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Relationship Between Metabolic Activity, Cellularity, Histopathological Features of Primary Tumors and Distant Metastatic Potential in Breast Cancer

Meme Kanserinde Primer Tümörün Metabolik Aktivitesinin, Hücreselliğinin ve Histopatolojik Özelliklerinin Uzak Metastaz Potansiyeli ile İlişkisi

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Abstract

Objectives: The aim of this study was to evaluate the relationship between the types of distant metastatic spread, histopathological features, and imaging features of primary tumor on positron emission tomography/magnetic resonance imaging (PET/MRI) for primary staging in newly diagnosed breast invasive ductal carcinoma (IDC) patients.

Methods: Data from 289 female patients were retrospectively evaluated. Maximum standardized uptake value, metabolic tumor volume (MTV), total lesion glycolysis (TLG), and minimum apparent diffusion coefficient (ADC_{min}) values of primary tumors were obtained from PET/MRI. The patients were grouped as non-metastatic, oligometastatic (1-5 metastatic lesions) and multimetastatic (>5 metastatic lesions) disease according to the number of distant metastases, and divided into two groups as isolated bone metastasis (IBM) and mixed/soft tissue metastasis (M-SM) groups according to the sites of metastatic spread.

Results: Metabolic parameters had higher values and ADC_{min} had lower values in the multimetastatic and oligometastatic groups than in the non-metastatic group. MTV was the only parameter that showed significant difference between the multimetastatic and oligometastatic groups. MTV and TLG were significantly higher in the M-SM group than in the IBM group. ^{18}F-fluorodeoxyglucose PET parameters had significantly higher values in grade 3, hormone receptor negative, human epidermal growth factor receptor 2 positive, triple negative, and highly proliferative (Ki-67 ≥14%) tumors. The prediction models that included imaging parameters to predict the presence of distant metastasis had higher discriminatory powers than the prediction models that included only histopathological parameters.

Conclusion: Primary tumors with higher metabolic-glycolytic activity and higher cellularity were more aggressive and had higher metastatic potential in breast IDC. Compared with histopathological parameters alone, the combination of imaging parameters and histopathological features of primary tumors may help to better understand tumor biology and behavior.

Keywords: ^{18}F-FDG PET/MRI, breast cancer, oligometastasis, multimetastasis, bone metastasis, soft tissue metastasis

Öz

Amaç: Bu çalışmanın amacı, yeni tanı meme invaziv duktal karsinom (İDK) hastalarında primer evreleme pozitron emisyon tomografisi/manyetik rezonans görüntüleme (PET/MRG) görüntülerinden elde edilen görüntüleme parametrelerinin, histopatolojik özelliklerin ve uzak metastatik yayılım tipleri arasındaki ilişkinin değerlendirilmesidir.

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Yöntem: İki yüz seksen dokuz kadın hastanın verileri retrospektif olarak değerlendirildi. Primer tümörün maksimum standartlaştırılmış alım değeri, metabolik tümör volümü (MTV), toplam lezyon glikolizisi (TLG) ve minimum görünür difüzyon katsayı (ADC_{min}) değerleri PET/MRG'lerden elde edildi. Uzak metastaz sayısına göre hastalar non-metastatik, oligometastatik (OM) (1-5 metastatik lezyon) ve multimetastatik (>5 metastatik lezyon) olarak gruplandı. Uzak metastazı bulunan hastalar ayrıca metastatik yayılım bölgelerine göre izole kemik metastazı (İKM) ve mikst/yumuşak doku metastazı (M-YDM) olarak iki gruba ayrıldı.

Bulgular: Multimetastatik ve oligometastatik gruplarında non-metastatik grubuna göre metabolik parametreler daha yüksek değerler gösterirken, ADC_{min} değeri anlamlı olarak daha düşüktü. MTV, multimetastatik ve oligometastatik grupları arasında anlamlı farklılık gösteren tek parametreydi. M-YDM grubunda MTV ve TLG değerleri İKM grubuna göre anlamlı olarak daha yüksekti. ^{18}F-florodeoksiglukoz PET parametreleri grade 3, hormon reseptör negatif, insan epidermal büyüme faktörü reseptör 2 pozitif, triple negatif ve yüksek proliferatif (Ki-67 ≥%14) tümörlerde anlamlı olarak daha yüksek değerlere sahipti. Uzak metastaz varlığını öngörmek için oluşturulan ve görüntüleme parametrelerini içeren modellerin ayırıcılık gücü, sadece histopatolojik özellikleri içeren öngörü modelinden daha yüksek olarak bulundu.

Sonuç: Meme İDK'de yüksek metabolik-glikolitik aktivite ve yüksek hücresellik gösteren primer tümörler daha agresif ve daha yüksek metastatik potansiyele sahiptir. Tek başına histopatolojik parametrelere kıyasla primer tümörün histopatolojik özelliklerinin ve görüntüleme parametrelerinin kombinasyonu tümör biyolojisi ve davranışının daha iyi anlaşılmasına yardımcı olabilir.

Anahtar kelimeler: ^{18}F-FDG PET/MRG, meme kanseri, oligometastaz, multimetastaz, kemik metastazı, yumuşak doku metastazı

Introduction

Breast cancer is the most common type of malignancy in women and is one of the most common causes of cancer-related deaths (1). Invasive ductal carcinoma (IDC) is the most common subtype and constitutes approximately 75% of all breast cancers (2). Distant metastasis (stage IV disease) at the time of diagnosis can be detected in approximately 3.5% to 7% of newly diagnosed patients (3). The median overall survival times may vary significantly in patients with distant metastasis (4). Some prognostic factors that may affect survival include tumor biology, metastatic tumor load, and the localization of distant metastases (5).

