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IMMUNOHISTOPHENOTYPING AND ^{18}F-FDG PET-CT IN CHARACTERIZING MALIGNANT BREAST TUMORS: PRELIMINARY RESULTS

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Abstract – *Objective:* *Malignant breast tumors are associated with a poor prognosis. Accurate tumor localization and characterization of the disease phenotype may avert inappropriate futile surgery and toxic treatment. This study evaluated the roles of standardized uptake value (SUVmax) and flurodeoxygenase (FDG) and immunohistochemical markers in assessing malignant breast tumors.*

Patients and Methods: *This was a prospective study of 21 consecutive patients who underwent ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) prior to treatment. Tissue biopsies were sought from patients with BIRADS 4/5 score on mammogram. Tumor SUVmax ^{18}F-FDG PET-CT was assessed for potential correlation with the histological and immunohistochemical categories.*

Results: *We investigated 21 patients (18 malignant, 3 benign) with a mean age of 54.48 ± 12.1 years. In the immunohistochemical categorization, tumors were HER positive (42.86%), HER negative (42.86%) and benign (14.29%). The sensitivity, specificity (on a per patient and per lesion basis), positive predictive value and negative predictive value for the primary lesion by CT and 18F-FDG PET-CT were 82.3%, 20%, 77.8%, 25% (on per patient basis); 88.2%, 25%, 88.3%, 66.7% (on per lesion basis); and 100%, 100%, 100%, 100% (on per patient basis); 100%, 75%, 94.1%, 100%, respectively. The sensitivity, specificity, positive predictive value and negative predictive value for CT and 18F-FDG PET-CT were 15.4%, 50%, 66.7%, 8.33% and 100%, 50%, 92%, 100%, respectively. There was no significant difference in the mean SUV max between HER positive and HER negative immunohistochemical phenotypes, but these values were significantly higher in single hormone receptor (HR), HER negative or HER positive tumors than in benign entities ($p<0.05$).*

Conclusions: *^{18}F-FDG PET-CT and immunohistophenotyping are potentially important surrogate markers for characterizing malignant breast disease and axillary lymph node metastasis.*

KEYWORDS: *FDG PET-CT, 18F-FDG PET-CT, Immunohistophenotyping, Breast cancer, HER positive, HER negative.*

INTRODUCTION

Immunohistophenotyping and ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) are important molecular markers for localizing and characterizing malignant breast tumors and in assessing the tumor landscape. This disease is a major public health problem worldwide[1]. The most prevalent cancer diagnosed in women and the second most common cause of mortality resulting from cancer is breast cancer (BC)[2]. A well-established fact is that BC is an array of diseases with distinct histopathologies and phenotypes. By associating clinical, pathologi-

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cal and outcome data with phenotyping patterns in the different BC subtypes, this may contribute to the definition of important differences in cell biology and tumor behavior in different tumor subtypes, thus enabling personalized treatment strategies. By virtue of the large-scale clinical application of BC disease stratification, classification into subtypes is largely dependent on traditional histopathological methods that assess the expression of three common molecular markers: estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2)[3]. In addition to facilitating the most pertinent therapeutic strategy, accurate diagnosis and staging also determine a patient's prognosis and survival. The standard assessment for operable invasive BC involves a thorough clinical examination and conventional imaging, i.e. bilateral mammogram and ultrasound with or without breast MRI for accurate disease localization and characterization. Hybrid imaging, which incorporates Tc^{99m} hydroxydiphosphonate (HDP) ,^{18}F-FDG PET-CT, as well as abdominal and pelvic CT, may be beneficial in certain cases, in particular when conventional imaging modalities are equivocal. The use of ^{18}F-FDG PET-CT staging for breast carcinoma is, therefore, important to ascertain stage II or III BC patients with the detectable lymph node metastases outside axillary levels I and II as well as cryptic metastases. The standardized uptake value (SUVmax) of ^{18}F-FDG PET is a semi-quantitative measure of the metabolic profile of altered glucose metabolism in tumor cells[4,5]. The biological diversity of BC and its varied aetiological development pathways may be better understood by assessing evolving molecular imaging pathways, which in turn affect the patient prognosis and provide personalized care[6,7].

