Original Article

Role of pathologic prognostic factors in breast cancer patients with isolated bone metastasis and relationship between SUVmax and prognostic factors

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ABSTRACT

Introduction: ^{18}F-FDG PET/CT provides very effective results in detecting metastases of breast cancer. In our study, we investigated the relationship between maximum standard uptake value (SUVmax) and prognostic pathologic factors in breast cancer cases with isolated bone metastasis and whether there was any difference in terms of prognostic pathologic factors between the group with and without bone metastasis.

Methods: Between 2013 and 2016, isolated bone metastases (55 female; 56±12 years; 32-87), and non-metastatic (46 female; 55±13 years; 30-81) patients who were referred to department of nuclear medicine and underwent ^{18}F-FDG PET/CT for staging were included in the study. PET/CT images of patients and pathologic prognostic factors were evaluated retrospectively. SUVmax value of the most intense activity from metastatic bone lesions was calculated. $p < 0.05$ was considered statistically significant.

Results: In the metastatic group, there was no statistically significant relationship between measured SUVmax value of bone metastasis and pathologic prognostic factors. A statistically significant difference was found between the metastatic group and the non-metastatic group in terms of lymph node stage, lymphovascular/perineural invasion. The lymph node stage in the metastatic group was higher than the non-metastatic group. The presence of lymphovascular/perineural invasion in bone metastasis cases was more than in the non-metastatic group.

Conclusion: In our study, it was determined that there was a relationship between the lymph node stage, lymphovascular/ perineural invasion and formation of bone metastasis in breast cancer. Between SUVmax values and other factors in the metastatic group, no significant relationship was detected.

Key words: Breast cancer; Bone metastasis; ^{18}F-FDG; SUVmax

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INTRODUCTION

Breast cancer is the most common type of cancer in women. Among cancer deaths in women, it comes after lung cancer. It is known that approximately 1.4 million people are diagnosed with breast cancer every year in the world [1]. Distant organ metastasis is frequently seen in breast cancer. Metastasis is present at the time of diagnosis in 6% of the cases [2]. The most common sites of metastasis are bone, liver, lung, brain and soft tissues. Approximately 25-40% of breast cancer metastases are bone metastases. Bone metastasis is present in approximately 60-80% of patients with recurrence [3, 4]. Isolated bone metastases are common in breast cancer. Breast cancer cells that enter the bloodstream show a very high affinity to the bones. Even 30-40% of early stage breast cancer cases have tumor cells in the bone marrow. Most of these cells may undergo apoptosis, while some may develop micrometastatic proliferation [3]. Patients with isolated bone metastases have a better prognosis than patients with other visceral organ metastases [5].

Since breast cancer is a heterogeneous disease, there are many clinical and pathological factors that can predict the development of prognosis and metastasis [6, 7]. There are studies in the literature that some of these factors may be effective in the development of isolated bone metastases [8-10]. Neville et al. [9] found a relationship between the presence of estrogen receptor, lymphovascular invasion and the development of bone metastasis. It has been shown that bone metastasis develops more frequently in luminal group A patients with histologic subtype [11]. In the study of Tanriverdi et al, a positive correlation was found between carcinoembryogenic antigen (CEA), cancer antigen 15-3 (CA 15-3) tumor marker levels and the development of bone metastasis [12].

F-18-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET/CT) is a hybrid method that provides imaging using glucose metabolism in the tumor cell. Breast cancer cells express a high level of glucose transporter in the cell membrane and hexokinase activity in the cytoplasm is higher than normal cells. High ^{18}F-FDG uptake shows glucose hypermetabolism [13]. It is known that ^{18}F-FDG uptake is high in primary breast mass and this shows tumor aggressiveness [14]. There are also studies showing a correlation between ^{18}F-FDG uptake and prognostic factors [15]. However, there are no studies showing the relationship between ^{18}F-FDG uptake observed in bone metastases of breast cancer, tumor behavior and prognotic factors. The standardized uptake value (SUV) is a semiquantitative parameter reflecting ^{18}F-FDG uptake in the lesion. In many studies, the correlation between SUVmax of malignant breast masses and histopathological/immunohistochemical parameters has been shown [15-17].

In this study, we aimed to investigate the relationship between SUVmax and prognostic pathological factors in breast cancer patients with isolated bone metastases, and to determine whether there is a difference in prognostic pathological factors between patients with and without bone metastases.

