Association of breast cancer with different molecular subtypes and Ki67 proliferation with 18F-FDG PET/CT

18F-FDG PET/CT in breast cancer

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Abstract

Aim: The main molecular factors affecting the aggressiveness of breast cancer are estrogen receptor, progesterone receptor, and human epidermal growth factor-2. We wanted to study how molecular subtypes make a difference in tumor metabolism and staging in 18F-FDG PET/CT.

Materials and Methods: Between 2023 and 2024, 110 patients with breast cancer who presented to our nuclear medicine clinic for staging were included in the study.

Results: There was no statistically significant correlation between the molecular classification of the patients and the SUVmax levels of the primary breast tumor (p = 0.055). There was a significant correlation between breast molecular types and the presence of lymph node metastasis (p = 0.032). Triple-negative and Luminal B type patients had a higher risk of lymph node metastasis compared to other molecular subtypes. There was a significant correlation between Ki67 proliferation and molecular subtypes (p = 0.000). We also found a significant correlation between Ki67 index and breast tumor and lymph node SUVmax levels (p = 0.000, p = 0.03). There was a significant correlation between Ki67 proliferation and the presence of lymph node metastasis (p = 0.000).

Discussion: In the present study, we demonstrated that different molecular subtypes show different metabolic characteristics. We also revealed that tumor Ki67 levels cause metabolic differences, and tumors with high Ki67 levels on 18F-FDG PET/CT have an increased likelihood of lymph node metastasis. We think that Ki67 levels should be taken into consideration when interpreting lymph node positivity in these patients.

Keywords

breast cancer, Ki67, 18f -fdg pet/ct, moleculer classifica

Introduction

Breast cancer is the most common type of cancer in women and accounts for approximately 15.5% of cancer deaths in women [1]. The main molecular factors affecting the aggressiveness of breast cancer are estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor-2 (HER-2) [2]. Approximately 70% of breast cancers are ER-positive, and the majority of them also have a positive PT. The prognosis of this group of breast cancers is much better than the others [3]. HER-2 positivity is associated with an extremely poor prognosis. These molecules determine the treatment option and prognosis [4]. As treatment options are related to molecular subtypes, staging is also very important in treatment. Therefore, ultrasonography, mammography, computed tomography, and magnetic resonance imaging, which are traditional imaging methods, are used in the staging of breast cancer. However, the lack of whole-body imaging may lead to errors in staging and, therefore, errors in treatment selection.

Fluorine-18 (F18) fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is a non-invasive functional imaging system used in the diagnosis, staging, and evaluation of response to treatment of various cancers [5]. In addition to tumor staging, PET/CT imaging allows quantitative assessment of glucose metabolism [6]. Although 18F-FDG PET/CT imaging in breast cancer is recommended for stage IIB and stage III breast cancer in the SNNMI and EANM guidelines, it is not recommended for stage I [7]. However, in a recent systematic review and meta-analysis by Han et al., it changed the initial stage in 25% of newly diagnosed breast cancer patients and changed the treatment management in 18 [8].

We wanted to study how molecular subtypes make a difference in tumor metabolism and staging in 18F-FDG PET/CT.

Materials and Methods

Between 2023 and 2024, 110 patients who were diagnosed with breast cancer by biopsy and applied to our nuclear medicine clinic for staging were included in the study. PET/CT imaging was performed at least 1 week after biopsy. In addition, the patients included in the study had not received any treatment for breast cancer and did not have any other concomitant malignancies.

Classification of Molecular Subtypes

The subtypes were classified by ER, PR, and HER-2 studies on tissues obtained from breast tumors by the Tru-Cut biopsy method. Molecular subtypes were divided into 4 classes as luminal A, luminal B, HER-2 positive, and triple negative.

Luminal A: estrogen receptor positive/progesterone receptor positive and HER-2 negative.

Luminal B: estrogen receptor±/progesterone receptor ± and c-erbB-2 ±.

HER-2 positive: estrogen receptor negative/progesterone receptor negative and HER-2 positive.

