18F FDG PET/CT after Neoadjuvant Chemotherapy and Pathological Responses are Predictive Factors for Disease-Free Survival and Overall Survival in Patients with Locally Advanced Breast Cancer: A Prospective Study

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ABSTRACT

We investigated the prognostic value of interim and post-neoadjuvant chemotherapy (NAC) 18F FDG PET/CT and the complete pathological and metabolical response after NAC for disease-free survival (DFS) and overall survival (OS) in patients with locally advanced breast cancer (LABC) receiving NAC. Patients who were decided to receive NAC were evaluated with baseline (PET1), after 2-3 cycles of chemotherapy (interim-PET2), and after NAC-before surgery (PET3) with 18F FDG PET/CT. The primary tumor SUV and the total metabolic tumor volume (MTV) of the primary tumor+axillary lymph nodes were calculated and defined for PET1-2-3 as SUV1-2-3 and MTV1-2-3. We also calculated Δ%SUV and Δ%MTV for PET1-2 and PET1-3. The relation between parameters and survival was evaluated with Cox regression analysis. Patients were grouped as a complete metabolic response or not (metCR/non-metCR) according to PET3 and as PCR/non-PCR according to the presence of residual invasive tumor as a result of pathology after NAC. Forty-two patients were analyzed (46.36±10.4 years old). The median follow-up time was 94.3 months. For DFS and OS, only MTV from post-NAC PET/CT was an independent predictor. For MTV3 ≤ 2.1 mL vs. > 2.1 mL, 7-year DFS and OS were 81.3% - 50%, (p= 0.038) and 88.2% and 55.6%, (p= 0.042) respectively. Survival was statistically significantly different in the PCR/non-PCR patient groups. There was no difference in DFS between patients with metCR/non-metCR, only between groups for OS (Log-rank). MTV (≤ 2.1mL vs. > 2.1mL) obtained from 18F FDG PET/CT after NAC-pre-surgery and complete pathological response might distinguish patients with poor prognosis.

Keywords: Breast cancer, Neoadjuvant chemotherapy, Fluorodeoxyglucose, PET/CT, Survival

INTRODUCTION

Neoadjuvant chemotherapy (NAC) has become a standard for locally advanced breast cancer. The essential goals of NAC are to increase the rate of breast-conserving surgery and predict the prognosis by monitoring the response of the tumor to treatment.[1,2] In breast cancer patients receiving NAC, complete pathological response (pCR) is an important prognostic indicator for long-term disease-free and overall survival.[3,4] However, PCR is an essential predictor of prognosis; the recurrent disease may be seen in some patients with pCR.[5] Therefore, there is a need for additional predictive markers other than pCR for early relapse in patients receiving NAC.

18F FDG PET/CT can quantify the glucose metabolism that reflects malignant tumors' metabolic activity and growth potential. With standard uptake value (SUV), we can detect and quantify changes in FDG uptake as the cytotoxic effect of chemotherapy reduces cellular glycolysis before tumor shrinkage occurs.[6,7]

Although SUVmax, a semi-quantitative parameter derived from 18F FDG PET/CT, is the most popular indicator in current practice, SUVmax only represents the most prominent point of metabolic activity within the tumor. It cannot be used to assess the overall metabolic tumor burden. Therefore, total metabolically active tumor volume (MTV) has also been used for prognosis.[8] Data obtained from interim 18F FDG PET/CT in patients with breast cancer have been reported to have prognostic value for survival.[9-11] Studies show that 18F FDG PET/CT, but not interim 18F FDG PET/CT, is prognostic for survival after NAC.[12-14]

Our study aimed to investigate the predictive value of SUVmax and MTV obtained from baseline, interim, and end-NAC PET/CT for disease-free survival (DFS) and overall survival (OS) in breast cancer patients receiving NAC. It also investigated the prognostic value of complete metabolic response (metCR) after NAC and PCR detected after surgery for DFS and OS.