The common treatments for BC patient revolve around chemotherapy, endocrine, and targeted therapy. Luminal ER positive (luminal A and luminal B), HER2 enriched, and triple negative are the preferred immunohistochemical subtype classifications of BC, which provides information on the proliferative rate and the expression of cytokeratins, and includes the evaluation of Ki67 (a marker of cell proliferation) and a cut-off of proliferation of less than 20% as factors associated with the luminal B, HER2-negative subtype[8, 10-15]. The potent marker HER2 is present in normal breast cells, in which its function is to promote cell proliferation, which could lead to the uncontrolled breast cell growth if it is not tightly regulated[16,17]. There are reports stating that HER(+) breast cancer, regardless of hormonal status, is associated with higher Ki67 expression, and HER +/- status may be a surrogate marker for the Ki67 proliferative index[18-22]. The aim of this study was to establish the role of ^{18}F-FDG PET-CT (SUVmax) as a staging tool in BC and to demonstrate correlations between immunohistochemical markers as potential surrogate metabolic markers that could be used to assess breast carcinoma aggressiveness.

PATIENTS AND METHODS

Study design

This study assessed consecutive 21 patients with primary breast carcinoma and recurrent breast carcinoma who underwent ^{18}F-FDG PET-CT imaging for diagnostic and staging purposes. All patients consented and Ethical approval to conduct the study was approved by the local authority.

Study subjects were recruited from the patients who attended the endocrine clinic of a tertiary center from June 2015 to October 2016. All patients were provided with a patient information sheet and a detailed explanation of the study.

Inclusion criteria

All patients had undergone biopsy of a breast mass (mammogram criteria BIRADS 4 and 5). Recurrent breast carcinoma was proven by biopsy.

Exclusion criteria

The following patients were excluded from the study: patients undergoing chemotherapy, underlying diabetes mellitus, pregnancy, aged 12 years or younger.

Methodology

Patients were required to fast for at least 6 hours. The blood glucose level was evaluated with a glucometer and was preferably less than 10 mmol/dL. Vital signs, i.e. blood pressure, heart rate, and blood oxygen saturation were recorded. For patients who had history of relevant allergy to the contrast media, premedication with oral prednisolone 40 mg at 12 and 2 hours before the procedure was prescribed. An intravenous line was set using a 23 branula in the antecubital fossa or the dorsum of the hand for contrast injection during the ^{18}F-FDG PET-CT scan.

Scanning parameters

CT imaging was done utilizing a 64-slice multidetector computed tomography (MDCT) scanner (Siemens Biograph/Acquisition-64, Munich, Germany)

and image analysis CT scans were acquired with a helical scan protocol (5.0 mm slice thickness reconstruction and a total active detector length pitch of 0.8. After the scanogram was performed, the range of scanning was determined from head to mid-thigh. The images were obtained using CT at 120 kVp and 240 mAs. Then, 100 mL of Iohexol 350 mg (Omnipaque 350 mg I/mL, Bayer Pharma AG Berlin, Germany) was injected using a power injector (Mallinckrodt) at 3.0 mL per second followed by 100 mL of normal saline at 3.0 mL per second. Image acquisition was commenced after a fixed delay of 80 seconds from the initiation of contrast injection. Three sets of images were acquired by PET-CT. The first set of images was attenuation correction CT followed by PET whole body and fused PET-CT whole body. The stacked images were reconstructed into 5.0 mm thick slices.

Image evaluation

Images were evaluated using a Leonardo Workstation with a Syringo MMWP VE50A GX340 monochromic LCD monitor of diagnostic quality. The monitor had a resolution of 1536 x 2048. Images were analyzed by a senior radiologist experienced in interpreting ^{18}F-FDG PET-CT images. All images (Figures 1-4) were read in separate reading sessions. The images with a slice thickness of 5.0 mm (whole body PET-CT, PET and CT images) are displayed side by side. The radiologist was blinded to the histopathological findings.