METHODS

Patient selection

^{18}F-FDG PET-CT patients with breast cancer who were admitted to the Department of Nuclear Medicine between 2013 and 2016 were screened retrospectively. Fifty-five patients with isolated bone metastases (mean±SD= 56 ± 12 years; range: 32-87 years old) and 46 non-metastatic (mean±SD= 55 ± 13 years; range: 30-81 years old) female patients who underwent ^{18}F-FDG PET-CT for staging purposes were included in the study. In patients with bone metastases, other visceral organ metastasis was not observed in FDG PET-CT examinations performed during 3 years follow-up. No metastatic focus was observed in the follow-up examinations in the group without metastasis. Patient files were reviewed retrospectively. Pathology reports after mass excision/breast conserving surgery/radical mastectomy were reviewed. Pathological prognostic factors were evaluated. Tumor histologic type (ductal, lobular, other), presence of carcinoma insitu, nuclear grade, histological grade, primary tumor size (<20 mm, 20-50 mm, > 50 mm), lymph node stage (N0, N1, N2), lymphovascular/ perineural invasion, estrogen (ER)/progesterone (PR) receptor, cerbB2 positivity, P53 presence, Ki67 proliferation index values were obtained. Four histological subgroups were created in accordance with the recommendations of the 12th International Breast Conference [18]:

1. Luminal A: ER + and/or PR +, cerbB2 -, Ki67 <14%
2. Luminal B: ER + and/or PR +, cerbB2 -, Ki67> 14% or ER + and/or PR +, cerbB2 +, regardless of Ki67 expression
3. cerbB2 positive: ER- / PR-, cerbB2 +
4. Triple negative: ER- / PR-, cerbB2 –

^{18}F-FDG PET/CT imaging protocol

After fasting and resting for 6 h, the patients received 259–407 MBq (7–11 mCi) of ^{18}F-FDG intravenously when their fasting blood glucose level was < 200 mg/dL. All patients were screened 60 minutes after injection. Pre-injection activity and post-injection injector activity were counted in PET-CT. The actual dose of radioactivity given to the patient was thus calculated. The patients were examined using a dedicated PET/CT scanner (Gemini TF TOF PET/CT; Philips, Cleveland, OH; 3D mode, slice thickness of 5

mm, 4x4x22 mm LYSO crystal, number of crystals 28.336, 256x256 matrix (voxel size 2.6x2.6x2.4 mm^3), transverse FOV 576 mm and axial FOV 180 mm). Emission scans were acquired from the calvaria base to the middle of the thigh for 1.5 min per position without intravenous contrast medium injection. Transmission images were obtained by low-dose CT (50–120mAs, 90–140 kVp, 16 number of CT detectors, slice thickness of 5 mm). Attenuation correction was performed for PET images using CT findings and the ordered subsets-expectation maximization (OSEM) algorithm (33 subsets, 3 iterations). PET images were reconstructed by the iterative method. Transverse, sagittal, and coronal sections (5 mm thickness) were created from PET/CT fusion images and evaluated using Philips Fusion Viewer software (ver. 2.1; Philips Healthcare, Best, The Netherlands).

Image evaluation

Images of patients with bone metastasis identified in the ^{18}F-FDG PET/CT result report were evaluated visually. In PET images, activity involvement areas in the skeletal system showing high levels of ^{18}F-FDG uptake from the surrounding tissue and not considered physiological involvement were determined. In CT images, it was determined whether the involvement areas corresponded to sclerotic/lytic bone lesion. Activity involvement of sclerotic/lytic metastatic bone lesion was accepted as metastasis. SUVmax values of all metastatic lesions were calculated automatically. The SUVmax of the lesion showing the highest ^{18}F-FDG uptake was used for statistical evaluation.

Statistical analysis

SPSS for Windows software (ver. 17.0; SPSS Inc., Chicago, IL) was used for statistical analysis. Continuous variables are expressed as mean±standard deviation and categorical variables are expressed as numbers and percentages. When parametric test assumptions were provided, the significance test of the difference between two means was used to compare independent group differences; when parametric test assumptions were not provided, Mann-Whitney U test and Kruskal Wallis Variance Analysis were used to compare independent group differences. Differences between categorical variables were examined by Chi-square analysis. Spearman Correlation analysis was used to examine the relationships between continuous variables. In all analyzes, $p < 0.05$ was considered statistically significant.