Triple negative: estrogen receptor negative/progesterone receptor negative and HER-2 negative.

8F-FDG PET/CT Imaging Protocol: The patients were asked to fast for at least 4-6 hours, and their blood glucose levels were measured before imaging was performed. Only patients with fasting blood glucose levels below < 200 mg/dL were injected with radiopharmaceuticals. During 18F-FDG PET/CT examinations, the patients were administered an average of 10 mCi 18F-FDG. All the patients stayed in the relaxation room for 45-60 minutes after the injection. The General Electric Discovery PET/CT 600 device was used for imaging. CT imaging was performed with a spiral 16-slice scanner at 120 kV and 172 mAs for attenuation correction and anatomical correlation. Three-dimensional PET imaging was performed, covering the body parts from the skull to the proximal thigh. PET imaging was conducted for approximately 2 minutes in each bed position. Axial, coronal, and sagittal fusion images were created using the iterative reconstruction method. The maximum standardized uptake values (SUVmax) were calculated based on the PET images. An adaptive threshold setting of 42% of maximum regional metabolic activity was used for the PET images, and the region of interest (ROI) was placed within the primary tumor in the breast by avoiding the peripheral area.

The following formula was used to calculate the SUVmax: [Activity in ROI (mCi/mL) × Body Weight (grams)] ÷ Injected Dose (mCi)

Ethical Approval

An informed consent form was obtained from the patients for this study. This study was approved by the Ethics Committee of Tokat Gaziosmanpasa University (Date: 2025-05-27, No:15235480-050.04-579263).

Results

The mean age of the 110 patients included in the study was 54.18 years (range: 24-86). All patients had invasive ductal carcinoma breast cancer. Of the 110 patients, 66 (60%) had luminal type A, 25 (22.7%) had luminal type B, 12 (10.9%) had HER2-positive, and 7 (6.4%) had triple negative subtypes. There was no statistically significant correlation between the molecular classifications of the patients and the SUVmax levels of the primary breast tumor (p = 0.055) (Table 1). Although not statistically significant, the lowest SUVmax values were measured in the Luminal A group, while the highest SUVmax values were in the Triple negative group.

In 66 patients with Luminal type A breast tumors on PET/CT, the median SUVmax value was 4.7 (range 1-20.5). In 30 Luminal type A patients with lymph node metastases, the median SUVmax value for metastatic lymph nodes was 4 (range: 1-16.8). Luminal type A 7 patients with distant metastases had a median SUVmax value of 6.4 (range: 1.5-15.2). In 27 patients with Luminal type B breast tumors on PET/CT, the median SUVmax value was 7 (range: 1-39.8). In 20 Luminal type B patients with lymph node metastases, the median SUVmax value for metastatic lymph nodes was 5.3 (range: 1-19.7). In 5 Luminal type B patients with distant metastases, the median SUVmax value for distant metastases was 4 (range: 3.3-9.7). The median SUVmax value of breast tumor on PET/CT of 12 HER2-positive patients was 7.35 (range 2.1-15.2). The median SUVmax value of metastatic lymph nodes in 7 HER2-positive patients with lymph node metastasis was 5.9 (range: 1.7-12.9). In 2 HER2-positive patients with distant metastases, the median SUVmax value for distant metastases was 3.05 (range: 2-4.1). The median SUVmax value of breast tumor on PET/CT of 8 triple negative patients was 8.4 (range 4.1-13.2). In 5 triple-

Table 1. Relationship between MolecularMolecular Subtypes and 18F-FDG PET/CT Data

Molecular Subtype	Breast Tumor SUVmax Median (min-max)	Lymph node SUVmax Median (min-max)	Distant Metastasis SUVmax Median (min-max)
Luminal Type A	4.7	4	6.4
	(0-20.5)	(1-16.8)	(1.5-15.2)
Luminal Type B	7	5.3	4
	(1-39.8)	(1-19.7)	(3.3-9.7)
Her2 positive	7.35	5.9	3.05
	(2.1-15.2)	(1.7-12.9)	(2-4.1)
Triple Negative	8.4	4.9	4
	(4.1-13.2)	(2.3-10.2)	(4-4)
p value	P = 0.055	P = 0.630	P = 0,593

