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The Role of 18F-FDG PET/CT in Predicting the Neoadjuvant Treatment Response in Patients with Locally Advanced Breast Cancer

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Keywords
Neoadjuvant chemotherapy · 18F-FDG PET/CT · Prognostic factors · Survival · Breast cancer

Abstract

Purpose: Patients with locally advanced breast cancer (LABC) should be treated with neoadjuvant chemotherapy (NAC). Pathological complete response (pCR) is related to better disease-free survival (DFS). The best strategy for assessing the efficacy of NAC has not been established yet, but several studies have shown that 18F-FDG PET/CT is a potential imaging tool for assessing pCR. The aim of this study is to investigate the merits of 18F-FDG PET/CT imaging in predicting pCR in both axillary and breast tissue and to establish a threshold maximum standard uptake value (SUVmax) for predicting the response after completion of NAC. ***Methods:*** A total of 186 LABC patients, treated with an NAC regimen according to tumor subtype, were retrospectively analyzed in this study. All patients underwent 18F-FDG PET/CT imaging before and after completion of NAC. PET parameters were measured in the most FDG avid breast tissue and axillary lymph nodes. We analyzed the correlation between the tumor SUVmax of the PET/CT response and the pCR after surgery. DFS was also evaluated with respect to pCR. ***Results:*** Higher pCR rates were significantly associated with a higher tumor grade, an initial Ki-67 ≥20% ($p = 0.03$ and $p = 0.003$, respectively), a triple-negative subtype (32.9%), and a human epidermal growth factor receptor 2 (HER-2)-positive subtype (24.7%) ($p < 0.001$). There was a significant correlation between the pCR and a complete response in 18F-FDG PET/CT ($p < 0.001$). The overall sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of 18F-FDG PET/CT to determine the pCR after NAC were 100%, 72.2%, 85%, 75.2%, and 100%, respectively. We demonstrated a 1.1 cutoff SUVmax for breast tumors after NAC (OR: 3.94, 95% CI: 1.14–5.05, $p = 0.004$), the 18F-FDG PET/CT response to NAC (OR: 0.50, 95% CI: 0.25–0.99, $p = 0.003$), and the molecular subtype of breast tumors (OR: 0.58, 95% CI: 0.38–0.88, $p = 0.011$). ***Conclusion:*** Our results confirm that 18F-FDG PET/CT is a useful method for predicting the NAC response in LABC.

Introduction

Breast cancer is the most common cancer and the leading cause of cancer deaths among females. Recently, mortality rates are decreasing due to screening mammogra-

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phy and the new treatment approaches [1]. Breast cancer should evaluate for hormone receptor testing which is related with prognosis. Estrogen receptor (ER) positivity is defined by immunohistochemistry (IHC) for ER and progesteron receptor (PR) in more than 1 percent of tumor cells. HER2 expression is detected by uniform intense membrane staining of >30 percent of invasive tumor cells (IHC 3+) or the presence [2].

For patients with early-stage breast cancer, the main treatment is surgery. On the other hand, in patients with locally advanced breast cancer (LABC), neoadjuvant chemotherapy (NAC) followed by surgery is the main treatment option [3]. The best outcome for NAC is a pathological complete response (pCR), which is associated with disease-free survival (DFS) and overall survival of breast cancer patients [4, 5].

Some studies have shown that compared with patients without a pCR, patients who have achieved a pCR have an improved 5-year DFS rate of 87% and a 5-year overall survival rate of 89% [5]. Preoperatively, predicting pCR can be a surrogate marker of prognosis and can help to predict the surgical resection area and preserve mammary tissue and can help to decrease axillary nodal dissection. The diagnostic modalities for assessing the response to NAC are physical examination, mammography/ultrasonography, breast magnetic resonance imaging (MRI), and 18F-FDG (fluorodeoxyglucose) positron emission tomography/computed tomography (18F-FDG PET/CT) [6–9].

Although many studies have aimed to determine the optimal imaging method for evaluating the efficacy of NAC, there is still no consensus. The current literature shows that 18F-FDG PET can be used to assess the NAC response and to provide a predictive value for pCR. Thus, using 18F-FDG PET/CT may allow risk stratification and guide rational management pre- or postoperatively [9, 10].

The relationship of the sensitivity and specificity of the 18F-FDG PET/CT with a pCR has previously been evaluated, but to our knowledge the metabolic and/or anatomical treatment response and the maximum standard uptake value (SUVmax) predicting the pCR and a cutoff SUVmax have not previously been investigated in the literature [10–12]. The aim of this study was to determine the merits of 18F-FDG PET/CT imaging in predicting pCR in both axillary and breast tissue after completion of NAC and to establish a threshold SUVmax for predicting pCR and DFS.

Materials and Methods

Between 2015 and 2021, a total of 186 women, who were discussed in a multidisciplinary tumor board and decided to be treated with NAC before curative surgery, were included in this study. The eighth edition of the tumor, node, metastasis (TNM) staging system of American Joint Committee on Cancer (AJCC) was used in this study. LABC patients included the patients with stage IIB disease (T3N0) and patients with stage IIIA to IIIC disease [13]. Patients' data were retrospectively obtained from patients charts with respect to age, histopathological type and molecular subtype, tumor localization, initial and postoperative Ki-67 index, NAC regimen, and initial clinical TNM stage. All patients underwent an 18F-FDG PET/CT scan at the beginning of NAC and 2 weeks after the completion of the treatment. After the completion of NAC, all patients underwent breast-conserving surgery (BCS) or mastectomy (MRM) and axillary lymph node dissection (ALND) or sentinel lymph node biopsy. For each molecular subtype, the response to NAC treatment was evaluated using the SUVsmax of the axillary lymph nodes and primary tumors after NAC, and pCR was defined by the pathological Miller-Payne regression score [14]. Only patients with a positive 18F-FDG PET/CT scan at the beginning of NAC were included in this study. Patients who were under 18 years, who had oligometastasis, or who were not able to complete the NAC regimen were excluded from the study. In addition, 3 patients were not included due to insufficient clinicopathological information ($n = 1$) or lost to follow-up ($n = 2$). Written informed consent was obtained from all patients. The Local Ethics Committee of Istanbul Medipol University approved the study with the decision number E-10840098-772.02-65177.