Breast carcinoma is one of the most common osteotropic tumors, along with prostate cancer. In addition, bone is the first site of relapse in approximately 50% of patients with breast cancer (6). Breast cancer can also metastasize to soft tissues such as distant lymph nodes, liver, and lung (7). Localization of distant organs where breast cancer metastasizes has clinical and prognostic importance. Although there are several complications such as bone pain, hypercalcemia, and pathologic fractures in patients with isolated bone metastasis (IBM), survival rates are higher in this patient group than in those with soft tissue metastasis (SM) (5,6,8).

Although metastatic breast cancers are generally considered incurable, patients with higher survival rates can be observed within this group. This clinical condition can also be associated with oligometastatic disease. In 1995, Hellman and Weichselbaum (9) conceptualized oligometastatic disease as an intermediate state with a limited number of metastases in malignant tumors. In their view, oligometastatic tumors may not have the genetic and biological features to rapidly develop multimetastasis (9,10). Approximately 1-10% of newly diagnosed patients with metastatic breast cancer have "*de novo*" oligometastatic disease (3). With the combined use of systemic and aggressive local treatment options in patients with oligometastatic disease, higher progression-free and overall survival rates can be achieved. Recently, the use of imaging modalities has increased the frequency of detection of oligometastatic disease in various types of malignancies, such as ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) or PET/magnetic resonance imaging (MRI).

IBM and oligometastatic disease may be related to different biological features of the primary tumor in breast carcinomas, such as hormone receptor status, human epidermal growth factor receptor 2 (HER2) status, and proliferation index (6,11,12). ^{18}F-FDG PET-derived metabolic parameters also have significant relationships with histopathological features (molecular subtypes, proliferation and tumor grade) of primary tumors (13,14,15). However, to the best of our knowledge, studies that evaluated the relationship between ^{18}F-FDG PET/MRI-derived quantitative parameters, the number of distant metastatic lesions (oligometastatic vs. multimetastatic disease), and the localization of distant metastases [IBM vs. mixed/soft tissue metastasis (M-SM)] in primary staging are not numerous. Therefore, this study aimed to evaluate the relationship between the types of distant metastatic spread and the imaging features of the primary tumor on PET/MRI for primary staging in newly diagnosed patients with breast IDC. This study also aimed to evaluate the relationship between histopathological features, imaging parameters, and metastasis types.

Materials and Methods

Patients

We retrospectively reviewed patients with newly diagnosed, histopathologically confirmed breast cancer

who underwent ^{18}F-FDG PET/MRI for primary staging before surgery or neoadjuvant treatment in our department between 2016 and 2020. Patients who (a) had a history of another malignancy, (b) had a diagnosis of breast cancer other than IDC, (c) received any neoadjuvant treatment before ^{18}F-FDG PET/MRI were excluded from the study. A total of 289 female patients (mean age: 51.5±12.2 years) were included in the analysis. The histopathological data of the patients were recorded. This study was approved by the Gazi University Local Ethical Committee (decision no: 296, date: 11.05.2020).

^{18}F-FDG PET/MRI

PET/MRI of all patients was performed in accordance with the protocols recommended in international guidelines. According to the protocol used, patients fasted for 4-6 h and blood glucose levels were confirmed to be 180 mg/dL before intravenous injection of ^{18}F-FDG. All patients received a single injection of ^{18}F-FDG (median activity: 170 MBq; range: 78-310 MBq). PET/MRI were acquired using an integrated 3 Tesla PET/MRI scanner (GE Signa PET/MRI, GE Healthcare, Waukesha, Wisconsin, USA) with a time-of-flight PET detector 60 min after injection. Both whole body and breast dedicated PET/MRI protocols included an initial localizer scan and a 3D dual-echo fast spoiled gradient recalled echo liver-accelerated volume acquisition sequence (LAVA-FLEX) for MRI-based attenuation correction (MRAC). Whole-body PET/MRI was followed by a high-resolution axial T1-weighted 3D LAVA-FLEX sequence, coronal T2-weighted fast-recovery fast spin echo sequence, whole -body diffusion-weighted images (DWI) (b values: 50, 1000 s/mm^2), and apparent diffusion coefficient (ADC) mapping. The whole-body protocol included 5 or 6 bed positions. PET emission scans were recorded together with MRI sequences, and the acquisition time per bed position was 3 min. Breast-dedicated PET/MRI with an 8-channel breast coil included axial T1-weighted and high-resolution T2-weighted sequences, axial DWI (b values: 50, 800 s/mm^2), and ADC mapping in 1 bed position, with an acquisition time of 15 min. For the attenuation correction, an atlas-based attenuation correction map was used for the head, and a vendor-based algorithm using MRI-based attenuation correction data was used for the remaining body parts. The whole-body and breast-dedicated PET/MR images were acquired without contrast material injection.

