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Relation between Tumor SUVmax, TLR and TSR and Breast Carcinoma Molecular Subtypes in PET CT

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Abstract--Breast cancer is known to be one of the most cancer affecting women around the globe and the second most common cancer in general. In third worlds countries, breast cancer is the most cause of cancer death. Early diagnosis and accurate follow-up of these patients affect the management. There are multiple prognostic factors most important one is the immunohistochemical molecular markers in the specimens including human epidermal growth factor, progesterone, and estrogen receptors (HER 2, PR, ER). In breast cancer, the HER2 positive molecular subtype is associated with bad prognosis and aggressive histological features, yet while following neoadjuvant chemotherapy, it achieves an increased pathological complete response rate. 18F-fluoro-2-deoxy-d-glucose positron emission tomography (FDG PET) has proved to be an effective and accurate imaging technique for lymph node and distant metastasis assessment, tumor staging, restaging of recurrence, treatment response, and follow-up. In breast cancer, tumor molecular subtype, tumor size, proliferation index, and histological grade correlated with 18F-fluoro-2-deoxy-d-glucose (FDG) uptake. This study evaluates the possible correlation between tumor SUV max, tumor to liver and tumor to spleen (standardized uptake value) SUV max ratio and the four different molecular subtypes in patients with pathologically proven breast cancer. Tumor SUV max and tumor to liver and tumor to spleen SUV max ratio (TLR, TSR) were a significant parameter for

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HER2 molecular sub type identification (p value=0.003,0.0005 and 0.014 respectively) and luminal A molecular sub type identification (p value=0.027,0.016 and 0.037 respectively). Tumor SUV max, TLR and TSR appeared to be valuable for HER2- and luminal A molecular subtype detection. So, 18F-FDG PET/CT could be a beneficial tool for prediction of tumor biological characteristics that can help in management of breast cancer patients.

Keywords---Fluoro-deoxy-glucose uptake (FDG uptake), Positron emission tomography/computed tomography (PET/CT), HER2, Luminal A, breast cancer, SUVmax, TLR, TSR.

Introduction

Breast cancer is known to be one of the most cancer affecting women around the globe and the second most common cancer in general. In developing countries, breast cancer is the most cause of cancer death [1]. Management of breast carcinoma depends on tumor size and site, TNM staging, and the molecular subtype. It includes Surgery, radiation, and chemotherapy in various combinations, [2].

Molecular sub type classification of the breast carcinoma based on immunohistochemistry including the estrogen, progesterone, and human epidermal growth factor receptors (ER, PR, HER 2) is now widely used. According to the expression of these receptors, luminal A, luminal B, HER 2 positive, and triple-negative are the accepted molecular subtypes [3]. HER2 positive molecular subtype is associated with bad prognosis and aggressive histological features, yet while following neoadjuvant chemotherapy. So, accurate molecular subtype diagnosis is necessary for the development of specific treatments [4].

Positron emission tomography (PET) can detect abnormal metabolic activity, and 18F-2-deoxy-D-glucose (FDG) PET provides tumor-related quantitative and qualitative metabolic data that may help in the prognosis, diagnosis, and follow-up. PET and computed tomography (PET/CT) combined, has benefits over CT alone, as this combined system allows us to assess the functional information and morphological data, and it also has benefits over PET alone, because pathological areas of tracer uptake are accurately localized, and the image acquisition time is reduced [5].

PET/CT can detect the primary breast tumor, and the ability depends on tumor size and histology. It also has high sensitivity in detection of the axillary and internal mammary lymph nodes reaching up to 94% and 92% respectively [6]. In breast cancer, tumor molecular subtype, tumor size, histological grade, and proliferation index were correlated with 18F-fluoro-2-deoxy-d-glucose (FDG) uptake. Nevertheless, few studies have analyzed the diagnostic performance of F-18FDG-PET/CT-based predictions of molecular subtype. [7]. The aim of this study is to evaluate the possible correlation between tumor SUV max, tumor to liver and tumor to spleen SUV max ratio (TLR, TSR) and the different four different molecular subtypes in patients with pathologically proven primary breast cancer.

