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Detection of the Metabolic Relationship Between Primary Tumor in Breast Cancer According to Molecular Classification in Positron Emission Tomography; Retrospective Cohort Study

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Abstract: The main objective of the study was to investigate whether the maximum SUV emission tomography values of Positron differ between luminal molecular properties. The second objective was to examine the relationship between positron emission tomography SUV max and ki67 in primary tumors and axillary lymphadenopathy. In the study between January 2018 and December 2020, 158 patients with stage 1-2-3 breast cancer admitted to the outpatient clinic of general surgery and medical oncology Yüksek htisas University Medicalpark Ankara were retrospectively evaluated. The results of the study considering the relationship between molecular properties and metabolic activity of primary tumors, found a significant relationship between grade (p<0.005), estrogen receptor (p:0.019), and progesterone receptor (p:0.045). More important differences were observed in the luminal type, especially between such as basal and luminal A (p: 0.021). A significant correlation was found in the Pearson correlation test, which was performed between the primary tumor and the SUV values for maxillary axillary lymphadenopathy (p < 0.001, correlation coefficient: 0.331). For Ki67, there was a significant, albeit low, correlation between the SUV max primary tumors (p: 0.026, correlation coefficient 0.179). Although there is a statistically positive trend between Ki67 and axillary SUV max, there is no significant difference (p: 0.06 correlation coefficient: 0.157) In conclusion, we found a significant relationship between max. positron emission tomography SUV, estrogen receptor, progesterone receptor, grade, ki67, and molecular subtypes such as basal and luminal A of the tumor. We found a correlation between the primary tumor and the metabolic activity of axillary lymphadenopathy. It will be meaningful to plan treatment and follow-up according to these results.
Keywords: Breast cancer; positron emission tomography; fluorodeoxyglucose; SUV max; ki67.

INTRODUCTION

Breast cancer is one of the most common and deadly cancers in women (Van Mechelen M et al. 2020; Can A et al.2013). Tumor size and involved lymph nodes are important prognostic indicators in breast cancer. However, features related to tumor biology such as estrogen receptor (ER), progesterone receptor (PR), epidermal growth factor receptor 2 (HER2) are much more helpful and more precise prognostic indicators(Coates AS et al., 2015). The cornerstones are in the diagnosis and staging of early breast cancer, mammography, USG (ultrasound), and breast MRI (magnetic resonance). However, the use of PET CT (positron emission computerized tomography) has increased significantly in recent years (Muzahir S., 2020).

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Besides showing distant metastases, PET can also give an idea about tumor histopathology (Sasaki M et al., 2018). Many studies on this subject have shown that the SUV max (maximal standardized uptake value) value varies according to breast cancer's histological and biological characteristics. Invasive tumors have been shown to have a higher SUV max than low-grade tumors (Kitajima K et al., 2018). PET parameters are effective in predicting the behavior of breast cancer (Surov A et., 2018). As a matter of fact, in a study by Higuchi et al., (2016), it was found that patients with high SUV max values in operated breast cancer patients had a worse prognosis than patients with low SUV max values. PET CT can also predict response to chemotherapy (Wang J et al., 2017). The role of PET CT in molecular subtypes of breast cancer is not yet fully understood.

Our primary aim is to investigate whether the PET SUV max value differs between luminal molecular properties. Our second aim is to investigate the correlation between PET CT SUV max and ki67 in primary tumors and axillary LAPs.

MATERIALS AND METHODS

One hundred fifty-eight patients admitted to the general surgery and medical oncology outpatient clinic of Yüksek İhtisas University Medicalpark Ankara hospital between January 2018 and December 2020 were evaluated retrospectively.

Early-stage (stages 1,2,3) patients were evaluated as operable or suitable for neoadjuvant therapy. Patients between the ages of 18-80 were included in the study. Patients with histopathologically noninvasive ductal carcinoma subtypes and patients with distant organ metastases and diabetes were excluded from the study.

The patients' information was anonymized, and research permission was obtained from the hospital management board of Yüksek İhtisas University Medical Park Ankara.