^{18}F-FDG PET/MRI Image Analysis

All PET/MRI were visually and quantitatively evaluated by one experienced nuclear medicine specialist using vendor-based workstations (AW volume share 5, GE Medical Systems). For visual assessment, the number of ^{18}F-FDG-positive lesions that displayed pathological correlates on MRI and were consistent with distant metastasis at follow-up were recorded for each patient. The pathological correlates of ^{18}F-FDG-positive metastatic lesions on MRI were hypointensity on T1-w images and hyperintensity on T2-w images associated with increased signal intensity on DWI and diffusion restriction on ADC maps. Patients were grouped as non-metastatic, oligometastatic, and multimetastatic according to the number of distant metastatic lesions. For the definition of "*de novo*" oligometastatic disease, we used a cut-off of maximum of five PET-positive distant metastatic lesions (3). Patients with distant metastasis were also divided into two groups according to the localization of metastatic lesions: i) IBM, ii) M-SM. For quantitative evaluation, the maximum standardized uptake value (SUV_{max}), metabolic tumor volume (MTV), total lesion glycolysis (TLG), and minimum ADC (ADC_{min}) of primary tumors were extracted from PET/MRI data. SUV_{max}, MTV, and TLG were calculated on whole body images. For the calculation of MTV and TLG, the volumes of interest were automatically drawn over primary tumors using the program with a 42% threshold of SUV_{max}. ADC_{min} values (using b value: 800 s/mm^2) were extracted by manually drawing the region of interest around each primary tumor. There were no patients with bilateral breast tumors in the patient population. In patients with more than one tumor in the same breast, quantitative measurements were obtained from the tumor focus with the most intense ^{18}F-FDG uptake.

Statistical Analysis

Differences in categorical variables between metastatic groups were assessed using the chi-square test and Fisher's exact test. Differences in continuous variables between metastatic groups were analyzed using the Mann-Whitney U test and the Kruskal-Wallis test, with corrections for multiple pairwise comparisons. The likelihood of the presence of distant metastasis was modeled with logistic regression analyses using histopathological and imaging parameters. The discriminatory abilities of the prediction models were assessed by receiver operating characteristic (ROC) curve analysis. All statistical analyses were performed using IBM SPSS Statistics for Windows (version 23.0, IBM Corp., Armonk, New York) software. For all analyses a p value <0.05 was considered statistically significant.

Results

Patient Characteristics

The clinical and imaging characteristics of the patients are summarized in Table 1. The patients had a mean age of 51.5±12.2 years. There were no distant metastatic lesions in 220 patients (76.1%). Twenty-six patients (9%)

had oligometastatic disease, and 43 patients (14.9%) had multimetastatic disease. Of the 69 patients with distant metastasis, 29 (42%) had IBM and 40 (58%) had M-SM. Of the patients with oligometastasis (n=26), 20 had IBM and 6 had M-SM. Of the patients with multimetastasis (n=43), 9 had IBM and 34 had M-SM. While IBM was seen in 76.9% of the patients in the OM group, M-SM was seen in 79.1% of the patients in the MM group. This difference between the OM and MM groups was significant (p<0.001). Of the patients with M-SM, 27 had distant lymph node metastases, 25 had lung metastases, 13 had liver metastases, and 2 had brain metastases. Histopathological and/or clinical axillary lymph node metastasis was observed in 67.2% of patients (178/265). While there were no patients with distant metastasis in the axillary lymph node negative group, distant metastasis was detected in 33.7% of patients with axillary lymph node metastasis (p<0.001).

Table 1. The characteristics of patients

Age (mean ± SD) (range)	51.5±12.2 years (26-86 years)
	n (%)
Tumor grade	
Grade 1	32 (11.1%)
Grade 2	134 (46.4%)
Grade 3	114 (39.4%)
Missing	9 (3.1%)
Molecular subtype	
Luminal A	60 (20.8%)
Luminal B (HER2 negative)	133 (46%)
Luminal B (HER2 positive)	41 (14.2%)
HER2 overexpressed	23 (8%)
Triple negative	32 (11%)
Hormone receptor status	
Hormone receptor positive	234 (81%)
Hormone receptor negative	55 (19%)
HER2 status	
HER2 positive	64 (22.2%)
HER2 negative	225 (77.8%)
Ki-67 index	
Low (<14%)	67 (23.2%)
High (≥14%)	222 (76.8%)
Metastatic status	
Non-metastatic group (M0)	220 (76.1%)
Oligometastatic group	26 (9%)
Multimetastatic group	43 (14.9%)
The type of distant metastasis	
Isolated bone metastasis	29 (42%)
Mixed-soft tissue metastasis	40 (58%)

HER2: Human epidermal growth factor receptor 2, SD: Standard deviation

Relationship Between Imaging Parameters and Metastasis Groups

SUV_{max}, MTV, TLG, and ADC_{min} values of primary breast tumors had significant differences among metastatic groups (Table 2). SUV_{max}, MTV, and TLG were higher and ADC_{min} was lower in the multimetastatic group than in the oligometastatic and non-metastatic groups (Figures 1, 2). For the comparison between the multimetastatic and non-metastatic groups, SUV_{max}, MTV, TLG, and ADC_{min} demonstrated significant differences (p=0.01, p<0.001, p<0.001, and p<0.001, respectively). For the comparison between the oligometastatic and non-metastatic groups, SUV_{max}, MTV, TLG, and ADC_{min} had significant differences (p=0.021, p<0.001, p<0.001, p=0.033, respectively). For the comparison between the multimetastatic and oligometastatic groups, MTV was the only parameter with significantly higher values in the multimetastatic group (p=0.048). The median values of MTV and TLG were significantly higher in patients with M-SM than in those with IBM (Table 2). In patients with oligometastasis, TLG was the only imaging parameter that had a significant difference between the IBM and M-SM groups, with higher median values in the M-SM group (70.7 vs. 42.3, p=0.02).