PATIENTS and METHODS

Patients

Patients diagnosed with breast cancer were included between November 2012 and November 2014 who planned to receive NAC. Patients with clinically or radiologically distant metastases were excluded. The staging was performed according to the American Joint Committee on Cancer (AJCC) seventh edition.[15]

We performed 18F FDG PET/CT (PET1) to stage patients. Oncologists evaluated patients whose primary tumor showed FDG uptake and no clinically and radiologically distant metastases. Written consent was obtained from the patients who decided to receive NAC. We applied interim 18F FDG PET/CT (PET2) to the patients for 2-3 cycles [36 patients (85%) had two cycles, 6 had 15(%) 3 cycles] approximately three weeks after chemotherapy. Approximately three weeks after the end of NAC, 18F FDG PET/CT (PET3) was applied again. Afterward, the patients were referred for surgery. Adjuvant treatment was performed with or without radiotherapy according to the stage, clinical findings, and tumor biology after the surgery. The patients were followed up regularly by the oncology clinic. For DFS, we calculated the time from the diagnosis to the development of recurrence and the diagnosis to the last follow-up date if there was no recurrence. For OS, we calculated the time from diagnosis to the date of death from disease.

Pathological Response Assessment

Modified radical mastectomy and, if necessary, axillary lymph node dissection was performed on the patients. We defined the absence of residual invasive tumor as the complete pathological response (PCR) and accepted the presence of carcinoma in situ as PCR.[16] We defined PCR as BreastOnlyPCR for primary breast tumor, NodeOnlyPCR for axillary lymph node, and BreastAndNodePCR for breast+axillary lymph node.[17]

18F FGD PET/CT Imaging Protocol

All patients were requested to fast for at least 6 hours before imaging. Before the 18F-FDG injection, blood glucose was ≤ 180 mg/dl. Patients were scanned from the base of the skull to the mid-thigh in the supine position (3 minutes per bed position) with a 128x128 matrix. Iterative image processing was applied to images (2 iterations, 21 subsets). CT images were obtained with a 4-slice device (140 kV, 80 mA). Attenuation correction was performed with CT slices. In PET1, FDG uptake time was median 85.5 minutes (45 to 128 minutes); in PET2, 91 minutes (62 to110 minutes); in PET3, 88 minutes (47 to 110 minutes).

Imaging Assessment

Two nuclear medicine physicians with over 20 years of expertise and a research assistant evaluated the images at the AW-46 workstation (GE Healthcare, USA). All PET/CTs of the patients were evaluated simultaneously. Evaluators were unaware of clinical data, pathology results, and other images (MRI, mammography, ultrasound). When there was disagreement among the evaluators, the final decision was reached by consensus. We drew a volume of interest (VOI) from the breast to cover the entire tumor. We measured SU-

Vmax and named it SUV1, SUV2, and SUV3 for PET1, PET2, and PET3. We also generated VOI for each breast tumor and axillary lymph node, thus calculating the metabolic volume (MTV) separately, then collected all MTVs and obtained the total metabolic tumor volume (MTV), defined as MTV1, MTV2, and MTV3. We made manual corrections for each VOI to distinguish each lesion from the surrounding soft tissue using the adaptive threshold method.[18] We calculated the % change of parameters between PET/CTs according to the formula.

Δ% SUV1-2: (SUV2-SUV1)/SUV1*100,

Δ% SUV1-3: (SUV3-SUV1)/SUV1*100

Δ% MTV1-2: (MTV2-MTV1)/MTV1*100,

Δ% MTV1-3: (MTV3-MTV1)/MTV1*100

Metabolic Response Assessment

For the complete metabolic response, we used the criteria of breast tumor or axillary lymph node showing low FDG uptake from blood pool activity and indistinguishable from surrounding tissue.[19] In PET3, we defined complete metabolic response as BreastOnlymetCR only in breast tumor, NodeOnlymetCR only in the axillary lymph node, and BreastAndNodemetCR in the absence of residual invasive tumor in all breast and axilla.

