The Value of F-18-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography for the Detection of Residual Breast Tumor or Axillary Metastasis after Neoadjuvant Chemotherapy in Invasive Ductal Carcinoma of the Breast

Memenin İnvazif Ductal Karsinomunda 18F- florodeoksiglukoz Pozitron Emisyon Tomografisi/Bilgisayarlı Tomografi'nin Neoadjuvan Kemoterapiden Sonra Kalan Meme Tümörünü ve Aksilla Metastazını Belirlemedeki Değeri

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ABSTRACT

Introduction: Accurate evaluation of pathological response after neoadjuvant chemotherapy would aid in treatment and surgical planning as well as prediction of outcomes. This study examined the value of F-18-fluorodeoxyglucose positron emission tomography/computed tomography (F-18-FDG PET/CT) in predicting pathologically confirmed residual tumor in breast or presence of axillary metastasis when performed after completion of neoadjuvant therapy in patients with invasive ductal carcinoma (IDC) of the breast cancer.

Methods: This retrospective study included 52 IDC of the breast who received neoadjuvant chemotherapy and underwent F-18-FDG PET/CT between 2015 and 2019 after completion of neoadjuvant chemotherapy. Diagnostic performance parameters of F-18-FDG PET/CT for predicting residual tumor or presence of axillary metastasis were estimated based on histopathological findings.

Results: All patients had IDC. F-18-FDG PET/CT exhibited high specificity for both locations (89.5% and 93.8% and for breast and axilla, respectively). The sensitivity of the method, on the other hand, was low for both locations (66.7% and 30.0% for breast and axilla, respectively), particularly for axilla. False-negative rate (i.e., missing rate) for breast and axilla was 9.1% and 0% for the tumors >8 mm in diameter.

Conclusion: F-18-FDG PET/CT does not seem to provide reliable information on the presence of a residual tumor or node metastasis when performed after the completion of neoadjuvant treatment in IDC of the breast. New diagnostic modalities utilized at different time points or including a combination of different imaging methods are warranted.

Keywords: F-18-fluorodeoxyglucose positron emission tomography/computerized tomography, breast cancer, neoadjuvant chemotherapy, residual tumor, complete response, axillary metastasis, invasive ductal carcinoma

ÖZ

Amaç: Neoadjuvan kemoterapiden sonra patolojik yanıtın doğru değerlendirilmesi hem cerrahi planlanmasına hem de tedavi sonuçların tahmin edilmesine yardımcı olacaktır. Bu çalışma F-18-fluorodeoksiglukoz pozitron emisyon tomografisi/ bilgisayarlı tomografi'nin (F-18-FDG PET/BT), memenin invazif duktal karsinomu (İDK) olan hastalarda, neoadjuvan tedavinin tamamlanmasından sonra yapıldığında, cerrahi sonrası patolojik olarak doğrulanmış memede kalan tümörü ve aksillada metastaz varlığını tahmin etmedeki değerini incelemiştir.

Yöntemler: Bu retrospektif çalışmaya 2015 ve 2019 yılları arasında neoadjuvan kemoterapi almış ve kemoterapi sonrasında F-18-FDG PET/BT yapılmış 52 memenin İDK'si dahil edilmiştir. F-18-FDG PET/BT'nin kalan tümörü ya da aksillada metastaz varlığını tahmin etmek açısından, histopatolojik bulgular esas alınarak, diyagnostik performans parametreleri hesaplanmıştır.

Bulgular: Tüm hastalarda İDK tanısı mevcuttu. F-18-FDG PET/ BT'nin özgüllüğü her iki lokasyon için de yüksek bulunmuştur (sırasıyla meme ve aksilla için %89,5 ve %93,8). Yöntemin duyarlılığı ise her iki lokasyon için, özellikle de aksilla için düşük idi (sırasıyla, meme ve aksilla için %66,7 ve %30,0). Sekiz milimetreden büyük tümörler incelendiğinde ise yanlış negatif oranı (gözden kaçan tümörler) meme için %9,1, aksilla için %0 idi.

