Utility of ^{18}F-FDG PET/CT in pre-surgical risk stratification of patients with breast cancer

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Abstract

Objective: To determine the correlation between fluorine-18-fluorodeoxyglucose (^{18}F-FDG)uptake values and clinicopathological prognostic markers using preoperative ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) in primary breast cancer (BC). **Subjects and Methods:** One hundred and twelve patients with primary BC were studied prospectively. Pretreatment ^{18}F-FDG PET/CT was performed. Maximum standardized uptake values (SUVmax) were compared with various clinicopathological variables. **Results:** In a univariate analysis, SUVmax correlated well with the following prognostic variables: T stage, absence of progesterone receptor (PR), absence of estrogen receptor (ER), triple negative lesions (ER/PR and Her 2 negative) and high histologic grade. Metastatic lesions and ductal lesions had higher SUVmax than lobular carcinoma. No significant correlation was found between SUVmax, and human epidermal growth factor receptor 2 (Her-2) status or perineural and lymphovascular invasion. Multivariate analyses showed that breast density, tumor size and PR negativity were significantly correlated with SUVmax (P=0.046 and 0.009, respectively). **Conclusion:** The pre-treatment tumor SUVmax could be utilized as an independent imaging biomarker of the tumor aggressiveness and poor prognosis. Risk stratification based on this index could play a pivotal role in alteration of treatment planning, such as neoadjuvant chemotherapy (precision oncology).

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Introduction

Cancer of the breast (BC) is the most common non-cutaneous cancer in the world in women with an age-standardized incidence rate (ASR) of 39.0 per 100,000, more than double that of cervical cancer, the second ranked (ASR=15.2 per 100,000)[1, 2]. Incidence rates are higher in the West, but the disability-adjusted life years (DALY's) are highest in middle-income countries, because incidence rates are increasing and there is a higher proportion of patients with late stage at diagnosis [3].

In India, it is the most common cancer among urban women and in rural areas, it is the second most common malignancy after cervical carcinoma. One in 22 women in India develops carcinoma of the breast in her lifetime[4].

Tumors with different histopathological characteristics show variable prognosis and therapeutic response. Invasive ductal carcinoma is the most common histological type (70%-80%), second is invasive lobular carcinoma (6%-10%) and last is medullary carcinoma (about 3%) [5]. Invasive BC may present as a single, multifocal or multicentric disease. Patients with locally advanced disease which includes tumors with direct extension to the chest wall or skin (stage T4); advanced nodal disease and inflammatory carcinomas have dismal prognosis because the majority of the patients suffer from distant metastatic disease.

The National Comprehensive Cancer Network (NCCN) has published guidelines for the evaluation of women with newly diagnosed breast malignancy. Their recommendations include history and physical examination, bilateral mammogram, ultrasound and breast magnetic resonance imaging (MRI) (optional),review of pathology, and determination of estrogen receptor (ER)/progesterone receptor (PR) status, nuclear grade and human epidermal growth factor receptor 2 (Her-2/Neu) status. For the detection of distant metastases, standard of care requires chest radiography, abdominal ultrasound and bone scintigraphy with plain bone radiographs (if necessary). To assess suspicious findings, imaging procedures include computed tomography (CT) and MRI.

Distant metastases will develop in 45%-50% of all patients[6].The extent of axillary nodal metastases is an independent marker of distant metastases. The prevalence of detectable metastases increases from stage I to stage III. In women with stage I cancer there has

been reported a 0.5% incidence of metastases by bone scan and a 0.1% incidence by chest X-rays. For stage II disease these figures were 2.4% and 0.2%, respectively [6]. The presence of distant metastases is a significant prognostic factor since patients with localized disease have a 5 years relative survival rate of more than 80% compared with 25% for those with metastases [7,8]. The study was performed to find an effective non invasive tool for staging the carcinoma breast, in view of its high incidence in India.

In addition to metastases, prognosis depends on the size and grade of the primary tumor, estrogen receptor status, perineural and lymphovascular invasion and axillary lymph node involvement.