NAC Regimen and Patients Follow Up

NAC consisted of taxanes following anthracycline. Postoperative radiotherapy was applied, and hormone therapy was given to patients with hormone receptor-positive breast cancer. Patients with HER2-positive breast cancer were treated with a trastuzumab-based regimen. Mammography, breast ultrasound, CT, whole-body bone scan, or FDG-PET/CT were used for follow-up. Suspected lesions were either biopsied or confirmed by clinical follow-up.

Statistical Analysis

We evaluated the relationship of PCR and metCR with DFS and OS using Kaplan-Meier method (log-rank test) curves and found p and chi-square values. The relationship between SUV, MTV, Δ% SUV, and ΔMTV to DFS and OS was evaluated by Cox regression analysis. We first evaluated the relationship between parameters DFS and OS with univariate Cox regression and included parameters with a p-value < 0.2 in the multivariate analysis, then created a model with the Backward LR method. The p significance value was accepted as 0.05. We used the receiver operating characteristic (ROC) curve to determine the optimal threshold value for the predictor of recurrence and death due to disease for the parameter found as an independent prognostic predictor in the multivariate analysis. Patient groups were dichotomized according to these threshold values. 7-year DFS and OS survival curves were estimated using the Kaplan Meier method and compared using the log-rank test. SPSS version 25 (IBM Corp. in Armonk, NY.) was used.

Ethics committee approval was obtained from the Hacettepe University ethics committee for this prospective and single-center study (Permission number GO 13/45-29).

RESULTS

We applied baseline 18F FDG PET/CT to 46 patients. 1 patient died of colitis after two cycles of chemotherapy. Data of 3 patients were missing. We included 42 patients (46.36±10.4 years old) in the analysis. The median follow-up was 94.3 months (7.6-108.6 months). The diagnosis of 36 patients was invasive ductal carcinoma, and 6 of them were mixed carcinoma (ductal+lobular). Twenty-three patients had T2, 15 had T3, and four had T4 tumors. While the tumor was grade 2 in 16 patients, it was grade 3 in 26 patients. Tumors were multifocal/multicentric in 8 patients and unifocal in 34 patients. While 28 patients were premenopausal, 14 patients were postmenopausal. Patient clinical information is given in Table 1.

Disease-Free Survival Analysis: *We performed a DFS analysis on 36 patients*

Univariate Analysis: SUV (1,2,3), MTV (1,2,3), Δ%SUV (1-2, 1-3) ve Δ%MTV (1-2, 1-3) were included into the analysis. MTV3 (p= 0.002, HR: 1.846, 95%CI: 1.259-2.709), Δ%SUV1-3 (p= 0.019, HR: 1.051, 95%CI: 1.008-1.095) and

Δ%MTV1-3 (p= 0.041, HR: 1.053, 95%CI: 1.002-1.107) were statistically significant.

Multivariate Analysis: We included MTV3, Δ%SUV1-3, Δ%MTV1-3, SUV3 Δ%SUV1-2 in the multivariate analysis. Only MTV3 was the independent predictor for DFS (p= 0.005, HR: 2.224, 95%CI: 1.270-3.895). ROC curve was performed to determine the optimal threshold value for the recurrence predictor of MTV3. For MTV3 ≤ 2.1mL vs > 2.1mL, the sensitivity was 66.7% and the specificity was 68.4% (AUC= 0.810, p= 0.009, 95%CI: 0.640-0.980). Patients were dichotomized as MTV3 ≤ 2.1mL vs.> 2.1. In the Kaplan-Meier (log-rank) analysis, the 7-year DFS for the MTV3 ≤ 2.1mL vs. > 2.1 patient groups was 81.3% and 50%, respectively (p= 0.038, χ^2= 4.315) (Figure 1). Univariate and multivariate analysis summary is given in Table 2.

