Original Article Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.2023102175-186

Association of Standardized Uptake Values of Primary Breast Cancer on [18F]FDG PET/CT With Immunohistochemistry and Molecular Subtypes

Nishita Goyal[a], P. Gokulakrishnan[a], Arunan Murali[a], Leena Joseph Dennis[b], Rajeswaran Rangasami[a], Bhawna Dev[a*]

[a]*Center of Excellence in Radiology and Imaging Sciences (CERIS), Sri Ramachandra Institute of Higher Education and Research, Porur, Chennai, India*

[b]*Department of Pathology, Sri Ramachandra Institute of Higher Education and Research, Porur, Chennai, India*

ARTICLE INFO

Received:
16 January 2023
Revised:
9 March 2023
Accepted:
10 March 2023

Keywords:
breast cancer, molecular subtype, 18F-FDG, immunohistochemistry, Positron-Emission Tomography, metastasis

ABSTRACT

Background: The prognostic factors for breast cancer include pre-treatment staging, nodal and distant metastasis, hormone receptor status, ki67 index, and molecular subtype. For adequate treatment, [18F]FDG PET/CT is now being used to prognosticate the course and response of treatment in breast cancer patients. Our study aims to find the association between the metabolic activity of primary breast tumors as PET/CT SUV uptake and prognostic factors such as ER/PgR/Her2neu receptor status, molecular subtypes, ki67 labelling index, and nodal/distant metastasis.

Methods: A retrospective observational study at our tertiary care institute included 228 breast cancer patients from March 2017 to April 2021. Pre-treatment PET/CT imaging was done. The immunohistochemical analysis was performed on a biopsy/surgical specimen to determine the molecular subtype of breast cancer. Further, statistical analysis was performed to find the association between PET/CT findings with immunohistochemistry and, thus, molecular subtypes of breast cancers.

Results: Significantly higher SUV max was seen in tumors with ER-negative (Mean SUVmax-11.6; P-value=0.002), PgR negative (Mean SUVmax-11.1; p value-0.0005), triple-negative receptor status (Mean SUVmax-13.7; P-value=0.004) and high Ki67 index (P-value=<0.01). Further Luminal A (Mean SUV max:6.0±5.5 & Median SUV max:3.9±3.6) and Luminal B (Mean SUV max: 8.9±4.9 & Median SUV max:7.6±4.0) subtypes showed lower SUV max as compared to Her2neu (Mean SUV max: 9.4±5.5 & Median SUV max:8.6±6.2) and TNBC (Mean SUV max: 13.7±12.4 & Median SUV max:10.0±7.6) subtypes. However, only a weak correlation was found for axillary nodal spread p-value – 0.02) and no significant correlation was seen for Her2 receptor status (Mean SUVmax-9.7; p value-0.178) and distant metastasis (P-value=0.26).

Conclusion: The values for different molecular subtypes can be used as Mean SUV or Median SUV uptake. However, owing to data skewing in practical scenarios, we suggest the use of median values with interquartile range for predicting the molecular subtypes of breast cancer on PET/CT imaging: Luminal A – Median SUV – 3.9 (IQR – 3.6); Luminal B – Median SUV – 7.6 (IQR – 4.0); Her2neu Enriched – Median SUV 8.6 (IQR - 6.2); Triple-negative breast cancer - Median SUV 10.0 (IQR - 7.6).

***Address for correspondence:**
Dr. Bhawna Dev, MD, DNB (Radio diagnosis)
Professor, Centre of Excellence in Radiology and Imaging Sciences (CERIS), Sri Ramachandra Institute of Higher Education and Research, Porur, Chennai.600116, India.
E-mail: bhawnadev@gmail.com,

INTRODUCTION

The prognostic factors for breast cancer include pretreatment staging, nodal and distant metastasis, histopathological type, hormone receptor status, ki67 proliferation index, and molecular subtypes. For

adequate treatment, staging and metastatic workup are two important considerations. Histopathological examination (HPE) and immunohistochemistry (IHC) markers are considered the gold standard for diagnosing breast cancer histology and further receptor status. Hormone receptors for breast cancer are the Estrogen receptor (ER), Progesterone receptor (PgR), and Her2neu receptor (Her2), which are further used to characterize molecular subtypes as Luminal A, Luminal B, Her2 Enriched, and Triple negative.

Knowledge of the receptor status and imaging characteristics like size, morphology, and vascularity is vital in guiding the treatment plan. Previously, the use of 18- Fluorodeoxyglucose positron emission tomography / computed tomography ([18F]FDG PET/CT) was limited to pre-treatment, interim, and post-treatment response assessment for cancers. However, the role of PET/CT can be expanded to predict the molecular subtype based on PET/CT uptake values. In the current era, PET/CT is used to prognosticate the affected individuals by correlating it with the HPE and IHC markers.[1,2]

This study aims to find the association between metabolic activity of primary tumors as Standardized uptake value (SUV) on PET/CT and prognostic factors such as ER, PgR, and Her2neu receptor status, molecular subtypes, ki67 index, and nodal/distant metastasis. This correlation will help in the management of patients concerning treatment planning, prediction of response, survival, and recurrence rates of breast cancer.

METHODS

Under a waiver of consent by the institutional ethics committee, a retrospective observational study was done at the Department of Radio-diagnosis in our tertiary care institute. The study recruited 228 breast cancer patients from March 2017 to April 2021. The cases under study were either pathologically proven cases of breast cancer who were referred to the radiology department for whole-body PET/CT imaging or were suspicious on imaging for breast cancer and later underwent biopsy/surgical management.

Patients who were undergoing primary breast cancer evaluation with PET/CT (i.e., with no prior treatment for presenting breast complaints) and those with complete IHC panels were included in this study. Patients who obtained any form of treatment before undergoing PET/CT investigation or those without required IHC data were excluded.