This study was planned to evaluate if uptake values on fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) whole-body examination correlates with the (tumor biology namely histopathological grade, ER/PR and Her2 neu receptors, lymphovascular and perineural invasion.

Subjects and Methods

This was a prospective study performed from April 2010 to March 2012 at the Army Hospital (Research & Referral), Delhi Cantt, a tertiary care hospital caring for all the three wings of Armed Forces in India. The study was performed after clearance from the ethical committee. Written consent was obtained for all procedures from all patients. Demographic and clinical details were entered in the database.

Patients with primary BC referred to the Oncology Department, Army Hospital (Research & Referral) were included in the study. Presence of BC was confirmed initially by FNAC/Trucut biopsy. Demographic and clinical details were entered in the database.

Inclusion and exclusion criteria
Eligible patients were 18 years old or older, of both genders, with histopathological/cytological diagnosis of BC.

Patients were excluded if they had undergone prior chemotherapy, radiotherapy or surgery, were pregnant or lactating, unable to lie supine for imaging with PET/CT, unable to provide informed consent, had claustrophobia, dual malignancy, active tuberculosis, were on antitubercular treatment, were immunocompromised, or had blood glucose level (random) >150mg%.

Procedure followed during staging by PET/CT-Methods

Initial workup
Thorough clinical examination was performed in all patients. Diagnosis of BC was confirmed by FNAC/TRUCUT biopsy. Patients were diagnosed based on clinical signs and/or symptoms with additional investigations namely Mam-

mogram, ultrasound of breast and axilla, chest radiograph, ultrasound abdomen, bone scan. Positron emission tomography/CT were performed in all the patients. Complete blood count and liver function tests were also done.

Whole body PET/CT imaging
After clinical examination and conventional investigations, whole body ^{18}F-FDG PET/CT scan was done. Standard procedures were followed for the performance of imaging [8]. a) Fluorine-18-FDG injection protocol: After measurement of random blood glucose level, with the patient in a resting state in a quiet room, a dose of 296-370MBq of ^{18}F-FDG was injected intravenously (i.v.) depending on the weight of the patient (mean±SD 325±4.07MBq). After about 60 minutes, patients were placed in the scanner (range: 45-60 minutes). b) Acquisition protocol of PET/CT scans was performed with a dedicated PET/CT scanner (Siemens, Biograph 2) which has a LSO (lutetium oxyorthosilicate Lu$_2$SiO$_5$:Ce) detector with attenuation coefficient 0.89/cm, photofraction 30% decay constant 40ns. The energy resolution at 511keV (%FWHM) was 10mm. Images from CT were obtained using 130kV and 25 mAs (mean) without administration of oral or i.v. contrast. Computed tomography based attenuation correction was performed. Images were reconstructed using standard iterative algorithm (OSEM) and reformatted into axial, coronal and sagittal sections. A 3D image and fusion images of PET and CT were obtained. Positron emission tomography acquisition was done for 2 minutes per bed position. c) Imaging by PET makes it possible to calculate "standardized uptake value" (SUV) which represents the uptake in a given region of interest related to the average uptake throughout the body. Maximal SUV provides an approximate indicator that correlates with ^{18}F-FDG metabolism. The rate of ^{18}F-FDG uptake and trapping is a semi-quantitative indicator of glucose metabolism.

Image analysis
Images were acquired and analyzed as CT and PET images read separately as well as with fusion. All PET/CT images were analyzed by two Nuclear Medicine physicians. Any area of focal, abnormal or asymmetric uptake, greater than the background normal of breast tissue uptake or more than the mediastinal blood pool uptake was considered as a malignant lesion and recorded accordingly. Maximal SUV of each lesion was recorded separately. No cut off SUVmax was used to segregate malignancy from artifact. The uptake values of these lesions were compared with histopathological findings like tumor grade, tumor type, ER, PR Her2Neu receptor status, perineural and lymphovascular invasion, in order to identify if their was any significant correlation with the abovementioned parameters.