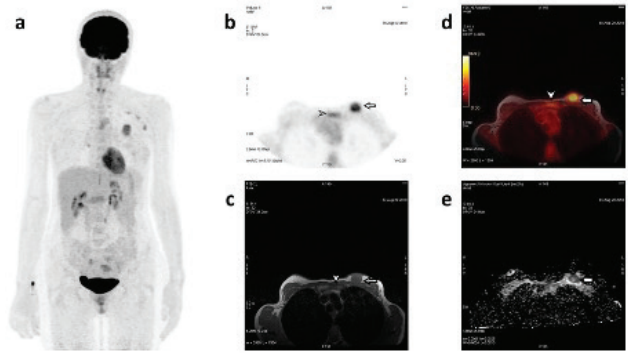

Figure 1. MIP (a), axial ^{18}F-FDG PET (b), axial T1 weighted MRI (c), axial fusion (d), and ADC mapping (e) whole body and breast dedicated PET/MRI of a 41-year-old female patient with invasive ductal carcinoma in left breast (arrows). SUV_{max}, MTV, TLG, ADCmin values of tumors were 5.9, 6.9 cm^3, 25.7 g, $0.42x10^{-3}$ mm^2/s, respectively. Histopathological features of tumor: grade 2, Ki-67 expression level 30%, ER and PR positive, HER2 negative. ^{18}F-FDG uptakes in left axillary lymph nodes were also seen on MIP image. The patient was included in oligometastatic and isolated bone metastasis groups, with one distant metastatic focus on manubrium of sternum (arrowheads)

MIP: Maximum intensity projection, ^{18}F-FDG: ^{18}F-fluorodeoxyglucose, PET: Positron emission tomography, MRI: Magnetic resonance imaging, ADC: Apparent diffusion coefficient, SUV_{max}: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2

Relationship Between Histopathological Parameters and Metastasis

There was no significant association between tumor grade categories (low-intermediate grade: grade 1-2 vs. high grade: grade 3) and metastatic groups (p>0.05). In patients with distant metastasis (n=69), a significant association was found between hormone receptor status and distant metastatic sites (p=0.01). In metastatic patients with hormone receptor-positive tumors (n=57), the proportions of IBM and M-SM were 49.1% (28/57) and 50.9% (29/57), respectively. However, in metastatic patients with hormone receptor negative tumors (n=12), these proportions were 8.3% (1/12) and 91.7% (11/12), respectively. Distant metastasis was observed in 20.5% (46/224) of HER2-negative patients. This ratio was 35.4% (23/65) in patients with HER2 positivity (p=0.02). In patients with distant metastasis, patients with HER2 amplification had a significantly higher ratio of having M-SM (18/23, 78.3%) than those without HER2 amplification (22/46, 47.8%) (p=0.02). In the triple negative cancer group (n=32), distant metastasis was seen in only 3 patients, and all of these patients had M-SM.

Distant metastasis was observed in 7.8% (5/64) of the patients with low proliferation index levels (Ki-67 <14%), and this ratio was 27.8% (61/219) in the patients with high proliferation index (Ki-67 ≥14%) (p<0.001). In patients with oligometastasis, Ki-67 index levels were significantly higher in the M-SM group than in the IBM group (60% vs. 25%, respectively; p=0.015). However, in patients with multimetastasis, Ki-67 index levels did not demonstrate significant differences between the IBM and M-SM groups (30% vs. 30%, respectively; p>0.05).

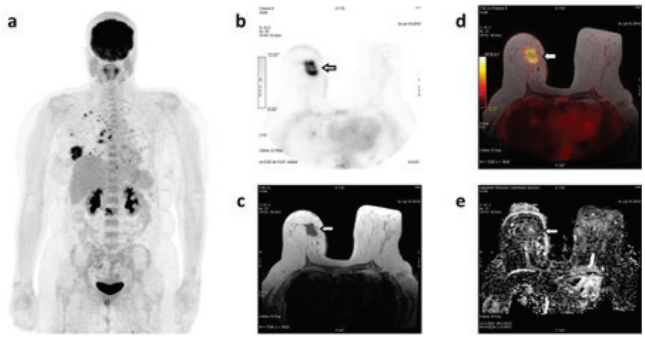

Figure 2. MIP (a), axial ^{18}F-FDG PET (b), axial T1 weighted MRI (c), axial fusion (d) and ADC mapping (e) whole body and breast dedicated PET/MRI images of a 50-year-old female patient with invasive ductal carcinoma in right breast (arrows). SUV_{max}, MTV, TLG, ADC_{min} values of tumors were 16.0, 12.2 cm^3, 109.7 g, 0.67x10^{-3} mm^2/s, respectively. Histopathological features of tumor: grade 2, Ki-67 expression level 50%, ER and PR positive, HER2 positive. ^{18}F-FDG uptakes in right axillary lymph nodes were also seen on MIP image. The patient was included in multimetastatic and mixed-soft tissue metastasis groups, with multiple distant metastatic foci on mediastinal lymph nodes, bilateral lungs, manubrium of sternum and L2 vertebra

MIP: Maximum intensity projection, ^{18}F-FDG: ^{18}F-fluorodeoxyglucose, PET: Positron emission tomography, MRI: Magnetic resonance imaging, ADC: Apparent diffusion coefficient, SUV_{max}: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2

Relationship Between the Histopathological and Imaging Parameters

SUV_{max} and TLG were found to be significantly higher in grade 3 tumors than in grade 1-2 tumors, in hormone receptor -negative tumors than in positive tumors, in HER2-positive tumors than in negative tumors, and in triple-negative tumors than in non-triple-negative tumors. Higher MTV and lower ADC_{min} values were found in high-grade tumors, with marginal significance (p=0.06 and p=0.054, respectively). SUV_{max}, MTV, and TLG were significantly

