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The relationship of 18F-FDG PET/CT SUVmax values with molecular subtypes and hormone receptors in breast cancer patients

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Abstract

Positron Emission Tomography–Computed Tomography (PET-CT) serves as a complementary imaging modality in breast cancer staging and therapeutic monitoring. SUV (standardized uptake value) represents the concentration of 18F-fluorodeoxyglucose (18F-FDG) radiotracer per tissue volume, normalized for injected dose and body weight. This study explored associations between 18F-FDG PET/CT (derived SUVmax measurements and breast cancer molecular classifications, assessing metabolic variations across subtypes characterized by hormone receptor expression patterns. We enrolled breast cancer patients who underwent 18F-FDG PET/CT scanning at the Surgical Oncology Department, Health Sciences University Faculty of Medicine, Gulhane Training and Research Hospital. We investigated relationships between maximum standardized uptake values (indicating metabolic activity) and molecular classifications. Additionally, we examined correlations between SUVmax and immunohistochemical markers such as Ki-67 proliferation index, HER2 (human epidermal growth factor receptor 2), ER (Estrogen receptor) and PR (progesterone receptor) expression. Our analysis encompassed 102 patients. Molecular subtype categorization demonstrated statistically significant SUVmax differences ($p<0.001$). Triple-negative malignancies showed notably elevated SUVmax compared with Luminal A ($p<0.001$), Luminal B HER2(-) ($p<0.001$), Luminal B HER2(+) ($p<0.001$), and HER2-enriched ($p<0.001$) categories. Similarly, isolated HER2(+) cases displayed higher SUVmax than Luminal A ($p<0.001$), Luminal B HER2(-) ($p<0.001$), and Luminal B HER2(+) ($p<0.001$) subtypes. Negative correlations emerged between SUVmax and ER/PR expression, whereas positive relationships were found with Ki-67 index. From a clinical perspective, SUVmax functions as a biomarker representing tumor biological characteristics rather than simply a quantitative measurement. Our results suggest that 18F-FDG PET/CT warrants expanded integration in comprehensive breast cancer care. The demonstrated elevated metabolic activity in aggressive subtypes highlights this modality's utility as an adjunctive prognostic tool.

Keywords: Positron emission tomography, suvmax, molecular subtypes, tumor biology

Introduction

Global epidemiological data indicate that breast malignancies account for roughly one-quarter of all cancers, making this the most prevalent cancer type among women [1]. Despite its frequency, this disease exhibits considerable heterogeneity regarding molecular profiles and histopathological features. Numerous risk factors have been established encompassing demographic characteristics (female sex, increasing age), genetic susceptibility (familial history, mutation carriers), hormonal exposures, reproductive patterns and lifestyle factors such as adiposity, smoking and physical inactivity. Earlier research has shown that patients presenting with identical tumor stages may demonstrate substantial survival outcome variations [2]. Even among individuals with small primary tumors and node-negative disease, early systemic dissemination and diminished survival suggest additional prognostic factors exist.

Based on this understanding, Perou et al. introduced the first molecular classification system for breast cancer in 2000 [3]. This framework prioritized tumor biology above morphological characteristics, employing DNA (Deoxyribose nucleic acid) sequencing, gene expression profiling and immunohistochemical analysis. ER (Estrogen receptor), PR (progesterone receptor),

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HER2 (human epidermal growth factor receptor 2) and Ki-67 proliferation marker constitute the principal molecular indicators for tumor characterization. Breast malignancies are classified into luminal A, luminal B, HER2-enriched and triple-negative categories according to ER, PR and HER2 profiles. In 2001, preliminary data regarding molecular subtype prognostic significance appeared showing that Luminal B malignancies displayed more aggressive characteristics than Luminal A, yet maintained better outcomes compared with triple-negative disease [4]. These observations have driven extensive subsequent investigations on breast cancer molecular classifications. Subsequently, the 2011 St. Gallen consensus recommended hormone receptor-based molecular subtype categorization [5].

Positron emission tomography combined with computed tomography (PET/CT) has become a valuable adjunctive imaging technique for breast cancer staging and post-treatment surveillance. This methodology exploits increased glucose metabolism and glycolytic activity in malignant cells and certain benign proliferative states, utilizing the glucose analogue 18F-fluorodeoxyglucose (18F-FDG) which enters cells via glucose transporters and undergoes hexokinase phosphorylation [6]. Nevertheless, given limited sensitivity and substantial cost, PET/CT is not advocated as a primary breast cancer imaging approach [7].