Statistical analysis
Statistical analyses performed using STATA 14 (StataCorp. 2015. *Stata Statistical Software: Release 14.* College Station, TX: StataCorp LP). Descriptive analysis of categorical variables comprised the calculation of simple and relative frequencies. The numeric variables were described as mean, standard devi-

ation (SD), minimum and maximum. To compare scalar variables between two groups Student's t test was utilized (or the Mann Whitney non-parametric test, as indicated). To compare a variable among three or more groups, the Analysis of Variance (ANOVA) or the Kruskal-Wallis non-parametric test was utilized. Those results with probability of type I error=5% (P=0.05) were considered as being statistically significant.

Results

A hundred and fifteen subjects initially enrolled in this study (113 females, 2 males). Considering histopathology subtypes, one of the males had IDC and the other "papillary carcinoma". Since none of the female subjects had "papillary carcinoma" subtype and considering the significance of gender in BC biology, both male subjects were excluded from the analysis.

Demographics
The average age of the included 113 female subjects was 51 years (SD=11; min=23; max=81). The 54% of subjects were older than 50 years. The majority of subjects had "invasive ductal carcinoma" (100 cases, 88.5%), followed by "metaplastic BC" (5 cases), and "invasive lobular carcinoma" (4 cases). Two cases had "pleomorphic BC" and two had "lobular carcinoma in-situ", respectively.

Blood glucose level and ^{18}F-FDG dose
The measured blood glucose level ranged 73-149mg/dL (mean=107.4mg/dL; 95% CI=104.1-110.7mg/dL). There was no statistically significant difference between blood glucose level of subjects younger than 50 years old (n=51; mean=106.7mg/dL; 95% CI=101.9-111.5mg/dL) and subjects older than 50 years old (n=59; mean=108.0mg/dL; 95% CI=103.4-112.7 mg/dL). There was no statistically significant correlation between the measured blood glucose level and SUVmax of main lesion (P value =0.30).

The dose of injected ^{18}F-FDG ranged 293-370MBq (mean=325MBq; 95% CI=325.6-333MBq). There was no statistically significant difference between injected ^{18}F-FDG dose of the subjects younger than 50 years old (n=51; mean= 328.93MBq; 95% CI=323.75-334.11MBq) and the subjects older than 50 years old (n=59; mean=329.3MBq; 95% CI= 324.12-334.11MBq) using t-test (P value=0.96).

Univariate analysis

Progesterone receptor and SUVmax
Patients with positive progesterone receptor histopathology (n=35) had significantly lower SUVmax (mean±SD 6.23±0.65) compared to negative PR group (n=75) (mean± SD 9.71±0.71; t-test P value=0.003). This difference in SUVmax between PR-positive and PR-negative patients maintained significant in subgroup of patients with "Intraductal Carcinoma" (6.92±0.67 vs 9.75±0.77; t-test P value=

0.02) as well of "non-IDC" subgroup (2.08±0.39 vs 9.43±1.73; t-test P value<0.01).

Estrogen receptor and SUVmax
Patients with positive estrogen receptor histopathology (n=38) had significantly lower SUVmax (mean±SD 6.74± 0.66) compared to negative ER group (n=72) (mean±SD 9.59±0.73; t-test P value=0.012). This difference in SUVmax between PR-positive and PR-negative patients maintained significant in the subgroup of patients with "Intraductal Carcinoma" (7.25±0.66 vs 9.67±0.79; t-test P value=0.05) but not among the "non-IDC" subgroup (4.03±1.98 vs 8.8±1.86; t-test P value=0.1). Of note, we had limited number of subjects in this subgroup (ER-positive=6 vs ER-negative=7) and this could explain lack of statistical power, even though the trend was observed.

Her-2 Neu and SUVmax
Patients with positive Her-2 Neu histopathology (n=47) had similar SUVmax (mean±SD 8.87±0.73) compared to negative Her-2 Neu group(n=63) (mean±SD 8.42±0.78; t-test P value=0.68).

T-staging and SUVmax
To assess whether SUVmax was significantly different among the subjects grouped based on T-staging, Analysis of Variance (ANOVA) was applied, which indicated this difference as statistically significant (R-squared=0.08, Adjusted R-squared=0.05, P value=0.04) (Table 1).