Sonuç: F-18-FDG PET/BT memenin İDK'de neoadjuvan tedavinin tamamlanmasından sonra yapıldığında rezidü tümör ya da nodal metastaz varlığını göstermede güvenilir bilgi veriyor gibi görünmemektedir. Değişik zaman noktalarında kullanılacak veya değişik görüntüleme yöntemlerini kombine edecek yeni tanısal yöntemlere gereksinim vardır.

Anahtar Kelimeler: F-18-fluorodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi, meme kanseri, neoadjuvan kemoterapi, rezidü tümör, tam yanıt, aksilla metastazı, invazif duktal karsinom

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Introduction

Breast cancer is the most common malignancy among women in the developed world (1). Advanced diagnostic modalities and new treatment strategies resulted in a decrease in breast cancer-related mortality, although its incidence is on the rise (1). Neoadjuvant therapy is increasingly used for the treatment of patients with breast cancer (2). It helps to downsize the tumor in early breast cancer, thereby increasing chances for breast-conserving surgery (3). Also, it has the potential to convert metastatic lymph nodes to pathologically negative status in a substantial proportion of patients with locally advanced breast cancer (4).

Accurate evaluation of pathological response after neoadjuvant treatment would aid in treatment and surgical planning (5). Correct prediction of the residual tumor site and size would enable successful resection as well as breast tissue preservation as much as possible. Also, it will give an idea of disease prognosis. Several imaging modalities such as magnetic resonance imaging (MRI), positron emission tomography/computerized tomography (PET/CT), ultrasonography, and mammography is currently being used to examine response to neoadjuvant chemotherapy in breast cancer (6). Although widely used, mammography and ultrasonography seems to overestimate tumor volume due to chemotherapy-induced fibrosis and necrosis (7). On the other hand, MRI may overestimate or underestimate the residual tumor in an essential proportion of the patients; thus, it also has some limitations, particularly its inability to discriminate between viable tumor tissue from scar tissue (7). Nevertheless, MRI and F-18-FDG PET/CT are often used to evaluate response after neoadjuvant chemotherapy for breast cancer (8,9).

F-18-FDG PET/CT provides a quantitative estimation of metabolic changes in the tumor tissue; thus, it has the potential to detect such changes occurring early in the course of chemotherapy (10). Several studies demonstrated the advantage of changes in standardized uptake values in predicting pathological response to neoadjuvant chemotherapy (11, 9, 12). On the other hand, FDG-PET has been shown to have low sensitivity for small lesions (13). To date, several studies examined the role of PET/CT in predicting response to neoadjuvant chemotherapy when performed after the completion of neoadjuvant chemotherapy and before surgery, with inconsistent findings, most of them comparing the findings with that of MRI (6,14-19).

This study aimed to examine the value of 18-FDG PET/CT in predicting pathologically confirmed residual tumor in breast and presence of axillary metastasis when performed after completion of neoadjuvant therapy in patients with invasive ductal carcinoma (IDC) of the breast.

Methods

Patients

This retrospective study included 51 female patients (52 tumors) diagnosed with IDC of the breast who received neoadjuvant chemotherapy and underwent F-18-FDG PET/CT between the years 2015 and 2019. Patients were eligible for the study if they fulfill the following criteria: Biopsy-confirmed diagnosis of invasive stage IIA, IIB, or IIIA breast carcinoma

with no distant metastasis. Patients with inflammatory breast carcinoma, invasive lobular carcinoma, invasive mucinous carcinoma, and patients with distant metastasis were excluded. F-18-FDG-PET/CT was performed 2-3 weeks after the completion of neoadjuvant chemotherapy. Patients were subjected to either breast-conserving surgery or modified radical mastectomy with sentinel node biopsy and/or axillary lymph node dissection after neoadjuvant chemotherapy. The study protocol of this study was approved by the Anadolu Medical Center Local Ethics Committee (decision no: ASM-EK-19/123, date: 11.12.2019). Informed consent was waived since the trial included retrospective data analysis. Data on patient demographics, tumor histology, assessment of tumor by metabolic response on 18F-FDG-PET/CT imaging was collected.