PET/CT plays a significant role in advanced breast cancer care; nevertheless, routine utilization is not recommended for early-stage presentations (T1–T2, N0–N1) as standard imaging techniques—mammography, ultrasonography and MRI—sufficiently address local staging, with minimal additional benefit from 18F-FDG PET/CT [8,9]. Conversely, 18F-FDG PET/CT is recommended in locally advanced cases (T3–T4 and/or N2–N3 nodal involvement) or in triple-negative and HER2-positive subtypes, due to the increased risk of systemic spread [10]. This is because, in these patients the sensitivity of 18F-FDG PET/CT for detecting distant metastases can reach up to 93% with a specificity of up to 95% [11]. Compared with conventional imaging it provides enhanced sensitivity for the detection of bone, liver and mediastinal lymph node metastases [12]. Additionally it can be effectively used to assess early treatment response and to investigate recurrence in patients showing elevated serum tumor markers but no detectable lesions on other imaging modalities [13]. Furthermore, variables such as lesion size below 10 mm, Ki-67 index, hormonal profile and tumor subtype can alter how sensitively 18F-FDG PET/CT detects breast cancer [7].

This study aimed to investigate associations between 18F-FDG PET/CT parameters and molecular tumor classifications in breast cancer patients. Specifically, we assessed metabolic activity variations among molecular subgroups according to hormone receptor expression patterns. Additionally, we analyzed how 18F-FDG PET/CT diagnostic performance varies with hormone receptor expression, evaluating its role in subtype differentiation and determining optimal SUV thresholds for receptor status.

Material and Methods

Study Population and Patient Selection

We conducted a retrospective analysis of breast cancer patients who received 18F-FDG PET/CT scans for diagnostic evaluation or disease monitoring at the Surgical Oncology Department of Health Sciences University Gulhane Training and Research Hospital spanning January 2023 and May 2025. In our institution, 18F-FDG PET/CT examinations are performed for patients fulfilling established criteria based on international oncology guidelines and published evidence. These encompass all locally advanced and inflammatory breast cancer presentations regardless of molecular characteristics, cT1c N0 HER2-negative and triple-negative patients, and those with ≥cT2 or N(+) Luminal-positive disease. Patients with stage 4 and who underwent PET CT were not included in the study. Since 18F-FDG is structurally similar to glucose, patients maintain a 6-hour fasting period before PET/CT to minimize false-negative results and reduce SUV measurement variability. Pre-imaging fasting glucose concentrations are targeted below 150 mg/dL. For patients exceeding this threshold, imaging is deferred until satisfactory glycemic control is attained. Among 154 patients meeting these criteria, eight were excluded owing to incomplete pathology reports lacking ER, PR, HER2 receptor status or Ki-67 index data. Since macrophages and fibroblasts participating in wound healing demonstrate high glucose uptake potentially causing spurious tumor uptake, 12 recurrence cases and 32 patients evaluated by 18F-FDG PET/CT for postoperative surveillance were excluded, producing a final cohort of 102 patients. All patients included in the study were operated after neoadjuvant treatment.

Classification of Molecular Subtypes

For hormone receptor evaluation, ≥1% positive nuclear staining in malignant cells was deemed positive for ER and PR by immunohistochemistry. HER2 status received scores ranging from 0 to 3+ based on membrane staining intensity; 3+ was considered positive whereas 2+ cases underwent FISH confirmation. Ki-67 index represented the proportion of nuclear-stained tumor cells. Following St. Gallen International Breast Cancer Conference criteria, patients were categorized into molecular subtypes: Luminal A [ER(+) and/or PR(+), HER2(−), Ki-67<14%], Luminal B HER2-negative [ER(+) and/or PR(+), HER2(−), Ki-67 ≥ 14%], Luminal B HER2-positive [ER(+) and/or PR(+), HER2(+), any Ki-67], HER2-enriched [ER(−), PR(−), HER2(+)], and basal-like (triple-negative) [ER(−), PR(−), HER2(−)].

Study Design

This investigation was performed as a retrospective, single-institution, observational study. Enrolled patients received

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invasive breast cancer diagnoses between January 2023 and May 2025 at the Surgical Oncology Clinic of Gulhane Training and Research Hospital, Health Sciences University, underwent surgical intervention, and received 18F-FDG PET/CT imaging preoperatively. The primary aim was investigating relationships between breast cancer molecular subtypes and SUVmax parameters, which quantify metabolic activity. Furthermore, associations between SUVmax and immunohistochemical parameters including Ki-67 index and ER/PR positivity rates were explored; for variables showing significant relationships, optimal cut-off values were determined via ROC curve analysis. The Scientific Research Evaluation Committee of Gulhane Training and Research Hospital approved this study (Decision No: 13-1 / Date: 02.07.2025). This retrospective investigation followed Declaration of Helsinki ethical principles.

Statistical Analysis

SPSS version 22.00 was utilized for statistical computations. Kolmogorov–Smirnov and Levene tests evaluated continuous variable normality and homogeneity. For non-normally distributed continuous variables Mann–Whitney U test addressed two-group comparisons whereas Kruskal–Wallis test handled multiple-group analyses. Post-hoc Bonferroni tests investigated statistically significant differences among multiple groups. Spearman correlation assessed continuous variable relationships with linear regression analyzing their associations. ROC curve analysis determined sensitivity and specificity cut-off values. Statistical significance was established at $p<0.05$.

