

Original Article

The Relation Between Tumor and Axillary Lymph Node SUV Values with the Presence of Distant Metastases in Staging F18 FDG PET/CT in Breast Cancer

Meme Kanserinde Evreleme F18 FDG PET/BT İncelemesinde Tümör ve Aksiller Lenf Nodu SUV Değerlerinin Uzak Metastaz ile İlişkisi

Bedriye Büşra Demirel, Hüseyin Emre Tosun, Gülin Uçmak

Ankara Oncology Research and Training Hospital, Department of Nuclear Medicine

ABSTRACT

Introduction: We aimed to investigate the relation between primary tumor and axillary lymph node maximum standardized uptake values (SUVmax) with the presence of distant metastases at initial staging of breast cancer.

Materials and Methods: Fifty-seven women who were referred to our clinic for staging positron emission tomography/computed tomography (PET/CT) with diagnosis of breast cancer were included in the study. Immunohistochemical (IHC) features of the primary tumor [hormone receptor (HR), human epidermal growth factor receptor type-2 (HER2), Ki67 index] were reviewed retrospectively. All patients' HR status was positive and HER2 status was negative. Primary tumor SUVmax (Tmax) and axillary lymph node SUVmax (Nmax) values and primary tumor-to-axillary lymph node (T/N) ratios were calculated in PET/CT. Patients were divided into two groups as metastatic and non-metastatic according to PET/CT findings. The differences between groups in terms of age, Ki67 index and SUV values were statistically analyzed.

Results: The mean age of the patients was 52±14.4 (range 25-79 years). According to PET/CT findings, the patients were divided in two groups, 57% metastatic (n = 33) and 43% non-metastatic (n = 24). While no statistically significant difference was observed between the two groups in terms of age, Ki67 index and Tmax averages, statistically significant differences were found between Nmax values (p <0.001) and T/N ratios (p=0.001). Cut-off value in association with distant metastasis was 7,8 for Nmax value and 8,5 for T/N ratio on ROC curve analysis.

Discussion: Accurate staging is important in terms of treatment plan and prediction of disease prognosis in breast cancer. In our study, it was thought that the difference in Nmax values and T/N ratios, independent of Tmax values, could be a determinant in terms of the overlooked and possible early metastatic disease indicator in the patient group without known distant metastasis.

Keywords: breast cancer, positron emission tomography, metastasis

ÖZET

Giriş: Meme kanseri evrelemesinde primer tümör ve aksiller lenf nodu SUVmax parametrelerinin uzak metastaz varlığı ile ilişkisini araştırmak amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya kliniğimize meme kanseri tanısı ile evreleme amaçlı positron emisyon tomografi /bilgisayarlı tomografi (PET/BT) incelemesi için refere edilen 57 kadın hasta dahil edildi. Hastaların immünohistokimyasal özellikleri [hormone reseptörü (HR), human epidermal büyüme factor reseptörü tip-2 (HER2), Ki67 indeksi] geriye dönük olarak tarandı. Hastaların tümü HR-pozitif, HER2-negatif idi. PET/BT'de primer tümör SUVmax(Tmax), aksiller lenf nodu SUVmax (Nmax) değerleri ve tümör/aksiller lenf nodu SUVmax (T/N) oranları hesaplandı. Hastalar PET/BT bulgularına göre metastatik ve non-metastatik olarak iki gruba ayrıldı. Gruplar arası yaş, Ki67 indeksi ve SUV değerleri açısından farklılık istatistiksel analizi yapıldı.

Bulgular: Hastaların yaş ortalaması 52 ± 14.4 (aralık 25-79) idi. PET/BT bulgularına göre hastalar %57'si metastatik (n=33), %43'ü non-metastatik (n=24) olmak üzere iki grupta izlendi. İki grup arasında yaş, Ki67 indeksi ve Tmax ortalamaları açısından istatistiksel olarak anlamlı fark izlenmezken ortalama

Nmax değerleri ve T/N oranları arasında istatistiksel olarak anlamlı fark bulundu (sırasıyla $p < 0.001$, $p = 0.001$). Uzak metastaz varlığı açısından ROC analizde Nmax için kesme değeri 7.8, T/N oranı için 8.5 olarak bulundu.