Patients and Methods

Patients: this study is retrospective study included 25 female patients with pathologically proven primary breast cancer underwent ^{18}F -FDG PET/CT imaging at the radiology department of Ain Shams University Hospitals from the time interval between August 2019 and June 2021. Data were collected after having patients' written informed consent following rules of ethical committee. We excluded patients who received chemotherapy or radiotherapy, underwent surgical tumoral intervention, post splenectomy status or unavailable histopathological reports

^{18}F FDG PET/CT imaging:

Patients' preparation:

- Patients were required to fast for 5 hours.
- Avoid severe physical activities one day before F-18 FDG-PET/CT acquisition.
- Blood glucose levels before scanning were less than 200 mg/dL.
- Before injection of the ^{18}F -FDG, the patient should seat in a quiet room.

PET/CT examination

In our university we used a reliable hybrid PET/CT scanner [(GE discovery IQ 5 rings) and enhanced helical CT (optima 540 16-slice)]. Patients were positioned supine on the table. Single-phase contrast material-enhanced helical CT using a standardized protocol [28-30 mAs; 120 kV; slice thickness 5 mm] was conducted after injection of 125 mL of a low osmolarity iodinated contrast medium (Optiray 350) at a rate of 4 mL/sec by using a power injector. A whole-body CT examination including neck, chest, abdomen, and pelvis scanning was performed. The related PET imaging instantly followed over the same body parts without repositioning the patient on the table. In the three-dimensional acquisition mode, six to seven-bed positions were planned for scanning the entire patient within five to seven minutes of acquisition per each bed position. PET images were performed with shallow breathing. Attenuation was corrected using the CT images, and the images were reconstructed.

Image interpretation

Image data were interpreted by at least two nuclear medicine radiologists using a workstation with fusion software GE workstation (Advantage window 4.7) which provided multi-planar reformatted images and displayed PET images, CT images, and PET/CT fusion images. Contrast enhanced CT images were interpreted to detect any enhancing lesions and bone window was used to evaluate any bony pathologies. For semi-quantitative analysis, estimating the maximum standardized uptake value of the IBC (tumor SUV max) on axial images by drawing a region-of-interest (ROI) that contained as much of the tumor area that showed the most intense area of F-18FDG accumulation and it was recorded automatically by the workstation, if multifocal disease was present, the ROI was placed over the largest visible tumor for calculation of the SUVmax value. In

addition, the liver SUVmax was calculated by drawing a circular ROI 3.0 cm in diameter over the relatively homogenous intense slice of the right lobe of normal liver parenchyma on PET images, avoiding the partial volume effect (PVE) caused by adjacent organs on the margins of the liver. The SUVmax of the spleen was measured similarly. TLR and TSR were calculated as ratios of the tumor SUV max to the liver and spleen SUVs max, respectively.

Histopathological and Immuno-histo-chemistry analysis

Tumor histology parameters were evaluated from the needle biopsy samples taken from the breast tumor or malignant axillary lymph nodes. We obtained the histopathological findings, including the ER and PR receptor status, HER2neu and proliferation index of the primary tumor by reviewing the pathology reports. According to the ER, PR, and HER2 status, IBCs were categorized into four molecular subtypes as follows:

- luminal A (ER-positive and/or PR-positive, HER2 negative),
- luminal B (ER-positive and/or PR-positive, HER2 positive),
- HER2-positive (ER-negative, PR-negative, and HER2 positive),
- triple-negative (ER-negative, PR-negative, and HER2 negative).

Statistical analysis

In this study, we used SPSS (Statistical package for social science) program version 23 for data analysis. Quantitative data were introduced as median & range to illustrate the studied sample. Qualitative data were introduced as count & percentage. Also, we used the Chi-square statistic to test relationships between categorical variables, and One-Way ANOVA test to compare parametric quantitative data between more than two groups. An ideal cut-off value established on maximal sensitivity and specificity was determined to detect HER2/Neu molecular subtype, using the highest area under the receiver operating characteristic (ROC) curve. We identified significance as a P value of less than 0.05 and high significance as a P value less than 0.01.