Using univariate regression model, SUVmax showed significant increase by advancement of T-staging (beta-coefficient=1.24±0.49; P value=0.013).

There was a statistically significant correlation between SUVmax and T-staging of the subjects (correlation coefficient=0.23; P value=0.013).

Peri-neural invasion and SUVmax.
There was no statistically significant difference between SUVmax of subjects with peri-neural invasion (n=32; 8.66± 1.12) and subjects without peri-neural invasion (n=78; 8.59±0.62; t-test P value=0.95).

Lymphovascular invasion and SUVmax
There is no statistically significant difference between SUVmax of cases with lymphovascular invasion (n=30; 8.26±1.17) and subjects without lymphovascular invasion (n=80; 8.74±0.61; t-test P value=0.70).

### Lymph node involvement and SUVmax of main tumor
There was no statistically significant difference between SUVmax of the main tumor subjects with positive lymph node invasion (n=54; 7.91±0.73) and subjects without lymph node invasion (n=24; 7.15±0.94; t-test P value=0.54).

SUVmax of main tumor and SUVmax of axillary lymph node
There was a statistically significant correlation between SUVmax of main lesion and axillary lymph node (correlation

Table 1. *Profile of patient population.*

T Stage	Number of cases	SUVmax (mean)	SUVmax (SD)	Compared to T1	Compared to T2	Compared to T3
T1	9	4.39	0.85	-----	-----	-----
T2	47	7.84	0.85	0.09	-----	-----
T3	11	9.23	1.74	0.05	0.47	-----
T4	42	10.09	0.87	< 0.01	0.06	0.7
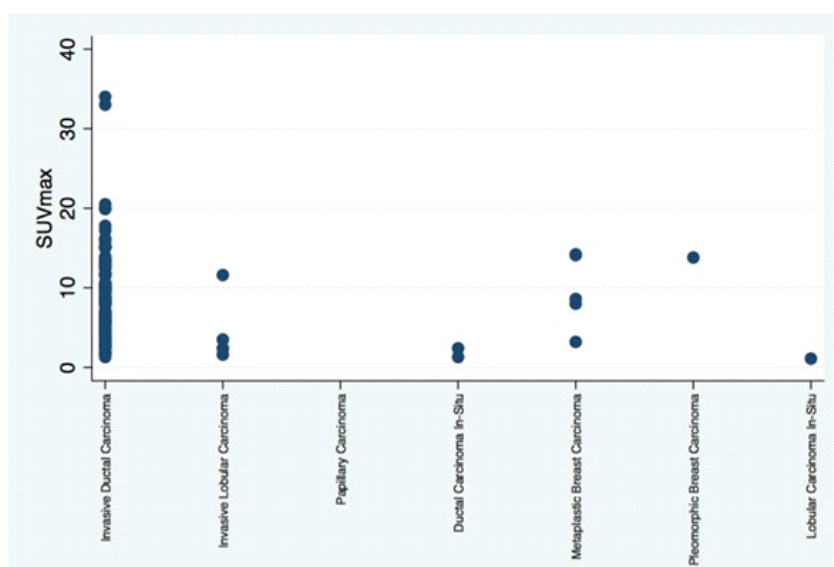
Figure 1. Tumor SUVmax scatter-plot grouped based on by histopathology types (X-axis).

coefficient=0.48; P value<0.01).

Using univariate regression model, SUVmax of lymph node could be predicted based on SUVmax of tumor using the following formula:

SUVmax (Lymph node)=0.37 * SUVmax (Tumor) +1.43; P value<0.01.

SUVmax of primary tumor and pathological grade
Implementing analysis of variance (ANOVA) there was no statistically significant difference in SUVmax of primary tumor among the subjects with grade I histopathology (n=6; 5.72±1.91), grade II (n=36; 7.91±1.00) and grade III (n=68; 9.23±0.68), P value=0.24.

SUVmax and tumor histopathology types
There was no statistically significant difference in SUVmax of primary tumor among the subjects grouped based on histopathology (ANOVA, P value=0.43) (Figure 1).