18F-FDG PET/CT Protocol and Image Analysis

The breast cancer patients underwent 18F-FDG PET/CT, at baseline and after treatment. The patients fasted for a minimum of 4 h and had blood glucose levels less than or equal to 200 mg/dL just before the intravenous injection of 18F-FDG (3.7 MBq/kg [0.1 mCi/kg]). After an uptake phase of 18F-FDG of approximately 60 min, a combined whole-body PET/CT scan (Gemini TF PET/CT, Philips Medical Systems) was performed. A single whole-body CT scan was performed with a sixteen-slice multidetector helical scanner for attenuation correction purposes. A CT transmission map was generated for image fusion. Emission data were acquired for 1.5 min at each bed position. PET images were reconstructed. PET assessment was reviewed by nuclear medicine physicians. Regions of interest (ROIs) were placed semiautomatically in attenuation-corrected images. The tumor was first identified on a pre-treatment FDG-PET scan, and subsequently an ROI was placed in the tumor bed on a post-treatment FDG-PET scan. The slice with the highest radioactivity concentration within the tumor was identified. SUVs were calculated using the maximum (SUVmax) activity values within the ROIs, normalized to the injected activity and patient's body weight. FDG-PET results were obtained for two SUV thresholds: SUV 2.0 and SUV 1.5. A positive PET result was defined as an SUV equal to or above the threshold level. A negative PET result was defined as an SUV below the threshold level. Histopathology served as a reference standard, as described above. To assess the metabolic response, the PET Response Criteria in Solid Tumors (PERCIST) were used [15]. To assess the anatomical response, the CT images of the PET scans were used.

Pathological Evaluation

Histopathological classification was done by IHC. The luminal group was classified as HER2 negative and ER positive and was then further subclassified as luminal A if Ki-67 was low (<20%) and luminal B if Ki-67 was ≥20%. HER2 positivity was defined as IHC 3+ or SISH positive. The triple-negative (TN) subtype was defined as having no ER, PR, and HER2 expression. The Miller-Payne regression score was used to evaluate the pCR in histopathological specimens. A pCR was defined as a response with no evidence of residual invasive cancer in breast tissue as Miller-Payne score V with no evidence of residual cancer in lymph nodes, in other words

Table 1. Patient and tumor characteristics regarding the presence of pCR after NAC

Characteristics	*N* (%)	pCR, *n* (%)	Non-pCR, *n* (%)	*p* value
Total patients	186	85 (45.7)	101 (54.3)	
Menopausal status				
Premenopause	127 (68.3)	58 (68.2)	67 (66.3)	0.31
Postmenopause	59 (31.7)	27 (31.8)	34 (33.7)	
Histopathological type				
Invasive ductal carcinoma	131 (70.4)	47 (55.2)	84 (83.1)	
Invasive lobular carcinoma	34 (18.3)	28 (32.9)	6 (6.1)	0.17
Others	21 (11.3)	10 (11.9)	11 (10.8)	
Tumor grade				
Grade 1	12 (6.5)	0	12 (11.9)	
Grade 2	99 (53.2)	40 (47)	59 (58.4)	**0.03**
Grade 3	75 (40.3)	45 (48.2)	30 (29.7)	
Initial Ki-67 index status				
<20%	38 (20.5)	10 (11.8)	32 (31.7)	**0.003**
≥20%	148 (79.5)	75 (88.2)	69 (68.3)	
Ki-67 index status after surgery				
<20%	128 (68.8)			
≥20%	58 (31.2)			
Molecular phenotype				
Luminal A	22 (11.8)	3 (3.7)	19 (18.8)	
Luminal B-HER-2 negative	56 (30.1)	15 (17.6)	36 (35.6)	
Luminal B-HER-2 positive	36 (19.4)	18 (21.1)	20 (19.8)	**<0.001**
HER-2 positive, ER negative	28 (15.1)	21 (24.7)	9 (8.9)	
TN	44 (23.2)	28 (32.9)	17 (16.8)	
Initial clinical TNM stage				
Stage II	58 (31.2)	29 (34.2)	30 (29.8)	0.09
Stage III	128 (68.8)	56 (65.8)	71 (70.2)	
Initial T status				
T1	31 (16.8)	15 (17.8)	16 (15.9)	
T2	59 (31.7)	21 (24.7)	38 (37.6)	0.61
T3	57 (30.6)	26 (30.5)	31 (30.6)	
T4	39 (20.9)	23 (27.0)	16 (15.9)	
Initial nodal status				
N0	58 (31.1)	27 (31.7)	31 (30.6)	
N1	54 (29.0)	22 (25.8)	32 (31.6)	0.53
N2	41 (22.0)	19 (22.3)	22 (21.7)	
N3	33 (17.9)	17 (20.2)	16 (16.1)	
Surgery type after NAC				
BCS	96 (51.6)	50 (58.8)	40 (39.7)	**0.003**
Modified/subcutaneous mastectomy	90 (48.4)	35 (41.2)	61 (60.3)	
Axillary surgery				
SLNB	80 (43.1)	52 (61.2)	36 (35.7)	**0.002**
ALND	106 (56.9)	33 (38.8)	65 (64.3)	
FDG-PET/CT response				
Metabolic CR	43 (23.1)	25 (29.4)	18 (17.8)	
Metabolic anatomic CR	52 (28.0)	42 (49.4)	10 (9.9)	**<0.001**
Partial response	88 (47.3)	18 (21.2)	70 (69.3)	
No response	3 (1.6)	0	3 (3.0)	

pCR, pathological complete response; CR, complete response; TNM, tumor node metastasis status; ALND, axillary lymph node dissection; SNLB, sentinel lymph node biopsy; NAC, neoadjuvant chemotherapy.

ypT0N0. A partially response was defined as a response with more than 30% therapeutic effect in the breast tissue (i.e., Miller-Payne score 2–4) with residual cancer in lymph nodes. No response was defined as a response with Miller-Payne score 1 and no therapeutic effect in the lymph nodes [14].