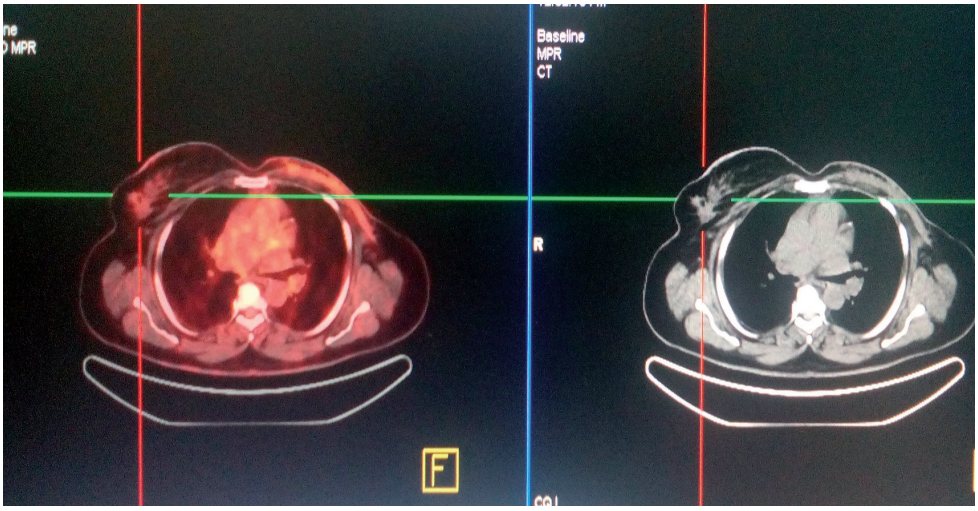

Fig. 1. Axial PET-CT and CT images of patient categorized as a true positive.

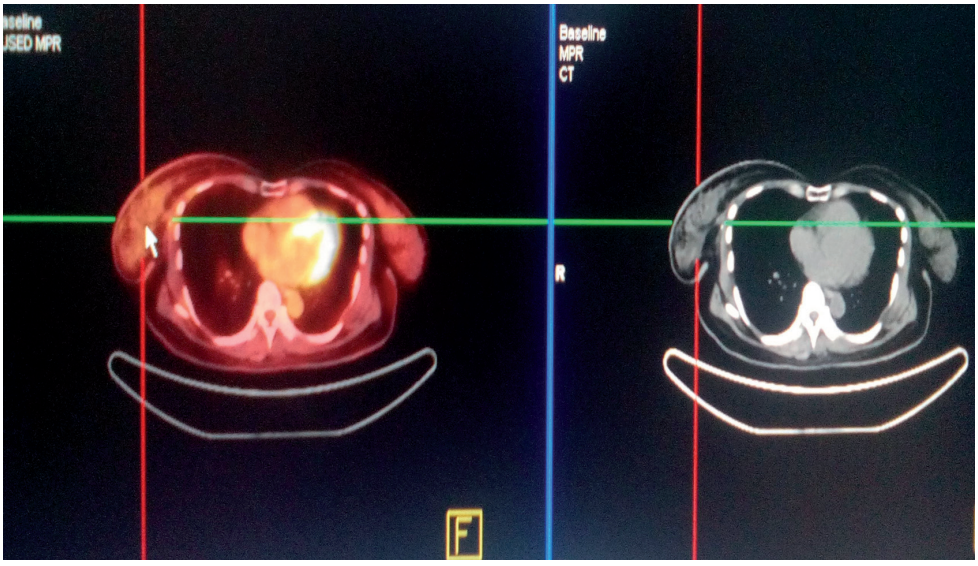

Fig. 2. Axial PET-CT and CT images of patient categorized as a false positive.