All the PET/CT imaging was done using Siemens Biograph Horizon TRUE V PET/CT scanner and Syngo.via version VB30A software. In all the studies, 18F-Fluorodeoxyglucose (dose: 185-555MBq) radiotracer and Iohexol-350mg/dl (dose: 1.5mg/kg) IV contrast agents were used. Post IV contrast administration low dose whole body CT scan with 16 slice CT scanner was performed to acquire slices with 5mm thickness which were reconstructed into 1.5mm thickness slices. Approximately, 1-2 minutes was the routine time to acquire the CT data. PET count acquisition was done in 6 to 7 beds of ~20cm length with exposure time lasting ~2 minutes for each. Detector sensitivity was 7.6cps/kBq at the rate of 435keV with a resolution of 4.2mm. The routine time taken for PET count acquisition was 7-8 minutes. The PET and CT image fusion was done by the software (syngo.via) in the Siemens PET/CT workstation. For measuring the [18F]FDG uptake in a primary lesion, lymph nodes, and distant metastasis, a region of interest (ROI) iso contour was drawn, including the entire lesion. The system calculated and displayed the SUV max of the lesion under consideration. The staging was done according to the AJCC Staging Manual (8th edition).

Histological assessment and interpretation of data were done, and an appropriate block was chosen. Sections of 3µ thickness were cut and immunohistochemical staining was performed using monoclonal antibodies (MAB) at a dilution of 1:100 to the Estrogen Receptor (ER) {rabbit MAB – Alpha (clone EP1) (BioGenex, CA)}, PgR {mouse MAB to PgR (clone PR88) (BioGenex, CA)}, Her2 {rabbit MAB (BioGenex, CA)} and Ki67% {mouse MAB (clone MIB-1) (BioGenex, CA)}. Tumors with >1% nuclear staining were defined as ER and PgR positive (+). Tumors with 2+/3+ positivity were defined as Her2 positive and confirmed by FISH (Fluro in-situ Hybridization). For Ki67%, scoring was done relatively as a percentage of tumor cells positivity with a cut-off of 15%. St. Gallen International Expert Consensus on the primary Therapy of Early Breast Cancer 2011 was used to define the molecular subtypes.

The collected data were analyzed with IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp). Descriptive statistics frequency analysis, and percentage analysis were used for categorical variables, and the mean and standard deviation (SD) were used for continuous variables. SUV max differences were calculated by the Kruskal-Wallis test. Spearman's rho was used to Correlate the Ki-67 index and SUV max. Unpaired sample t-test was used to find the significant difference between the bivariate samples in independent groups. For skewed data, the normality of data was verified with Shapiro-Wilk's Test. Median values with interquartile range (IQR) were also calculated for the data. For multivariate analysis, the one-way ANOVA with Tukey's Post-Hoc test was used. In the above statistical tools, the probability value 0.05 was considered significant.

RESULTS

The mean SUV uptake values were found to be significantly higher for ER/PgR negative and triple negative IHC receptor status. However, no significant association was found for isolated Her2neu receptor status (P-value = 0.17 > 0.05) (Table 1).

A significant association was found for a higher Ki67 index (>15%) with higher [18F]FDG uptake (P<0.001). (Table 1).

Table 1. Mean SUV max with SD & Median SUV max with IQR for each receptor status and Ki 67% proliferative index (with 15% as the cut-off).

Receptor Status		No of cases	Percent-age	Mean SUV max	SD	P-value*	Median SUV max	IQR	P-value*
ER	Positive	137	60.1	7.88	5.37	0.002	6.2	4.8	<0.001
	Negative	91	39.9	11.60	10.04		9.6	7.5	
PgR	Positive	108	47.4	7.37	5.21	0.0005	6.6	5.0	<0.01
	Negative	120	52.6	11.15	9.18		9.3	7.5	
HER2	Positive	80	35.1	8.57	4.51	0.178	7.9	5.2	<0.68
	Negative	148	64.9	9.79	9.06		7.1	6.6	
Triple Negative	TN	49	21.5	13.73	12.43	0.004	10	7.1	<0.01
	Non-TN	179	78.5	8.17	5.37		7.6	5.2	
Ki 67 index	<15%	42	18.5	6.0	2.6	<0.01	4.8	5.7	<0.001
	>15%	186	81.5	10.6	6.4		7.7	5.8	

*P<0.05=significant

ER: Estrogen receptor, PgR: Progesterone receptor, HER2: Human epidermal growth factor Receptor 2, TN: Triple negative, N-TN: Non-triple negative, Ki 67 index: Tumor proliferation index, Mean SUV: Mean Standardized Uptake value (maximum), SD: Standard deviation, Median SUV: Median Standardized Uptake value(maximum), IQR: Inter quartile range.

We considered median values with inter-quartile range best suited for skewed data. It revealed similar results for statistical significance (P<0.001) with few variations in absolute value. In our experience, the difference between the close values of Luminal B and Her2neu molecular subtype was better delineated with median values.

A significant difference (P< 0.001) was found in the mean SUV uptake values to differentiate Luminal A, Luminal B, Her2neu enriched, and TNBC molecular variants of breast cancer (Table 2).

Table 2. Mean SUV max with SD and Median SUV max with IQR for each molecular subtype of breast cancer

Molecular subtype status	No. of cases	Percentage	Mean SUV max	SD	95% Confidence Interval for Mean		Median SUV max	IQR	P-value
					LB	UB			
Luminal A	52	22.8	6.0	5.5	4.5	7.6	3.9	3.6	<0.001
Luminal B	90	39.5	8.9	4.9	7.9	9.9	7.6	4	<0.001
Her 2 neu enriched	37	16.2	9.4	5.5	7.6	11.2	8.6	6.2	<0.001
Triple-negative	49	21.5	13.7	12.4	10.2	17.3	10	7.6	<0.001

*P<0.05 = significant association

Mean SUV: Mean Standardized Uptake value (maximum), SD: Standard deviation, Median SUV: Median Standardized Uptake value(maximum), IQR: Inter quartile range.