Tartışma: Meme kanserinde tedavi planı, hastalık prognozu açısından evrelemenin doğru şekilde yapılması önem arz etmektedir. Çalışmamızda Nmax değerinin ve T/N oranının, Tmax değerlerinden bağımsız olarak farklılık göstermesi, uzak metastaz saptanamayan hasta grubunda gözden kaçan ve olası erken metastatik hastalık göstergesi açısından belirleyici olabileceği düşünülmüştür.

Anahtar kelimeler: meme kanseri, pozitron emisyon tomografi, metastaz

Introduction

Breast cancer is the most frequent cancer type in women [1]. In 2020, 2.3 million women were diagnosed with breast cancer and 685 000 of them died globally [2]. Although many strong treatment options such as surgery, radiation therapy, chemotherapy, hormone therapy, targeted therapy etc. are achievable, precise staging is a necessity to plan optimal management of the disease.

During the last years, 18F-fluorodeoxyglucose (FDG) positron emission tomography /computed tomography (PET/CT) has gained an important role in the pretreatment staging of breast cancer. FDG-PET/CT has shown high accuracy in detecting axillary-extra axillary lymph nodes and distant metastases. Also, FDG-PET/CT allows on a single “whole-body” examination to assess for locoregional as well as distant metastases with a positive predictive value exceeding 80% [3-6].

Except nodal and distant metastasis status, it was known that biological characteristics of tumor such as size, grade, histological subtype, hormone receptor status are significance determinant in selecting treatment option and prognosis. Tumor subtypes of breast cancer patients have been reported to show different outcomes, including poor prognosis for the basal-like subtype and a significant difference in the outcome for the HR-positive groups [7,8].

We retrospectively evaluated the utility of tumor and axillary lymph node maximum

standardized values (SUVmax) on FDG-PET/CT and clinicopathological characteristics for predicting distant metastasis in patients with breast cancers.

Materials and Methods

Fifty-seven women who were referred to our clinic for PET/CT for staging purposes with diagnosis of breast cancer were included in the study. Patients with prior excisional biopsy of breast were excluded from the study.

This study was approved by the ethics committee of our institution (2022-03/64).

Age and immunohistochemical (IHC) features of the primary tumor such as hormone receptor (HR), human epidermal growth factor receptor type-2 (HER2) status and Ki67 index were recorded from the institution patient information system, retrospectively. All patients included in the study were HR positive and HER2 negative.

PET/CT Imaging Procedure

Patients were imaged on an integrated PET/CT scanner (Siemens Biograph 6-True Point PET/CT systems). Patients were fasted for at least 6 hours prior to injection of $90 \mu\text{Ci/kg}$ 18F-FDG by using automatic infusion system (Intego PET Infusion System). The blood glucose levels were less than 150 mg/dl in all patients at the time of the FDG injection. Unenhanced CT images were acquired for attenuation correction from the vertex of the skull to distal thigh using 3 mm slice thickness and calculated effective mAs due to patient weight. The PET and CT images

Table 1. Patient and tumor characteristics according to metastatic and non-metastatic groups

	metastatic (n:33) mean±SD	non-metastatic (n:24) mean±SD	p value
Age	50,2±15	55,2±13,3	0,2
Ki67 index (%)	31,9±23,7	32,9±23,8	0,6
Tmax	8,4±4,2	7,3±4,9	0,1
Nmax	5,5±3,9	2,5±2,8	<0,001
T/N	2,3±2,2	5,1±4,2	0,001

Tmax: primary tumor SUVmax, Nmax: axillary lymph node SUVmax, T/N: primary tumor-to-lymph node SUVmax ratio

were reviewed on a workstation (Syngovia, Siemens Medical Solutions) in all standard planes along with maximum-intensity-projection images and were visually and quantitatively by two specialists experienced in interpreting PET/CT scans.