Patients' age, tumor TNM staging, nuclear grade, ki67, hormone receptor status, HER 2, primary tumor, and axillary PET CT SUV max values were recorded. PET CT evaluation was done in a single center and by the same nuclear medicine specialist. The same pathologist made pathological evaluations in all patients.

Molecular classification of groups

According to the different combinations of ER, PR, and HER-2 status and according to the recommendations of the 12th International Breast Conference (Goldhirsch A et al.2011), patients were divided into five subgroups:

1. Luminal A: ER(+) and/or PR(+), HER2(−), Ki-67 low (<14 %)
2. Luminal B-HER2(−): ER(+) and/or PR(+), HER2(−) and Ki-67 high (≥14 %)
3. Luminal B-HER2(+): ER(+) and/or PR(+), HER2(+), and any Ki-67 index
4. HER2(+) like ER(−), PR(−), and HER2(+)
5. Basal-like: ER(−), PR(−), and HER2(−)

Positron Emission Tomography

According to the standard protocol, all patients underwent Fluorine-18–Fluorodeoxyglucose (18F-FDG) PET/CT scanning. Patients fasted for at least 6 hours before scanning, and blood glucose levels were checked using a fingertip blood glucose meter before 18F-FDG injection. It was ensured that the blood sugar level was lower than 160 mg/dl. The dose of 18F-FDG was 0.10 mCi/kg, and that dose was intravenously injected into each patient under appropriate glycemic control. It was ensured that each patient drank at least 1 liter of fluid. Whole-body PET/CT scan was obtained at 60 minutes by a special PET scanner (Siemens Biograph 2, USA) with 3 minutes of acquisition for every 8-9 bed position (patient supine, arms at patient's side, from top to thigh position). The spatial resolution for the PET scanner was 5 mm. A

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contrast-enhanced CT scan was obtained in 1 minute with a low dose of 70-120 kVp and tube current of 10-90 mAs.

Statistics

The SPSS-22 program was used for statistical evaluations. Kolmogorov-Smirnov test was used in the assessment of normal distribution between groups. Kruskal Wallis test was used for group means. Spearman correlation test was used for the relationship and correlation between the groups. A P value below 0.05 was considered significant.

RESULTS AND DISCUSSION

The mean age of the patients included in the study was 55 (range; 26-83). When the stages of the patients were examined, 10.7% (17) were stage 1, 50.6% (80) were stage 2, and 38.6% (61) were stage 3 (Table 1).

When the receptor status of the patients was examined, 76.6% (121) had estrogen receptor, 74.1% (117) had progesterone receptor, 21.6% (34) had HER 2 positivity. When looking at the patients from the luminal point of view, 22.8% (36) were luminal A, 55.1% (87) were luminal B, 15.2% (24) were HER 2-like type, and 7% (11) were basal-like. Of the patients, 25.3% (40) were grade 1, 18.4% (29) were grade 2 and 56.3% (89) were grade 3. The mean ki67 level in the patients was 24.2% (range; 1-90) (Table 1).

Considering the relationship between molecular properties and metabolic activity of the primary tumor, a significant relationship was found between grade ($p<0.005$), ER (p:0.019), and PR (p:0.045). A significant correlation was found between the metabolic activity of the primary tumor in luminal subtypes (p:0.049) (Table 2). It was observed that, especially in luminal types, the significance was more obvious between basal-like type and luminal A (p:0.021) (Figure 1).

When looking at tumor SUV max in PET CT, primary tumor SUV max average was 4.88 (range: 0-28.3), axillary SUV max was 2.61 (0-20.4). A moderately significant correlation was found in the Pearson correlation test performed between the primary tumor and axillary LAP SUV max ($p <0.001$, correlation coefficient 0.331). For Ki67, there was a significant correlation, albeit at a low level, between the primary tumor SUV max (p:0.026, correlation coefficient 0.179). Although there was a statistically positive trend between Ki67 and axillary SUV max, there was no significant difference (p:0.06 correlation coefficient 0.157).