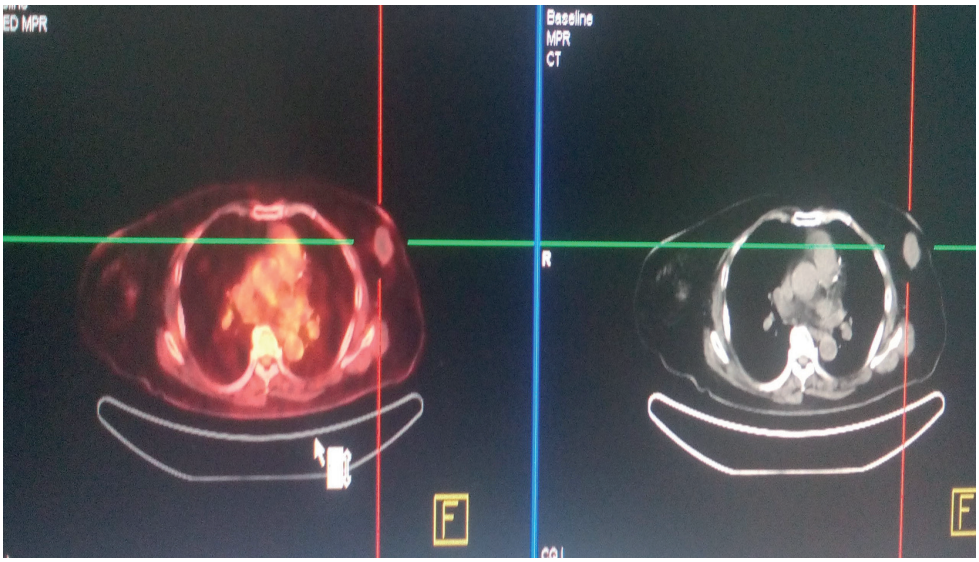

Fig. 3. Axial PET-CT and CT images of patient categorized as a true negative.

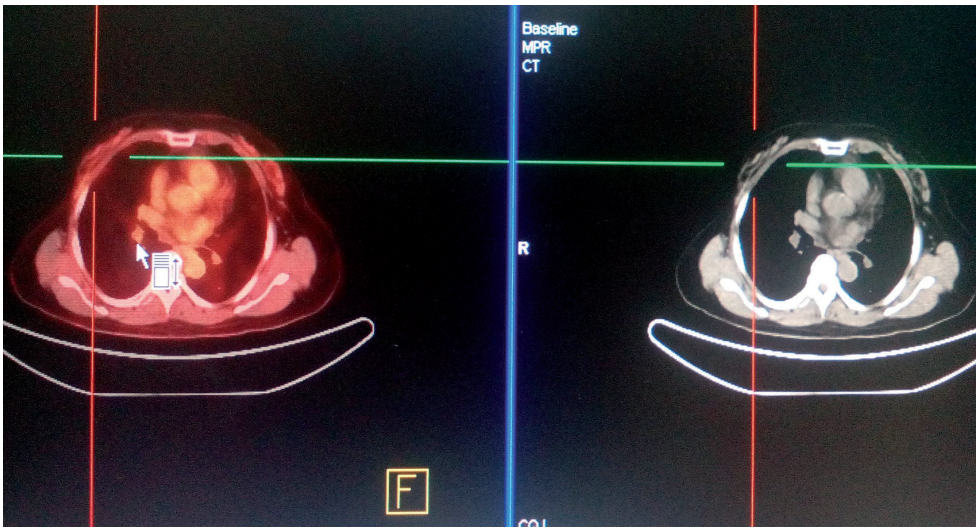

Fig. 4. Axial PET-CT and CT images of patient categorized as a false negative.

Criteria defining malignant lesions on PET-CT

The following aspects were considered for malignant lesions on PET-CT (Figures 1-4): maximum standardized uptake (SUVmax) value > 1.5, lesion size > 1 cm, and non-physiological uptake.

Gold standard

Based on the inferring status of HER status reflecting the proliferation index of the cellular landscape of the primary tumor or recurrence tumor and the axillary lymph nodes, we tested the diagnostic accuracy of ^{18}F-FDG PET-CT *vs.* CT.

Statistical analysis

Demographic data, immunohistochemical type, histological type (subject dichotomisation into benign or malignant), SUVmax, primary or recurrent disease, mammogram BIRADS type, and ^{18}F-FDG PET-CT lesion size, were inserted into SPSS Version 20.0 (IBM Corp., Armonk, NY, USA) and analyzed. The SUVmax values differences derived from both tracers were analyzed by one-way analysis of variance (ANOVA). We used a post hoc test (Tukey's method) and specified that the family of group comparisons should collectively produce a family-wise error rate of 0.05. The adjusted *p*-value identifies the group comparisons that were significantly different while limiting the family error rate to the significance level. When the adjusted

