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Investigation of Clinical Histopathologic Features and Metabolic Parameters of ^{18}F-FDG PET/CT in Invasive Breast Carcinoma with a Micropapillary Component

Mikropapiller Komponentli İnvazif Meme Kanserinde Klinik, Histopatolojik Özellikler ile ^{18}F-FDG PET/BT Metabolik Parametrelerin İncelenmesi

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Abstract

Objectives: The aim of this study was to evaluate the correlation between clinical histopathologic features and micropapillary (MP) ratio with the maximum standardized uptake value (SUV_{max}) derived from ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in treatment naïve breast cancer.

Methods: Twenty-nine patients diagnosed with breast cancer with a MP component who underwent PET/CT imaging before any local and/or systemic treatment were included in this retrospective study. All clinical histopathological features were recorded. SUV_{max} values were measured from ^{18}F-FDG PET images for primary tumors and metastatic axillary lymph nodes.

Results: MP component percentage did not correlate with any clinical histopathological features except age. At early ages, the MP component ratio was significantly higher. Our results showed that there is no significant correlation between the SUV_{max} value and MP component percentage.

Conclusion: A high SUV_{max} value is generally expected in aggressive malignancies. However, this assumption may not be valid for the MP subgroup, which has an aggressive course compared to other subgroups in breast cancer.

Keywords: ^{18}F-FDG, micropapillary, breast cancer, PET/CT, SUV_{max}

Öz

Amaç: Bu çalışmanın amacı, tedavi uygulanmamış meme kanserinde klinik, histopatolojik özellikler, mikropapiller (MP) komponent oranı ile ^{18}F-florodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografiden (^{18}F-FDG PET/BT) elde edilen maksimum standardize tutulum değeri (SUV_{maks}) arasındaki ilişkiyi değerlendirmektir.

Yöntem: Bu retrospektif çalışmaya herhangi bir lokal ve/veya sistemik tedavi uygulanmadan önce PET/BT görüntülemesi yapılan MP komponentli meme kanseri tanılı 29 hasta dahil edildi. Tüm klinik, histopatolojik özellikler kaydedildi. Primer tümörlerin ve metastatik aksiller lenf nodlarının SUV_{maks} değerleri ^{18}F-FDG PET görüntülerinden ölçüldü.

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Bulgular: MP komponent oranı yaş dışında herhangi bir klinik-histopatolojik özellik ile korele değildi. Erken yaşlarda, MP komponent oranı anlamlı olarak daha yüksekti. Sonuçlarımız SUV_{maks} değeri ile MP komponent oranı arasında anlamlı bir ilişki olmadığını gösterdi.

Sonuç: Agresif malignitelerde genelde yüksek düzeyde SUV_{maks} değeri beklenir. Ancak bu varsayım meme kanserinde diğer alt gruplara kıyasla agresif seyir gösteren MP alt grup için geçerli olmayabilir.

Anahtar kelimeler: ^{18}F-FDG, mikropapiller, meme kanseri, PET/BT, SUV_{maks}

Introduction

Invasive micropapillary carcinoma (MPC) of the breast is an infrequent type of breast cancer. It was described as a different entity having 'exfoliative appearance' by Fisher et al. (1) in 1980 and included in the classification of breast tumors in 1993. These cases present with larger tumor volumes, higher histological grade, and a higher percentage of lymphovascular invasion (2,3).

^{18}F fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is an extensively used imaging modality that shows glucose metabolism. PET data could uncover underlying histopathologic features by revealing metabolic tumor characteristics. Whether the MP component ratio negatively influenced disease prognosis is not clear in the literature. High ^{18}F-FDG uptake generally indicates poor prognosis, as is well known. In this context, we planned a retrospective study to investigate the relationship between the percentage of MP component in treatment-naïve breast cancer patients and metabolic parameters derived from the primary tumor and lymph node metastases derived from the initial ^{18}F-FDG PET study.

Materials and Methods

Study Population

Cases diagnosed with invasive ductal carcinoma with MP features who did not receive any systemic/local therapy were included in the study. The study period of interest was from 2016 to 2021. The duration between pretreatment PET/CT imaging and histopathological analysis of the surgical specimen was 30 days. Cases with secondary malignancies were excluded from the study.