Neoadjuvant Treatment Protocols

The patients in the luminal group were treated with four cycles of epirubicin (75 mg/m^2) or adriamycin (60 mg/m^2) with cyclophosphamide (600 mg/m^2) (AC/EC) every 3 weeks, followed by four cycles of docetaxel (100 mg/m^2) every 3 weeks or 12 cycles of paclitaxel (80 mg/m^2), every week. Patients whose tumors were

Table 2. Median SUVsmax before and after NAC in PET/CT

	Median SUVmax breast (range)	Median SUVmax axilla (range)	*p* value
Before NAC	9.1 (2.3–48.5)	5.1 (2.6–30.7)	<0.001
After NAC	3.14 (0–16.2)	1.76 (0–14.8)	<0.001

NAC, neoadjuvant chemotherapy.

Table 3. Performance of 18F-FDG-PET/CT in determining the pCR

Performance	pCR	Non-pCR
True-positive, *n*	67	–
True-negative, *n*	–	3
False-positive, *n*	–	98
False-negative, *n*	18	–
Sensitivity, %	72.2	
Specificity, %	100	
PPV, %	75.2	
NPV, %	100	
Accuracy, %	85	

pCR, pathological complete response; PPV, positive predictive value; NPV, negative predictive value.

HER2 positive received AC/EC followed by docetaxel with dual blockage (trastuzumab 8 mg/kg loading dose, followed by 6 mg/kg; pertuzumab 840 mg loading dose, followed by 420 mg; every 3 weeks). TN breast cancer patients received a dose-dense regimen defined as four cycles of AC/EC followed by four cycles of paclitaxel every 2 weeks or 12 cycles of paclitaxel, every week.

Statistical Analysis

SPSS 22.0 (SPSS Inc., Chicago, IL, USA) software was used for all statistical analyses. Parameters were described with their median values. Because the distribution of the study parameters was non-normal distribution, nonparametric tests were used. The median SUVsmax before and after NAC were compared using the Wilcoxon test. The relationship between clinicopathological factors and the presence of pCR was compared by means of the χ^2 test and Fisher's exact test. Survival analysis and curves were performed according to the Kaplan-Meier method and compared by the log-rank test. DFS was defined as the time from curative breast surgery to disease progression or recurrence, or to the date of death or loss to follow-up. Univariate analyses to assess the significance of pCR and other clinicopathological features as prognostic factors were carried out. After that, the multivariate logistic regression analysis was performed in order to further evaluate all of the significant factors for predicting to pCR. A receiver operating characteristic (ROC) analysis was performed to detect the best cutoff value of SUVmax for predicting pCR for both primary breast tumors and axillary lymph node. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All *p* values were two-sided in tests, and *p* values less than or equal to 0.05 were considered to be statistically significant.

Results

In this study, 186 patients were included, of whom 68% (n = 127) were postmenopausal and 59% were premenopausal, with a median age of 45 years (range: 27–81 years). Histopathologically, 70.4% (n = 131) of the tumors were invasive ductal carcinomas, while 18.3% (n = 34) were invasive lobular carcinomas. Twenty-one of the tumors (11.3%) belonged to other subtypes of invasive breast carcinomas. The number of patients with Ki-67 values above 20% at baseline and after operation was 148 (88.2%) and 58 (68.3%), respectively; the number of patients below 20% was 38 (11.8%) and 128 (31.7%), respectively.

The molecular subtypes of the patients were as follows; 22 patients (11.8%) were in the luminal A group, 56 patients (30.1%) in the luminal B HER2-negative group; 36 patients (19.4%) in the luminal B HER2-positive group, 28 patients (15.1%) in HER2-positive ER-negative group; and 44 patients (23.2%) were in the TN group. At the time of diagnosis, 128 patients (68.8%) were classified as stage 3 and 58 patients as stage 2 (31.2%). The number of patients with clinical T1, T2, T3, T4 tumors at baseline was 31 (16.8%), 59 (31.7%), 57 (30.6%), 39 (20.9%), respectively. In addition, 58 (31.1%) patients regarding clinical nodal staging were classified as N0, and 54 patients as N1 (29.0%), 41 patients as N2 (22.0%), and 33 patients as N3 (17.9%) at the time of diagnosis.