RESULTS

There was a statistically significant difference between metastatic and non-metastatic groups in terms of lymph node stage, lymphovascular/perineural invasion ($p < 0.05$) (Table 1). The lymph node stage was higher in the metastatic group, whereas the presence of lymphovascular /perineural invasion was found in more cases than the non-metastatic group. In the logistic regression analysis, when the effect of lymphovascular invasion, perineural invasion, nodal stage, histological grade, tumor size and age on metastatic status together, it was found that lymphovascular invasion, perineural invasion and nodal stage had a statistically significant effect (Table 2). In the metastatic group, no statistically significant relationship was found between the SUVmax value of the bone metastasis and pathological prognostic factors (Table 3). In the correlation analysis, no correlation was found between SUVmax and pathological prognostic factors (age, nuclear/histologic grade, tumor size, nodal stage, p53, Ki67) (Table 4).

DISCUSSION

In our study, a statistically significant difference was found between the isolated bone metastasis group (IBM) and the non-metastatic group in terms of lymph node stage, lymphovascular/perineural invasion. The lymph node stage was higher in the metastatic group, whereas the presence of lymphovascular/perineural invasion was found in more cases than the non-metastatic group. Bone metastasis is of clinical importance in breast cancer because it is highly prevalent. In breast cancer, isolated bone metastasis has a better prognosis than other distant metastases. However, significant morbidity may occur due to some complications [19]. Few studies have been conducted on the clinical and histopathological factors associated with the development of isolated bone metastasis in breast cancer. In the study of Coleman et al. [19], patients with isolated bone metastases were older, diagnosed with lobular carcinoma and had lower lymph node stage than multiple metastatic patients. However, this study did not compare with the non-metastatic group. Several studies have found a significant relationship between estrogen receptor positivity (ER+) and the development of isolated bone metastases [20-23]. In addition, it has been shown that bone metastasis occurs more frequently in cases with luminal subtype A among histological subtypes compared to other subtypes [9, 24]. In breast cancer patients with ER+ and luminal subtype A, genes associated with cellular proliferation show low expression and have a higher survival rate compared to other types [25]. This information supports the fact that isolated bone metastasis has a better prognosis than other organ metastases. ER/PR positivity in breast cancer is very important as it allows hormonotherapy. Generally, patients with ER/PR positivity respond well to hormonotherapy and their prognosis is good.

Table 1: Comparison of metastatic/non-metastatic groups in terms of prognostic factors.

Prognostic factors		Metastatic (n=55) N (%)	Nonmetastatic (n=46) N (%)	P value
Age		56.16±11.95	54.98±12.64	0.630
Histological type	Ductal carcinoma	35 (76.4)	38 (82.6)	0.639
	Lobuler carcinoma	6 (10.9)	2 (4.3)	
	Other	7 (12.7)	6 (13.1)	
Carcinoma in situ	Positive	31 (56.4)	30 (65.2)	0.360
	Negative	24 (43.6)	16 (34.8)	
Nuclear grade	2	21 38.2)	17 (37.0)	0.900
	3	34 (61.8)	29 (63.0)	
Histological grade	2	31 (56.4)	25 (54.3)	0.970
	3	24 (43.6)	21 (45.7)	
Tumor size	<20 mm	13 (23.6)	13 (28.3)	0.680
	20-50 mm	36 (65.5)	30 (65.2)	
	> 50 mm	6 (10.9)	3 (6.5)	
Lymph node stage	N0	8 (14.5)	21 (45.7)	**0.002***
	N1	22 (40.0)	15 (32.6)	
	N2	25 (45.5)	10 (21.7)	
Perineural invasion	Positive	19 (34.5)	7 (15.2)	**0.003***
	Negative	36 (65.5)	39 (74.8)	
Lymphovascular invasion	Positive	35 (63.6)	18 (39.1)	**0.003***
	Negative	20 (36.4)	28 (60.9)	
Estrogen receptor	Positive	46 (83.6)	40 (87.0)	0.640
	Negative	9 (16.4)	6 (13.0)	
Progesterone receptor	Positive	40 (72.7)	37 (80.4)	0.360
	Negative	15 (27.3)	9 (19.6)	
cerbB2	Positive	32 (58.2)	23 (50.0)	0.41
	Negative	23 (41.8)	23 (50.0)	
P53	<%20	11 (20.0)	22 (47.8)	0.300
	>%20	10 (18.2)	7 (15.2)	
	Negative	13 (23.6)	12 (26.1)	
	Unknown	21 (38.2)	5 (10.9)	
Ki67 proliferation index	<%20	14 (25.5)	18 (39.1)	0.290
	%20-50	16 (29.1)	14 (30.4)	
	>%50	7 (12.7)	6 (13.0)	
	Unknown	18 (32.7)	8 (17.4)	
Histological subtype	Luminal A	12 (21.8)	13 (28.3)	0.610
	Luminal B	34 (61.8)	28 (60.9)	
	cerbB2+/triple negative	9 (16.4)	5 (10.9)	