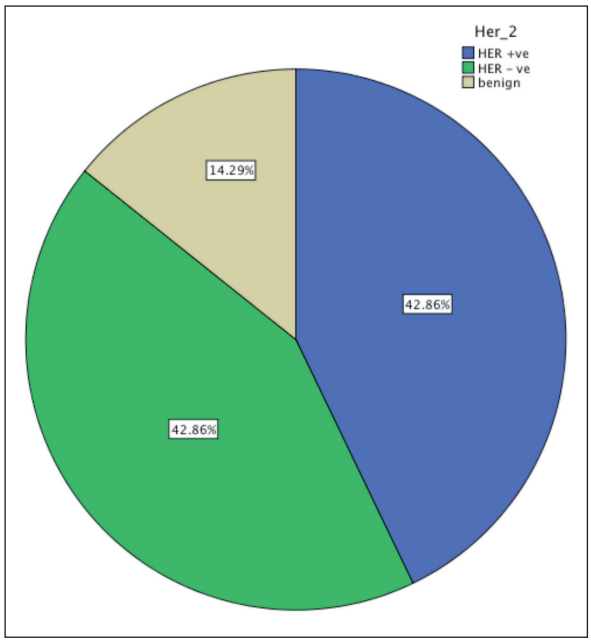

Fig. 5. Pie chart shows percentage or HER positive, HER negative and benign cases in the study population. There were 42.8% HER positive lesion, 42.8% (HER negative lesion which encompass the malignant tumur histology and 14.2% of benign lesion (Figure 5).

p-value was less than the significance level, the difference between those group means was statistically significant. The receiver operating characteristics curve (ROC) was used to determine the cut-off value of the SUVmax value between HER positive and negative parameters; an area under the curve (AUC) value of less than 0.05 was considered significant.

RESULTS

Twenty-one patients were recruited into this study. Of these, 66.7% had primary breast carcinoma and 33.3% had recurrent breast carcinoma. The age of the patients varied from 36 to 80 years with a mean age of 54.48 ± 12.1 years. A large number of the patients (85.7%) included in this study had malignant histology findings, whilst the remaining 14.3% patients had benign histological findings (Table 1).

The area under curve was 0.555 with $p < 0.01$ (p=0.71), which is not significant (Figure 6). The discriminator power of SUVmax to differentiate between HER positive and HER negative immunohistochemical phenotypes was low. Hence, PET-CT is not good discriminator between HER positive and HER negative immunohistochemical phenotypes.

TABLE 1. Descriptive patient characteristics (n=21).

N	*Age*	*Primary disease*				*Axillary lymph nodes (histology) M/NM/I*
		Histology	*Immunophenotype*			
			ER	*PR*	*HER2*	
1	56	IDC	+	+	+	M
2	59	IDC	+	+	-	M
3	55	Benign	-	-	+	-
4	73	IDC	+	+	-	M
5	46	IDC	+	+	-	M
6	60	IDC	+	+	+	M
7	48	Benign	-	-	-	-
8	47	IDC	+	+	+	M
9	48	IDC	+	+	+	M
10	62	IDC	+	+	-	M
11	53	IDC	+	+	-	M
12	64	IDC	+	+	-	M
13	69	Benign	-	-	-	-
14	40	IDC	+	+	+	NM
15	36	IDC	+	+	-	M
16	41	IDC	+	+	+	M
17	41	IDC	+	+	-	I
18	57	IDC	-	-	+	NM
19	80	IDC	-	-	+	NM
20	69	IDC	-	-	+	NM
21	40	IDC	-	-	-	M

Note: infiltrative ductal carcinoma (IDC), metastatic (M)/non-metastatic (NM)/inflammatory (I), oestrogen (ER), progesterone (PR), human epidermal growth factor receptor 2 (HER2).