SUVmax was used to quantify FDG uptake. Primary tumor SUVmax (Tmax) and axillary lymph node SUVmax (Nmax) were calculated in PET/CT. Primary tumor-to-lymph node SUVmax (T/N) ratios were measured.

Patients were divided into two groups as metastatic and non-metastatic according to PET/CT findings.

Statistical Analysis

The distributions of variables were tested for normality using Kolmogorov-Smirnov test. Student's t-test and Mann-Whitney U-test were used to compare differences in normally distributed and non-normally distributed variables, respectively. The data were presented as the mean ± standard deviation. The differences between groups in terms of ages were statistically analyzed by using t-test. The differences between Ki67 index, Tmax, Nmax values and T/N ratio according to the presence of distant metastasis were analyzed by Mann-Whitney U test. p values < 0.05 were considered to be statistically significant. Receiver Operating Characteristic (ROC) curve analysis was used to mark the cut-off values of Nmax and T/N in association with the presence of distant metastasis. The

statistical analysis was performed using commercial software (SPSS 25.0, IBMSPSS Statistics for Windows, Version 25.0. Armonk NY: IBM Corp.).

Results

The mean age of the patients was 52±14.4 with a range of 25-79 years. All patients of the study were HR-positive and HER2-negative.

PET/CT detected distant metastasis in 33 of 57 patients. According to PET/CT findings, the patients were divided in two groups, 57% metastatic (n = 33) and 43% non-metastatic (n = 24).

Prognostic factors candidates such as age, Ki67 index were evaluated for each group. No statistically significant difference was observed between the two groups in terms of age and Ki67 index (Table 1).

The average primary tumor SUVmax (Tmax) values in metastatic and non-metastatic groups were 8.4±4.2 (mean±SD) and 7.3±4.9 (mean±SD), respectively. No significance difference was observed in Tmax between two groups (p=0.12). The presence of distant metastasis was analyzed for its association with axillary lymph node SUVmax (Nmax) and primary tumor-to-axillary lymph node ratio (T/N). We observed that Nmax was significantly higher in patients with distant metastasis than in patients without distant metastasis (mean±SD 5.5±3.9 vs. 2.5±2.8, respectively, p < 0.001). Based on ROC curve analysis, cut-off values in association of distant