All clinical data of patients were recorded, including age, location of the tumor (right-left breast), percentage of MP component, histological grade, nuclear grade, Ki-67 value, estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 receptor statuses, molecular subtypes, axillary lymph node status, tumor size, and metastatic lymph node size (Table 1). All lymph node metastases were verified as histopathological.

Patient Imaging and PET/CT Data Analysis

Patients were injected with 3.7 MBq/kg of ^{18}F-FDG after fasting for at least 6 hours (h) with blood glucose level <180 mg/dL and scanned approximately 60 minutes after injection on PET/CT scanners (Ingenuity TF, Philips Healthcare, Cleveland, Ohio, USA). CT was first acquired using a low-dose technique without contrast agent injection, and a PET scan was obtained immediately after

Table 1. All patients clinical, histopathological, and PET characteristics

	No. of patients	SUV_{max} value median (range)
Lateralization		
Right breast	15	9.4 (2.0-20.2)
Left breast	14	8.3 (2.7-32.6)
Tumor size		
T1	11	6.9 (2.0-15.3)
T2	13	10.6 (2.1-21.4)
T3	2	14.6 (9.0-20.2)
T4	3	9.4 (6.6-32.6)
Hypermetabolic axillary lymph node		
Positive	18	8.0 (1.6-41.2)*
Negative	11	
Ki-67		
<15	3	9.7 (7.7-15.1)
>15	26	8.4 (2.0-32.6)
Subtypes		
Luminal A	4	12.4 (7.7-21.4)
Luminal B	24	7.7 (2.0-32.6)
HER-2 positive	0	-
Triple negative	1	20.2
MPC percentage		
100%	15	9.4 (2.0-32.6)
80%	1	2.1
50%	1	2.9
40%	2	9.1 (7.5-10.6)
25%	2	5.9 (4.5-7.2)
20%	4	7.8 (7.1-15.3)
15%	1	15.2
10%	3	11.4 (7.7-21.4)

SUV_{max} value of axillary lymph nodes. PET: Positron emission tomography, HER-2: Human epidermal growth factor receptor 2, MPC: Micropapillary carcinoma

the CT scan. Attenuation correction was performed on the PET images using the corresponding CT images.

The standardized uptake value (SUV) is a commonly used parameter for semi-quantitative analysis of PET images and is calculated either as the ratio of tissue radioactivity concentration to the injected dose adjusted by body weight. The maximum SUV (SUV_{max}) is obtained for a 1-pixel region of interest corresponding to the maximum pixel value in the tumor.

Initial PET/CT was analyzed by 2 experienced nuclear medicine specialists who were blinded to patients' clinicopathological information and percentage of MP component. SUV_{max} was measured separately for the primary tumor and metastatic lymph nodes. If there were multiple hypermetabolic primary tumors and metastatic lymph nodes, the lesion with the highest SUV_{max} was selected.

University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Ethics Committee approved this study (decision no: 2023.01.43).

Statistical Analysis

The median values and ranges for quantitative variables are presented. The Mann-Whitney U test was used to compare MP component percentage between lymph node metastasis -positive and -negative cases. SUV_{max} clinicohistopathologic features were compared using Spearman correlation matrix. The r value was interpreted as 0.00-0.19 very weak, 0.20-0.39 weak, 0.40-0.59 moderate, 0.60-0.79 high, 0.80-1.0 very high level correlation. Statistical analyzes were performed using IBM SPSS-25 software (SPSS Inc, Chicago, IL, USA). Any p-value <0.05 was considered statistically significant.

Results

Twenty-nine patients with a median age of 55 (range: 27-76) were included in this study. All patients were female. In 52% of the cases (n=15), the tumor was located in the right breast. Bone metastases were detected in 3 patients, and bone and lung metastases were detected in 1 patient. The median tumor size was 2.5 cm (range: 0.4-14). Percentages of MP components ranged between 10-100%. SUV_{max} values of the tumor ranged between 2.0-32.6 (median 9.0). The median SUV_{max} value for patients with 100% MP component (n=15) was 9.4 (range: 2-32.6); for patients with 10% MP component (n=3) was 11.4 (range: 7.7-21.4). The clinical, histopathological, and PET characteristics are listed in Table 1.