Overall Survival Analysis: *We analyzed OS in 39 patients*

Univariate Analysis: SUV (1,2,3), MTV (1,2,3), Δ%SUV (1-2, 1-3) ve Δ%MTV (1-2, 1-3) were included. MTV3 (p= 0.002, HR: 1.887, 95%CI: 1.258-2.832) and Δ%MTV1-3 (p= 0.049, HR: 1.057, 95%CI: 1.000-1.117) were statistically significant.

Multivariate Analysis: MTV3, Δ%MTV1-3, and Δ%SUV1-3 were included. Only MTV3 was independent predictor (p= 0.003, HR: 1.870, 95%CI: 1.243-2.813) for OS. ROC curve was performed to determine the predictor of MTV3 for death from disease. For MTV3 ≤ 2.1mL vs. >2.1mL cutoff, sensitivity was 75% and specificity was 76.2% (AUC= 0.804, p= 0.013, 95%CI: 0.597-1.000). Patients were dichotomized as MTV3 ≤ 2.1mL vs.> 2.1. The 7-year OS for MTV3 ≤ 2.1mL vs.> 2.1 patient groups was 88.2% and 55.6%, respectively (p= 0.042, χ^2=4.144) (Figure 2). Univariate and multivariate analysis summary is given in Table 3.

The Value of Pathological and Metabolic Response in Prognosis

We detected BreastOnlyPCR in 12 patients, NodeOnlyPCR in 22 patients, and BreastAndNodePCR in 11 patients. We observed BreastOnlymetCR in 19 patients, NodeOnlymetCR in 24 patients, and BreastAndNodemetCR in 13 patients.

Table 1. Patient and tumor characteristics

Parameter	n (%)
Histology	
IDC	36
Mixt (Ductal+lobular)	6
Hormon Reseptor status	
HR- positive	27
TN	7
HER-2	8
Grade	
2	16
3	26
Menopausal status	
Pre	28
Post	14
T Stage	
T2	23
T3	15
T4	4
N Stage	
N0	6
N1	19
N2	5
N3	12
Tumor Focality	
Unifocal	34
Multifocal/multicentric	8

IDC= invasive ductal carcinoma; Mixt= invasive ductal+lobuler carcinoma; HR= hormone reseptör; TN= triple-negative; Her-2= Human epidermal growth factor receptor 2

Disease-Free Survival Analysis: Kaplan Meier analysis showed that, DFS was longer in the BreastOnlyPCR (p= 0.011, χ^2= 6.399), NodeOnlyPCR (p< 0.001, χ^2= 12.460), BreastAndNodePCR (p= 0.019, χ^2= 5.544) patient groups compared to the non-PCR group (Figure 3). In the BreastOnlymetCR (p= 0.071, χ^2= 3.261), NodeOnlymetCR (p= 0.560, χ^2 =0.339), BreastAndNodemetCR (p= 0.136, χ^2= 2.221) patient groups, DFS was not statistically different from the non-metCR group.

Overall Survival Analysis: OS was longer in the BreastOnlyPCR (p= 0.039, χ^2=4.244), NodeOnlyPCR (p= 0.001, χ^2= 10.454) patient groups com-

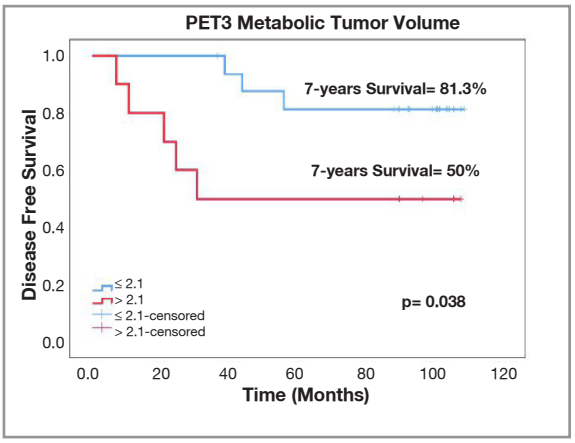

Figure 1. Kaplan-Meier graph showing disease-free survival in patients grouped by metabolic tumor volume (≤ 2.1 mL vs. > 2.1mL)