SUVmax: Standard Uptake Value, $p < 0.05$, significant

Table 2. Relationship between Histologic Subtypes and K67 Proliferation

Histologic Subtype	Ki67 Proliferation (< 15%)	Ki67 Proliferation (≥ 15%)	Total	p value
Luminal Type A	33	32	65	
	-51%	-49%		
Luminal Type B	3	22	25	
	-12%	(% 88%)		p = 0.000
Her2 positive	1	11	12	
	-8%	(% 92%)		
Triple Negative	0	7	7	
	0%	-100%		
Lymph node Metastasis Presence/ Absence				
Positive Lymph Node	8	51	58	
	-22%	-71%		p = 0.000
Negative Lymph Node	29	21	50	
	-78%	-29%		

$p < 0.05$, significant

negative patients with lymph node metastases, the median SUVmax value for metastatic lymph nodes was 4.9 (range: 2.3-10.2). The median SUVmax value of a 1 triple-negative patient with distant metastasis was 4. No significant correlation was found between breast cancer molecular subtypes and the SUVmax values of lymph node and distant metastases (p = 0.630, p = 0.593) (Table 1).

While 59 (89.4%) of 66 patients with luminal type A had no distant metastasis, 7 (10.6%) had distant metastasis. Luminal type B 20 (80%) of 25 patients had no distant metastasis, while 5 (20%) had distant metastasis. While 10 (83.3%) of 12 HER2-positive patients had no distant metastasis, 2 (16.7%) had distant metastasis. While 6 (85.7%) of 7 triple-negative patients had no distant metastasis, 1 (14.3%) had distant metastasis. No significant association was found between breast molecular subtypes and the presence of distant metastasis (p = 0.689). Of 66 patients with luminal type A, 37 (56.1%) had no lymph node metastasis, and 29 (43.9%) had lymph node metastasis. While 6 (24%) of 25 patients with luminal type B had no lymph node metastasis, 19 (76%) had lymph node metastasis. While 5 (41.7%) of 12 HER2-positive patients had no lymph node metastasis, 7 (58.3%) had lymph node metastasis. Of the 7 triple-negative patients, 2 (28.6%) had no lymph node metastasis, while 5 (71.4%) had lymph node

metastasis. There was a significant association between breast molecular subtypes and the presence of lymph node metastasis (p = 0.032). The risk of lymph node metastasis was higher in triple-negative and Luminal B type patients compared to other molecular subtypes.

Ki67 proliferation index was less than 15% in 37 patients and more than 15% in 72 patients. The Ki67 index of 1 patient was not available. Of the 37 patients with Ki67 proliferation less than 15%, 34 (91.9%) had no distant metastasis, while 3 (8.1%) had distant metastasis. Of 72 patients with Ki67 proliferation greater than 15%, 60 (83.3%) had no distant metastasis, while 12 (16.7%) had distant metastasis. There was no significant correlation between i67 proliferation and the presence of distant metastasis (p = 0.219). Of 37 patients with Ki67 proliferation less than 15%, 8 (22%) had lymph node metastasis, while 29 (78%) had no lymph node metastasis. Of 72 patients with Ki67 proliferation greater than 15%, 21 (29%) had no lymph node metastasis, while 51 (71%) had lymph node metastasis. There was a significant correlation between Ki67 proliferation and the presence of lymph node metastasis (p = 0.000) (Table 2).

Of 65 luminal type A patients, 33 (51%) had less than 15% Ki67 proliferation, and 32 (49%) had more than 15% Ki67 proliferation. Luminal type B was less than 15% in 3 (12%) and more than 15% in 22 (88%) of 25 patients. In 1 (8%) of 12 HER2-

positive patients, Ki67 was less than 15% and in 11 (92%), Ki67 was more than 15%. In all 7 triple-negative patients (100%), Ki67 was more than 15%. There was a significant association between Ki67 proliferation and molecular subtypes (p = 0.000) (Table 2). We also found a significant correlation between Ki67 index and breast tumor and lymph node SUVmax levels (p = 0.000, p = 0.03).