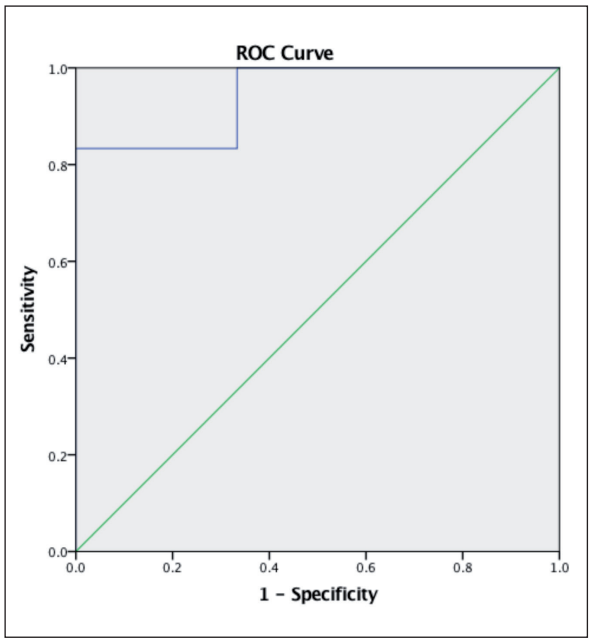

Fig. 6. Receiver operating curve (ROC curve) for malignant and benign histological types. The area under the curve is very large, AUC = 0.938, and the p-value is 0.019 (p<0.05), which is significant. The discriminatory power of SUVmax to differentiate between malignant and benign is high.

SUV of primary lesion and lymph nodes

We then compared SUV primary lesions and lymph nodes in single hormone receptor HER negative and single hormone receptor HER positive cases (Table 2).

The mean SUVmax for HER positive and HER negative immunohistochemical subtypes were 2.79 ±0.85 and 2.95 ± 0.81, respectively (Figure 7). Nevertheless, the mean SUVmax for HER positive and HER negative lymph nodes on the right were 2.07 ±0.57 and 2.38 ± 1.01, respectively, while on the left the mean SUVmax were 1.16±0.40 and 1.41± 0.56, respectively, without significant differences.

The Shapiro-Wilk test was used to test for normality; it showed a normal data distribution for this study population. Due to the normal distribution of SUVmax values of the primary lesion and lymph nodes for both HER positive and negative cases, ANOVA was used to compare the differences between these two immunohistochemical phenotypes. This test revealed that the SUVmax for the HER positive (1.69±0.59) immunohistochemical phenotype was higher than the SUVmax of the benign histology type (1.53±0.59) with p <0.05 (p=0.04). In addition, the SUVmax value for HER-negative immunohistochemical phenotype was also higher than the SUVmax of the benign histology type (1.69 ± 0.60) with p < 0.05 (p=0.02). A p >0.05 was observed for the SUVmax for HER positive and HER negative immunohistochemical phenotypes and thus there was no statistically significant difference between the SUVmax of HER positive and HER negative immunohistochemical phenotypes, as demonstrated in Table 3.

Tables 4 and 5 demonstrate the superiority of ^{18}F-FDG PET-CT over CT in localizing the primary tumor, on both a per lesion and per patient basis. ^{18}F-FDG PET-CT had a very high specificity in predicting false negative lesions.

DISCUSSION

In the current era of oncology, appropriate staging and treatment are essential to offer a better prognosis for the patient[23]. Hybrid imaging tools offer significant insight and impact in fulfilling this requirement. The imaging method that is currently most in demand is ^{18}F-FDG PET-CT, as it provides both anatomical and metabolic information that undoubtedly facilitates screening, diagnosis, and treatment[24].

Subjects in this study were in mixed categories of primary BC or recurrent disease. Besides an assessment of primary or recurrent BC, axillary lymph node involvement is also important to ensure the prognostication of treatment efficacy[25]. The previously used traditional axillary dissection has been replaced by sentinel lymph node biopsy. However, this method has been shown to have few disadvantages, namely an extensive pathological work-up, the need for lymphoscintigraphy, and increased surgical duration[22]. The emergence of ^{18}F-FDG PET-CT has substituted single lymph node biopsy, but the former may yield more false negative patients at risk of cancer recurrence and more false positive patients who would then undergo unnecessary axillary lymph node bi-

TABLE 2. The mean SUVmax for single hormone receptor HER positive single hormone receptor HER negative primary breast lesions and lymph nodes on the right and left sides with their respective standard deviation values.

Phenotyping	*Primary tumor SUV (MAX) g/dL mean ±SD*	*RTLN SUVmax mean ±SD*	*LTLN SUVmax mean ±SD*	*p-value*
HER +ve	2.79 ±0.85	2.07 ±0.57	1.16±0.40	p>0.05
HER -ve	2.95 ±0.81	2.38 ±1.01	1.41±0.56	

Notes: RTLN (right lymph node; LTLN (left lymph node).