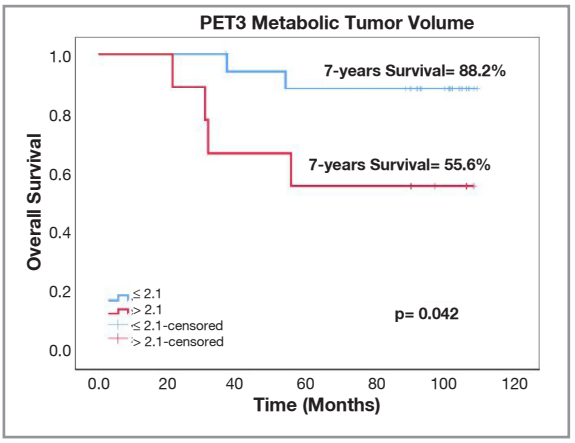

Figure 2. Kaplan-Meier graph showing overall survival in patients grouped by metabolic tumor volume (≤ 2.1 mL vs. > 2.1mL)

pared to the non-PCR group. In the BreastAndNodePCR (p= 0.060, χ^2= 3.544) group, OS was border statistically significantly longer compared to the non-PCR group. OS was longer in BreastOnlymetCR (p= 0.036, χ^2 =4.414) and BreastAndNodemetCR (p= 0.014, χ^2=6.064) patients compared to the non-metCR group (Figure 4). However, OS in NodeOnlymetCR (p= 0.194, χ^2= 1.685) patients was not statistically significantly better than the non-metCR group.

DISCUSSION

In this prospective study, we investigated the predictive value of SUV, MTV obtained from pre-NAC, interim, and post-NAC-pre-operative 18F FDG PET/CT and the Δ% change of these two parameters between 18F FDG PET/CTs for DFS and OS. We also investigated the predictive value of PCR and metCR detection after NAC for OS and DFS.

Table 2. Summary of univariate and multivariate analysis for disease-free survival

	DISEASE-FREE SURVIVAL					
	Univariate Analysis			Multivariate Analysis		
Parameter	p	HR	95%CI	p	HR	95%CI
SUV1	0.945	0.995	0.872-1.136			
SUV2	0.266	1.119	0.918-1.364			
SUV3*	0.114	1.260	0.946-1.680	0.078	0.355	0.112-1.124
MTV1	0.862	1.001	0.986-1.017			
MTV2	0.467	1.020	0.967-1.076			
MTV3*	0.002	1.846	1.259-2.709	0.005	2.224	1.270-3.895)
Δ%SUV1-2*	0.190	1.014	0.993-1.036	0.494	1.012	0.978-1.046
Δ%SUV1-3*	0.019	1.051	1.008-1.095	0.577	0.982	0.920-1.048
Δ%MTV1-2	0.279	1.014	0.989-1.040			
Δ%MTV1-3*	0.041	1.053	1.002-1.107	0.363	1.030	0.967-1.097

** Parameters included in multivariate analysis.*
SUV= standardized uptake value; MTV= metabolic tumor volume (primary tumor+axillary lymph node)

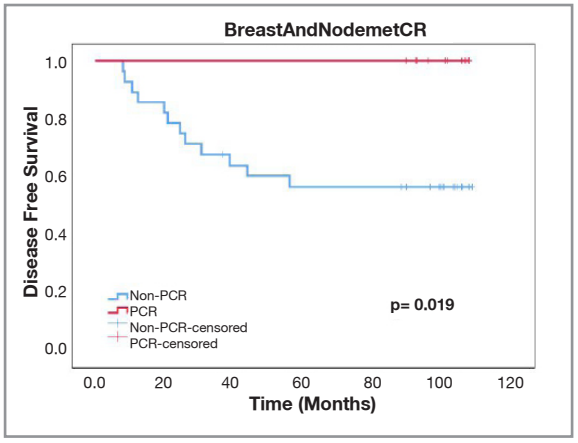

Figure 3. Kaplan-Meier graph showing disease-free survival in patients grouped by complete pathological response