Discussion

Breast cancer exhibits highly heterogeneous pathologic and molecular features. According to these characteristics, treatment modalities and prognosis of patients are determined. Breast tumors with different molecular subtypes may have different uptake levels of 18F-FDG in PET/CT.

In the present study, although we did not find a statistically significant relationship between molecular subtypes and SUVmax, according to our results, the highest tumor SUVmax was calculated in the triple negative subtype, while the lowest tumor SUVmax was calculated in the luminal A type. This is consistent with other studies in the literature. Akin et al. found that luminal type B and triple negative type breast cancer had higher SUVmax values than luminal type A [9]. Oner et al. in their study, the breast tumor SUVmax value of luminal type B, HER-2 positive, and triple negative patients was higher than the SUVmax value of luminal type A patients [10]. Consistent with the results of our study, Koo and Kitajima et al. also found lower SUVmax values in luminal type A patients compared to luminal type B and triple negative tumor SUVmax [11,12].

In the present study, there was a significant relationship between molecular subtypes and lymph node metastasis. In the study by Koo et al., lymph node involvement was found to be 1.67 times higher in HER-2 and triple negative patients compared to luminal type A patients. In our study, statistically significant triple-negative patients had the highest lymph node metastasis rate. 2. The highest probability of lymph node metastasis was found in HER2-positive patients. The lowest lymph node metastasis rate was in luminal type A patients [11]. In addition, the incidence of lymph node metastasis was higher in patients with high Ki67 in our study. In the Aktaş et al. study, the lymph node SUVmax value was higher in patients with high Ki67 compared to those with low Ki67 [13]. Similar to the results of our study, Aktaş et al. found a significant correlation between primary tumor SUVmax and metastatic lymph node SUVmax values and molecular subtypes.

In contrast to our study, Topuz et al. did not find a significant correlation between breast tumor and lymph node SUVmax and Ki67. We found a significant correlation between Ki67 elevation and the frequency of lymph node metastasis. Topuz et al. did not find a significant correlation between Ki67 and axillary lymph node involvement in their study [14]. Shen et al. also found a significant correlation between breast tumor SUVmax and elevated Ki67 [15].

Consistent with the results of our study, Li et al. also found a relationship between Ki67 elevation and molecular subtypes [16]. In George et al.'s study, as in our study, the highest rate of Ki67 elevation was observed in triple negative patients and the lowest in the luminal type A group [17]. No significant

correlation was found between Ki67 and the presence of lymph node metastasis in Tuzcu et al. However, in our study, there was a significant correlation between Ki67 elevation and lymph node metastasis [18].

Limitations

We could not perform a prognosis study because our study was retrospective. Although the 8th edition of the American Joint Committee on Cancer (AJCC) staging guidelines does not include 18F-FDG hypermetabolism as a prognostic factor in breast cancer, increasing evidence suggests that SUV max is useful in predicting prognosis. Studies are needed in this regard.

Conclusion

Molecular classification in breast cancer is very important in the treatment and prognosis follow-up of the disease. In our study, we demonstrated that different molecular subtypes show different metabolic characteristics. We also revealed that tumor Ki67 levels cause metabolic differences, and tumors with high Ki67 levels on 18F-FDG PET/CT have an increased likelihood of lymph node metastasis. We think that Ki67 levels should be taken into consideration when interpreting lymph node positivity in these patients.

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Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content, including study design, data collection, analysis and interpretation, writing, and some of the main line, or all of the preparation and scientific review of the contents, and approval of the final version of the article.

Animal and Human Rights Statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Data Availability Statement
The datasets used and/or analyzed during the current study are not publicly available due to patient privacy reasons but are available from the corresponding author on reasonable request.

Conflict of Interest
The authors declare that there is no conflict of interest.

Ethics Declarations
This study was approved by the Ethics Committee of Tokat Gaziosmanpasa University (Date: 2025-05-27, No:15235480-050.04-579263)