Result

Patient Characteristics

The analysis incorporated 102 patients who underwent 18F-FDG PET/CT imaging for staging prior to neoadjuvant therapy following breast cancer diagnosis. Average patient age was 52.03 years (range: 31–85). Tumor distribution was equivalent between right and left breasts. Pathological examination identified invasive ductal carcinoma as the predominant histological variety comprising 88.2% of cases. ER positivity was identified in 79 patients (78.2%) with average ER expression of 60.34%. PR positivity occurred in 79.4% of patients with average PR expression of 51.03%. HER2 receptor tested negative in 82 patients. Average Ki-67 index measured 34.60%. Concerning molecular classification based on hormone receptor status, Luminal B HER2-negative represented the most frequent subtype at 39.2%. Prior to neoadjuvant therapy average tumor diameter measured 38.89 mm and average metastatic axillary lymph node count was 2.47. Average SUVmax value representing tumor metabolic activity on 18F-FDG PET/CT, was 5.24. Table 1 displays detailed demographic, clinical and pathological characteristic distributions for all patients.

Relationship Between Hormone Receptor Status, Molecular Subtypes, and 18F-FDG PET/CT SUVmax Values

Patients were categorized into molecular subtypes according to immunohistochemical findings. Distribution comprised 32 Luminal A, 40 Luminal B HER2-negative, 12 Luminal B HER2-positive, 8 isolated HER2-positive and 10 triple-negative patients. SUVmax value distribution measured by 18F-FDG PET/CT was investigated across molecular subtypes. Initially, Kolmogorov–Smirnov and Levene tests evaluated SUVmax value distribution and variance homogeneity. Both analyses revealed non-normal distribution and heterogeneous variances. Median SUVmax values by molecular subtype were: Luminal A: 3.1; Luminal B HER2-negative: 3.8; Luminal B HER2-positive: 4.5; isolated HER2-positive: 6.8; and triple-negative: 14.8. Statistically significant SUVmax distribution differences were identified among molecular subtypes ($p<0.001$). Post-hoc Bonferroni analysis demonstrated this difference originated from substantially elevated SUVmax values in the triple-negative cohort versus Luminal A ($p<0.001$), Luminal B HER2-negative ($p<0.001$), Luminal B HER2-positive ($p<0.001$) and isolated HER2-positive ($p<0.001$) cohorts along with higher SUVmax values in the isolated HER2-positive cohort compared with Luminal A ($p<0.001$), Luminal B HER2-negative ($p<0.001$) and Luminal B HER2-positive ($p<0.001$) cohorts.

SUVmax value distribution according to hormone receptor status among enrolled patients also showed statistical significance. Median SUVmax was 8.6 in ER-negative patients versus 3.8 in ER-positive patients ($p<0.001$). Similarly, median SUVmax measured 8.9 in the PR-negative cohort and 3.75 in the PR-positive cohort ($p<0.001$). SUVmax distribution by HER2 receptor status was also statistically significant; however this difference appeared less substantial compared with relationships with ER and PR receptors (Table 2).

Correlation of ER and PR Expression Percentages and Ki-67 Index with 18F-FDG PET/CT SUVmax Values

Associations between tumor SUVmax levels and ER/PR expression percentages along with Ki-67 index were assessed through correlation analysis. Significant negative correlations appeared between SUVmax and ER/PR expression percentages (rho=–0.610 and rho=–0.598, respectively; $p<0.001$). Conversely, significant positive correlation was identified between SUVmax and Ki-67 index (rho=0.638; $p<0.001$). Linear regression analysis based on these findings showed that each unit increase in Ki-67 index correlated with an average 0.730-unit SUVmax increase ($p<0.001$). Each unit increase in ER expression percentage corresponded to an average 0.651-unit SUVmax reduction and similarly each unit increase in PR expression percentage corresponded to a 0.617-unit SUVmax reduction ($p<0.001$ for both variables). These findings indicate tumor glycolytic activity significantly correlates with immunohistochemical markers (Table 3).

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ROC Curve Analysis of HER2, ER, and PR Receptors for SUVmax Levels

ROC curve analysis was performed to establish SUVmax discriminative performance as a tumor metabolism marker across cohorts categorized by ER, PR and HER2 expression. The SUVmax threshold for ER was determined as 4.65. ER negativity could be predicted in patients with SUVmax exceeding this threshold with 78.3% sensitivity and 81.0% specificity ($p<0.001$) (Figure 1a). Similarly, the SUVmax threshold for PR was established as 5.2. In patients with SUVmax surpassing this threshold, PR negativity was predicted with 85.7% sensitivity and 86.4% specificity ($p<0.001$) [Figure 1b]. SUVmax ROC curve analysis for HER2 status predicted HER2-positivity in patients with SUVmax above 4.55 with 70% sensitivity and 70.7% specificity (Figure 1c).