In eighteen cases, hypermetabolic axillary lymph nodes were detected on PET images, which were histopathologically verified as metastasis. In one case, because of the temporal resolution, PET could not detect lymph node metastasis whose size was 0.2 cm. The median metastatic lymph node size was 1.9 cm (range: 0.2-4.0). SUV_{max} values of metastatic lymph nodes ranged from 1.6 and 41.2 g/mL (median 8.0 g/mL).

The median Ki-67 value was 33 (range: 10-70). Four cases were luminal A, only one was triple negative, and the rest were luminal B.

At early ages, Ki-67 values and probability of hypermetabolic lymph node detection were higher (r=-0.38, p=0.04; r=-0.39, p=0.03; respectively). Between Ki-67 value and nuclear grade, axillary lymph node metastasis had a moderate positive correlation (r=0.50, p=0.01; r=0.48, p=0.01; respectively).

Luminal B and triple-negative cases were prone to axillary lymph node metastasis (p=0.03). Tumor size was positively correlated with tumor SUV_{max} value (r=0.42, p=0.02). There were no data showing that more axilla lymph node metastases were detected in cases with high tumor SUV_{max} value (r=0.26, p=0.18).

There was no significant correlation between MPC percentage and tumor SUV_{max} value (r=-0.02, p=0.91). When the cases were grouped as positive and negative lymph node metastases, no significant difference was found in the percentages of MPC (p=0.50). No significant differences were detected between MPC percentage, clinical histopathologic features, and SUV_{max} values. There was a negative correlation between age and MPC (r=-0.40; p=0.03).

Two demonstrative cases are shown in Figures 1 and 2.

Discussion

The pure form of MP breast cancer is rare (0.9-2.0%) among other types of breast carcinoma (2). In our series, which included only patients with MPC, 51.7% (n=15) of cases presented with pure invasive MPC.

One of the largest studies with pure invasive MPC showed regional lymph node metastasis in 55.2% of the cases (4). This ratio was 65.5% in our study. This difference could be attributed to the fact that PET/CT was performed in patients with a high risk of metastasis.

Many previous studies have reported that MPC tends to be in the luminal B category (5,6,7). Consistent with the literature, most of our cases (82.8%, n=24) were in the luminal B category.

Vingiani et al. (8) reported that tumor size was higher in invasive MPC patients than in invasive ductal cancer

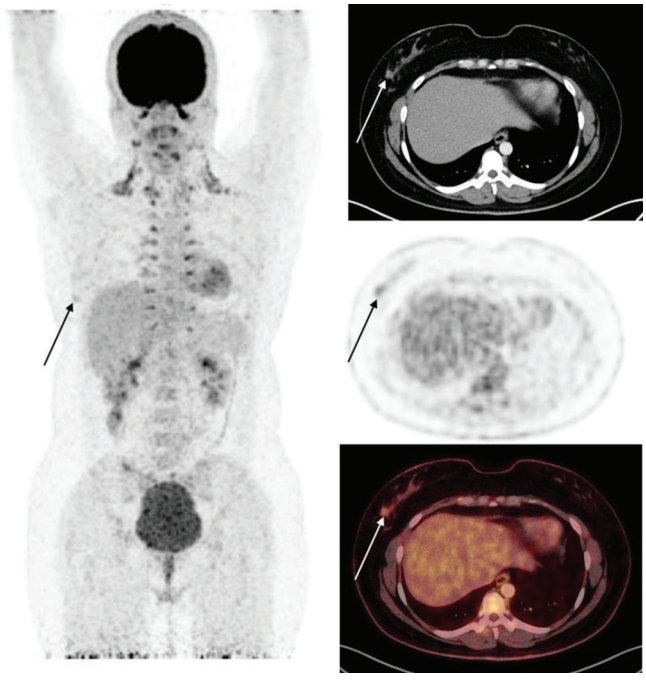

Figure 1. Twenty-seven-year-old-female, stage IIA 80% micropapillary component, 20% invasive ductal component breast cancer patient. Mildly hypermetabolic lesion located in the right breast was shown (SUV_{max}: 2.1 mg/dL; arrow)
Left column: MIP image, right column: Axial CT, PET, and fusion images.
CT: Computed tomography, MIP: Maximum intensity projection, PET: Positron emission tomography