Results

Patient and tumor characteristics

A total of 25 patients were included, their demographic factors and tumor characteristics are reviewed in Table 1. The 25 IBCs were categorized according to their molecular subtype as follows: luminal A, 11 (44%); luminal B, 5 (20%); HER2-positive, 6 (24%); and triple-negative, 3 (12%). The maximal tumor diameters ranged from 10-60 mm, with a median of 36 mm.

Table 1
Patient demographic factors and tumor characteristics

Characteristic	Number (%)
Age mean, range	53.36 (29 – 79)
Size median, range	36 (10-60)
<i>Location</i>	
Right	10 (40.0%)
Left	11 (44.0%)
Bilateral	4 (16.0%)
<i>Histopathology</i>	
Invasive Ductal	21 (84.0%)
Invasive Lobular	4 (16.0%)
<i>Grade</i>	
I	1 (4.0%)
II	15 (60.0%)
III	9 (36.0%)
<i>Immuno-histo-chemistry</i>	
Luminal A	11 (44%)
Luminal B	5(20%)
Tripple negative	3(12%)
HER2/Neu	6(24%)

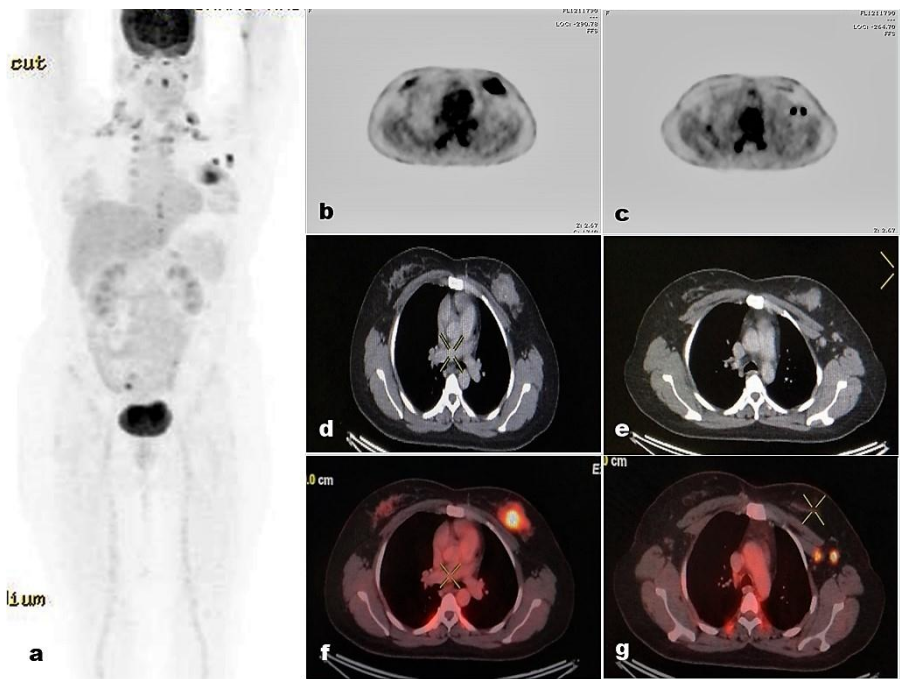


Figure (1): 50 years old patient with recently diagnosed left sided HER2 positive breast carcinoma. TLR=3.2 and TSR=3. (a) Maximum intensity projection. (b) and (c) Trans axial PET images corresponding axial CT cut in (d) and (e) shows left breast retro-areolar heterogenous enhancing soft tissue mass lesion with foci of calcifications. It measures about 5.5x3.5 cm associated with enlarged suspicious looking two left axillary lymph nodes. The largest measures about 1x1.1cm. (f) fused PET/CT axial cut shows left breast retro areolar FDG avid lesion displaying SUVmax~ 9.3. (g) fused PET/CT axial cut show two FDG avid axillary lymph node displaying SUVmax ~ 11.14.