Ninety-six patients (51.6%) had undergone BCS (i.e., lumpectomy or partial mastectomy), and the remaining patients had undergone modified or subcutaneous mastectomy. Although 128 patients had axillary lymph node metastasis at the initial diagnosis, 106 patients underwent ALND after the completion of NAC. Histopathological analysis of surgical specimens after NAC revealed pCR in 85 cases (45.6%). pCR rates were significantly higher in patients with a high tumor grade and an initial Ki-67 index ≥20% before NAC (p = 0.03 and p = 0.003, respectively). When the molecular subgroups were evaluated, the pCR rate after NAC was significantly higher in the TN (32.9%) and HER2-positive groups (24.7%) (p < 0.001). The pCR rates in the luminal B HER2-positive, luminal B HER2-negative, and luminal A groups were determined as 21.1%, 17.6%, and 3.7%, respectively. After the subgroups with or without pCR were compared among themselves, significant differences were detected between pCR and non-pCR tumors with respect to the initial Ki-67 index status, tumor grade, molecular subtype, 18F-FDG-PET/CT response, surgery type after NAC, and axillary surgery type. In other words, the prevalence of BCS was significantly higher in patients with pCR than in patients without pCR (58.8% vs. 39.7%, p = 0.003). More-

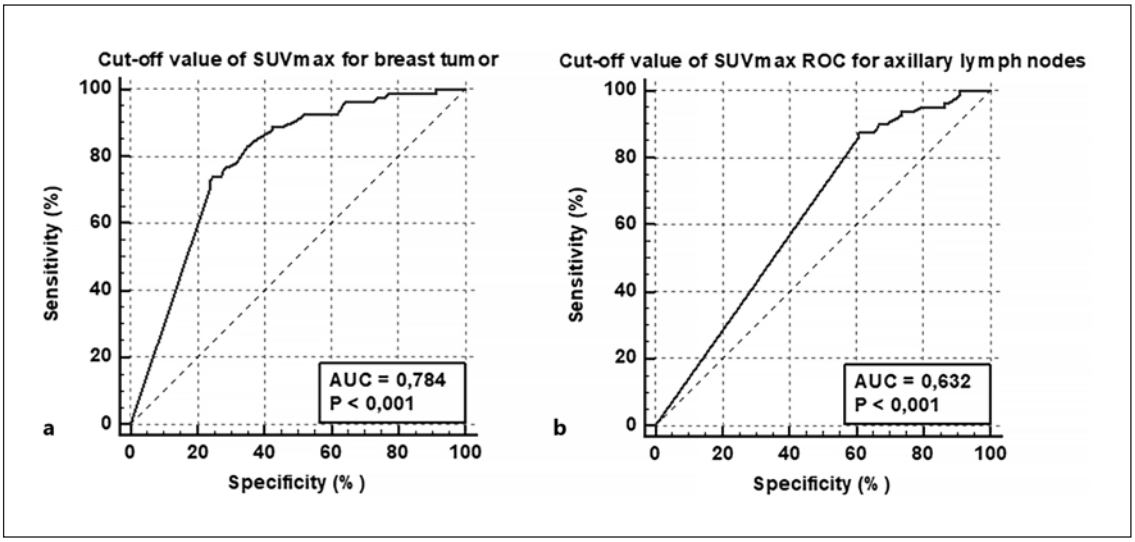

Fig. 1. ROC analysis showing the sensitivity and the specificity of the PET/CT for breast tissue (**a**) and axillary lymph nodes (**b**).

over, the ALND rate was found to be significantly higher in the non-pCR group than in the pCR group ($p = 0.002$) (Table 1).

The median SUVsmax measured in 18F-FDG PET/CT imaging before NAC in primary breast tumors and axillary lymph nodes were 9.1 (range: 2.3–48.5) and 5.1 (range: 2.6–30.7), respectively. Furthermore, the median SUVsmax measured in 18F-FDG PET/CT imaging after NAC was completed were 3.14 (range: 0–16.2) in primary breast tumors and 1.76 (range: 0–14.8) in axillary lymph nodes. Thus, after NAC, both SUVsmax in both primary breast tumors and axillary lymph nodes were significantly decreased ($p < 0.001$ and $p < 0.001$, respectively) (Table 2).

There was a significant correlation between the pCR and the complete metabolic and/or anatomical response in 18F-FDG PET/CT imaging ($p < 0.001$). In 18F-FDG PET/CT imaging, 78.8% of the patients with a metabolic or metabolic plus anatomical response achieved a pCR, while 27.7% did not achieve a pCR. In 70 out of 88 patients who had a partial response on 18F-FDG PET/CT imaging, no pCR was obtained (21.2% pCR vs. 69.3% non-pCR). These results were statistically significant. The overall sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of 18F-FDG PET/CT to determine the pCR after NAC were 100%, 72.2%, 85%, 75.2%, and 100%, respectively (Table 3).

The ROC analysis showed that the sensitivity and the specificity of the presence of pCR with a cutoff value of 1.1 SUVmax for breast tumors were 74.7% (95% CI: 63.1–83.2) and 75% (95% CI: 64.9–83.9) (AUC = 0.784, $p < 0.0001$), respectively. These values with a cutoff value of 1.2 SUVmax for axillary lymph nodes during 18F-FDG PET/CT were 87.5% (95% CI: 78.2–93.8) and 39.8% (95% CI: 28.8–50.1) (AUC = 0.632, $p < 0.0001$), respectively (Fig. 1).

Logistic regression analysis was performed in order to further evaluate all of the significant prognostic factors that might be predicted pCR after NAC. It demonstrated that the cutoff SUVsmax for breast tumors after NAC (odds ratio[OR]: 3.74, 95% CI: 1.05–15.05, $p = 0.004$), 18F-FDG PET/CT response to NAC, and molecular subgroups of breast tumor were predictive factors for pCR. In other words, HER2-positive, ER-negative (OR: 3.36, 95% CI: 0.51–12.8, $p = 0.03$), and TN (OR: 4.38, 95% CI: 1.05–18.2, $p = 0.012$) groups were associated with higher pCR rates. Moreover, complete metabolic (OR: 14.1, 95% CI: 3.76–51.1, $p < 0.001$) and complete anatomic plus metabolic response (OR: 13.8, 95% CI: 3.81–49.9, $p < 0.001$) to NAC in 18F-FDG PET/CT were significantly predicted to pCR (Table 4).