Table 2. The relationship between imaging parameters of primary tumors, metastatic groups and distant metastasis types

	Median SUV_{max} (range)	p	Median MTV (range) (cm^3)	p	Median TLG (range) (g)	p	Median ADC_{min} (x10^{-3} mm^2/s) (range)	p
Metastatic groups								
Non-metastatic (M0) group (n=220)	6.2 (0.6-31.7)	**0.001**	3.0 (0.3-152.0)	**<0.001**	10.1 (0.2-1126.3)	**<0.001**	0.71 (0.1-1.11)	**<0.001**
Oligometastatic group (n=26)	8.8 (3.0-32.6)	-	8.3 (1.3-59.0)	-	52.1 (3.3-885.6)	-	0.51 (0.02-0.89)	-
Multimetastatic group (n=43)	10.0 (1.4-26.0)	-	14.4 (0.7-220.0)	-	64.6 (1.8-2076.8)	-	0.46 (0.01-0.73)	-
Distant metastasis types								
IBM group (n=29)	8.1 (3.0-32.6)	0.141	8.2 (0.7-220.0)	**0.008**	41.5 (1.8-2076.8)	**0.01**	0.46 (0.02-0.89)	0.502
M-SM group (n=40)	10.4 (1.4-30.8)	-	16.3 (2.1-104.0)	-	100.8 (6.8-1456.3)	-	0.53 (0.01-0.89)	-

The bold entries indicate a significant result. SUV_{max}: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, ADC: Apparent diffusion coefficient, IBM: Isolated bone metastasis, M-SM: Mixed or soft tissue metastasis

higher, and ADC_{min} was significantly lower in tumors with high Ki-67 index compared with tumors with low Ki-67 index (Table 3).

Regression Analyses and Prediction Models

In multivariate regression analysis using only histopathological parameters (model 1), Ki-67 index category (<14% vs. ≥14%) and HER2 positivity were significant predictive factors for distant metastasis [odds ratio (OR) with 95% confidence interval (CI): 4.57 with 1.66-12.6, p=0.003 for higher Ki-67 category, and 5.0 with 1.1-22.8, p=0.036 for HER2 positivity]. In multivariate analysis using only PET/MRI parameters (model 2), SUV_{max} (OR with 95% CI 1.12 with 1.03-1.22, p=0.006), MTV (1.08 with 1.02-1.15, p=0.007), TLG (1.02 with 1.0-1.04, p=0.025), and ADC_{min} (0.6 with 0.48-0.75, p<0.001) were found to be significant predictive factors. In another multivariate analysis using histopathological parameters and imaging parameters together (model 3), imaging parameters of primary tumors were found to be significant predictive factors.

In ROC curve analysis, the area under the curve (AUC) values of the prediction models for distant metastasis were 0.66 (95% CI, 0.56-0.75; p=0.008) in model 1, 0.85 (95% CI, 0.78-0.92; p<0.001) in model 2, and 0.90 (95% CI, 0.84-0.95; p<0.001) in model 3. These values indicated the strong discriminatory ability of models 2 and 3. The AUCs of prediction models 2 and 3 were higher than those of model 1 (Figure 3).

Discussion

Distant metastasis causes most cancer-related deaths. There are some important theories about the metastatic spread of tumors. In 1889, Paget's "seed and soil" hypothesis stated that circulating tumor cells released from primary tumors would seed to an amenable organ microenvironment. In 1894, Halstead stated that cancer metastasis was a progressive anatomical process of contiguous seeding by direct spread from the primary tumor to the regional lymph nodes and then to distant sites. The "systemic theory of metastasis", suggested by Keynes, stated that widespread dissemination occurs from the beginning of cancer and primary tumor is an early manifestation of systemic disease (16,17). In contrast to these theories, in 1994, Hellman developed the "spectrum theory" of cancer metastases, which was first described for breast cancers. According to

Table 3. The relationship between imaging parameters and histopathological features of primary tumors

	Median SUV_{max} (range)	p	Median MTV (range) (cm^3)	p	Median TLG (range) (g)	p	Median ADC_{min} ($x10^{-3}$ mm^2/s) (range)	p
Histopathological tumor grade								
Low-intermediate grade (grade 1-2) (n=166)	5.6 (0.6-31.7)	**<0.001**	3.6 (0.3-152.0)	0.06	11.2 (0.2-1456.3)	**0.001**	0.69 (0.01-1.11)	0.054
High grade (n=114)	9.7 (0.8-32.6)	-	4.9 (0.5-220.0)	-	31.8 (0.7-2076.8)	-	0.66 (0.1-0.97)	-
Steroid hormon receptor status								
Hormone receptor positive (ER and/or PR +) (n=234)	6.7 (0.6-32.6)	**<0.001**	3.8 (0.3-220.0)	0.399	14.5 (0.2-2076.8)	**0.034**	0.67 (0.01-1.11)	0.198
Hormone receptor negative (ER and PR -) (n=55)	9.9 (0.8-30.8)	-	4.8 (0.5-152.0)	-	28.4 (0.7-1126.3)	-	0.73 (0.24-0.97)	-
HER2 status								
HER2 negative (n=225)	6.8 (0.6-32.6)	**0.002**	3.7 (0.3-220.0)	0.125	14.4 (0.2-2076.8)	**0.017**	0.67 (0.01-1.11)	0.456
HER2 positive (n=64)	8.9 (1.1-29.2)	-	5.5 (0.6-82.5)	-	27.4 (0.7-643.8)	-	0.73 (0.24-0.97)	-
Triple negative status								
Triple negative (n=32)	10.4 (0.8-30.8)	**0.005**	5.8 (0.5-152.0)	0.119	43.2 (0.7-1126.3)	**0.032**	0.69 (0.50-0.97)	0.367
Non-triple negative (n=257)	6.9 (0.6-32.6)	-	3.9 (0.3-220.0)	-	14.8 (0.2-2076.8)	-	0.68 (0.01-1.11)	-
Ki-67 index status								
<14% (n=67)	3.6 (0.7-17.0)	**<0.001**	2.2 (0.3-43.8)	**<0.001**	6.4 (0.2-271.2)	**<0.001**	0.75 (0.01-0.99)	**0.005**
≥14% (n=222)	8.7 (0.6-32.6)	-	4.8 (0.3-220.0)	-	27.0 (0.3-2076.8)	-	0.66 (0.02-1.11)	-

