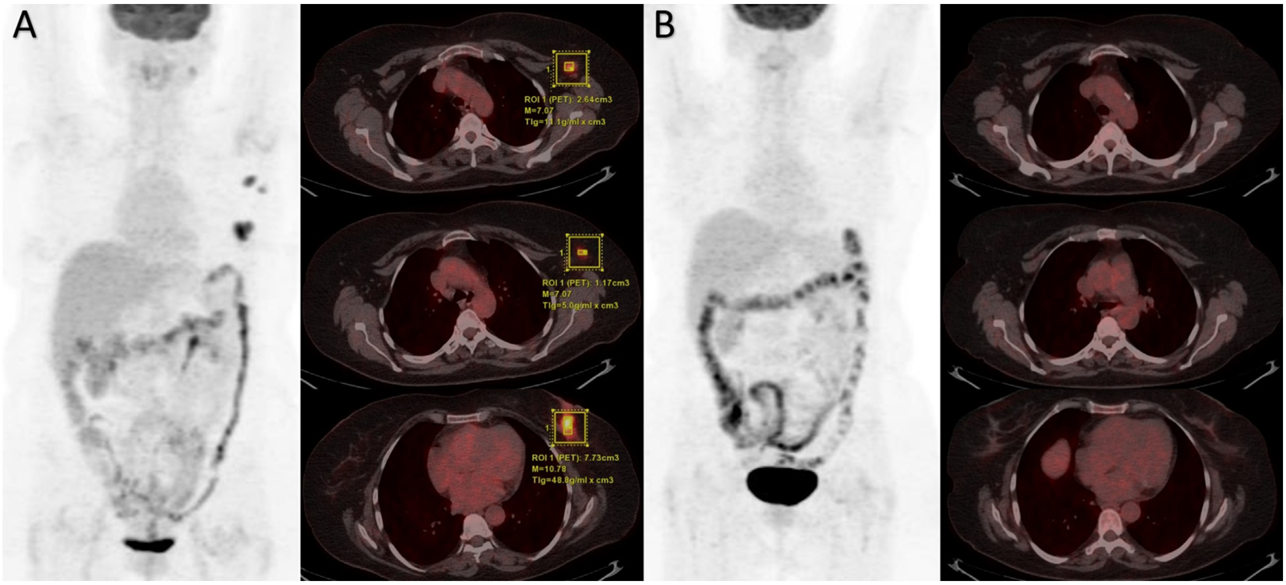

Fig. 2. Maximum intensity projection and axial PET/CT images at baseline (A) and after chemotherapy (B) in a 51-year-old woman with invasive ductal carcinoma of the left breast. The reduction rate of SUVmax, TLG, and MTV noticed after chemotherapy was 100% (primary lesion and metastatic lymph nodes are indistinguishable from the surrounding glandular tissue). After surgery, the patient was classified as RCB-0 according to the RCB classification.

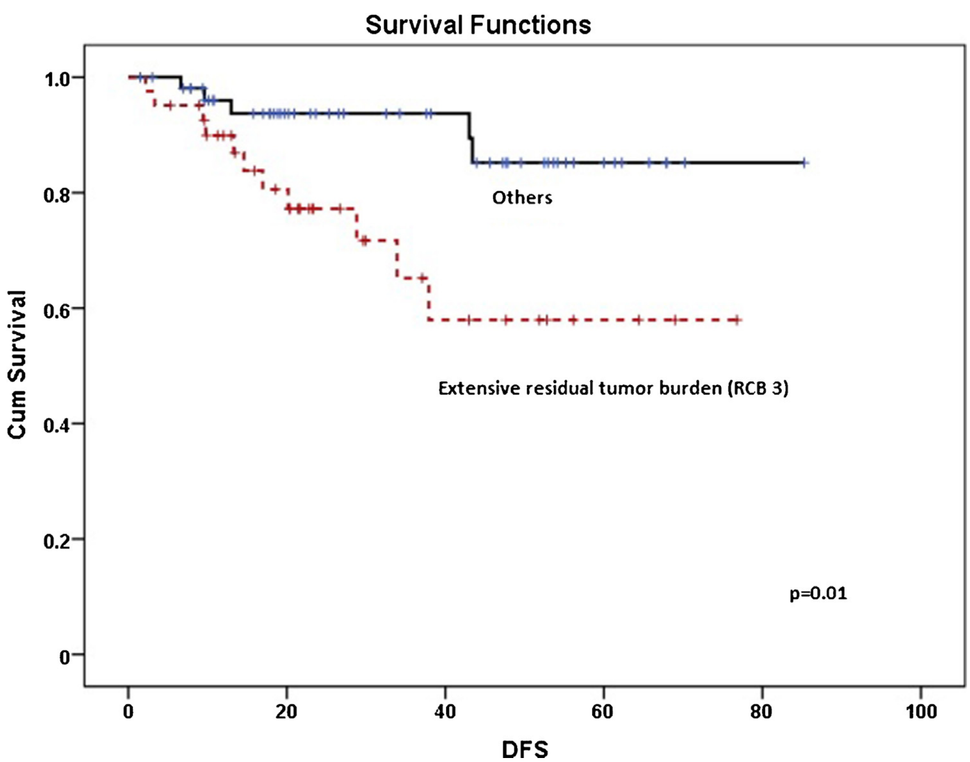

Fig. 3. Disease-free survival was significantly lower in the Extensive Residual Cancer Burden (RCB3) group compared to the pathological responder group (p = 0.01).