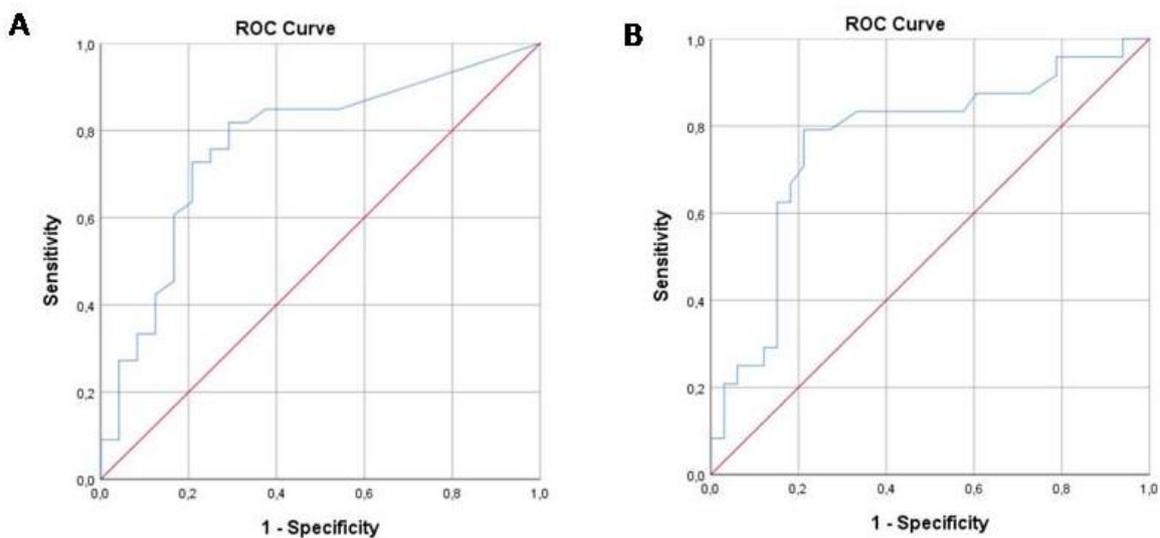


Figure 1. ROC curves demonstrate the cut off values for axillary lymph node SUVmax (A) and primary tumor-to-lymph node SUV ratios (T/N) (B) in association with the presence of distant metastasis. The cut off value for Nmax was 7.8, area under the curve was 77%. The cut off value for T/N ratio was 8.5, area under the curve was 76%.

metastasis were calculated as 7.8 for Nmax (sensitivity: 27%, specificity: 96%, area under the curve (AUC): 0.769) (Figure 1). Also, according to T/N ratios we found significant difference between metastatic and non-metastatic groups (mean \pm SD 2,3 \pm 2,2 and 5,1 \pm 4,2, respectively, $p=0,001$). Cut-off value in association of distant metastasis was calculated as 8.5 for T/N ratio on ROC curve analysis (sensitivity: 20%, specificity: 97%, area under the curve (AUC): 0.764).

Discussion

F-18 FDG PET/CT has an important role in initial staging of breast cancer and it can detect distant metastasis with superior success compared to conventional imaging methods [5,9]. In recent study, FDG PET/CT was compared with conventional imaging modalities for ability of detecting distant metastases, and it was shown that the sensitivity and specificity were 87% and 83% versus 48% and 93% [10]. It was observed that FDG PET/CT determined unexpected

metastases and changed the clinical stage in 52% of the patients, especially with locally advanced disease, in another study [11]. Compatible with literature, in our study the detected distant metastasis via FDG PET/CT was 57% of the patients with newly diagnosed breast cancer.

Breast cancer has high structural and molecular heterogeneity between tumors and also within a single tumor. Gene expression profiling enables defining and characterizing of main intrinsic molecular subtypes with different clinical outcomes and responses to treatment. The distinction between subtypes is based on expression of estrogen and progesterone HR and HER2 [7,8]. The highest survival rate is observed among women with HR+/HER2- subtype, while triple negative subtype has the worst survival rate [12]. Despite this ongoing acceptance, it is striking that, in our patient population whom all of HR+/HER2- the distant metastasis rate was 57% at the time of diagnosis.

In routine clinical practice, immunohistochemical evaluation of Ki-67 is frequently utilized to assess proliferative features of tumor cells. It has been used for many years for breast cancer to decide the therapy option. The results of the studies investigating the effect of Ki-67 on survival outcomes were conflicting with each other. Although some of the researchers showed prognostic effects of Ki-67 expression on survival outcomes, the others did not demonstrate any correlation [13-15]. In the current study, no correlation was found between the presence of metastasis and Ki67 index in patients with HR+/HER2- breast cancer at initial staging.

Several studies have shown correlations between the avidity of FDG uptake and some tumor characteristics of breast cancer such as tumor type, grade, HR status, and HER2 status [16-18]. In previous studies, high tumor grade, HR negativity, HER2 positivity and high Ki-67 index, in summary, high mitotic activity was associated with increased SUV values [19]. As a predictor for postoperative clinical outcome, SUVmax on FDG-PET/CT is useful for diagnosing high-grade malignancy and predicting the prognosis in breast cancer patients. It was reported that SUVmax and the HR status were useful for predicting malignancy grades and prognosis of patients with breast cancer [20]. Nevertheless, Tmax values were not found associated with the presence of distant metastasis in our study.