The mean SUV max uptake for nodal metastasis was found to be higher in patients with Her2 enriched and TNBC variants compared to the Luminal A and B subtypes (Table 3). On multiple intergroup comparisons of mean SUV max uptake for nodal metastasis, statistical difference was found between Luminal A versus TNBC (P= 0.02). However, no statistical difference was found for Luminal A and Luminal B (P=0.7), Luminal A versus HER2 (P=0.06), Luminal B versus HER2 (P=0.18), and TNBC versus Luminal B (P= 0.07) and HER2 (P= 0.9)

The median SUV max uptake for distant metastasis was almost similar in all the molecular subtypes. On multiple intergroup comparisons of mean distant metastasis SUV max uptake, no statistical difference could be found (P-value- 0.26 >0.05) between the various molecular subtypes of breast cancer (Table 3).

DISCUSSION

According to our study, we found that as the [18F]FDG uptake increases in the primary breast lesion, it tends to become more aggressive pathologically. In a study conducted by Brock *et al.*[1], it was found that tumors with high [18F]FDG uptake are more aggressive and therefore [18F]FDG uptake on PET/CT scans can be utilized for assessing the

prognosis of the disease. According to the study conducted by Oshida *et al.*,[2] the lesions with lower SUV uptake have a better disease-free survival rate, which fits the criteria of a better prognosis of breast cancer.

Table 3. Mean SUV max with SD and Median SUV max with IQR for nodal and distant metastasis in different molecular subtypes.

Category	Number of cases	Nodal metastasis		Distant metastasis	
		Mean SUV max uptake	SD	Mean SUV max uptake	SD
Luminal A	52	3.01	3.923	1.832	4.364
Luminal B	90	4.608	4.012	1.967	3.851
Her 2 neu enriched	37	7.295	8.089	2.778	4.112
Triple-negative	49	6.441	6.151	3.085	5.114

Mean SUV: Mean Standardized Uptake value (maximum), SD: Standard deviation, Median SUV: Median Standardized Uptake value(maximum), IQR: Inter quartile range

ER receptor status and [18F]FDG uptake correlation

In studies conducted by Mauri *et al.*[3] and Clahsen *et al.*[4] ER positivity status was shown to have a higher disease-free survival rate in the affected patients. In the current study, we found a significant association of ER-negative status with increased [18F]FDG uptake on PET/CT scan (Table. 1) as was also demonstrated in studies conducted by Ekmekcioglu *et al.*[5], Kitajima *et al.*[6], Koolen *et al.*[7], Ueda *et al.*[8], Abubakar *et al.*[9], Groheux *et al.*[10], Mavi *et al.*[11], Osborne *et al.*[12], Keam *et al.*[13], Ugurluer *et al.*[14] and Dondi *et al.*[15] (Table 4). However, no significant association between ER-negative status and [18F]FDG uptake was found by Buck *et al.*[16], Heudel *et al.*[17], and Utech *et al.*[18] (Table 4).

PgR receptor status and [18F]FDG uptake correlation

The current study found a significant association between PgR negative hormone status with increased [18F]FDG uptake on PET/CT imaging (Table 1) which is in concordance with the results of Ekmekcioglu *et al.*[5], Kitajima *et al.*[6], Koolen *et al.*[7], Abubakar *et al.*[9], Groheux *et al.*[10], Ugurluer *et al.*[14], Dondi *et al.*[15] and Heudel *et al.*[17] (Table 4). In comparison to this, studies conducted by Buck *et al.*[16] (Table 4), Mavi *et al.*[11], and Keam *et al.*[13] did not find a significant association between PgR negative status and SUV max uptake in breast cancer patients.

HER2 gene overexpression and [18F]FDG uptake correlation

Koo *et al.*[19] stated that HER2-positive breast cancers are characterized by HER2 gene overexpression, which promotes tumor growth and progression. According to the study conducted by Osborne *et al.*,[12] Her2 overexpression is associated with poor prognosis and aggressive disease, which shows comparatively higher uptake of [18F]FDG as compared to ER and PR hormone-positive receptor status. Kitajima *et al.*[6] (P=0.0002) and Ueda *et al.*[8] (P=0.006) found a significant association between Her2 overexpression and increased [18F]FDG uptake (Table 4). As opposed to this, no significant association between the two factors could be determined by our study (Table 1) as well as studies conducted by Ekmekcioglu *et al.*[5], Koolen *et al.*[7], Abubakar *et al.*[9], Mavi *et al.*[11], Osborne *et al.*[12], Buck *et al.*[16], Berriolo-Riedinger *et al.*[20], Dondi *et al.*[15] and Keam *et al.*[13] (Table 4). Groheux *et al.*[10] suggested that HER2 has no major role to play in glycolysis, which can be a reason why its overexpression is not significantly associated with higher [18F]FDG uptake.

In a study conducted by Kumar *et al.*[21], no significant relationship was found between PET results and tumor type, Her2, and ER/PgR receptors.

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Table 4. The comparison between the current and previous studies conducted for receptor status, Ki67% index, and axillary and distant metastasis.