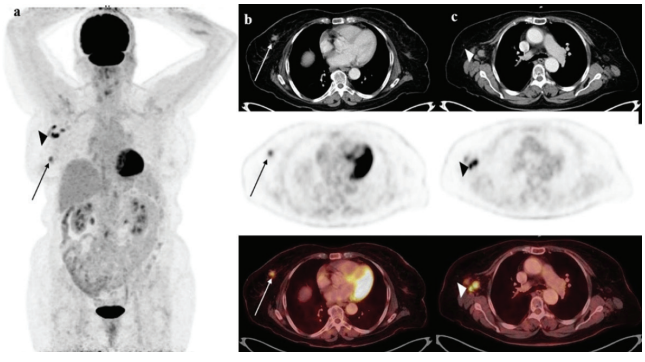

Figure 2. Seventy-six-year-old-female, stage IIIA 20% micropapillary component, 80% invasive ductal component breast cancer patient. Markedly hypermetabolic lesion located in the right breast was shown (SUV_{max}: 5.3 mg/dL; arrow). Metastatic axillary lymph nodes showed intense ^{18}F-FDG uptake (SUV_{max}: 10.1 mg/dL; arrow head).
Column a: MIP image, column b and c: Axial CT, PET, and fusion images
CT: Computed tomography, MIP: Maximum intensity projection, PET: Positron emission tomography, ^{18}F-FDG: ^{18}F-fluorodeoxyglucose

patients. Our data showed that tumor size did not significantly change with MPC percentage. In these cases, even if the MP component rate is low, close follow-up is important in terms of aggressive prognosis.

Breast cancer with MPC presents with a higher histological grade, lymphovascular invasion, and higher percentage of lymph node metastasis (2,3). Worse recurrence-free survival was attributed to a higher incidence of lymph node recurrence in the MPC group (9,10).

It is still not clear whether locoregional recurrence negatively influenced the overall survival of patients with MPC compared with other subtypes of breast cancer with similar nodal stage. Although there are some discrepancies in the literature, one recent meta-analysis demonstrated no statistically significant difference in overall survival and disease-free survival between patients with MPC and those with invasive ductal carcinoma (11). Our results showed that MPC percentage did not differ with any histopathologic features and SUV_{max} value of tumor/lymph nodes. Only younger patients had a statistically higher rate of MPC. These results led us to believe that there may not be a significant difference between the prognosis of cases with pure form and mixed components.

To our knowledge, the largest study in the literature with sixteen PET/CT imaging in MPC cases revealed that the mean SUV_{max} value of the primary tumor was 11.2, which is similar to our result 9.0 mg/dL (12). High ^{18}F-FDG uptake is an indicator of poor prognosis in breast cancer (13,14,15,16). SUV_{max} did not correlate with MPC ratio, only tumor size was positively correlated with SUV_{max} value. Kaya et al. (17) stated that there was no significant difference in demographic characteristics, tumor diameter, lymph node metastasis status, histological grade, multicentricity, local recurrence, distant metastasis, and overall survival between their groups (group 1: MPC ratio 10-75%; group 2: MPC ratio >75%). These findings made us think that MPC might not be an aggressive subtype in which to expect high ^{18}F-FDG uptake.

There is limited literature regarding the metabolic imaging features of breast carcinoma with MPC. As far as we know, this is the biggest cohort in the literature.

Study Limitations

The number of cases in our study may be considered small. It must be taken into consideration that the incidence of MPC is quite low. To increase the case number and statistical examination reliability, we included cases with under 1 cm tumor size. This could be considered a study limitation because of the partial volume effect.

Conclusion

Our results showed that the MPC percentage did not show a significant correlation with the tumor SUV_{max} value. In light of the ^{18}F-FDG PET findings, we believe that the MP

subtype ratio is not a poor prognostic factor for breast cancer. New studies are needed to evaluate whether a high SUV_{max} could indicate a poor prognosis with the same MPC percentage.

Ethics

Ethics Committee Approval: University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Ethics Committee approved this study (decision no: 2023.01.43).

Informed Consent: Patient consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.A., G.A., E.C.K.T., T.S.A., E.Ş., E.Ar., Concept: E.A., E.Ar., Design: E.A., E.Ar., Data Collection or Processing: E.A., G.A., E.C.K.T., Analysis or Interpretation: E.A., T.F.Ç., E.Ar., Literature Search: E.A., Writing: E.A.

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