At a median follow-up time of 28.9 months (range: 6.5–169.2 months), the 3-year DFS rate was found to be statistically longer in patients with a pCR after NAC treatment than in patients with a non-pCR (84.4% vs. 60%) (Fig. 2). The 3-year DFS rates were 90.3%, 81.9%, and 69.6% in patients who obtained complete metabolic plus anatomical response, complete metabolic response, and partial response in 18F-FDG PET/CT, respectively. In other words, DFS rates in patients with a complete metabolic or complete metabolic plus anatomical response were significantly longer than in patients with a partial response ($p < 0.001$). On the other hand, 3-year DFS rates were not significantly different among molecular subgroups regardless of pCR ($p = 0.35$). The findings were as follows: 86.3% in luminal A, 80% in luminal A HER2-

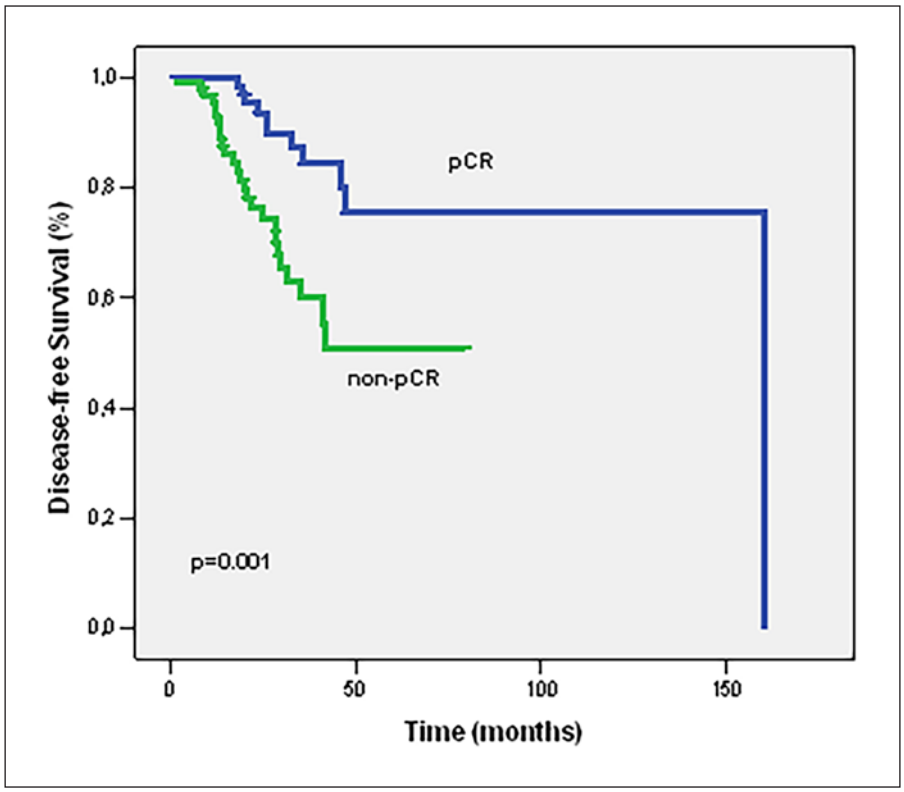

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Fig. 2. DFS curve according to the pCR after NAC.

Table 4. Predictive factors for pCR in patients with breast cancer who received NAC

Factors	Coefficient β	Wald χ^2	*p* value	OR	95% CI
Cutoff SUVmax for breast tumor after NAC	1.45	3.98	**0.004**	3.74	1.05–15.05
Cutoff SUVmax for ALN after NAC	−0.023	0.28	0.59	0.97	0.89–1.06
PET/CT response to NAC		17.9	**0.003**		
No response or partial response	0.90	1.89	0.16	2.46	0.68–8.89
Metabolic CR	2.96	14.6	**<0.001**	14.1	3.76–51.1
Metabolic + anatomic CR	2.62	16.0	**<0.001**	13.8	3.81–49.9
Molecular subgroup		9.53	**0.011**		
Luminal A	−1.01	1.29	0.25	0.36	0.06–2.07
Luminal B-Her2 negative	0.85	2.07	0.15	4.47	0.58–34.3
Luminal B-Her2 positive	1.32	1.34	0.24	2.34	0.55–9.97
Her2 positive, ER negative	1.47	1.98	**0.03**	3.36	0.51–12.8
Triple-negative	1.49	4.11	**0.012**	4.38	1.05–18.2
Initial Ki-67 index status	−0.07	0.25	0.62	0.99	0.96–1.02
Tumor grade	0.95	3.45	0.06	2.59	0.95–7.06

OR, odds ratio; CI, confidence interval; pCR, pathological complete response; CR, complete response; NAC, neoadjuvant chemotherapy; ALN, axillary lymph node, ER, estrogen receptor.

negative, 54% in luminal A HER2-positive, 76.5% in HER2-positive, ER-negative, 63.8% in TN subgroup.

Figure 3 shows 18F-FDG PET/CT images of a 41-year-old patient with locally advanced TN breast cancer and FDG uptakes before and after NAC in breast tissue. Figure 4 shows images of a 38-year-old woman with locally advanced HER2-positive and ER-positive breast cancer and FDG uptakes before and after NAC in both breast and axillary tissue.