Neoadjuvant Chemotherapy

Patients received anthracycline-based, taxane-based, or anthracycline and taxane combination neoadjuvant treatment. Selected patients with high hormone receptor positivity and advanced age received only hormone therapy. In patients with HER2 positivity, trastuzumab ± pertuzumab was added.

18-FDG PET/CT Examination after Neoadjuvant Treatment

Patients fasted for at least 6 hours, and the blood glucose level had to be <150 mg/dL. F-18-FDG (3.7 MBq/kg) was administered through the arm opposite to breast tumor using a venous line to prevent extravasation. Imaging started approximately 60 min after injection and was performed from mid-thigh level to the base of the skull with arms raised. An integrated PET/CT scanner (Discovery 690, GE Healthcare, Wisconsin, USA) was used for imaging. CT data were acquired first (120 kV;20-120 mAs, determined automatically based on attenuation). Only an oral contrast agent was used. PET emission data were acquired in a 3-dimensional mode, with 3 min per bed position, and reconstructed using iterative reconstruction algorithm with 5 mm slice thickness. Attenuation-corrected images were normalized for injected dose and body weight, and subsequently converted into SUV, defined as: [tracer concentration (kBq/mL)] / [injected activity (kBq) / patient body weight (g)]. The 3D volume of interest was automatically drawn around the primary tumor and around the axillary lymph nodes, when present.

Postoperative Pathological Examination

All cases were diagnosed by tru-cut biopsy. Estrogen receptor and progesterone receptor positivity, the grade of differentiation, and Ki-67 were determined by immunohistochemical (IHC) staining. HER-2 status was accepted as "positive" if strong (3+) membranous staining was seen on IHC. Fluorescence *in situ* hybridization analysis (FISH) was done in samples with moderate (2+) membranous staining on IHC, and HER-2 status was accepted as "positive" if FISH showed amplification. All postoperative specimens were microscopically evaluated to identify the residual invasive tumor. pCR was defined as no residual invasive tumor cells in the breast or axillary nodes. Pathological responses other than pCR were defined as incomplete response (non-pCR).

Assessment of Metabolic Response

Regions of interest were identified and outlined for both primary tumor and axillary lymph node areas, and SUV values were calculated.

Adjacent breast or axillary tissue without activity was identified, and SUV values were calculated to serve as a background activity. When SUV value for the region of interest is two times or more of background activity, the activity in the region of interest was considered pathological and evidence for residual tumor/metastasis.

Statistical Analysis

Statistical analyses were performed using SPSS software for Windows (Version 21.0; SPSS Inc., New York, New York, USA). Descriptive data were presented as mean ± standard deviation or number (frequency), where appropriate. The sensitivity and specificity of the F-18-FDG PET/CT examination following the completion of neoadjuvant chemotherapy were calculated for the diagnosis of histologically confirmed residual tumor in axilla or breast.

Results

Table 1 shows patient and tumor characteristics. All patients were female and diagnosed with IDC of the breast. Half of the patients received neoadjuvant treatment with anthracycline and taxane combination, whereas 13.5% and 32.7% of them received anthracycline-based and taxane-based neoadjuvant therapy. Only two patients received hormone therapy. Trastuzumab ± pertuzumab was added in 36.5% of patients due to HER2 positivity. Postoperative histopathological examination identified residual invasive tumors in the breast in almost two-thirds of the patients (63.5%). On the other hand, metastasis was present in the axilla in slightly more than one-third of the patients (38.5%).

Table 2 shows diagnostic parameters for F-18-FDG PET/CT for the detection of residual invasive tumor in breast and metastasis in the axilla. F-18-FDG PET/CT exhibited high specificity for primary tumor and axilla (93.8% and 89.5%, respectively). The sensitivity of the method, on the other hand, was low for both locations (66.7% for primary tumor and 30.0% for axilla). Around one-quarter of the residual invasive tumors/metastases were missed at these locations. When only the patients with histologically positive residual invasive tumor/metastasis were analyzed separately (n=20 and 33 for axilla and breast, respectively), a false negative rate (i.e., missing rate) for axilla and breast was 0% and 9.1% for the tumors >8 mm in diameter. Among 33 residual invasive tumors in the breast, 22 of them were >8 mm (66.7%); on the other hand, only 4 of 20 axillary metastases were greater than >8 mm (20.0%).