Table 2: Logistic regression analysis.

Prognostic factors	P value	O.R.	95% C.I.for O.R.	
			Lower	Upper
Lymphovascular invasion	0.015*	2.845	1.224	6.612
Perineural invasion	0.030*	3.032	1.117	8.231
Lymph node stage (N2)	0.045*	3.433	1.029	11.448
Lymph node stage (N3)	0.007*	6.844	1.672	28.008
Age	0.365	1.018	0.980	1.057
Histolojical grade (3)	0.997	1.002	0.417	2.408
Tumor size (20-50 mm)	0.747	0.841	0.294	2.405
Tumor size (> 50 mm)	0.969	0.966	0.167	5.582

*p<0.05 statistically significant; O.R: Odds Ratio; C.I: Confidence Interval

Table 3: Relationship between SUVmax value and pathologic prognostic factors of bone metastasis.

Prognostic factors	Groups (n)	SUVmax (Mean±standard deviation)	p value
Histological type	Ductal carcinoma (n=42)	6.25±2.38	0.77
	Lobular carcinoma (n=6)	6.10±1.36	
	Other (n=7)	7.94±4.61	
Histological subtype	Luminal A (n=12)	5.71±1.43	0.45
	Luminal B (n=34)	6.39±2.59	
	cerbB2/ triple negative (n=9)	7.67±3.92	
Carcinoma in situ	Positive (n=31)	6.39±2.17	0.72
	Negative (n=24)	6.54±3.27	
Lymphovascular invasion	Positive (n=35)	6.57±2.84	0.74
	Negative (n=20)	6.23±2.41	
Estrogen receptor	Positive (n=46)	6.21±2.35	0.26
	Negative (n=9)	7.67±3.92	
Progesterone receptor	Positive (n=40)	6.11±2.22	0.24
	Negative (n=15)	7.36±3.56	
cerbB2	Positive (n=32)	6.53±2.54	0.56
	Negative (n=23)	6.34±2.92	
P53	<%20 (n=11)	5.72±1.57	0.58
	>%20 (n=10)	6.96±2.38	
	Negative (n=13)	5.99±2.61	
	Unknown (n=21)	6.88±3.28	
Ki67 proliferation index	<%20 (n=14)	5.95±1.76	0.82
	>%20 (n=23)	6.59±2.45	
	Unknown (n=18)	6.67±3.51	
Nuclear grade	Grade 2 (n=21)	5.91±2.19	0.28
	Grade 3 (n=34)	6.78±2.92	
Histological grade	Grade 2 (n=31)	6.29±2.33	0.82
	Grade 3 (n=24)	6.66±3.11	
Tumor size	<20 mm (n=13)	5.80±1.95	0.37
	20-50 mm (n=36)	6.51±2.97	
	>50 mm (n=6)	7.49±2.04	
Lymph node stage	N0 (n=8)	6.46±2.29	0.85
	N1 (n=22)	6.06±2.24	
	N2 (n=25)	6.79±3.15	

Table 4: Correlation between SUVmax and prognostic variables in the metastatic group (Spearman correlation analysis).