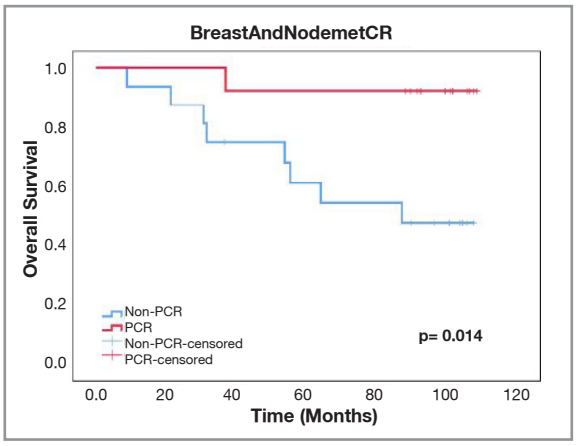

Figure 4. Kaplan-Meier graphs showing overall survival in patients grouped by complete metabolic response

SUV and MTV obtained from pre-NAC and interim 18F FDG PET/CT were not predictors for survival. Also, there was no statistically significant correlation between Δ%SUV1-2, 1-3 and Δ%MTV1-2, 1-3 and survival. Only MTV3 was an independent predictor for DFS and OS. In a study including 130 patients, SUV after NAC was associated with DFS, while SUV before NAC was unrelated in Her2+ and TN patients. Unlike our study, no evaluation was made with interim PET/CT in this study.[20] The study included 66 patients; the SUV change obtained from 18F FDG PET/CTs before and after NAC was a predictor for DFS, regardless of hormone receptor type.[21] A study including 72 patients with evaluated SUV and MTV before and after NAC stated that no parameter was a predictor for survival in the multivariate analysis.[8] In a study in which 262 patients with luminal type (A, B) breast cancer were evaluated, pretreatment SUVmax was a predictor for OS. They grouped the patients as SUVmax ≤ 6 and > 6. The 5-year survival rates were statistically significantly different.[22] A study evaluating 82 patients stated that the best predictor for survival was SUVmax after 2-3 cycles of chemotherapy.[11] In a prospective study evaluating 23 patients with inflammatory breast cancer, patients were evaluated with baseline, after three courses of chemotherapy and after NAC, before surgery 18F FDG PET/CT. Baseline, interim, after NAC PET/CT parameters, were not associated with OS, only Δ% PET1-3.[12] In another study, the patients were evaluated with baseline after two courses and the end-of-the NAC PET/CT. Only the end-of-the NAC PET SUV was a predictor for OS and DFS, ΔSUVPET1-2 was not a predictor for survival, and ΔSUVPET1-3 was associated with DFS. The authors stated that post-NAC or ΔSUVPET1-3 parameters might be related to survival.[13] A study evaluated the relationship between SUV and MTV from PET/CT before and after NAC with DFS (n= 132). MTV from PET CT after NAC was an independent predictor of DFS, regardless of tumor subtype and stage. The MTV treshold was determined as 0.2 cm^3 for the prognosis.[14] As observed in the studies mentioned in the above paragraph, which investigated the prognostic value of PET/CT in patients with breast cancer, different results have been reported. The reasons for this can be listed as heterogeneity in patient inclusion criteria (differences according to histological subtype or hormone receptor status), differences between treatments, and timing of interim PET. In addition, there are still several technical limitations to the quantitative PET imaging analysis method. Both MTV and SUVmax calculations are affected by many factors, such as the definition of volume of interest, uptake time, and plasma glucose level. The volume of interest segmentation method for determining MTV is still evolving, and there is currently no validated method.