Discussion

This study examined the diagnostic value of F-18-FDG PET/CT in predicting residual tumor or presence of axillary metastasis after the completion of neoadjuvant treatment in patients with IDC of the breast. F-18-FDG PET/CT exhibited high sensitivity but low specificity in this setting, with a high false-negative rate; however, its diagnostic value seems better for residual tumors or axillary metastasis >8 mm.

To date, several other studies examined the diagnostic value of F-18-FDG PET/CT in predicting residual tumor after the completion of neoadjuvant therapy; and most studies compared F-18-FDG PET/CT with MRI. Choi et al. (20) compared the performances of PET/CT and MRI for response evaluation after neoadjuvant treatment in breast cancer. Imaging studies were performed before and after neoadjuvant

treatment, and their diagnostic value in predicting complete/partial response (responders) and stable/progressive disease (non-responders) was evaluated based on postoperative pathological findings. PET/CT exhibited lower specificity and accuracy and higher sensitivity when compared to MRI in response evaluation, although these differences between the two methods did not reach statistical significance (20).

A recent study compared two PET methods [ring-type dedicated breast PET (dbPET) vs whole-body PET-CT (WBPET)] for the assessment of residual tumor after neoadjuvant chemotherapy for breast cancer (14). dbPET was more sensitive than WBPET when quantitative methods

Table 1. Patient and tumor characteristics

Characteristics	n=52
Age, y (mean ± SD)	48.9±10.8
Tumor receptor characteristics	
Estrogen receptor-positive	34 (65.4%)
Progesterone receptor positive	24 (46.2%)
HER2 positive	19 (36.5%)
Triple-negative tumor	12 (23.1%)
Luminal A	7 (13.5%)
Luminal B	15 (28.8%)
Chemotherapy type	
Anthracycline-based	7 (13.5%)
Taxane-based	17 (32.7%)
Anthracycline taxane combined	26 (50.0%)
Hormone	2 (3.8%)
Trastuzumab ± pertuzumab	19 (36.5%)
Histological examination	
Residual invasive tumor in axilla	20 (38.5%)
Residual invasive tumor in the breast	33 (63.5%)
Residual invasive tumor diameter in axilla, mm, (mean ± SD)*	5.8±5.7
Residual invasive tumor diameter in the breast, mm, (mean ± SD)*	17.5±13.0

Unless otherwise stated, data presented in n (%).
HER2: human epidermal growth factor receptor 2, *: for patients with histologically positive residual invasive tumor, SD: standard deviation, Luminal A: hormone-receptor positive (estrogen-receptor and/or progesterone-receptor positive), HER2 negative, and has Ki-67 ≤14, Luminal B: hormone-receptor positive (estrogen-receptor and/or progesterone-receptor positive), and either HER2 positive or HER2 negative, Ki-67 >14

Table 2. Diagnostic value of F-18-fluorodeoxyglucose positron emission tomography/computed tomography for the detection of residual invasive tumor or presence of axillary metastasis after neoadjuvant chemotherapy

	Primary tumor	Axilla
True positive, n (%)	22 (42.3%)	6 (11.5%)
True negative, n (%)	17 (32.7%)	30 (57.7%)
False positive, n (%)	2 (3.8%)	2 (3.8%)
False negative, n (%)	11 (21.2%)	14 (26.9%)
Sensitivity, % (95% CI)	66.7 (48.2-82.0)	30.0 (11.9-54.3)
Specificity, % (95% CI)	89.5 (66.9-98.7)	93.8 (79.2-99.2)

CI: confidence interval

(84% vs 26%) or qualitative methods (58% vs 21%) were used; however, these figures may still be considered relatively low for the detection of a residual tumor (14).