Table 1. Demographic and clinicopathological distribution of the patients

Age, year, mean±SD, range	**52.03±11.25 (31-85)**
Tumor Lateralization, n(%)	
Left	51 (50%)
Right	51 (50%)
Pathology, n(%)	
İnvasice Ductal Cancer	90 (88.2%)
İnvasice Lobular Cancer	12 (11.8%)
ER, n(%)	
Absent	23 (22.5%)
Present	79 (77.5%)
ER expression percentages, mean±SD, range	60.34±37.08 (0-95)
PR, n(%)	
Absent	21 (20.6%)
Present	81 (79.4%)
PR expression percentages, mean±SD, range	51.03±34.41 (0-95)
HER2, n(%)	
Absent	82 (80.4%)
Present	20 (19.6%)
Ki-67 proliferation index, nb, mean±SD, range	34.60±24.73 (5-90)
Molecular Subgroups, n(%)	
Luminal A	32 (31.4%)
Luminal B HER2(-)	40 (39.2%)
Luminal B HER2(+)	12 (11.8%)
HER2(+)	8 (7.8%)
Triple negative	10 (9.8%)
Preoperative Tumor size, mm, mean±SD, range	38.89±13.16 (12-59)
Preoperative axillary metastasis, nb, mean±SD, range	2.47±1.15 (0-5)
SUVmax, nb, mean±SD, range	5.24±3.73 (1.6-18.9)

SD: Standard deviation, SUVmax: Standardized Uptake Value, ER: Estrogen receptor, PR: Progesterone receptor

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Table 2. Distribution of molecular subgroups and hormone receptors according to suvmax values

Clinicopathological Factors	SUVmax, median, range	P value
Molecular Subgroups, n(%)		
Luminal A	3.1 (1.6-6.7)	p<0.001H
Luminal B HER2(-)	3.8 (2.3-6.2)	
Luminal B HER2(+)	4.5 (3.6-5.8)	
HER2(+)	6.8 (6.1-8.9)	
Triple Negative	14.8 (13.1-18.9)	
Post-Hoc Multiple Comparisons (Bonferroni) Test		
Molecular Subgroups	**Mean Difference**	**Significance**
Luminal A		
Luminal B HER 2(-)	-0.4350	1.000
Luminal B HER2(+)	-1.1208	0.084
HER2 (+)	-3.9250	<0.001
Triple Negative	-1.9975	<0.001
Luminal B HER2(-)		
Luminal A	0.4350	1.000
Luminal B HER2(+)	-0.6858	0.936
HER2(+)	-3.49	<0.001
Triple Negative	-11.5625	<0.001
Luminal B HER2(+)		
Luminal A	1.1208	0.084
Luminal B HER2(-)	0.6858	0.936
HER2(+)	-2.8042	<0.001
Triple Negative	-10.8767	<0.001
HER2(+)		
Luminal A	3.9250	<0.001
Luminal B HER2(-)	3.49	<0.001
Luminal B HER2(+)	2.8042	<0.001
Triple Negative	-8.0725	<0.001
Triple Negative		
Luminal A	11.9975	<0.001
Luminal B HER2(-)	11.5625	<0.001
Luminal B HER2(+)	10.8767	<0.001
HER2(+)	8.0725	<0.001
ER, n(%)		
Absent	8.6 (2.6-18.9)	p<0.001U
Present	3.8 (1.6-6.7)	
PR, n(%)		
Absent	8.9 (3.6-18.9)	p<0.001U
Present	3.75 (1.6-6.7)	
HER2, n(%)		
Absent	3.8 (1.6-18.9)	p<0.001U
Present	5 (3.6-8.9)	

U: Mann Whitney U test; H: Kruskal Wallis-H test <0.001H ; This significance difference is due to the association of the triple negative group with Luminal A (p<0.001), Luminal B HER2(-)(p<0.001), Luminal B HER2(+)(p<0.001), HER2(+)(p<0.001) groups and the association of the HER2(+) group with Luminal A (p<0.001), Luminal B HER2(-)(p<0.001), Luminal B HER2(+)(p<0.001) groups according to the Post-Hoc Bonferroni test