Prognostic factors		SUVmax
Age	r*	0.029
	p	0.833
	n	55
Nuclear grade	r	0.147
	p	0.283
	n	55
Histological grade	r	0.047
	p	0.733
	n	55
Tumor size	r	0.158
	p	0.251
	n	55
Lymph node stage	r	0.032
	p	0.815
	n	55
p53	r	0.077
	p	0.575
	n	55
Ki67	r	0.071
	p	0.606
	n	55

*r: Correlation coefficient

In our study, no significant difference was found between the groups with no metastasis and isolated bone metastases in terms of ER+, PR+ and histological subtypes. According to our findings, it is noteworthy that ER/PR positivity in breast cancer with isolated bone metastases is similar to that in the nonmetastatic group. This shows that ER+, PR+ levels are high in patients with bone metastases and may benefit from hormone therapy. HER2/neu oncogen (c-erbB-2) is a member of the erbB-like oncogen family and is associated with the epidermel growth factor receptor. Amplification of c-erbB-2 is an important prognostic factor in breast cancer and its positivity is associated with poor prognosis. In our study, no significant difference was found between IBM and nonmetastatic group in terms of cerb-B2 receptor expression. The fact that cerb-B2 expression is not higher in the IBM group than in the nonmetastatic group may suggest that the prognosis in IBM is not significantly worse.

In our study, the presence of lymphovascular/perineural invasion in the IBM group was significantly higher than in the non-metastatic group. Neville et al. [9] found a significant relationship between the development of bone metastasis and the presence of lymphovascular invasion. The presence of lymphovascular invasion in the primary tumor is a parameter indicating that the tumor can metastasize outside the breast tissue and is an important factor in the planning of breast cancer treatment [26]. The presence of lymphovascular invasion in patients with IBM is higher than in non-metastatic patients, which is consistent with the literature.

In our study, we found that the lymph node stage was higher in the IBM group. In the literature, there are studies showing that lymph node stage is lower in IBM cases compared to other organ metastases [19]. However, there was no study showing the relationship between IBM and non-metastatic patients. Bone metastasis is common in the early period as a result of cancer cells reaching the bloodstream and bone marrow. Axillary lymphatic metastasis is also common due to the lymphatic richness of breast tissue. The association of lymph node and bone metastasis is thought to be common for this reason.

^{18}F-FDG PET/CT is a hybrid imaging method that is frequently used in the diagnosis, follow-up and prognosis of many types of cancer. Since FDG is a glucose analogue, imaging is based on showing an increase in glucose metabolism in malignant cells [27]. SUVmax is a semiquantitative parameter and reflects ^{18}F-FDG uptake in the lesion. There are many studies showing that SUVmax value of primary malignant breast mass correlates with prognostic factors (tumor stage, high histologic grade, Ki67 index, presence of p53, high mitosis number, etc.) [28-31]. However, there are few studies investigating the relationship between SUVmax of metastatic lesions and clinical/histopathological prognostic factors in

breast cancer [32-34]. Zhang et al. [32] found a strong correlation between molecular subtype and SUVmax in their study with 244 metastatic breast cancer patients. They also argued that SUVmax can be used as a prognostic indicator in patients with early metastasis. In the 176 disease study of Izmir oncology group [33], a significant relationship was found between SUVmax and ER, PR, CerbB2 positivity, histological subtype in metastatic breast cancer patients. They showed that SUVmax value in metastatic lesions with cerbB2+ and triple negative group was higher than luminal A and B. In Zhang et al. study [34], 134 hormone receptor positive metastatic breast cancer patients were evaluated and no significant correlation was found between SUVmax and molecular subtype. In all three studies, all organ metastases were evaluated together and no separate group was formed for IBM. In our study, no significant correlation was found between SUVmax of bone metastases and prognostic factors. In correlation analysis, no correlation was found between SUVmax and some independent prognostic factors. In the literature, there are no studies showing the association of SUVmax with prognostic factors in the IBM group. According to our data, SUVmax was not an independent prognostic parameter in IBM cases. However, there are some limitations of our study. First, a retrospective study was conducted. Secondly, the number of our patients was lower than the literature on metastatic breast cancer studies. Since only bone metastases were detected at the time of diagnosis, the number of patients in other studies could not be reached. Third, pathological examination of lesions considered bone metastasis on ^{18}F-FDG PET/CT was not performed. Metastasis was diagnosed according to the anatomic and metabolic characteristics of the lesion on PET and CT images. Despite these limitations, our study is the first study to investigate the relationship between SUVmax and pathological prognostic factors in IBM cases.

CONCLUSION

There was a statistically significant difference between metastatic and non-metastatic groups in terms of lymph node stage, lymphovascular/perineural invasion. While the lymph node stage was higher in the IBM group, the presence of lymphovascular/perineural invasion was higher than the non-metastatic group. There was no significant relationship between SUVmax and pathological prognostic factors in the IBM group.

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