The bold entries indicate a significant result. SUV_{max}: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, ADC: Apparent diffusion coefficient, ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2

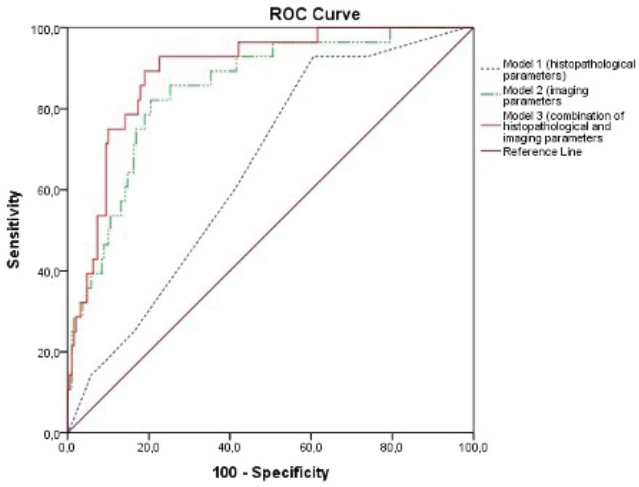

Figure 3. Receiver operating characteristic curves for multivariable prediction models in discriminating the presence of distant metastasis. The AUCs were 0.66 for model 1, 0.85 for model 2 and 0.90 for model 3, respectively
ROC: Receiver operating characteristic, AUC: Area under the curve

this evolutionary theory, cancer progression is a multistep process, ranging from indolent disease to widespread metastasis (16,18). Based on this theory, in 1995, Hellman and Weichselbaum (9) described oligometastatic disease as an intermediate state in the spectrum of metastatic disease. At the oligometastatic stage, tumors may not have aggressive biological features adequate to develop widespread metastasis, and the metastatic potential is limited with low burden disease. With the combined use of systemic and aggressive local treatment options in patients with oligometastatic disease, higher progression-free and overall survival rates can be achieved compared with multimetastatic disease (19). The biological characteristics of primary tumors are considered to be one of the most important factors in determining the type of metastatic spread due to the microenvironmental conditions in the primary tumor and the circulating tumor cells released from the primary tumor (16). Therefore, we aimed to investigate the relationship between histopathological markers, ^{18}F-FDG PET/MRI-derived imaging parameters of primary tumors as *in vivo* markers, and the types of distant metastases. There is no consensus on a strict definition of oligometastatic disease, and different cut-offs were used in the literature. For the definition of oligometastatic disease, we used the cut-off of maximum five ^{18}F-FDG PET-positive metastatic lesions (3). To obtain a more homogeneous patient population, only patients with IDC of the breast were included in our study because ^{18}F-FDG uptakes of primary tumors were found to be different among various histopathological types of breast carcinoma in previous studies (14,20).

Lactate is considered a metabolic key player in tumor metabolism. Altered glucose metabolism is pivotal for tumor growth. Warburg reported that cancer cells could maintain a high rate of glycolysis and their capacity to convert glucose to lactate at high speed, which was closely related to tumor aggressiveness, known as the "Warburg effect" (21). Lactate reduces cytotoxic T-cell function and contributes to the escape of tumor cells from immune cells. Furthermore, tumor cell motility is enhanced by lactate-induced mechanisms, and it was found that the lactate content of tumors was significantly correlated with the incidence of distant metastasis (22). In our study, we found that primary tumors in the multimetastatic state had higher metabolic-glycolytic activity compared with those in other groups and in the oligometastatic state compared with those in the non-metastatic disease. Our results suggest that the presence and number of distant metastatic lesions may be related to the degree of metabolic and glycolytic activity of the primary tumor. This may be explained by higher glycolysis and lactate production that stemmed from the primary tumor, and other biological factors. Besides ^{18}F-FDG PET-derived metabolic parameters, ADC_{min} also had significant differences among metastasis groups in our study. We found that the ADC_{min} values of primary tumors decreased with increased metastatic spread. ADC, which inversely correlates with tissue cellularity, represents a different aspect of the biological features of tumor cells from glucose metabolism (23). In a previous study using a breast cancer mouse model (24), it was shown that the reduction in tumor burden via primary tumor resection stopped metastatic progression and increased the immune response to cancer cells. Considering the literature and our results, it can be concluded that some of the important factors that determine the metastatic potential and metastatic spread are biological and metabolic features of the primary tumor.