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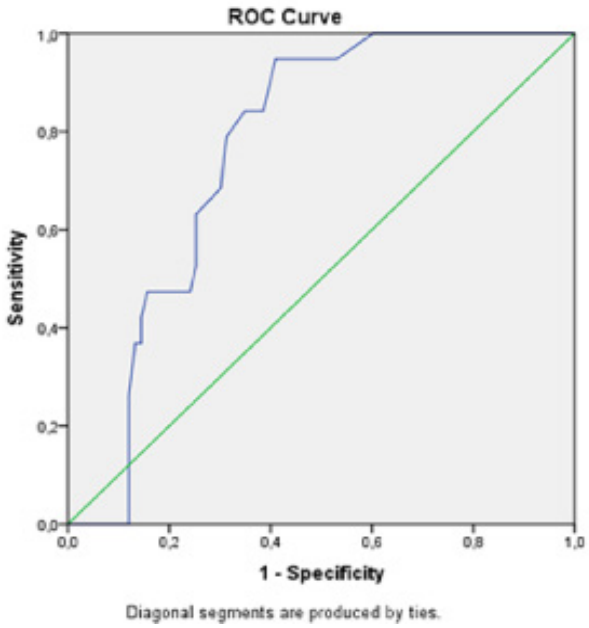
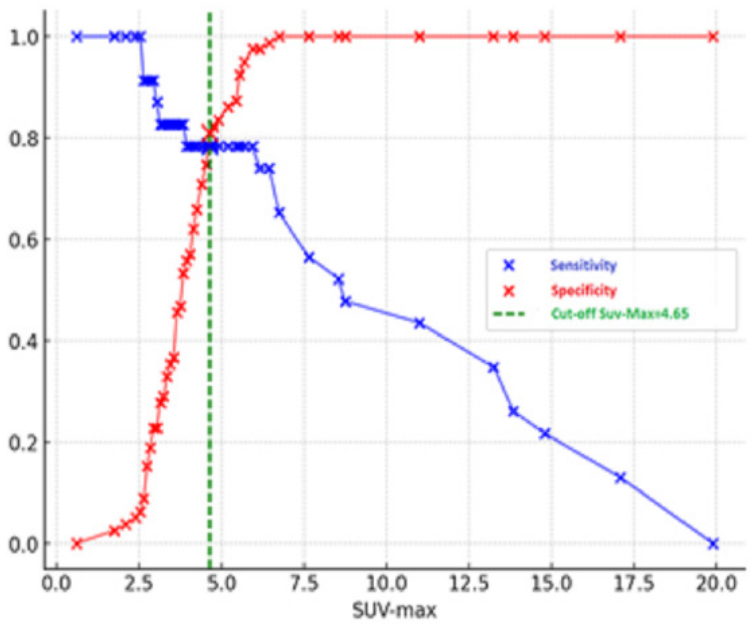
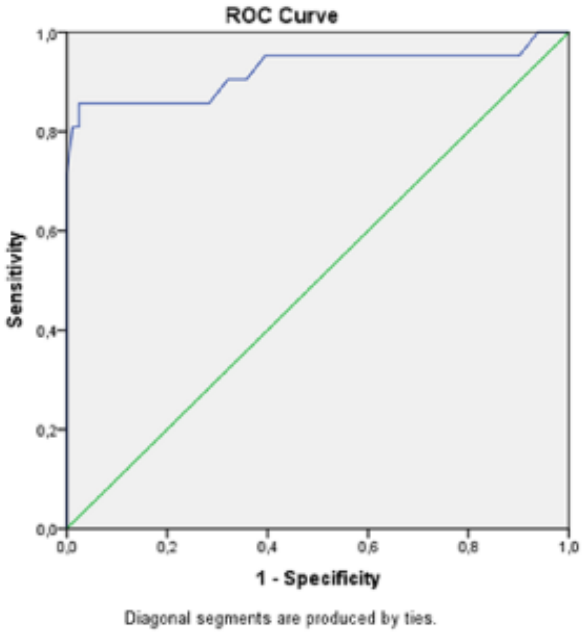
A. ROC Curve Analysis of the Relationship Between SUVmax and ER Status

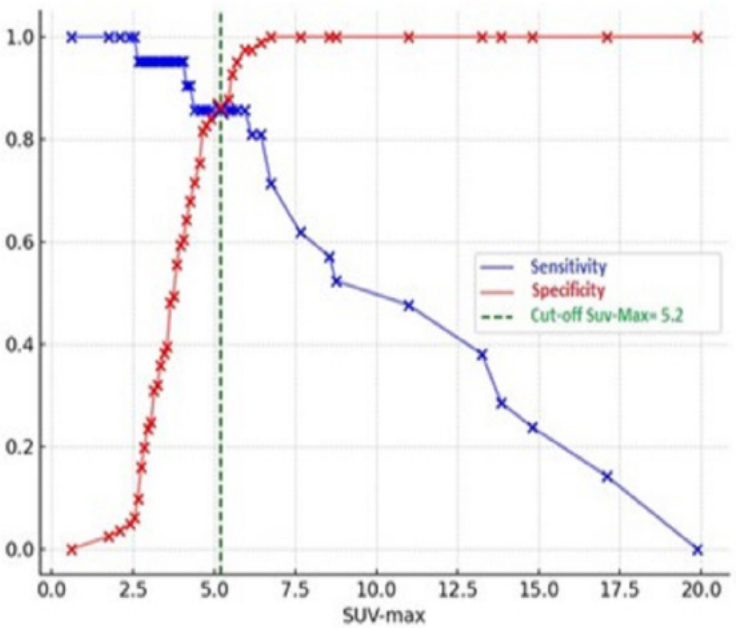




Variable	Sensitivity	Specificity	Area Under Curve	95% CI		Cut-off value	P value
				Lower Bound	Upper Bound		
ER negative	78.3%	81%	0.832	0.698	0.966	4.65	<0.001