The possibility of predicting tumor behavior and tumor biology based on PET findings is very important. In particular, SUV max value can be an important biomarker if it can reflect the tumor's proliferation activity and biological subtype. Theoretically, the metabolic activity of the tumor is expected to be predictive of the cellular activity and proliferation of the tumor. However, glucose metabolism may not be directly related to cell proliferation because ki67 is only just one of the proliferation markers. Glucose metabolism is expected to be a stronger marker than other proliferation markers such as ki67.

There are quite inconsistent results in the literature regarding the relationship between PET parameters and ki67 expression. Fewer than 100 patients were recruited and evaluated İn most studies. In the meta-analysis conducted on this subject, a moderate correlation (0.40) was found between SUV max value and ki67 (Surov A et al., 2018). There was also a significant low-level correlation between ki67 and primary tumor SUV max in our study.

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Table 1: General Features

	N:158 (100%)
Age-mean	55
Range	(26-83)
Estrogen receptor	
Positive >%1	121 (76.6 %)
Negative	37 (24.4%)
Progresterone receptor	
Positive >%1	117 (74.1 %)
Negative	41 (25.9%)
Cerbb2 -HER2	
Positive (ihc +++)	34 (21.6 %)
Negative(ihc -,+,++, fısh-)	124 (78.4%)
Grade	
Grade 1	40 (25.3 %)
Grade 2	29 (18.4 %)
Grade 3	89 (56.3%)
Kİ67 %	24.2 (1-90)
Primary Tumor SUV max -median	4.88(0-28.3)
Axillary LAP suv max-median	2.61 (0-20.4)
Luminal Type	
Luminal A	36 (22.8%)
Luminal B	87 (55.1%)
Her 2 like	24 (15.1%)
Bazal like	11 (7 %)
T	
T1	32 (20.3%)
T2	101 (63.9%)
T3	12 (7.6%)
T4	13 (8.2%)
N	
N0	59 (37.3 %)
N1	47 (29.7 %)
N2	30 (19 %)
N3	22 (13.9 %)
Stage	
1a	15 (9.5 %)
1b	2 (1.3 %)
2a	43 (27.2 %)
2b	37 (23.4 %)
3a	26 (16.5 %)
3b	13 (8.2 %)
3c	22(13.9 %

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Table 2: Metabolic Evaluation in PET CT According to Histopathological Evaluations

	N	Mean Suv max	P value
Grade			
Grade 1	40	4.8	0.005
Grade 2	29	5.1	
Grade 3	89	7.7	
Estrogen receptor			
Negative	39	8.3	0.019
Positive	119	5.9	
Progesterone receptor			
Negatif	43	7.9	0.045
Positive	115	6	
HER 2 status			
Negative	87	6.7	0.323
Positive	71	6.3	
Ki67			
>%15	50	7.1	0.076
≤ %15	108	5.1	