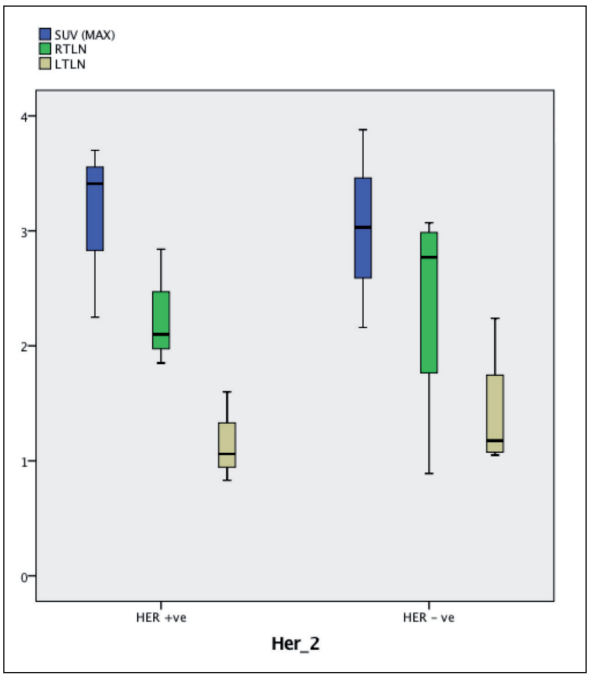

Fig. 7. Boxplot of SUV in the primary lesion and lymph nodes of HER negative and HER positive cases.

opsy[22]. In this study, we assessed the accuracy of ^{18}F-FDG PET-CT *vs.* CT in detecting axillary lymph nodes based on the gold standard of inferring the proliferative index by HER status. The sensitivity and specificity for CT were only 15.4% and 50%, respectively, which improved to 100% and 50%, respectively, with ^{18}F-FDG PET-CT. The positive predictive value in this study population was 66.7% for CT and 92% for ^{18}F-FDG PET-CT. To assess the number of truly negative cases, negative predictive values were calculated, with 8.33% for CT and 100% for ^{18}F-FDG PET-CT. This provides evidence that ^{18}F-FDG PET-CT is more sensitive and specific for lymph node assessment than conventional CT. Although preventing the need for two sequential operations for sentinel lymph node biopsy and axillary lymph node dissection in FDG-positive PET-CT patients, previous studies have shown that there may be more false positive patients who would undergo unnecessary axillary lymph node biopsy if PET-CT was utilized

TABLE 3. *p*-values of SUVmax for HER positive and HER negative immunohistochemical phenotypes.

Phenotypes	*SUVmax mean std. error±SD*	*p-value*
Benign	-1.53 ±0. 59	$p<0.005$
HER (+)	-1.69 ±0.59	

prior to the single lymph node biopsy. However, in a study, average ultrasound sensitivity was 69-71% and specificity was 75-86% *vs.* the higher sensitivity and specificity of ^{18}F-FDG PET-CT in our study, which were 100% and 50%, respectively; these results are comparable to those of Copper et al[26].

More importantly, ^{18}F-FDG PET-CT sensitivity per patient and per lesion (100% for both) for detecting lesions was far superior to CT (sensitivity 82.3% and 88.2%, respectively). The specificity per lesion can be affected by false positive results due to inflammation. Despite this, the sensitivity of ^{18}F-FDG PET-CT per lesion was higher than CT per lesion (75% *vs.* 25%). On the per patient and per lesion basis, ^{18}F-FDG PET-CT provided a positive predictive percentage of 100% and 94.1% as compared to CT (77.8% and 88.3%). The proportion of actual negative primary or recurrent BC was 100% per patient and per lesion, while it was much lower for CT (25% and 66.7%, respectively). In a study done by Veronesi et al [22], the sensitivity and specificity of BC detection on ^{18}F-FDG PET-CT was 37% and the specificity was 96%. Regarding the localization of axillary lymph nodes, our study recorded a sensitivity of 100% and specificity of 50% for axillary lymph node detection by ^{18}F-FDG PET-CT. This shows that, based on our study, ^{18}F-FDG PET-CT is a potential surrogate marker for lymphoscintigraphy for sentinel lymph node or invasive lymph node dissection.