B. ROC Curve Analysis of the Relationship Between SUVmax and PR Status





Variable	Sensitivity	Specificity	Area Under Curve	95% CI		Cut-off value	P value
				Lower Bound	Upper Bound		
PR negative	85.7%	86.4%	0.922	0.830	1.000	5.2	<0.001

Figure 1. ROC curve analysis of the relationship between SUVmax and ER, PR, HER2 Status, (b). ROC curve analysis of the relationship between SUVmax and PR status

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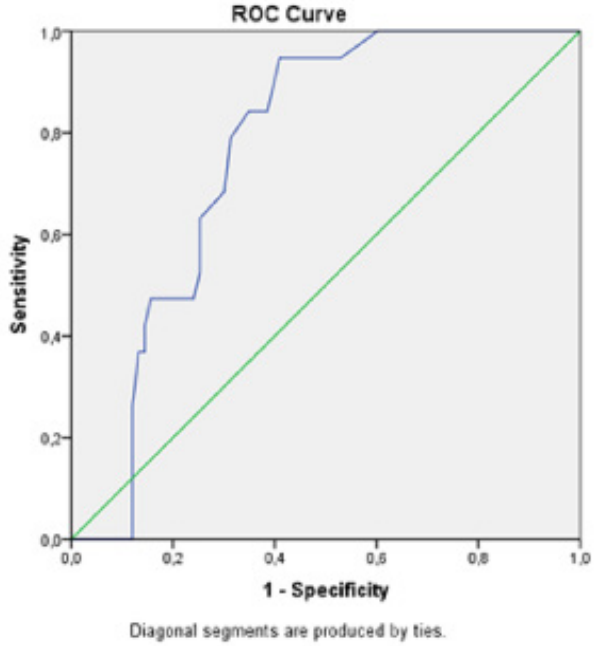
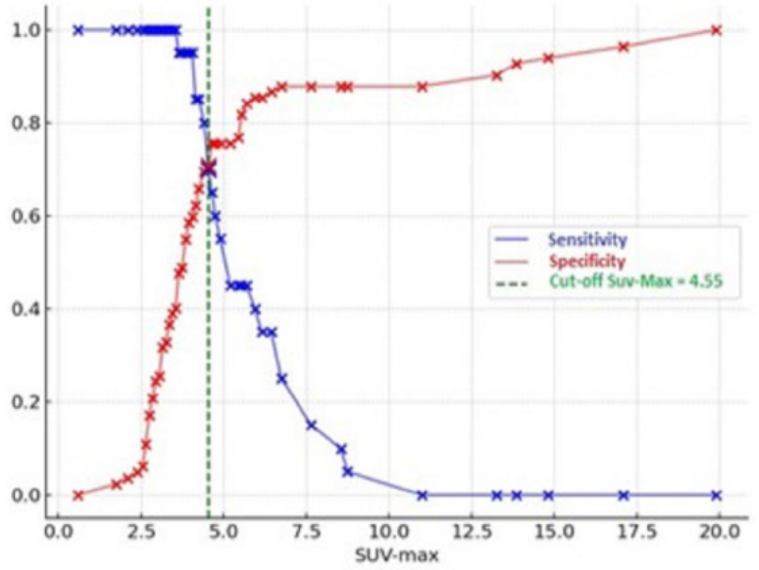
C. ROC Curve Analysis of the Relationship Between SUVmax and HER2 Status





Variable	Sensitivity	Specificity	Area Under Curve	95% CI		Cut-off value	P value
				Lower Bound	Upper Bound		
HER2 positive	70%	70.7%	0.766	0.676	0.857	4.55	<0.001

Figure 1. ROC curve analysis of the relationship between SUVmax and ER, PR, HER2 Status, (b). ROC curve analysis of the relationship between SUVmax and PR status

Table 3. Correlation and linear regression analysis between SUVmax Value and Ki-67 Proliferation Index, ER and PR expression percentages

Correlation Analysis of SUVmax Value					
Molecular subgroup parameters		**N**		**rho**	**p value**
1- Ki-67 proliferation index		102		0.638	<0.001
2- ER expression percentages		102		-0.610	<0.001
3- PR expression percentages		102		-0.598	<0.001
Linear Regression Analysis					
Dependent Variable	**Independent Variable**	**Beta**	**95% CI**	**t**	**p value**
1- SUVmax	1-Ki-67 proliferation index	0.730	0.09-0.131	10.692	<0.001
	2-ER percentages	-0.651	-0.081-0.05	-8.574	<0.001
	3-PR percentages	-0.617	-0.084-0.05	-7.841	<0.001

Discussion

Traditionally, breast cancer was conceptualized as a localized disease; however, contemporary understanding recognizes it as a heterogeneous entity arising from integrated histopathological, genetic, immunological, and molecular factors [14]. Particularly, the molecular classification system developed by Perou et al. has been fundamental in understanding heterogeneity in breast cancer biology. This molecular framework has shown that despite morphological resemblances, distinct tumor subtypes display marked prognostic differences and critically affect treatment decisions concerning chemotherapy and hormonal interventions. Numerous published investigations have explored relationships between molecular subtypes and various demographic,

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histopathological, immunological or clinical parameters [15]. The current investigation focused on evaluating relationships between SUVmax obtained through 18F-FDG PET/CT and breast cancer molecular subtypes. These insights may improve tumor heterogeneity understanding and guide clinical decision-making. This significance derives from the breast being a complex organ encompassing not only aesthetic and lactational roles but also numerous histopathological, biological and immunological processes. This multifaceted structure contributes to breast cancer biological diversity and highlights personalized treatment approach necessity.