This study obtained that PCR is a predictor for DFS and OS. In a study including 221 patients, PCR was a predictor for DFS.[23] The review, which included

Table 3. Summary of univariate and multivariate analysis for overall survival

	OVERALL SURVIVAL					
	Univariate Analysis			Multivariate Analysis		
Parameter	p	HR	95%CI	p	HR	95%CI
SUV1	0.877	0.990	0.878-1.118			
SUV2	0.474	1.077	0.879-1.320			
SUV3	0.255	1.204	0.875-1.656			
MTV1	0.629	1.003	0.990-1.017			
MTV2	0.379	1.024	0.971-1.081			
MTV3*	0.002	1.887	1.258-2.832	0.003	1.870	1.243-2.813
Δ%SUV1-2	0.259	1.012	0.991-1.033			
Δ%SUV1-3*	0.082	1.036	0.996-1.077	0.485	0.975	0.910-1.046
Δ%MTV1-2	0.579	1.008	0.981-1.035			
Δ%MTV1-3*	0.049	1.057	1.000-1.117	0.252	1.041	0.972-1.116

** Parameters included in multivariate analysis.*

SUV= standardized uptake value; MTV= metabolic tumor volume (primary tuomor+axillary lymph node)

thousands of patients, reported that PCR was the prognostic predictor for survival.[24] Some authors have reported that the predictive value of PCR for survival may vary depending on the hormone receptor status.[17] On the other hand, some authors state that PCR is a good predictor of prognosis in studies including all hormone receptor subtypes, regardless of hormone receptor status16. Due to the limited number of our patients, we could not group and analyze the patients according to their hormone receptor subtypes. However, we still obtained the result that PCR was predictive for DFS and OS.

While some studies evaluated PCR for a tumor in the breast, others included axillary lymph nodes. [25-27] Similarly, we defined PCR separately for the primary tumor, axillary lymph node, and primary tumor+axillary lymph nodes. While focal invasive or in-situ tumor foci are considered PCR in some studies, some authors argue that invasive and non-invasive foci should be completely eradicated to mean PCR.[28 24,26,29] In this study, we accepted non-invasive tumors both in breast and lymph reported by pathology as PCR.

Besides investigating the prognostic value of PCR, we also examined the prognostic value of complete metabolic response in 18F FDG PET/CT after NAC- before surgery. We thought it would be helpful to compare these two parameters. In patients with metCR, DFS was not different from the non-metCR group. For OS, survival in the breastOnly-metCR and breastAndNodemetCR groups was statistically significantly better than the non-metCR group. Survival in the NodeOnlymetCR group was similar to the non-metCR group. A study evaluating 132 patients reported that complete metabolic response was not a predictor for OS and DFS 13. Another study stated that the complete metabolic response predicts survival.[30] In a study examining the survival relationship of metabolic complete response monitoring in interim PET/CT, 5-year survival values were found to be statistically different between CMR and non-CMR patient groups, regardless of hormone receptor type and when classified according to hormone receptor type (92% for ER[+]). /HER2(-) tumors and 80% for TN, respectively) 11. The level of FDG uptake in the tumor and the tumor volume showing FDG uptake reflect the amount of viable tumor cells, providing a reliable measure of tumor burden. Tumor metabolic activity remaining on 18F FDG PET/CT after treatment indicates active disease, whereas interim negative PET can be considered a predictor of successful treatment response.[11]

The limited number of our patients is our main limitation. This limitation affected the accuracy of our statistical results, and therefore we could not divide the patients into subgroups and analyze them

according to hormone receptor status, which has different treatment and prognosis in breast cancer.

In conclusion, our findings suggest that 18F-FDG PET/CT data after NAC may provide additional prognostic information and distinguish patients with a potentially poor prognosis. It is not yet known whether treatment decisions based on this information can improve patient outcomes. The role of metabolic tumor response in therapeutic decision-making in breast cancer patients undergoing NAC can be better understood with prospective studies with more patients.

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