In the oligometastatic state, the selectivity of tumor cells for metastatic organs is high. The metastatic potential of oligometastatic tumors is limited to certain distant sites that are the most suitable and receptive organs for tumor cells (16,18,19). Similar to this knowledge, in our study, we found that IBM was significantly higher than M-SM in patients with oligometastasis. In addition in multimetastatic patients, M-SM was observed to be significantly higher than IBM. Our results suggest that primary breast tumors, which have not yet reached their maximum metastatic potential, seem to metastatize primarily to the bones rather than soft visceral organs in an oligometastatic state. This may be related to the fact that bone is the most frequent site of distant metastasis in breast cancer and is the most amenable target organ for circulating tumor cells.

Our results also showed that high metastatic potential, which can be observed as widespread multimetastasis, had a significant relationship with metastatic spread to soft visceral tissues in breast cancer. These findings resemble the "seed and soil" and "spectrum" hypotheses of distant metastasis (16,18). In our study, the absence of distant metastasis in the axillary lymph node negative patient group may also bring Halstead's "contiguous seeding" hypothesis to mind (16,17).

Localization of distant organs where breast cancer metastasizes has clinical and prognostic importance. Patients with visceral metastases have a worse prognosis than those with IBM (5,25,26). The biology of the primary breast tumor was associated with the type of distant metastatic sites (6). As we expected, it was found that MTV and TLG of the primary tumor were significantly higher in patients with visceral metastasis (M-SM) than in those with IBM. SUV_{max} was also higher in the M-SM group, but this difference did not reach statistical significance. This finding seems to be related to the fact that SUV_{max} is based on a single voxel measurement. Unlike SUV_{max}, MTV and TLG, which were the combination of metabolic and volumetric features of the tumor, differed significantly between the groups. These results may be related to the aggressiveness and higher metastatic potential of the tumors, which had higher glycolytic activity and larger volumes. Similar to this finding, in oligometastatic patients (n=26), TLG was the only parameter that reached statistical significance, with higher values in the M-SM group than in the IBM group. TLG can provide information on both the tumor metabolic activity and tumor volume. This finding suggests that the presence of SM in oligometastatic patients is also associated with higher glycolytic activity and more aggressive tumor behavior.

Tumor grade, hormone receptor status, HER2 status, and proliferation index are considered important histopathological factors that determine the biological behavior of breast tumors. In our study, the metabolic-glycolytic activity of the primary tumor was positively correlated with tumor grade. This finding is in agreement with previous studies (14,27,28). In a previous study, it was reported that the expression of glucose transporter 1 (GLUT-1) was significantly associated with histological tumor grade (29) and our finding may be related to increased GLUT-1 expression in high-grade tumors. Tissue cellularity is another important component of tumor grade (30). Choi et al. (31) found that patients with high-grade tumors showed lower ADC mean values than those with low-grade tumors. Zhao et al. (32) also reported that lower ADC_{min} values were associated with higher histological grades. Similar to these studies, we found that ADC_{min} had lower values in high-grade tumors than in low-intermediate-grade tumors, but with marginal significance (p=0.054).

Steroid hormone receptor negativity in the primary tumor was significantly associated with GLUT-1 expression (33). Our study showed that hormone receptor-negative tumors had higher SUV_{max} and TLG than hormone receptor-positive tumors. This finding is similar to the findings of previous studies (14,20,27).

HER2 positivity in breast cancer is defined by high expression levels of the HER2 tyrosine kinase receptor as determined by immunohistochemistry and/or amplification of the *HER2* gene by fluorescence *in situ* hybridization. HER2-positive tumors have a highly aggressive disease course. Previous studies have demonstrated significant upregulation of glycolysis-related pathways in tumors with high HER2 expression (34,35). Groheux et al. (14) did not find a significant association between the HER2 status and SUV_{max} of primary tumors. We found a significant relationship between HER2 status and metabolic imaging parameters, with higher SUV_{max} and TLG in HER2-positive tumors, similar to previous studies (20,27,28). One of the anticancer effects of trastuzumab, an anti-HER2 agent, is the inhibition of glycolytic metabolism in HER2-positive breast cancer (36). Triple-negative breast tumors are considered very aggressive tumors with poor prognosis and lacking targeted therapy. GLUT-1 upregulation has also been reported in triple-negative breast cancer (33,37). Expression of other glycolysis markers, such as monocarboxylate transporters and carbonic anhydrase IX, was also found to be higher in triple-negative breast cancer than in other subtypes (29). Our study showed that triple-negative tumors had significantly higher SUV_{max} and TLG than non-triple-negative tumors. Increased tumor cell glycolysis rate, known as the Warburg effect, is one of the most important indicators of biological aggressiveness in triple negative breast cancer, and glycolytic markers may be possible molecular targets for therapy in this patient group (29,33).

Ki-67 expression is correlated with the tumor cell proliferation rate, and the Ki-67 index is considered a prognostic marker for breast cancer (38,39). A significant and positive relationship between the Ki-67 index and ^{18}F-FDG uptake in breast cancer has been reported in previous studies (20,40,41,42). Similar to previous studies, we found that breast tumors with a higher Ki-67 index (≥14%) demonstrated higher metabolic and glycolytic activity than those with a low Ki-67 index (<14%). This relationship between the Ki-67 index and ^{18}F-FDG uptake can be explained by the increased glucose consumption during the G1, G2, and S phases of the cell cycle. We also

found that ADC_{min} was significantly lower in tumors with a high Ki-67 index than in those with a low Ki-67 index. ADC values are inversely correlated with tumor cell density and tissue cellularity; therefore, it can be thought that increased cell proliferation rate has a significant relationship with lower ADC values.