STUDY	SUV for ER	SUV for PgR	SUV for HER2	SUV for TNBC	SUV for Ki67%	SUV for Axillary Lymph node	SUV for Distant metastasis
CURRENT (Mean) (n=228)	ER+7.8 ER–11.6 p = 0.002	PgR+7.3 PgR-11.1 p < 0.0005	HER2+8.5 HER2-9.7 p = 0.178	Non-7.1 TN-10.1 p < 0.001	<15-6.0 >15-10.6 p < 0.01	Weak association p <0.05	No association p = 0.2
CURRENT (median) (n=228)	ER+6.9 ER–9.5 p = 0.001	PgR+6.6 PgR-9.2 p < 0.001	HER2+7.7 HER2-7.1 p < 0.86	Non-7.1 TN-10.1 p < 0.001	<15-4.8 >15-7.7 p < 0.001	Weak association p = 0.05	No association p = 0.05
Koolen BB *et al.* (n = 214)	ER+5.7 ER-9.1 p ≤ 0.0001	PgR+5.4 PgR-8.8 p ≤ 0.0001	HER2+6.2 HER2-7.1 p = 0.31	TN-10.8 p ≤ 0.0001 Non (HER2)-6.2 (ER+/HER2-)-5.5	<10-5.4 >10-8.2 p ≤ 0.001	No association p = 0.17	Ab-6.6 Pr-11.1 p ≤ 0.006
Ekmekciog lu *et al.* (n = 136)	ER+9.6 ER–12.5 p = 0.004	PgR+10. 2 PgR-10.3 p = 0.21	HER2+11.6 HER2-9.8 p = 0.17	Non-9.6 TN-13.9 p ≤ 0.001	<20-5.8 >20-10.5 p = 0.002	Ab-5.1 Pr-10.1 p < 0.001	-
Koo HR *et al.* (n = 552)	ER+4.9 ER-8.8 p ≤ 0.001	PgR+4.9 PgR-7.5 p ≤ 0.001	HER2+7.3 HER2-5.8 p ≤ 0.001		<14-5.4 >14-8.8 p < 0.001	Ab-5.5 Pr-6.8 p ≤ 0.001	
Ueda S *et al.* (n = 152)	ER+4.0 ER–6.4 p = 0.001	PgR+4.1 PgR-5.4 p = 0.04	HER2+6.2 HER2-4.0 p = 0.006	-	-	Ab-3.9 Pr-5.7 p = 0.002	-
Kitajima K *et al.* (n = 308)	ER+4.7 ER-7.0 p ≤ 0.001	PgR+4.4 PgR-6.2 p ≤ 0.0001	HER2+4.9 HER2-7.0 p = 0.0002		<14-3.7 >14-6.1 p ≤0.0001	Ab–4.1 Pr-6.7 p ≤ 0.0001	
Abubakar ZA *et al.* (n = 219)	Hormone Receptor +13.3 Hormone Receptor - 9.5 p ≤ 0.05		HER2+11.4 HER2-11.0 p = 0.64		Low-7.2 High-11.9 p ≤ 0.05	Ab –7.8 Pr –12.5 p ≤ 0.05	No association p = 0.086
Heudel P *et al.* (n = 45) (median)	ER+2.4 ER–7.0 p = 0.0005	PgR+2.2 PgR-6.0 p = 0.002	HER2+3.7 HER2-3.5 p = 0.93	Non-2.8 TN-7.0 p = 0.0005	-	No association p ≥ 0.05	-
Buck A *et al.* (n = 76)	No associatio n p = 0.41	No associatio n p = 0.34	No association p = 0.79	-	<20%-7.1 >20%-11 p ≤ 0.001	No association p = 0.9	-

(P<0.05 = significant association)

n = the number of cases taken in the study, ER+ = Estrogen receptor-positive, ER- = Estrogen receptor negative, PgR+ = Progesterone receptor-positive, PgR- = Progesterone receptor negative, HER2+ = Isolated Her2 neu receptor-positive, HER2- = Isolated Her2 neu receptor negative, Non- = Non-Triple negative receptor type, TN or TNBC = Triple negative receptor type, Ki67% = Ki 67 proliferation index, Ab = Number of cases with nodal/ distant metastasis absent, Pr = Number of cases with nodal/ distant metastasis present, P = P-value of significance for each factor calculated and provided by the respective study, Weak/no association = Weak or no association was found between the factors under consideration with P-value > 0.05.

compared to ER and PR hormone-positive receptor status. Kitajima *et al.*[6] (P=0.0002) and Ueda *et al.*[8] (P=0.006) found a significant association between Her2 overexpression and increased [18F]FDG uptake (Table 4). As opposed to this, no significant association between the two factors could be determined by our study (Table 1) as well as studies conducted by Ekmekcioglu *et al.*[5], Koolen *et al.*[7], Abubakar *et al.*[9], Mavi *et al.*[11], Osborne *et al.*[12], Buck *et al.*[16], Berriolo-Riedinger *et al.*[20], Dondi *et al.*[15] and Keam *et al.*[13] (Table 4). Groheux *et al.*[10] suggested that HER2 has no major role to play in glycolysis, which can be a reason why its overexpression is not significantly associated with higher [18F]FDG uptake.

In a study conducted by Kumar *et al.*[21], no significant relationship was found between PET results and tumor type, Her2, and ER/PgR receptors.

Luminal subtype and [18F]FDG uptake correlation

In the current study, significant differences were found in [18F]FDG uptake on PET/CT imaging for Luminal type A (Fig.1a,1b and 1c, Fig.2) and Luminal B (Fig.3a, 3b and 3c, Fig.4) molecular subtypes (p<0.001) (Table 2). These findings were in agreement with the studies conducted by Koolen *et al.*[7]**,** Abubakar *et al.*[9], and Kitajima *et al.*[6] who found significantly different [18F]FDG uptakes for Luminal A and B subtypes (Table 5). In contrast, according to the study conducted by Koo *et al.*[19], no significant differences were found in [18F]FDG uptake values between Luminal A and Luminal B subtypes (P=0.158 > 0.05) (Table 5). It has been pointed out in the literature by previous studies that since Luminal A and B subtypes have a lower [18F]FDG uptake, sometimes PET/CT can give a false negative result in this type of breast cancer and there is a possibility of missing out these lesions as suggested by Basu *et al.*[23]

Table 5. The comparison between current and previous studies regarding mean/ median SUV uptake values on PET/CT for different molecular subtypes with sample size (n) in each study.