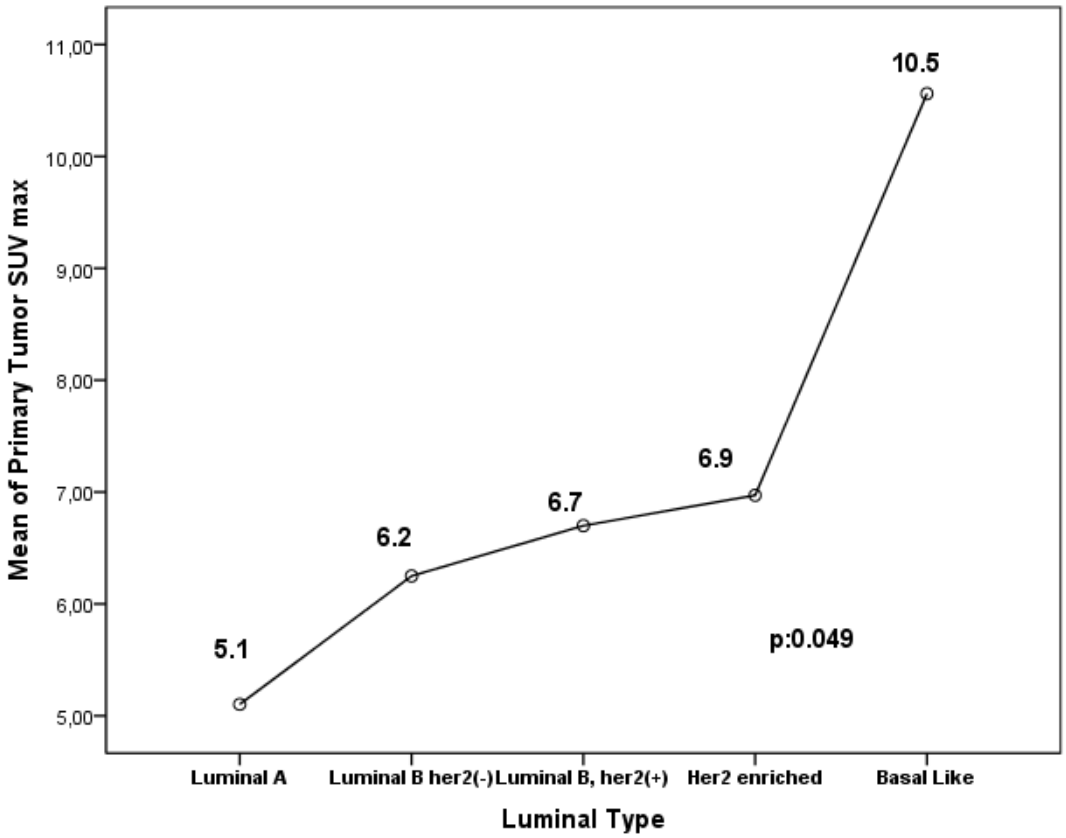

Figure 1. Mean SUV Max by Luminal Molecular Subtypes

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Heudel et al., (2010) observed significant correlations of SUV max with histological grade (P< 0.001), histological type (P= 0.001), tumor diameter (P< 0.0435), estrogen receptor (P< 0.0005) and progesterone receptor (P= 0.002) level . In our study, a significant correlation was found especially between ER, PR positivity and grade and ki67.

In the study by Higuchi T et al., (2016), it was determined that the prognosis of patients with high SUV max in the baseline 18F-FDG PET/CT examination was significantly worse than patients with low SUV max in operated breast cancers. However, subgroup analysis showed that the prognostic significance of SUV max was evident in the ER (+) and HER2(-) subgroups. In contrast, O JH et al., (2013) found that SUV max in primary breast cancer was not associated with recurrence within two years. According to Son SH et al., (2014) multivariate analysis found that SUV max was not an important prognostic factor for overall survival (Son SH et al., 2014). Similarly, the prognostic significance of SUVmax in primary tumors could not be demonstrated in the multivariate analysis by Kim et al. (Kim YH et al., 2015). According to the molecular correlation evaluation performed by Garcia Vicente AM et al., a significant correlation was found with the SUV max value according to the molecular subtypes of breast cancer. In this study, it has been stated that a higher SUV max value was associated with tumor aggressiveness (García Vicente AM et al., 2013).

In another study investigating the metabolic correlation between molecular subtypes and PET CT, its predictive value was found to be more significant, especially for luminal A and HER2 positives (Kitajima K et al., 2015). Our study found a significant relationship between basal-like and luminal A in terms of pet ct SUV max. We could not see this difference among other luminal subtypes.

The small number of patients for common cancer, such as breast cancer, and the fact that we made a retrospective evaluation are important limitations in our study. The fact that we did not provide survival and recurrence information is a deficiency in terms of prognosis assessment.

CONCLUSION

We found a significant correlation between PET CT SUV max metabolic activity and ER, PR, and grade. We found significant metabolic activity among luminal types, especially basal-like and luminal A. Also, we found a correlation between the primary tumor and axillary LAP metastasis, albeit at a low rate, in terms of metabolic activity. It will be meaningful to plan treatment and follow-up according to these results.

CONFLICT OF INTEREST

All of the authors have no conflict of interest

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