Discussion

NAC has become the standard treatment strategy for LABC before surgery. This approach provides BCS rather than MRM in many women. In addition, the response to NAC is associated with a longer DFS [5]. There is no consensus on how to determine the response to NAC before surgery. Previously, CT and MRI have been used to evaluate the response. However, the morphological response

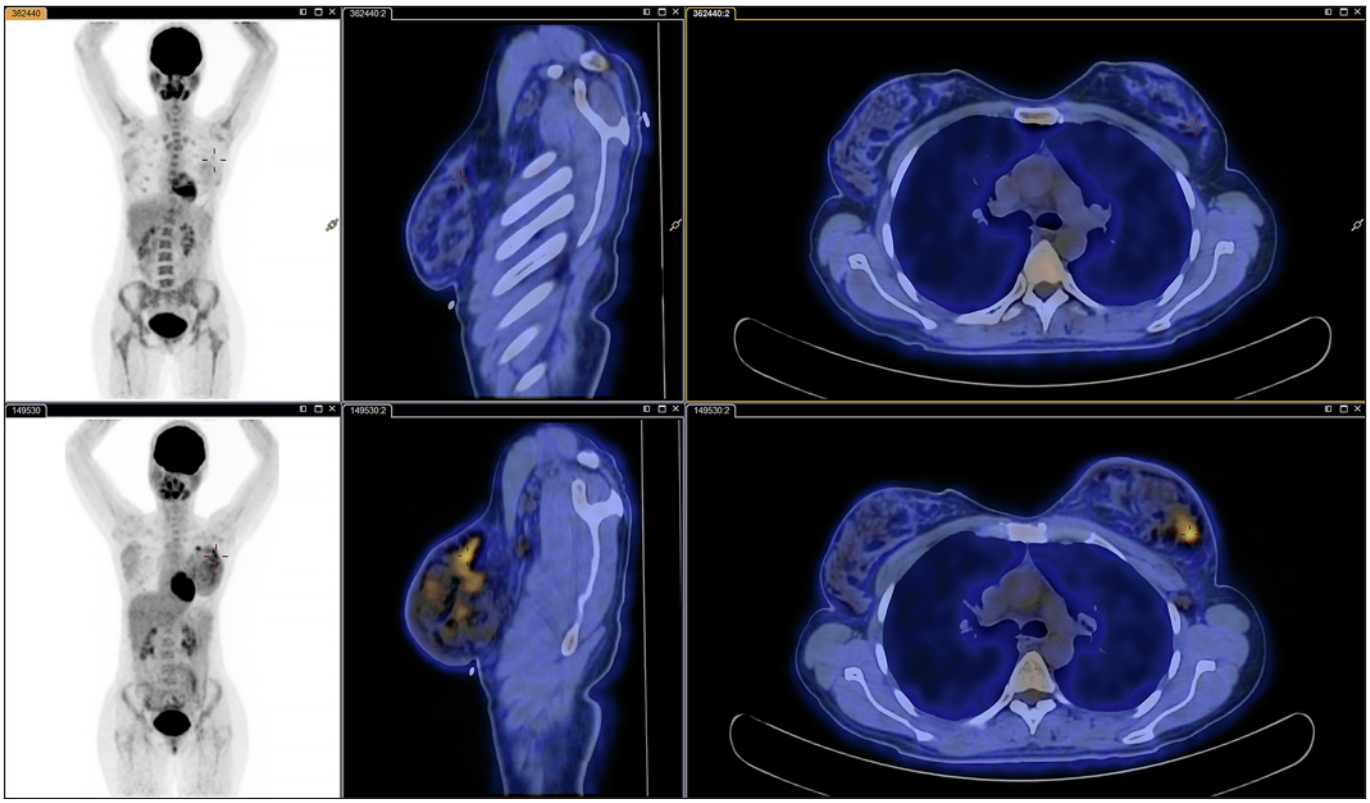

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Fig. 3. 18F-FDG PET/CT images of a 41-year-old woman with locally advanced TN breast cancer. Before NAC (lower image), the images show a high uptake of FDG in breast tissue without any FDG uptake in axillary tissue. After the patient received a dose-dense chemotherapy regimen (upper image), the images show metabolic and anatomical regression by which after-surgery pCR was obtained.

to NAC varies between 4 and 6 weeks, and morphological imaging cannot differentiate between fibrosis tissue and viable tumor tissue. Edema, an inflammatory reaction after NAC, also leads to confusion in determining the treatment response [7]. 18F-FDG PET/CT examination, which can also evaluate viable tumor cells, was therefore used to investigate the treatment response to NAC in patients with LABC [9–11].

According to a review of the literature, 18F-FDG PET/CT response evaluation has been performed at different times and with different parameters [12]. Berriolo-Riedinger et al. [16] evaluated the relationship between the decrease in FDG uptake (DeltaSUV) at the beginning and after the first course of NAC and pCR. They showed that a DeltaSUV (max-BSA-G) <60% predicted the pCR with an accuracy of 87%. However, Rousseau et al. [10] performed 18F-FDG PET/CT at baseline and after the first, second, third, and sixth courses of chemotherapy. When 60% of the SUVmax at baseline was used as the cutoff value, the sensitivity, specificity, and NPV of FDG PET were 61%, 96%, and 68% after one course of chemotherapy; 89%, 95%, and 85% after two courses; and 88%, 73%, and 83% after three courses, respectively [10].

Tumor regression or pCR was defined in different ways in different studies [12, 17]. Rousseau et al. [10] considered a good response if there was a tumor regression of more than 50%, while Berriolo-Riedinger et al. [16] regarded no residual invasive cancer as pCR. In our study, we defined tumor regression with the Miller-Payne score, which is a more evidence-based method, as described above [14].