Relation between tumor SUV max, TLR and TSR and the molecular subtype

Significant statistical relation was found between tumor SUV max and luminal A and HER2 positive molecular subtype ($P=0.027, 0.003$) respectively. We also found significant statistical relation was found TLR and TSR max ratio and luminal A molecular subtype ($P=0.016, 0.037$) respectively also between them and HER2 molecular subtype ($P=0.005, 0.014$) respectively as illustrated in table 2. The specificity and sensitivity of the TLR for identification of the HER2-positive subtype were 89.47% and 83.33%, respectively, when applying a cut-off value of more than 3.12. The AUC for identification of the HER2-positive subtype was 0.89, as illustrated in figure 2.

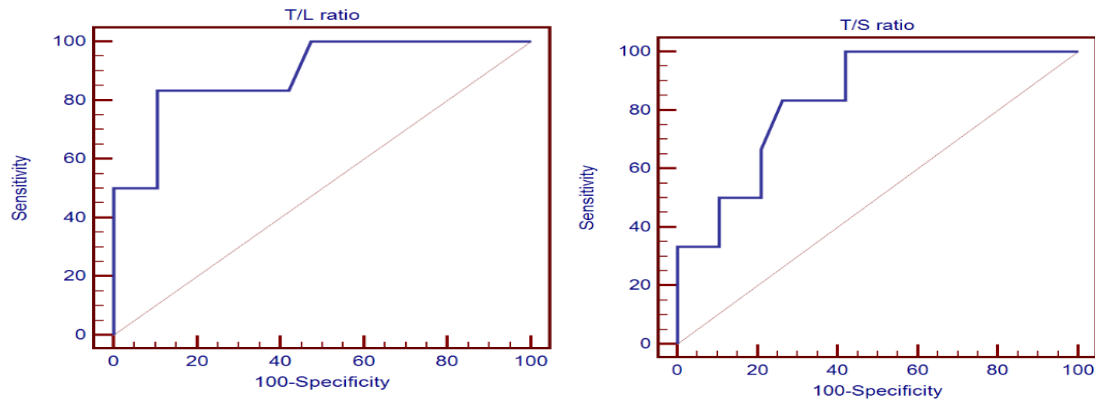


Figure (2): ROC curve of TLR and TSR as a predictor of Her2 molecular subtype

The specificity and sensitivity of the TSR for identification of the HER2-positive subtype were 57.89% and 100%, respectively, when applying a cut-off value of more than 2.43. The AUC for identification of the HER2-positive subtype was 0.84, as illustrated in figure 2.

The specificity and sensitivity of the TLR for identification of the luminal A positive subtype were 72.73% and 85.71%, respectively, when applying a cut-off value of more than 2.17. The AUC for identification of the luminal A subtype was 0.786, as illustrated in figure 3.

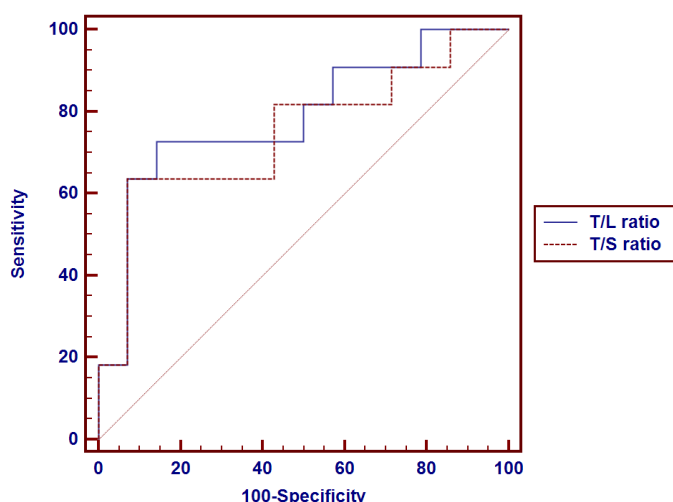


Figure 3. ROC curve of TLR and TSR as a predictor of luminal A molecular subtype

The specificity and sensitivity of the TSR for identification of the luminal A positive subtype were 63.64% and 92.86%, respectively, when applying a cut-off value of more than 1.6. The AUC for identification of the luminal A subtype was 0.747, as illustrated in figure 8.