Unlike metabolic imaging parameters, ADC_{min} values did not differ significantly between groups based on hormone receptor status, HER2 status, and triple negativity in our study. These results are in line with those of previous studies (20,27,43). This finding may be explained by the ^{18}F-FDG PET metabolic parameters and ADC values reflecting the different biological features of tumor cells. Hormone receptor status and HER2 status have major influences on glucose metabolism and glycolytic pathways. Therefore, it can be expected that ^{18}F-FDG uptake levels differ according to the biological characteristics of breast tumors. However, ADC represents the tumor cell density, not the metabolic activity of tumor cells. In addition, the ADC value also depends on the stromal components of tumors and cellularity (44).

Tumor histological grade, hormone receptor status, HER2 status, and Ki-67 index are considered biological factors that influence the distant metastasis type in breast carcinoma. In a previous study, it was reported that high-grade tumors were associated with SM and low-grade tumors were correlated with bone metastases (45). However, we did not find a significant association between tumor grade categories and metastatic groups. Wei et al. (6) reported that ER and PR expression was higher in patients with IBM than in those with visceral metastasis. In accordance with this study, we found that the ratio of patients with IBM was higher in the hormone receptor positive group than in the negative group (49.1% vs. 8.3%, respectively), while the ratio of M-SM was higher in the hormone receptor negative group than in the positive group (91.7% vs. 50.9%, respectively). We also found that the ratio of M-SM was significantly higher in the HER2-positive group than in the negative group (78.3% vs. 47.8%, respectively). Hormone receptor negativity and HER2 positivity are known to be poor prognostic factors and induce angiogenic pathways (46,47). High levels of Ki-67 indicate an aggressive tumor. In our study, the ratio of distant metastasis was higher in patients with a high proliferation rate (≥14%) than in those with a low proliferation rate (<14%) (27.8% vs. 7.8%, respectively). This finding is similar to that of a previous study (48). The Ki-67 index also seems to be related to distant metastatic sites. In our study, the Ki-67 index demonstrated significant differences between the IBM and M-SM groups (25% vs. 60%, respectively) in oligometastatic patients. Nishimura et al. (49) reported that Ki-67 index values of primary breast tumors for recurrent sites were lower in patients with bone metastasis than in those with liver or brain metastasis. We also obtained similar results in newly diagnosed patients.

In our study, it was found that multivariable prediction models that included imaging parameters (models 2 and 3) had strong discriminatory abilities for distant metastatic disease (the AUCs were 0.85 and 0.90, respectively). The discriminatory powers of these two prediction models were found to be higher than those of the prediction model that included only histopathological parameters (model 1). These findings show that imaging parameters that reflect the metabolic-glycolytic activity and cellularity of the primary tumor may be more effective than histopathological markers alone in explaining the aggressive biological behavior of the tumor in breast cancer patients.

Study Limitations

There are some limitations to our study. First, this was a retrospective single-center study. The second limitation was the lack of histopathological confirmation of distant metastatic lesions detected by ^{18}F-FDG PET/MRI. Although most of the PET positive findings were not histopathologically confirmed in patients with distant metastasis, PET positive lesions displayed pathological correlates on MRIs. Third, breast-dedicated PET/MRI were acquired without contrast injection; therefore, the contrast enhancement patterns and signal enhancement ratios of primary breast tumors could not be evaluated in our study. Therefore, this study did not provide full MRI information. Fourth, the immunohistochemical results of patients were obtained by tru-cut biopsy in 102 of 289 cases (35.3%); therefore, the histopathological features of the entire tumor might not have been evaluated in some patients. Fifth, we did not perform survival analysis because of the short follow-up time in most patients. Finally, although there was no distant metastatic lesion that was ^{18}F-FDG negative but was detected on MRI in our study, some millimetric metastases without ^{18}F-FDG uptake might have been missed and we might have underestimated the presence and number of metastatic lesions in some patients. Despite these limitations, our study included imaging and histopathological data of a large patient cohort in primary staging with PET/MRI. Simultaneous PET/MRI combines high-resolution anatomic and functional information from MRI with metabolic information from PET within the same imaging session. The combination of different imaging parameters of PET/MRI representing different biological features may allow better *in vivo* characterization of breast tumors.

Conclusion

Quantitative imaging parameters of primary tumors obtained from PET/MRI were associated with tumor biology, metastatic tumor load, and localization of distant metastases. Primary tumors with higher metabolic-glycolytic activity and higher cellularity were more aggressive and had a higher metastatic potential in breast IDC. While ^{18}F-FDG PET-derived metabolic-volumetric parameters had a strong relationship with histopathological prognostic factors, ADC only demonstrated a significant association with proliferation rate. Compared with histopathological parameters alone, the combination of PET/MRI parameters and histopathological features of primary tumors may help to better understand tumor biology and clinical course in breast carcinoma.

Ethics

Ethics Committee Approval: This study was approved by the Gazi University Local Ethical Committee (decision no: 296, date: 11.05.2020).

Informed Consent: Not applicable (Retrospective study).

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: U.A., S.G.A., O.K., Ü.Ö.A., P.U.G., L.Ö.A., Concept: U.A., O.K., P.U.G., L.Ö.A., Design: U.A., O.K., L.Ö.A., Data Collection or Processing: U.A., S.G.A., O.K., P.U.G., Analysis or Interpretation: U.A., S.G.A., Ü.Ö.A., Literature Search: U.A., S.G.A., Ü.Ö.A., Writing: U.A.

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