Study	Luminal A	Luminal B – her2-	Luminal B – her2+	Her2 enriched	Triple-negative	P-value*
CURRENT (n = 228)	Mean SUV = 6.0 (n = 52)	Mean SUV=8.9 (n = 90)		Mean SUV = 9.4 (n = 37)	Mean SUV =13.7 (n = 49)	P ≤ 0.001
	Median SUV= 3.9 (n = 52)	Median SUV=7.6 (n = 90)		Median SUV =8.6 (n=37)	Median SUV =10.0 (n = 49)	P ≤ 0.001
Koo HR *et al.*(19) (n = 552)	Mean SUV = 4.69 (n = 334)	Mean SUV = 6.51 (n = 66)		Mean SUV = 7.44 (n = 60)	Mean SUV = 9.83 (n = 92)	P ≤ 0.001
Koolen BB *et al.*(7) (n = 214)	Median SUV = 6.3 (n = 14)	Median SUV=8.9 (n = 16)		Median SUV =6.3 (n=6)	Median SUV =13.3 (n = 18)	P ≤ 0.007
Kitajima *et al.*(6) (n = 308)	Mean SUV = 3.41 (n = 87)	Mean SUV = 5.17 (n = 111)	Mean SUV = 6.57 (n = 31)	Mean SUV = 7.55 (n = 26)	Mean SUV = 6.97 (n = 53)	P ≤ 0.05
Abubakar ZA *et al.*(9) (n = 219)	Mean SUV = 7.75 (n = 23)	Mean SUV = 10.01 (n = 90)		Mean SUV =11.27 (n = 45)	Mean SUV =15.2 (n = 55)	P ≤ 0.001
Bitencourt *et al.* (22) (n = 59)	SUV max = 3.5 (n = 17)	SUV max = 4.9 (n = 27)		SUV max = 4.8 (n = 5)	SUV max = 11.9 (n = 9)	P ≤ 0.006

*(p < 0.05 = significant association)
Mean SUV: Mean Standardized Uptake value (maximum) and Median SUV: Median Standardized Uptake value (maximum)

Her2-enriched subtype and [18F]FDG uptake correlation

The Her2-enriched subtype is associated with higher recurrence rates and mortality. The randomized control trial by Gianni *et al.*[24] concluded that targeted treatment with Trastuzumab monoclonal antibodies has increased the survival rates in such patients. In our study, we found a significantly increased [18F]FDG uptake (P<0.002) in Her2 enriched subtype (Fig. 5a, 5b and 5c, Fig. 6) in comparison to hormone receptor-positive subtypes (Table 2). Similar results (with higher uptake in Her 2 enriched subtype) were demonstrated by Ueda *et al.*[8] (P <0.001), Bitencourt *et al.*[22] (P <0.006)**,** Koolen *et al.*[7] (P <0.0001) and Keam *et al.*[13] (Table 5)**.** However, the study conducted by Abubakar *et al.*[9] showed no significant difference in the Her 2 enriched subtype (Table 5). In a study by Kitajima *et al.*[6]**,** the Her2 subtype had maximum [18F]FDG uptake (P =0.0002) followed by the triple-negative subtype (P =0.0003) (Table 5).

Triple-negative breast cancers (TNBC) subtype and [18F]FDG uptake correlation

According to Haffty *et al.*[25], TNBC is associated with the most aggressive clinical course and poor prognosis. In our study, we found that the primary pretreated cancers with very high [18F]FDG uptake (Fig. 7a, 7b, and 7c) correlated with TNBC subtypes on immunohistochemistry (Fig. 8) (Table 2). The findings of our study were supported by studies conducted by Basu *et al.*[23], Koolen *et al.*[7], Ekmekcioglu *et al.*[5], Bitencourt *et al.*[22], Groheux *et al.*[10] and Keam *et al.*[13] (Table 5). Koolen *et al.*[7] pointed out that the most beneficial role of PET/CT is in assessing the TNBC since they show high uptake. In a study conducted by Basu *et al.*[23], the percentage change in SUV uptake was calculated for TNBC versus non-TNBC, and 100% PET sensitivity was found for TNBC with increased [18F]FDG uptake when compared to the hormone receptor-positive subtypes.

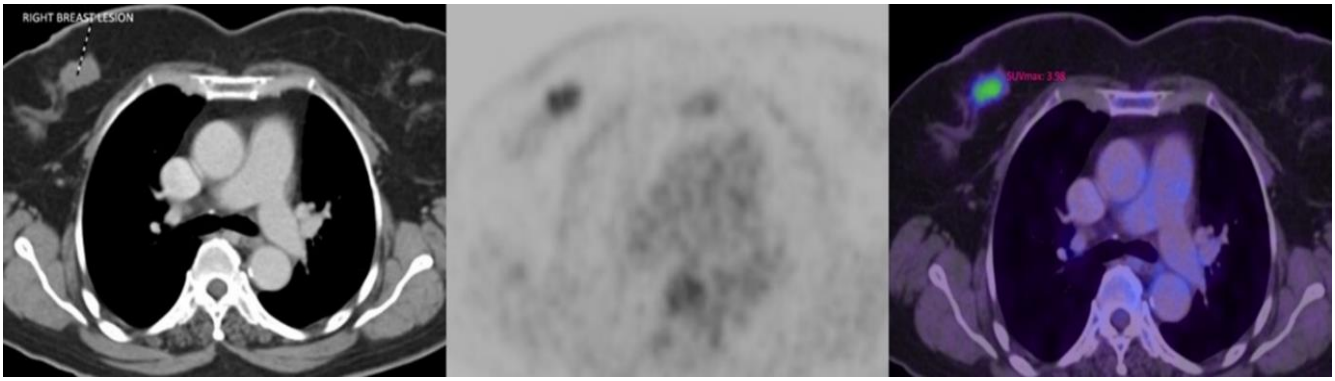

Figure 1. CT(1a), PET(1b), and fusion(1c) images with SUV max uptake of 3.98 in the right breast lesion.