Later studies investigated whether combining metabolic measurements with volumetric measurements could be a better predictor for the pathological response. The origin of this idea was that volumetric measurements reflect the whole tumor activity; while SUVmax reflects a single voxel.[11] However, it is still controversial to use volumetric indices in our daily practice due to the lack of standardization of measurement parameters. In our study, as we presented in Table 5, neither RR of TLG, RR of MTV nor the combination of them did not increase sensitivity or specificity for predicting residual cancer burden and did not contribute to RR of SUVmax alone in the detection of non-responders.

Several studies determined RR between baseline and interim values to be the main predictor for extensive residual cancer burden.[23,24] The timing of the interim PET/CT scans to assess the RR were variable in the literature. Some studies define that metabolic changes of tumors occur within the first chemotherapy cycle; so early evaluation can reflect early response. Therefore, interim evaluation is mostly done after the second cycle of chemotherapy.[25,26] On the contrary, the metaanalysis of Tian et al. showed some stud-

Table 6
Univariate and multivariate analysis of extensive residual cancer burden (RCB3).

	Univariate analysis			Multivariate analysis			
	n	95% CI	HR	*p* value	95% CI	HR	*p* value
Age, ≥60	15	0.73–6.93	2.2	0.15			
BMI, obesity	64	0.66–3.85	1.6	0.29			
Smoking, (+)	25	0.52–3.26	1.3	0.57			
Postmenopausal	37	0.62–3.31	1.44	0.50			
Tumor size, >2.5 cm	49	0.72–3.70	1.6	0.23			
Lymph node, positive	81	0.84–12.48	3.2	0.06			
Nuclear grade 3	42	0.40–2.21	0.9	0.95			
Ki67 expression, ≥30	33	0.45–3.68	1.3	0.62			
Subtypes							
Triple negative and HER2 (+)	55	0.31–2.80	1.0	0.77			
Baseline median values							
SUVmax, Low (<8.4)	47	0.19–1.12	1.3	0.05			
TLG, Low (<53633)	47	0.6–2.36	1.05	0.90			
MTV, Low (<10.1)	47	0.6–2.36	1.05	0.90			
Reduction rate (%)							
SUVmax, Low (<86)	45	2.35–13.99	5.7	0.000	1.06–18.20	4.4	0.04
TLG, Low (<95)	39	1.86–10.7	4.46	0.001	0.24–9.91	1.5	0.64
MTV, Low (<80)	42	1.21–6.54	2.8	0.014	0.85–5.19	2.1	0.81
Low TLG and/or MTV with Low SUVmax[a]	38	1.69–9.62	4.03	0.002	0.75–14.03	1.8	0.07

RR: reduction rate, BMI: body mass index, SUVmax: maximum standardized uptake value, TLG: total lesion glycolysis, MTV: metabolic tumor volume, HR: hazard ratio, CI: confidence interval.

[a] SUVmax RR is below 86% with TLG RR is below 95% and/or MTV RR is below 80%.

ies that evaluation after four or more cycles of chemotherapy can be accurate for predicting response similar to our work.[10,27,28] The basis of these studies, like our study, was to assess the response to treatment before changing the chemotherapy protocol.

The last issue we want to emphasize is the different pathological scoring systems were used in previous studies. RCB is a more reliable scoring system than Miller-Payne, especially in defining the non-responding group.[29,30] Miller-Payne scoring was able to detect only 11 of 41 patients who were pathologically unresponsive according to RCB scoring in our patient population. Because, presence of carcinoma in situ does not exclude pCR, and metastatic lymph nodes are not evaluated in Miller-Payne scoring. Therefore, some non-responder patients were accepted in pCR groups in this scoring. We believe that our results are more reliable than similar studies in the literature by using RCB scoring.

Conclusion

In conclusion, we found RR of SUVmax as an independent factor for predicting extensive residual cancer burden. We also want to emphasize that RR of SUVmax is the most powerful predictor of the treatment response after interim evaluation, and may be used to plan the next step of treatment. Besides, adding RR of TLG and RR of MTV to RR of SUVmax did not increase sensitivity and specificity for the detection of the RCB3 patient group.

It is very important to predict treatment-resistant patients earlier with non-invasive and easily accessible techniques in daily practice. RCB scoring should be adopted in clinical practice as a standard scoring system. We believe that the RCB3 patient group should be encouraged for clinical trials instead of continuing standard NACT in the future.

Statement of ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Appropriate local regulations were followed, and ethical review approval was obtained. All patients provided written informed consent.

Conflict of interest

The authors have no conflicts of interest to declare.

Funding sources

No funding has been provided for the preparation of this manuscript.

All procedures performed were in accordance with ethical standarts of institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

This study was performed with local ethics/ institutional review board approval (No. 09.2020.1110)

Written informed consent was obtained from all patients

Acknowledgement

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

The authors did not receive honoraria related to the preparation of this manuscript.

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