The reason for the ability of ^{18}F-FDG PET-CT to detect positively malignant lymph nodes is 50% more frequent than other attributes i.e. primary tumor or benign lesions. Infected and inflamed lymph nodes concentrate FDG too, but the degree of uptake is lower as measured by SUVmax[27].

TABLE 4. Sensitivity, specificity, positive predictive value and negative predictive value per patient and per lesion with CT and PET-CT analysis of the primary lesion.

	CT		*PET-CT*	
	Per patient	*Per lesion*	*Per patient*	*Per lesion*
Sensitivity	82.3%	88.2%	100%	100%
Specificity	20%	25%	100%	75%
Positive predictive value	77.8%	88.3%	100%	94.1%
Negative predictive value	25%	66.7%	100%	100%

TABLE 5. Sensitivity, specificity, positive predictive value and negative predictive value per lesion for the CT and PET-CT analysis of lymph nodes.

	CT	PET-CT
Sensitivity	15.4%	100%
Specificity	50%	50%
Positive predictive value	66.7%	92%
Negative predictive value	8.33%	100%

For the ^{18}F-FDG PET-CT detection of lymph nodes, the positive predictive value in our study was 92% and the negative predictive value was 100%. This shows that ^{18}F-FDG PET-CT is a powerful imaging modality for ascertaining malignant lymph nodes. This is in comparison with a study by Champion et al[28] that obtained positive predictive and negative predictive values of 94% and 74%, respectively. Hence, our study substantiates the fact that ^{18}F-FDG PET-CT is a potentially good discriminator for distinguishing benign lymph nodes from malignancy. Notwithstanding, it disclaims the notion that PET-CT can be omitted if clinically negative axillary lymph node detection occurs, due to its high negative predictive value.

In our study, we found that there was no significant difference between the mean SUVmax value for single hormone receptor (HER negative) and HER positive group. This is in contrast to other studies that found a significant difference in SUVmax values between these phenotypes[29,30]. The reason for these equivocal findings could be explained by the small sample size in our study, which did not provide adequate statistical power[30]. The ROC curve, which compared the single hormone receptor group with the HER positive group and the single hormone receptor HER negative group in our study had an AUC of 0.555 and $p = 0.71$ ($p > 0.05$); this could not determine a cut-off SUVmax value to differentiate between phenotypes. Besides the small sample size, the potential of low tumor proliferation in our study that was not substantial enough to affect SUVmax.

Poor spatial resolution still remains a major problem, as it can affect the detection of breast lesions or lymph nodes smaller than 10 mm. This makes ^{18}F-FDG PET-CT prone to false negative findings because of the low spatial resolution of PET. Therefore, ^{18}F-FDG PET-CT is not able to detect micrometastases in early BC cases. In addition, some BC histological types like lobular breast carcinoma (ILC) show no uptake and they are detected with significantly lower sensitivity by ^{18}F-FDG PET-CT. This can be explained by various factors such as a low level of GLUT-1 expression, a lower tumor cell density, diffuse infiltration of surrounding tissue, and a decreased proliferation rate in ILC. Osseous metastases in patients with ILC also demonstrate lower FDG avidity than those in invasive ductal carcinoma (IDC) patients. Non-FDG-avid sclerotic osseous metastases are significantly more common in untreated subjects with ILC than with IDC[7].

Given the preliminary results of our evaluation of ^{18}F-FDG PET-CT and immunophenotype in the evaluation the breast cancer aggressiveness, future studies are needed to compare the proliferative index (Ki67 expression) to ascertain the performance of the ^{18}F-FDG PET-CT *vs.* other modalities, i.e. MRI and ultrasound, in disease prognostication and the impact on the cost effectiveness of the patient management.

CONCLUSIONS

The role of ^{18}F-FDG PET-CT as a staging tool in characterizing aggressive (malignant) BC from a benign entity is strong and a potential surrogate marker for axillary lymph node metastasis and hence could be utilized as a surrogate marker for tumor aggressiveness.

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Conflict of Interest:

All authors declare that there is no conflict of interest.

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