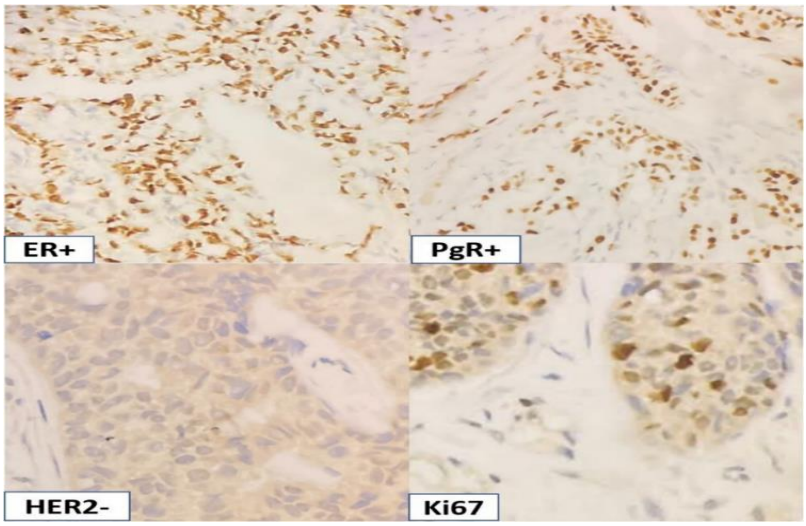

Figure 2. Luminal A Subtype on IHC – (From Upper left to right) (A, B) ER and PgR positive, (C) Her2 –Negative, (D)Ki67 <14%

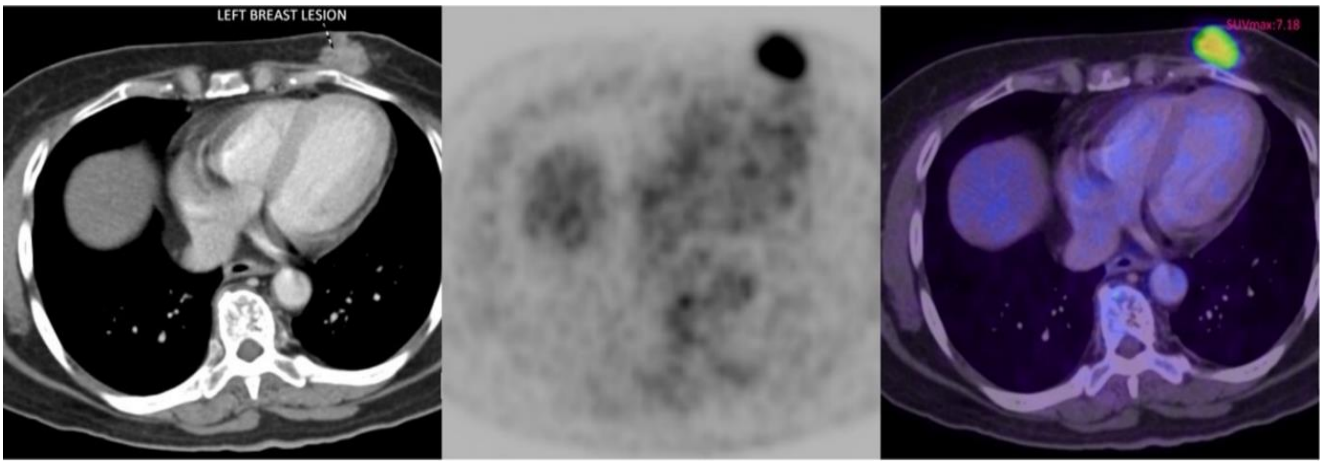

Figure 3. CT(3a), PET(3b), and fusion(3c) images with SUV max uptake of 7.18 in the left breast lesion.

Ueda *et al.*[8], Mavi *et al.*[11], and Basu *et al.*[23] demonstrated an increased [18F]FDG uptake in Her2neu and TNBC subtypes when compared to the hormone receptor-positive subtypes. Thus, as Basu *et al.*[23] suggested, PET/CT can be an important marker for tumor activity and treatment response in breast cancer patients.

Ki67 proliferation index and [18F]FDG uptake correlation

This is a proliferation marker for cancerous cells within the breast parenchyma. As the proliferation index value increases, the grade of carcinoma increases owing to the increased proliferation of malignant cells within the tissue. The cutoff for low and high ki67 has been variable in different studies (e.g., 14 / 15 or 20%) but in our studies, a value <14 % was taken to be a low index and a value ≥14 % as a high index. This marker has invariably shown a positive association with increased [18F]FDG uptake on PET/CT imaging including our study (Table 1) (Fig. 2,4,6 and 8) as well as studies by Ekmekcioglu *et al.*[5], Buck *et al.*[16], Koo *et al.*[19], Bitencourt *et al.*[22], Kitajima *et al.*[6], Koolen *et al.*[7], Shimoda *et al.*[26], Abubakar *et al.*[9] and Keam *et al.*[13] (Table 4).

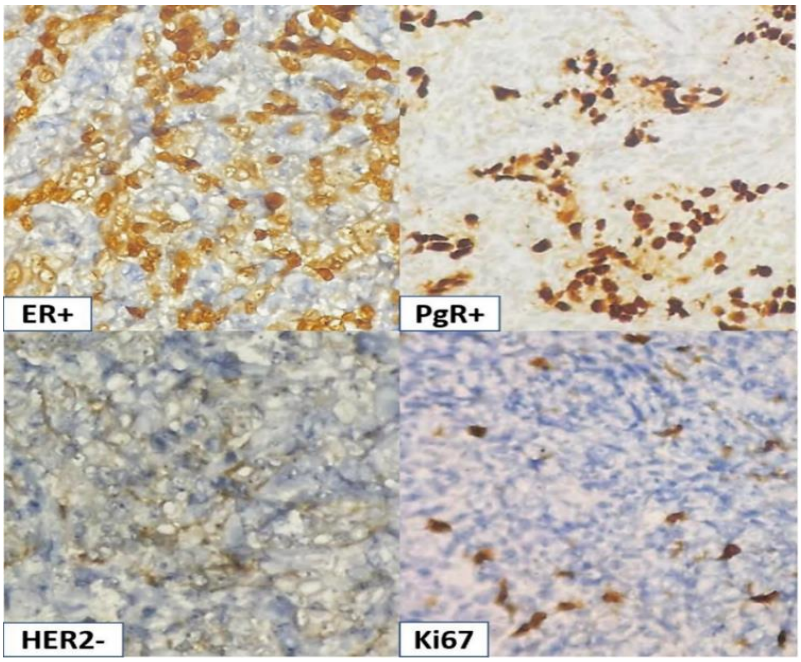

Figure 4. Luminal B Subtype on IHC – (From Upper left to right) (A, B) ER and PgR positive, (C)Her2 –Negative, (D)Ki67> 14%