In a meta-analysis of 19 studies, the sensitivity, specificity, PPV, NPV, and diagnostic OR of 18F-FDG PET/CT to predict a histopathological response in primary breast lesions were 84% (95% CI: 78–88), 66% (95% CI: 62–70), 50% (95% CI: 44–55), 91% (95% CI: 87–94), and 11.90 (95% CI: 6.33–22.36), respectively [17]. Performing 18F-FDG PET/CT early, after the first or second cycles of NAC, was significantly better than performing it later (accuracy 76% vs. 65%, $p = 0.001$) [17]. Nevertheless, PET was not administered at the end of treatment in any of the studies included in this meta-analysis, and the number of patients included in the studies was very low. In our study, we detected that the overall sensitivity, specificity, PPV, and NPV of 18F-FDG PET/CT to determine the pCR were 100%, 72.2%, 75.2%, and 100%, respectively, with an

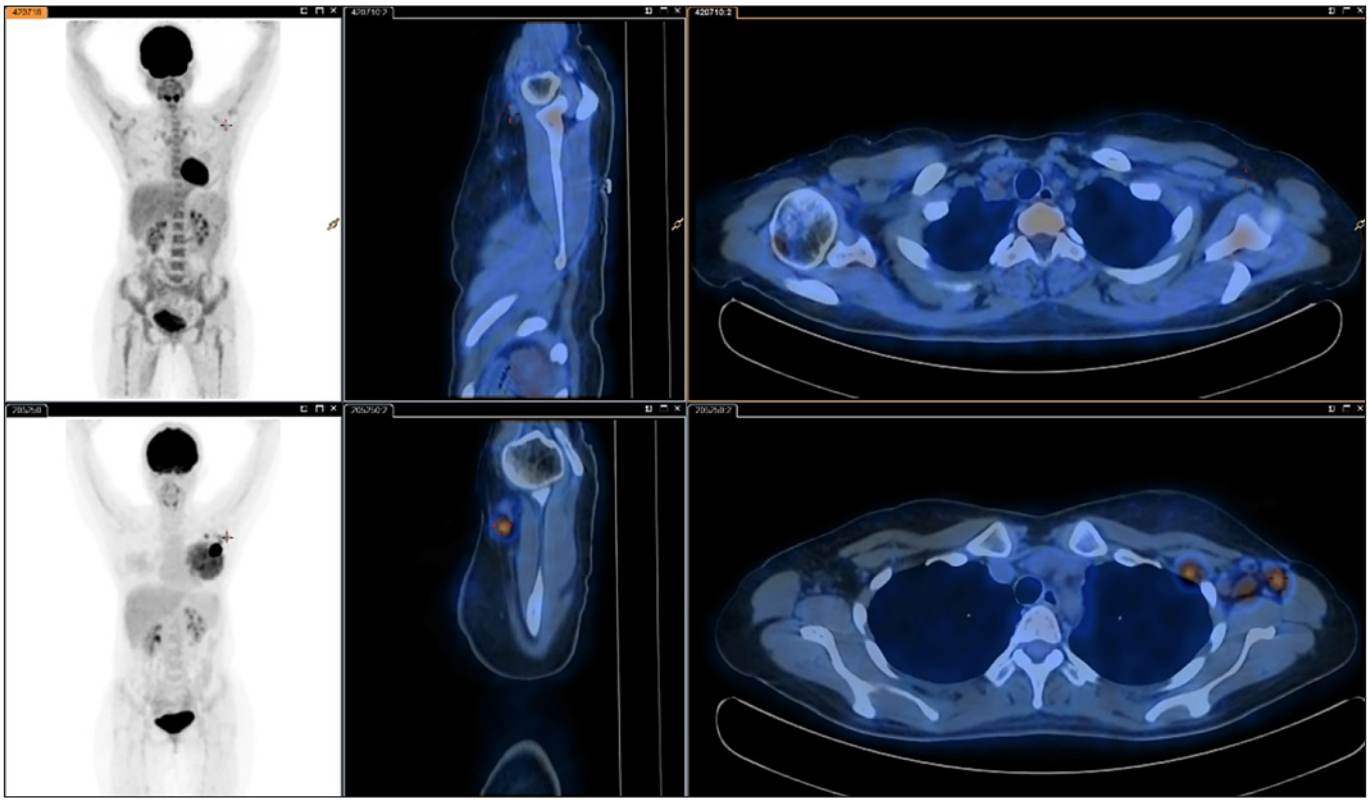

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Fig. 4. 18F-FDG PET/CT images of a 38-year-old woman with locally advanced HER2-positive and ER-positive breast cancer. Before NAC (lower image), the images show the FDG uptake in both breast and axillary tissue. After the patient received chemotherapy with a dual-blockage regimen (upper image), the images show metabolic and anatomical regression by which after-surgery pCR was obtained.

accuracy of 85%. The reasons for the high specificity and sensitivity of 18F-FDG PET/CT in our study might be the high number of patients included in the study and the patients receiving the most appropriate treatment according to their molecular subtypes. Another reason might be the timing of 18F-FDG PET/CT in our study. Although NAC treatment response assessment is done after one or two cycles in most studies [10, 11], it seems that evaluating after the completion of NAC treatment, which has become the standard of care for LABC patients, may be more effective in making the right decision before surgery [18]. Therefore, our study provides more appropriate data in terms of predicting PCR.

Furthermore, we found that the sensitivity and the specificity of the presence of pCR with a cutoff value of 1.1 SUVmax for primary breast tumors were 74.7% (95% CI: 63.1–83.2%) and 75% (95% CI: 64.9–83.9%), respectively, by ROC analysis (AUC = 0.784, $p < 0.0001$). Since no cutoff value was determined to predict PCR after NAC in other studies, we think that our study will contribute to the literature.