Clinicopathological parameters such as tumor size and lymph node status have been used as traditional prognostic factors for patients with breast cancer. Today several prognostic models based on clinical prognostic factors are available to estimate survival of breast cancer patients. But the clinical variables for each model are slightly different and the models also showed different prognostic performance [21]. To make an optimal treatment decision for especially early-stage

breast cancer, the main importance is to exclude the presence of distant metastasis and also to identify risk of recurrence. Despite the improvement of early diagnosis and a growing progress in treatment strategies, still today metastatic disease remains incurable and the main cause of breast cancer-related mortality.

Also, lymph node involvement has long been recognized as an important prognostic factor in breast cancer. The presence of positive axillary lymph nodes is a predictor of increased risk of local and distant recurrence, directly affecting mortality [22,23]. It has been shown that the overall 5-year survival for breast cancer patients with lymph node metastasis is 40% lower than that of patients who do not have metastasis to the lymph nodes [23]. The number of lymph nodes involved has traditionally been used for post-surgical staging of breast cancer. In addition, the lymph node ratio, defined as the ratio of positive lymph nodes to the total number of lymph nodes removed, has emerged as a prognostic factor in a growing number of studies. A higher lymph node ratio is associated with a poor overall survival and an increased risk of locoregional recurrence in breast cancer [22,24,25].

Several studies have reported the correlation of higher SUVmax of the primary tumor with poorer prognostic behavior in breast cancer [16]. Previously, it was showed that both primary tumor SUVmax and a combination of primary tumor SUVmax and axillary lymph node avidity were significant factors for predicting relapse [26]. However, in another study, it was reported that axillary lymph node SUVmax was the only significant independent factor for predicting relapse and that the optimal cut-off for axillary lymph node SUVmax was 2.8[27]. In our study, we observed that Nmax values and T/N ratios were significantly higher in patients with distant metastasis than without ones at initial staging and cut-off values in association of distant metastasis were measured as 7.8 for

Nmax and 8.5 for T/N. Several studies evaluated whether lymph node-to-primary tumor SUV ratio was a useful factor for prediction of relapse in breast cancer [27-29]. Furthermore, a recent study revealed that lymph node-to-primary tumor SUV ratio is a more accurate value for discriminating axillary lymph node involvement than axillary lymph node SUVmax value [28]. In another study, authors speculated that lymph node and primary tumor SUV ratio could be linearly related, and studied the clinical value of axillary lymph node-primary tumor SUV ratio for predicting disease-free survival in invasive ductal carcinoma with axillary lymph node metastasis [29]. In our study we found that, Nmax values and T/N ratios were significantly higher in HR+/HER2- breast cancer patients with distant metastasis than in patients without distant metastasis at the time of diagnosis. This study revealed that the presence of distant metastasis was associated with Nmax and T/N ratio and both Nmax value and T/N ratio were significant independent factors for predicting prognosis. Even if distant metastasis is not detected in the

staging FDG PET/CT with high Nmax and T/N ratio, it should be kept in mind that present distant metastasis may be occult and these patients should be followed more closely. We believe that the results of this study should be supported by studies with follow-up prognosis data. The other limitation of this study is that only patients with HR positive HER2 negative were selected in order to provide homogeneous data because the number of patients with other hormone status (such as HR negative HER2 positive) was insufficient. Further studies with larger number of patients including all hormone and receptor profiles may support our results.

In conclusion, accurate staging is important in terms of treatment plan and prediction of disease prognosis in breast cancer. In our study, it was thought that the difference in Nmax and T/N ratio, independent of Tmax values, could be a determinant in terms of the overlooked and possible early metastatic disease indicator in the patient group without known distant metastasis.

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Corresponding author e-mail: demirelbbusra@hotmail.com

Orcid ID:

Bedriye Büşra Demirel 0000-0002-6494-062X

Hüseyin Emre Tosun 0000-0002-0169-6316

Gölin Uçmak 0000-0002-0268-4747

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