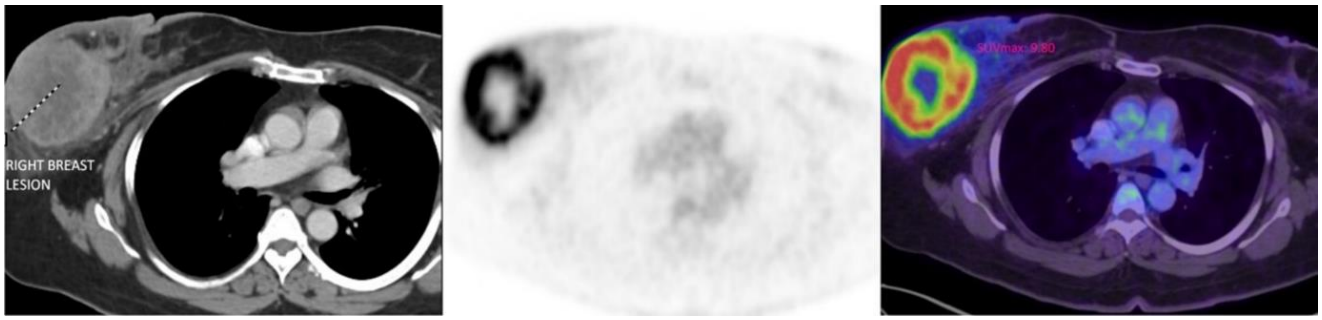

Figure 5. CT(5a), PET(5b), and fusion(5c) images with SUV max uptake of 9.80 in the right breast lesion.

Axillary lymph node involvement and [18F]FDG uptake correlation

Lymph node involvement is the prognostic factor with the most variable findings according to previous studies. The study by Heudel *et al.*[17] found no significant association between morphological and histological characteristics of axillary nodal involvement and the primary subtype of breast cancer (Table 4). However, increased sensitivity and specificity for the detection of nodal involvement were seen on PET/CT. Shimoda *et al.*[26] determined only a weak correlation between the two factors which corroborates with the findings of the current study (Table 3). According to Wahl *et al.*[27], [18F]FDG PET/CT has moderate accuracy for detecting axillary nodal involvement except for small and few axillary nodal metastases. Ekmekcioglu *et al.*[5], Abubakar *et al.*[9] Dondi *et al.*[15] and Crippa *et al.*[28]

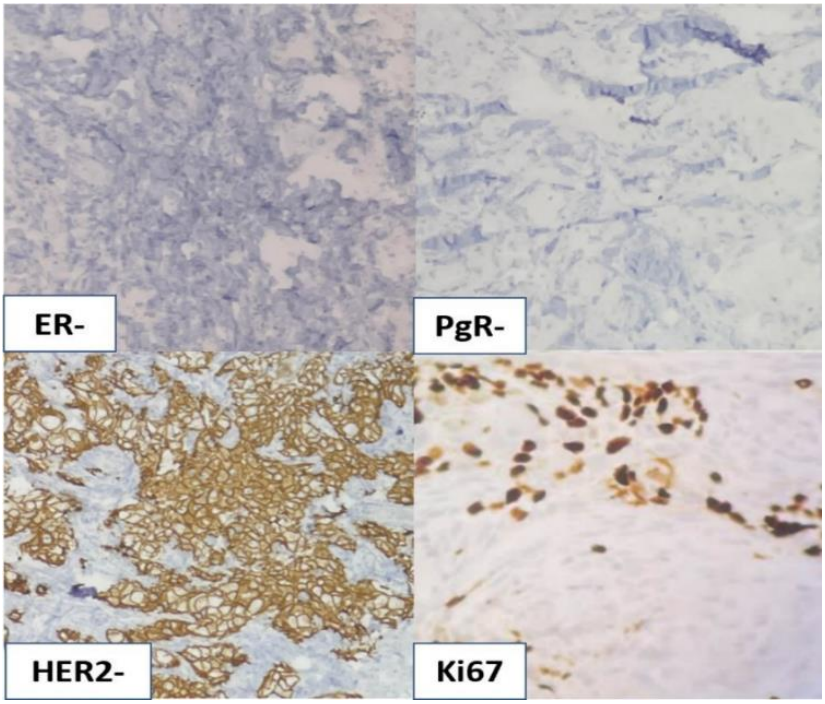

Figure 6. Her2neu Enriched Subtype on IHC– From Upper left to right) (A, B) ER and PgR – Negative, (C)Her2 – positive, (D)Ki67 ~ 40%

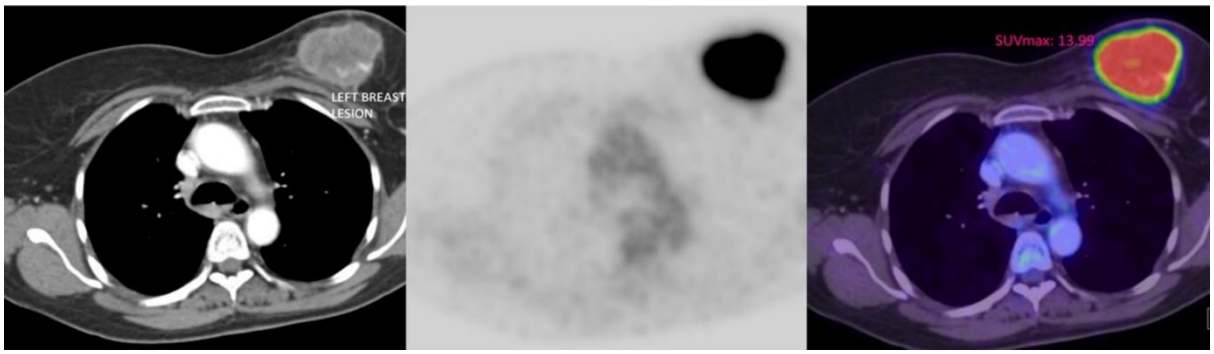

Figure 7. CT(7a), PET(7b), and fusion(7c) images with SUV max uptake of 13.99 in the left breast lesion.