18F-FDG PET/CT uptake differs between different molecular subtypes of breast cancer. Aggressive subtypes such as the TN and HER2-positive types are associated with significantly higher uptakes of 18F-FDG PET/CT than the luminal groups [19, 20]. Groheux et al. [19] investigating the 18F-FDG PET/CT response according to breast cancer subtypes showed that pCR was significantly more common in HER2-positive tumors (16 out of 33 patients: 48.5%) and TN breast tumors (20 out of 54 patients: 37%) than in ER-positive/HER2-negative tumors (4 out of 82 patients: 4.9%) ($p = 0.01$). In this study, also six 18F-FDG PET/CT parameters were tested: SUV, peak SUV (SUVpeak), mean SUV (SUVmean), metabolically active tumor volume, total lesion glycolysis, and SUVmax in breasts and axilla, which were all found to be much more predictive of pCR than the other parameters [19]. On the other hand, some studies showed that the change in FDG uptake was not able to predict pCR in the HER2-positive subtype as it did in the TN group of breast cancer [20]. Although most studies showed lower response rates in the luminal group, de Cremoux et al. [21] showed that the change in 18F-FDG uptake (ΔSUVmax) after 2 cycles of NAC was significantly associated with pCR in ER-positive/HER2-negative breast cancer subtype ($p = 0.008$). In our study, a significant relationship

was found between the molecular subtypes and pCR. In the HER2-positive and TN groups, the pCR rates were significantly higher than in the ER/PR-positive subtype group. This could be related to the low chemosensitivity of the luminal groups. Thus, we showed a significant association between pCR rates and the 18F-FDG PET/CT response after completion of NAC, especially in the HER2-positive and TN subtypes. Our findings were thus compatible with the literature with respect to molecular subtypes but not with respect to the timing of 18F-FDG PET/CT [18–22].

Although most studies described the response in primary breast tumors, pCR should be defined as the absence of invasive cancer cells in both breast tissue and axillary lymph nodes. The study evaluated 18F-FDG PET/CT responses of 76 patients at baseline (PET-1), after the second course of chemotherapy (PET-2), and after the last course of chemotherapy (PET-3), and no significant relationship was observed between the metabolic complete responses on PET-2 and PET-3 and the pCR ($p = 0.31$ and $p = 0.99$, respectively). Lymph node metabolism on PET-1 was not able to predict the final histopathological status [23]. In previous studies, a cutoff SUVmax that predicted pCR could not be obtained [8, 12, 16, 19]. In the present study, we evaluated changes in FDG uptake in both axillary lymph nodes and breast tissue. Axillary lymph node involvement was not associated with the NAC response. The median SUVmax was decreased significantly with NAC treatment. Furthermore, ROC analysis showed that the sensitivity and the specificity of the presence of pCR with a cutoff value of 1.2 for axillary lymph nodes during 18F-FDG PET/CT were 87.5% (95% CI: 78.2–93.8) and 39.8% (95% CI: 28.8–50.1), respectively (AUC = 0.632, $p < 0.0001$). However, the 18F-FDG PET/CT response after NAC was not a significant predictive factor for pCR in axillary lymph nodes. Moreover, the ROC analysis showed that the sensitivity and the specificity of the presence of pCR with a cutoff value of 1.1 SUVmax for breast tumors were 74.7% (95% CI: 63.1–83.2) and 75% (95% CI: 64.9–83.9), respectively (AUC = 0.784, $p < 0.0001$).

Ki-67 is a proliferation index that is used in clinical practice as a prognostic factor for breast cancer. Systematic review and meta-analysis in luminal group Ki-67 was a predictive factor for pCR [24]. Ki-67 was also evaluated in neoadjuvant setting and several studies demonstrated a high Ki-67 proliferation rate was predictive of higher probability of pCR [25]. In our study, the pre-NAC biopsy Ki-67 value was high, while the Ki-67 values were low in operation material after NAC. Although the relationship between Ki-67 and the NAC response was more pronounced in aggressive subtypes, it was found to be a statistically significant predictive factor for the Ki-67 NAC response in each group.

The most important limitation of our study is its retrospective design. Despite this limitation, the sufficient sample size makes our study strong. Additionally, the evaluation of pCR with the Miller-Payne regression scale provided a very valuable and more objective evaluation criterion in this study.

We believe that our results can contribute to the literature as we demonstrated the role of 18F-FDG PET/CT in predicting pCR by determining the cutoff SUVsmax by ROC analysis both in axillary and breast tissue. It should be noted that 18F-FDG PET/CT in the lymph node had a lower specificity. In addition, we showed that pCR was associated with a longer DFS in patients with a complete response in 18F-FDG PET/CT after NAC, similarly with previous studies [6].

Conclusion

In conclusion, our results confirm that 18F-FDG PET/CT is a useful imaging modality for assessing the pCR after completion of NAC. We showed a significant correlation between pCR and longer DFS. In addition, complete metabolic or complete metabolic plus anatomical response in 18F-FDG PET/CT after NAC may be surrogate factors for longer DFS in LABC. However, surgery after NAC is still gold standard modality and due to low specificity of 18F-FDG PET/CT in axillary tissue, SNLB is the best appropriate approach for axilla after NAC. Although prospective and randomized studies are needed, we think that in the future, evaluating the NAC response with both breast MRI and 18F-FDG PET/CT may be a tool for omitting the surgery for selected patients.

Statement of Ethics

The written informed consent was obtained from all participants. Local Ethics Committee of Istanbul Medipol University approved the study in June 2021 with decision number E-10840098-772-02-2508.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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Author Contributions

A. Bilici and S. Goktas Aydin conceived the statistical data analysis. A. Bilici was responsible for statistical analysis. S. Goktas Aydin, A. Bilici, and T. Cakir wrote the manuscript. O.F. Olmez, Y. Kutlu, J. Hamdard, P. Basim, B.B. Oven, and O. Acikgoz contributed substantial input to the conception and acquisition of the work. A. Cakir was responsible for pathologic evaluation. T. Cakir was responsible for imaging evaluation. All authors read and gave their stamp of approval for the submission of the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are not openly available. Further inquiries can be directed to the corresponding author.

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