In breast malignancies, 18F-FDG PET/CT functions as a complementary imaging modality across various clinical scenarios including advanced disease staging, internal mammary, supraclavicular or mediastinal lymph node involvement identification, distant organ metastasis evaluation, neoadjuvant therapy response monitoring and recurrence detection. Nevertheless, current international guidelines do not support routine PET/CT utilization in early-stage breast malignancies (T1–T2, N0). NCCN (National Comprehensive Cancer Network) and ESMO (European Society for Medical Oncology) guidelines indicate that PET/CT is unnecessary in early-stage patients owing to low systemic spread risk. They advocate its use only as a complementary imaging technique in advanced local disease (e.g., T3–T4 and/or N2–N3) or biologically aggressive subtypes including triple-negative and HER2-positive malignancies [8,9].

PET/CT diagnostic accuracy for breast malignancies depends on tumor subtype and size, with reported sensitivity ranging from 48%–96% and specificity spanning 73%–100% [16]. Therefore consistent with current guidelines and published literature, PET/CT is not routinely utilized for early-stage operable breast cancer patients in our institution. All patients enrolled in our investigation were either in advanced local stages scheduled for neoadjuvant therapy or belonged to high biological risk categories.

Our neoadjuvant therapy referral criteria were determined based on tumor molecular subtype and disease stage. For Luminal-type malignancies, primary selection parameters were tumor size exceeding 5 cm or presence of more than three axillary lymph node metastases identified radiologically or pathologically. Conversely irrespective of lymph node status, neoadjuvant therapy was indicated for isolated HER2-positive patients with malignancies larger than 1.5 cm and for triple-negative patients with tumors exceeding 1 cm. According to these parameters, molecular subtype distribution among our 102 study patients was: Luminal A, 31.4%; Luminal B HER2-negative, 39.2%; Luminal B HER2-positive, 11.8%; isolated HER2-positive, 7.8%; and triple-negative, 9.8%. Similar results have been documented in large-scale literature investigations examining molecular subtype distribution and neoadjuvant therapy response. For example in a multicenter pooled analysis by von Minckwitz et al. involving 5,161 patients, molecular subtype distributions were: ER and/or PR-positive/HER2-negative, 44%; ER and/or PR-positive/HER2-positive, 21%; HER2-positive/ER and PR-negative, 11%; and triple-negative, 24% [17]. In our investigation, the combined proportion of ER and/or PR-positive/HER2-negative subtypes (Luminal A and Luminal B HER2-negative) reached 70.6% notably exceeding the 44% documented by von Minckwitz et al. Conversely, HER2-positive and triple-negative subtype proportions were lower in our cohort. This discrepancy likely reflects various factors including patient selection parameters, ethnic and genetic variations, regional treatment practices and socioeconomic and demographic variables. Including only patients scheduled for neoadjuvant therapy may have created selective representation among subtypes and contributed to higher ER and/or PR-positive subtype proportions. Similarly a Japan-based investigation documented 7.9% triple-negative patients, whereas a Spanish investigation documented 9.6% [18]. Our investigation's subtype proportions generally correspond with international literature distributions. Subtype distribution differences likely arise from population-specific immunogenetic variations and disparities in socioeconomic status and educational levels.

In our investigation, we examined relationships between ER, PR, HER2 and Ki-67 proliferation index—which constitute molecular classification foundations—and SUVmax values detected on 18F-FDG PET/CT. Particularly, ER and PR positivity represent significant prognostic and predictive parameters in breast malignancies. This significance is reinforced by the observation that hormone receptor-positive malignancies respond better to endocrine therapy and generally correlate with more favorable prognosis. Literature has shown that estrogen binds to receptors in tumor cells thereby stimulating cellular proliferation [19]. In our investigation, SUVmax values were significantly lower in both ER-positive and PR-positive patients. Hormone receptor positivity appears to reduce tumor metabolic activity resulting in decreased SUVmax values as measured by 18F-FDG uptake. This relationship received additional statistical support from the significant negative correlation observed between ER/PR percentages and SUVmax values. Our regression analysis showed that each unit increase in hormone receptor positivity correlated with significant SUVmax level reductions. While most literature investigations report this relationship qualitatively, our investigation reinforced it quantitatively by presenting correlation coefficients and regression parameters. Our results also correspond with the investigation performed by Lee et al. in Korea. That investigation documented SUVmax levels in ER- and PR-positive patients to be markedly lower compared with hormone receptor-negative patients [20].