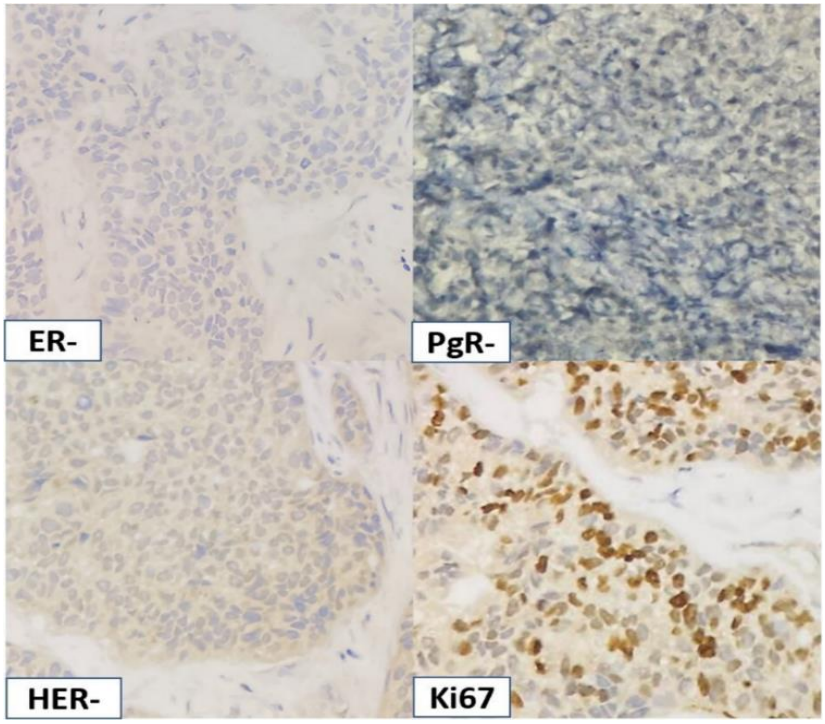

Figure 8. TNBC – (From Upper left to right) (A, B, C) ER and PgR Her2 – Negative, (D)Ki67 ~80 %

found a significant association between the high SUV max uptake and nodal enlargement whereas Koolen *et al.*[7] and Buck *et al.*[16] found no significant association between the two factors (Table 4). Kumar *et al.*[21] found no significant relationship between PET results with metastasis for sentinel or distant lymph nodes. Inoue *et al.*[29] found that the increased [18F]FDG uptake with nodal involvement is a predictor for poor prognosis in breast carcinoma. Veronesi *et al.*[30] concluded that PET imaging has high specificity, so patients with PET-positive axilla should have an axillary lymph node dissection rather than a sentinel node biopsy for axillary staging similar to the results of the study by Heudel *et al.*[17] However, due to the low sensitivity of [18F]FDG PET/CT for axillary metastases, PET-negative axillae should undergo sentinel node biopsy, which is also supported by Heusner *et al.*[31]

Distant metastasis and [18F]FDG uptake correlation

Few studies have considered and commented on the correlation between [18F]FDG uptake in distant metastasis involvement along with primary breast cancers. In our study, we found that distant metastasis has no significant association with a higher mean SUV max uptake of the primary breast lesion (P >0.05) (Table 3). These results are in concordance with the study conducted by Abubakar *et al.*[9], in which no significant association was seen between distant metastasis and increased FDG uptake (n = 219, P = 0.086) (Table 4). A study conducted by Dondi *et al.*[15] stated that 2 out of 46 cases had distant metastasis on PET/CT imaging with higher SUV max. However, the P -value was 0.2 (insignificant). In contrast, the study conducted by Koolen *et al.*[7] suggested that metastasis is seen in patients with ER-negative status and higher grades of primary breast cancer (n=214, P <0.006) (Table 4). However, further studies are required to establish a more confident correlation between the two factors.

CONCLUSION

In conclusion, significantly higher SUV max was seen in tumors with ER, PgR negative, triple negative receptor status, and high Ki67 index which is likely to predict poor prognosis in the patient. However, only a weak correlation was found for axillary nodal spread and no significant correlation was seen for distant metastasis.

The values for different molecular subtypes can be calculated and used as Mean or Median SUV uptake. However, owing to data skewing in practical scenarios, we suggest the use of median values (with interquartile range) can be applied for predicting the molecular subtypes of breast cancer on PET/CT Imaging.

Luminal A – Median SUV – 3.9 (IQR – 3.6)

Luminal B – Median SUV – 7.6 (IQR – 4.0)

Her2neu Enriched – Median SUV 8.6 (IQR - 6.2)

Triple-negative breast cancer - Median SUV 10.0 (IQR - 7.6)

ETHICAL CONSIDERATIONS

This study was approved by the institutional ethics committee of Sri Ramachandra Institute of Higher Education and Research. Oral consent was obtained from patients and their relatives (IEC number of approval: CSP-MED/17/NOV/40/144).

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ACKNOWLEDGEMENTS

I would like to acknowledge my parents and brothers for their constant guidance and moral support and my late grandmothers for their blessings.

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How to Cite This Article

Goyal N, Gokulakrishnan P, Murali A, Dennis LJ, Rajeswaran R, Dev B. Association of Standardized Uptake Values of Primary Breast Cancer on [18F]FDG PET/CT With Immunohistochemistry and Molecular Subtypes . Arch Breast Cancer. 2023; 10(2): 00-00.
Available from: https://www.archbreastcancer.com/index.php/abc/article/view/668