A recent meta-analysis reviewed the findings of 13 studies comparing MRI and PET/CT in predicting response after neoadjuvant treatment (15). The pooled sensitivity for PET/CT and MRI was 77% and 88%, respectively. Corresponding figures for specificity were 88% (PET/CT) and 69% (MRI). The authors recommended that MRI might be a more suitable method for predicting pathologic response to neoadjuvant chemotherapy. Another meta-analysis examining the prediction of pathological complete response to neoadjuvant chemotherapy by these two imaging modalities from six studies found a high sensitivity for PET/CT (86%), and the authors recommended combined use of these modalities for better predicting response to neoadjuvant treatment (16). Another meta-analysis that included ten studies compared the value of MRI and PET/CT in predicting pathological response. During the neoadjuvant treatment, the performance of PET/CT was similar to MRI in terms of sensitivity (91% vs 89%) and better in terms of specificity (69% vs 42%). On the other hand, MRI had better performance when either of the two methods was used after the completion of neoadjuvant treatment, with significantly higher sensitivity (88% vs 57%) (19). There is a wide range of sensitivity and specificity across studies, which may be attributed to the heterogeneity between studies (17).

Studies examining the value of diagnostic methods in predicting complete axillary response after neoadjuvant therapy for breast cancer are relatively few. A study by Vicente et al. (21) examined the predictive value of 18-FDG PET/CT for axillary lymph node response after neoadjuvant chemotherapy performed at different time points: before, during, and after neoadjuvant therapy. Predictive values of axillary response were low for both early and late evaluation (sensitivity, 52% vs 32%), in line with the findings of the present study. A systematic review included four studies with a relatively small sample. The reported positive predictive value (PPV) for complete axillary response ranged between 40% and 100% for different diagnostic methods. Among the studies included in the review, in the study by Hieken et al. (18), post neoadjuvant F-18-FDG PET-CT exhibited sensitivity, specificity, PPV, and negative predictive value of 85%, 63%, 61%, and 86%, respectively. You et al. (6) evaluated the axillary lymph node status after neoadjuvant chemotherapy and compared the diagnostic performances of ultrasound, MRI, and F-18-FDG PET/CT. The sensitivity of ultrasound, MRI, and PET/CT was 50%, 72%, and 22%, respectively. Corresponding figures for specificity were 77%, 54%, and 85%, with PET/CT having the highest specificity. On the other hand, a combination of the three methods had the highest sensitivity.

In this study, 18-FDG PET/CT exhibited relatively better performance for predicting tumors/metastases larger than 8 mm. This is in line with the findings of a study that demonstrated low sensitivity of 18-FDG PET/CT for small lesions. That study by Kumar et al. (13) examined the clinicopathological factors associated with false-negative FDG-PET in primary breast cancer and found that small tumor size (≤10 mm) and low tumor grade were independent predictors of false-negative results. This may also explain the low sensitivity found in our study, particularly for axillary metastasis. The substantial reduction of the tumor size

after neoadjuvant treatment seems to be responsible for this finding. Although sensitivity for detecting an invasive tumor in the breast is somewhat acceptable, sensitivity for detecting axillary metastases, in particular, is substantially low; probably, since only one-fifth of axillary metastases were >8 mm whereas, two-thirds of residual invasive tumors in the breast had such a great size.

This study has several limitations. Firstly, the sample size is relatively small for examining clinicopathological factors that may affect the predictive performance of PET/CT. Another limitation is that not all patients were node-positive at baseline before neoadjuvant treatment. Thus, any metastasis in axilla may not necessarily be considered residual after neoadjuvant therapy.

Conclusion

F-18-FDG PET/CT alone does not seem to provide reliable information on the presence of a residual tumor or node metastasis when performed after the completion of neoadjuvant treatment in IDC of the breast. Considering that preoperative restaging is essential in terms of treatment planning and outcome prediction, new diagnostic modalities utilized at different time points or including a combination of different imaging methods are warranted to predict response to neoadjuvant chemotherapy better.

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