SUVmax of primary tumor and patient age
There was no statistically significant correlation between patient age and SUVmax (P value=0.71). There was no statistically significant difference between SUVmax of subjects younger than 50 years old (n=51; 8.73±0.75) and subjects older than 50 years old (n=59; 8.50±0.79; t-test P value=0.83).

Axillary lymph node SUVmax (nSUVmax) and progesterone receptor
There was no statistically significant difference between nodal nSUVmax of the subjects with positive PR (n=32; 3.99±0.65) and negative PR (n=48; 4.32±0.58; t-test P value=0.71).

Axillary lymph node SUVmax (nSUVmax) and estrogen receptor
There was no statistically significant difference between nodal SUVmax (nSUVmax) of the subjects with positive ER (n=32; 3.93±0.62) and negative ER (n=48; 4.36±0.59; t-test P value=0.62).

Multivariate analysis

Estrogen-progesterone receptor discordance
We defined the discordance between ER and PR status as either (ER+/PR-) or (ER-/PR+). Among the patients with discordant ER/PR(n=15), there was no statistically significant difference in SUVmax of the tumor between ER positive (n=9; 7.80±1.23) and ER negative subjects (n=6; 5.35±0.46; t-test P value=0.14)

Similarly, among the patients with discordant ER/PR (n=15), there was no statistically significant difference in SUVmax of the tumor between PR positive (n=6; 5.35±0.46) and PR negative subjects (n=9; 7.80±1.23; t-test P value=0.14.

Triple negative (ER, PR and Her2 Neu) and SUVmax

There was statistically significant difference between subjects with triple negative subtype (n=38; 10.19±1.14) comparing to other subtypes (n=72; 7.77±0.56; t-test P value= 0.03). On average, triple negative subjects had 2.42 unite higher ^{18}F-FDG uptake.

Favored prognostic receptor combination (ER positive, PR positive, Her2 Neu negative) and SUVmax

There was statistically significant difference between subjects with ER+/PR+/Her2Neu- subtype (n=18; 5.15±0.77) comparing to other subtypes (n=92; 9.28±0.61; t-test P value<0.01). On average, ER+/PR+/Her2Neu- subjects had 4.13 unite lower ^{18}F-FDG uptake.

Triple negative and grade

There was no relation between the grade of tumor and the status of triple negative (Chi-2 test; P value=0.38).

Favored prognostic receptor combination and grade

There was no relation between grade of tumor and status of triple negative (Chi-2 test; P value=0.44).

Triple negative and tumor-stage

There was no relation between tumor stage and status of triple negative (Chi-2 test; P value=0.28).

Favored prognostic receptor combination and tumor-stage

Patients with ER+/PR+/Her2Neu- status had lower tumor-stage (more likely to have T1 andT2) comparing to the other subtypes (more likely to have T3 and T4), and this trend was statistically significant (Chi-2, P value=0.01) (Table 2).

Table 2. Receptor status in patient population.

	Number of cases	T1 or T2	T3 or T4
ER+/PR+/Her2Neu-	18	14	4
Other subtypes	92	43	49

Discussion

Of the 112 patients we finally studied whose tumor staging and grading was available, SUVmax values showed a statistically significant correlation with markers of tumor aggressiveness and poor prognosis (Figure 1, Table 1).

However, SUVmax value was independent of tumor size. We found similar uptake in patients with T2 tumors (2.1-5cm) and T3 (>5cm). Patients with T4 tumors had somewhat higher SUVmax values, but this did not reach significance. There also was no influence of axillary lymph node status on the SUVmax of the primary tumor. Kumar et al. (2004) found

a lower SUVmax value in small tumors. They, however, mentioned the impact of potential underestimation [9]. Our findings are similar to a study which found no influence of tumor size or lymph node status on baseline SUVmax in patients with BC tumors larger than 2cm [10].