Table 2
Four molecular subtypes and tumor SUV max,TLR and TSR SUV max ratios

	Tumor SUV max	P value	TLR SUVmax ratio	P value	TSR SUVmax ratio	P value
Luminal A	2.13(1.6-4.6) Range :0.9-15.9	0.027	1.4(1-2.7) Range :0.5-4.2	0.016	1.55(1.12-2.87) Range :0.56-5.3	0.037
Luminal B	4.7(4.2-5.8) Range:3.9-8.5	0.634	2.6(2.2-2.8) Range :2-3.4	0.587	2.43(2.2-3.8) Range :2-4.5	0.683
Triple negative	3.41(1.6-4.5) Range:1.6-4.5	0.259	2.27(0.8-2.6) Range :0.8-2.6	0.477	2.6(1-3) Range :1-3	0.544
HER2/Neu	9.1(6.6-9.9) Range:6.7-11.2	0.003	4.07(3.17-5) Range :2.2-6.62	0.005	3.83(3-5.5) Range :2.44-7.46	0.014

Discussion

18FDG PET/CT is a non-invasive imaging modality that evaluates the metabolic activity of tissues and their anatomical details [8]. In the literature, multiple studies have reviewed 18F-FDG uptake in patients with breast tumors and related it to tumor size, histopathological grade, and hormone receptor expression as prognostic factors. [9] Patients with HER2-positive and triple-negative subtype tumors have a higher rate of distant metastasis, local recurrence, and mortality than tumors with luminal A and B subtype-positive tumors [10].

In our study, we used the TLR and TSR as well as the tumor SUVmax. Patients with viable malignant tumors have a higher mean SUV in the liver and spleen as

they are organs with increased reticuloendothelial system activity [11]. TLR would provide a proper overview of the tumor metabolic activity and a more accurate diagnostic implementation than SUV_{max}. Using the TLR obviously remove the SUV limitation such as possible inaccuracies regarding scanner calibration, injected dose, and patient weight index (either actual body weight, lean body mass, or body surface area) [12],[13].

In our study, the mean TLR and TSR had statistically significant relation with the molecular sub type of the breast tumor with P value=0.018 and 0.061, it was found to be high among the HER2/Neu positive subtype tumors than among triple negative, luminal A and B subtype tumors. This finding agrees with Noda Y et al., (2017) who concluded a positive correlation between tumor to liver SUV_{max} of the lesion with the molecular subtype ($P = 0.0049$) and agreed also with Asmaa A et al., (2021) who concluded that “the mean TLR values were much higher in Her2neu +, GIII and TN molecular subtype patients ($P= 0.002, 0.0476, 0.005$ and 0.018 respectively) [14],[15].

There were a few limitations in our study. First, since this was a retrospective study with a small sample size and was conducted in a single medical centre, there was a higher risk of selection bias. More clinical trials with larger sample sizes may be required to confirm our preliminary findings. Second, our study included small tumors which are more susceptible to partial volume effect. Hence, the SUV_{max} may be underestimated.

Conclusion

Tumor SUV_{max}, TLR and TSR appeared to be valuable for HER2- and luminal A molecular subtype detection. Thus, 18F-FDG PET/CT could be a beneficial tool for prediction of tumor biological characteristics that help in management of breast cancer patients.

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Abbreviations:

(18F) FDG-PET/CT: fluorodeoxyglucose positron emission tomography/computed tomography.

SUV max: maximum mean standard uptake values.

IBC: invasive breast carcinoma

ER: estrogen receptor

PR: progesterone receptor

HER2: human epidermal growth factor receptor 2

TLR: tumor-to-liver ratio

TSR: tumor-to-spleen ratio

LN: lymph node.

Ki-67: Ki-67 labelling index