HER2 is a transmembrane receptor glycoprotein with tyrosine kinase activity that substantially contributes to cellular proliferation regulation and apoptosis resistance. Its overexpression represents a major causative factor in breast cancer development and progression [21]. In the current investigation, a significant positive relationship was identified between HER2 expression and SUVmax values obtained from 18F-FDG PET/CT. Patients with HER2-positive malignancies exhibited higher

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SUVmax measurements than those with HER2-negative disease. Similarly in the literature, Oner et al. documented a significant positive correlation between HER2 expression and SUVmax values. Nevertheless, in that investigation, this relationship achieved significance only in univariate analysis, and multivariate analysis did not demonstrate an independent HER2 effect on SUVmax [22].

Ki-67, a nuclear protein associated with cellular proliferation, expresses across active cell cycle phases (G1, S, G2, and M) but remains absent in resting (G0) cells. Its expression terminates upon mitosis completion. Therefore, Ki-67 proliferation index functions as a significant biomarker reflecting tumor cell proliferative activity and expresses as the proportion of proliferating to non-proliferating cells [23]. Elevated Ki-67 levels indicate increased cellular proliferation and generally correlate with more aggressive biological characteristics and poorer prognosis. Our results demonstrated a significant positive correlation between Ki-67 index and 18F-FDG PET/CT SUVmax levels consistent with the trend noted in HER2-positive cases. Statistical analysis showed that each one-unit increase in Ki-67 index correlated with an average 0.730-unit SUVmax increase. Literature review reveals investigations supporting our results; however in most previous investigations, Ki-67 was categorized only as positive/negative or high/low (e.g., using a 14% or 15% cut-off value). For instance, Abubakar et al. documented that patients with high Ki-67 index exhibited significantly elevated SUVmax values [24]. Similarly Alcin et al. classified Ki-67 into two groups as >15% and <15% [25]. In contrast, in our study we evaluated Ki-67 as a continuous variable and quantitatively assessed its correlation with SUVmax demonstrating this relationship statistically through regression analyses.

Evaluating all these parameters guided us to investigate relationships between molecular subtypes and 18F-FDG PET/CT SUVmax values. In our investigation, statistically significant differences were observed between breast cancer molecular subtypes and 18F-FDG PET/CT SUVmax levels. This difference primarily originated from the substantially higher SUVmax values observed in the triple-negative cohort compared with hormone receptor-positive cohorts as well as elevated metabolic activity seen in the isolated HER2(+) cohort relative to hormone-positive subtypes. Conversely, no significant difference in SUVmax values emerged between Luminal B HER2(-) and Luminal B HER2(+) cohorts. These results indicate that the primary determinant of elevated 18F-FDG PET/CT SUVmax levels is the malignancy's classification as triple-negative or isolated HER2(+) molecular subtype.

The primary limitation of this investigation lies in its retrospective nature and single-institution design, further influenced by including only patients who received neoadjuvant therapy and underwent 18F-FDG PET/CT before surgery. This circumstance resulted in a relatively limited sample size and some patients continued their surgical intervention at different institutions after completing neoadjuvant therapy. These cases were excluded from the investigation because surgery or follow-up was not completed at our institution.

Conclusion

Breast malignancies represent highly heterogeneous diseases shaped by morphological, histopathological, genetic, immunological and molecular factor interactions. This heterogeneous structure necessitates identifying molecular subtypes that determine disease course, treatment response and prognosis as well as investigating their associations with clinical and radiological parameters. In our investigation, relationships between SUVmax values obtained from 18F-FDG PET/CT and molecular subtypes, along with their defining markers such as ER, PR, HER2, and Ki-67, were clarified.

Our results demonstrated that hormone receptor-negative malignancies (triple-negative and isolated HER2-positive) exhibit substantially higher SUVmax values compared with hormone receptor-positive malignancies (Luminal A and Luminal B). Furthermore, analysis revealed a statistically significant positive relationship between Ki-67 index and SUVmax whereas ER and PR expression levels exhibited significant negative relationships. ROC analysis-derived cut-off values indicated that SUVmax levels could predict hormone receptor status. These results suggest that breast cancer biological characteristics are also reflected in imaging features, indicating that 18F-FDG PET/CT may have potential not only for staging but also for evaluating tumor biology.

The SUVmax value should be regarded in the clinical context not merely as a quantitative measurement but as a parameter reflecting tumor biological dynamics. These results indicate that PET/CT should assume a more comprehensive role in multidisciplinary breast cancer care. The demonstration that aggressive subtypes exhibit higher metabolic activity suggests that this modality could function as an adjunctive tool in prognostic evaluation. To substantiate these results and enable their translation into clinical settings, additional prospective research with larger cohorts is warranted.

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Conflict of Interests
The authors declare that there is no conflict of interest in the study.

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Ethical Approval
The study received ethical approval from the Ethics Committee of the Health Science University Gülhane Training and Research Hospital (Decision Nb: 13-1 / Date: 02.07.2025).

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