Tumor grade is a major prognostic factor in BC. In our series, we found a positive correlation between high histologic tumor grade and SUVmax value (SUVmax 9.7 for grade 3 vs 4.8 for grades 1+2 tumors; P<0.0001). This confirms previous reports [5, 10-15]. Grade is a composite parameter. Another group found a significant correlation of nuclear pleomorphism and of the number of mitoses but not of the architectural differentiation [10]. Breast cancer patients with tumors that are (ER)-positive and/or (PR)-positive have a better prognosis compared to women with ER- and/or PR-negative tumors [1-5, 16]. Clinical trials have also shown that the survival for women with hormone receptor-positive tumors is improved further by treatment with adjuvant hormonal and/or chemotherapeutic regimens [11, 17-19]. A recent study using data from the SEER program reported that joint ER/PR status was an independent predictor of outcome in a large group of women with BC [20]. We compared maximal SUV values obtained on PET/CT scan in all 112 patients were compared with hormonal receptor status of the tumor. Both ER/PR positive patients had statistically lower SUVmax (P value=0.01 and 0.001, respectively). Tumor-SUVmax in triple-negative (ER, PR and Her2 Neu) patients versus the rest(t-test P value=0.03). Tumor-SUVmax in patients with favored prognostic receptor combination (ER-positive, PR positive, Her2 Neu negative) versus the rest (t-test P value<0.01).

Maximal SUV of the main lesion correlates with ER/PER/Her2Neu status but not histopathology, implying that it correlates with molecular and cellular level rather than architectural/structural level in multi-scale pathologic model of cancer. Positron emission tomography CT has a role in pre surgical risk evaluation which has been identified by various studies.

Regarding the relationship between steroid hormone receptor status and ^{18}F-FDG uptake, there have been contradictory reports. Some studies showed no correlation between hormone receptor status and SUV values [21-26]. However, many recent series found higher SUV in ER-tumors [27-29]. The results from our study were concordant with a prior series which showed significantly higher ^{18}F-FDG uptake in ER- tumors than in ER+ tumors (P=0.003) [30]. Other investigators observed a significant correlation between GLUT1 and ER-alpha expression but not between GLUT1 and ER-beta expression [31]. In one study of 36 subjects, there was no significant association between SUV and PR status [7]. A study of a large number of patients found a significantly higher ^{18}F-FDG uptake in PR- tumors than in PR+ tumors (P=0.003) [30]. More investigations with more patients are necessary in order to understand the relationship between glucose metabolism and hormonal receptor status of BC.

Oncoprotein c-erbB-2 overexpression is a factor of tumor aggressiveness and poor prognosis. Ueda et al. (2008) found a significant relationship between ^{18}F-FDG uptake and c-erbB-2 oncogene expression [32]. However, 51% of tumors

we studied, were smaller than 2cm, which might have biased the results. In several other reports [13, 14, 30, 33-41], no significant influence of c-erbB-2 overexpression on SUV was found. This suggests that HER2 has no major influence on glycolytic pathways.

Triple-negative breast tumors (ER-, PR- and no overexpression of c-erbB-2) are of major interest because of their aggressiveness, poor prognosis and lack of targeted therapy. Most triple-negative tumors are of "the basal-like" molecular subtype. Our study showed that triple negative tumors had significantly higher SUVmax than other tumors (9.2 vs 5.8; P=0.0005). This was also reported by Basu and colleagues (2008).

Positron emission tomography CT has a role in pre surgical risk evaluation which has been identified by various studies, our study also suggests correlation with molecular pathology.

In conclusion, SUVmax of the main lesion correlates with stage but not the grade. Maximal SUV of the main lesion correlates with ER/PR/Her2Neu status but not histopathology types/sub-types (ductal, lobular); implying it correlates with molecular pathology rather than structural/morphological pathology. The relation between SUVmax of main lesion and lymph node is interesting. Particularly independence of nodal SUVmax to ER/PR/Her2Neu status (contrary to main lesion uptake and receptor status).

Whole body PET/CT stands a role in pre surgical evaluation of breast cancer patients in view of correlation between with various molecular markers with tumor SUVmax.

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Mexican female which doctor "smokes" patient and invokes powers of pagan and Christian divinities. She then sucks out evil from patient's head and cleanses body by passing egg or black hen over it. Museo National de Anthropologia, Mexico