Original Article

^{18}F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Features in Locally Advanced Breast Cancer and Their Correlation with Molecular Subtypes

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Abstract

Purpose: ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is now recognized as a staging investigation for locally advanced breast cancer. This retrospective review of data was performed to correlate the maximum standardized uptake value (SUV_{max}) of the primary tumor with the molecular subtype of breast cancer. **Materials and Methods:** Patients with biopsy-proven, treatment naïve, Stage III breast cancer, for whom ^{18}F-FDG PET/CT data and immunohistochemistry 4 was available were included in the study. Correlations were deduced between the SUV_{max} of primary tumor to the molecular subtypes. **Results:** Three hundred and two patients were included in the study. Fifty-two (17.2%) tumors were Luminal A (LA), 131 (43.4%) Luminal B (LB), 42 (13.9%) human epidermal growth factor receptor-2 enriched (HE), and 77 (25.5%) basal-like (BL). SUV_{max} of the primary tumor differed significantly between LA and other subtypes (SUV_{max}: LA Median 7.4, LB 11.65, HE 13.5, BL 15.35, $P < 0.001$). Estrogen receptor (ER) and progesterone receptor (PR) positivity were inversely correlated to the SUV_{max} of the primary (SUV_{max}: ER + Median 10.4, ER - 14.2, $P < 0.001$, PR + 9.65, PR − 13.9, $P < 0.001$). There was a strong positive correlation observed between Ki67 and SUV_{max} (Pearson Coefficient 0.408, $P < 0.001$). A SUV_{max} value of 9.65 was determined as a cutoff on receiver operating characteristic curve to differentiate between LA and other subtypes with a sensitivity of 92.3% and specificity of 70.6%. **Conclusions:** SUV_{max} of primary showed a statistically significant difference between LA subtypes when compared to other subtypes. However, there was overlap of values in each subgroup and thus ^{18}F-FDG PET/CT cannot be used to accurately assess the molecular characteristics of the tumor.

Keywords: *^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, locally advanced breast cancer, molecular subtypes*

Introduction

Breast cancer has become the number one cancer in women in urban India with an age-adjusted breast cancer rate of 37.5/100,000 in Chandigarh.[1] The estimated burden of breast cancer in India for the year 2015 was 134,214 new cases.[2] Accurate staging is critical for management decisions and prognosis in patients with newly diagnosed breast cancer. In locally advanced breast cancer (LABC) ^{18}F-Fluorodeoxyglucose Positron emission tomography/computed tomography (^{18}F-FDG PET/CT) can detect distant metastases in about a quarter of cases and change their management plan.[3] ^{18}F-FDG PET/CT is now recommended as an acceptable alternative to CT chest and abdomen and bone scan for staging LABC.[4]

Breast cancer is a heterogeneous disease based on morphology and clinical behavior. Tumor biology has always been considered to be very important in patients with breast cancer. The description of different molecular subtypes based on DNA microarray and their prognostic significance has led to wide acceptance of these subgroups in clinical practice.[5,6] The use of DNA microarray technology has not gained widespread acceptance in routine clinical practice and immunohistochemistry (IHC) is often used as a surrogate marker to define these molecular subtypes.[7]

^{18}F-FDG is the most commonly used and most extensively studied radioisotope used in PET/CT. ^{18}F-FDG uptake is considered a

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marker for the aggressiveness of tumor as it is dependent on GLUT-1 transporter expression, hexokinase activity, vascularity, degree of necrosis, density of tumor cells, mitotic index, type and grade of tumor and is inversely correlated with disease-free survival.[8-11]

We have been using ^{18}F-FDG PET/CT to stage all our patients with LABC for about 5 years. The present study aims to look at the ^{18}F-FDG PET/CT features in patients with LABC and correlate them to the molecular subtypes as determined by IHC.

Materials and Methods

After institutional review board approval, a retrospective analysis was performed on patients with a clinical diagnosis of LABC and infiltrating duct carcinoma on biopsy, selected from the database in the Department of Surgery, PGIMER, Chandigarh, a tertiary health-care center in Northern India. All patients underwent PET/CT as part of their staging. Patients for whom the clinical staging, histopathological diagnosis, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2), Ki67 status, and ^{18}F-FDG PET/CT findings were available were included for analysis. Patients with incomplete records were excluded.

Core biopsy was performed for diagnosis and ER, PR, HER2, and Ki67 results were reported as assessed by IHC. All patients with HER2 result of 2+ on IHC were subjected to FISH for confirmation and final classification. Based on the IMPAKT working group statement,[7] the patients were then classified into Luminal A (LA), Luminal B (LB), HER2 enriched (HE), and Basal-like (BL) subtypes.

^{18}F-FDG PET/CT examinations were performed using a PET/CT scanner (Discovery 710; GE Healthcare, Milwaukee, WI, USA). Approximately 370 MBq of ^{18}F FDG was injected, and images were acquired after 1 h. CT images were acquired using multidetector CT equipment with tube voltage of 120 kV and smart mA (range 150–300 mA), a tube rotation time of 0.5 s per rotation, a pitch of 0.984, and a section thickness of 3.75 mm. Emission PET data were acquired for 2 min per bed. Attenuation correction of PET images was done using CT data. Reconstruction of PET images was done using an ordered-subset expectation maximization iterative reconstruction algorithm with 24 subsets, 3 iterations, Gaussian post filtering (FWHM 5.5 mm), matrix size of 192 cm × 192 cm and 70 cm transaxial field of view. Maximum standardized uptake value (SUV_{max}) of the primary tumor and lymph nodes, size of primary and lymph nodes and presence and location of metastases were studied on the PET-CT images.

Statistical analysis

All statistical analyses were performed on SPSS statistical software 19.0 (SPSS Inc., Chicago, Illinois, USA). Kolmogorov–Smirnov and Shapiro–Wilk tests were used to check for the normality of the data. Kruskal–Wallis test and Mann–Whitney U-test were used to compare the parameters obtained on ^{18}F-FDG PET/CT to molecular subtypes and ER, PR, and HER2 status of the tumors. The correlation between Ki67 values and parameters obtained on ^{18}F-FDG PET/CT was determined using Pearson coefficient. The relationship between the presence of axillary lymph nodes and presence of distant metastases to individual molecular subtype was derived using Chi-square test. Receiver operating characteristic (ROC) curve analysis was performed to examine the diagnostic performance of SUV_{max} of the primary tumor to differentiate LA subtype from others. Statistical significance was defined as $P < 0.05$.

Results

Over a period of 55 months (December 1, 2012–June 30, 2017), 302 female patients fulfilling the selection criteria were analyzed.

The mean age of the patients was 48.6 ± 11.0 years (range 24–75). Out of the 302 tumors studied, 176 (58.3%) were found to be ER positive, 132 (43.7%) to be PR positive, and 183 (60.6%) were hormone receptor (HR) positive (ER/PR positive). A total of 109 (36.1%) tumors were found to be HER2 positive out of which 63 (57.8%) were found to be ER positive, 41 (37.6%) were found to be PR positive, and 67 (61.5%) were HR positive. On the basis of IHC characteristics, 52 (17.2%) patients were found to have LA tumors, 131 patients (43.4%) to have LB, 42 patients (13.9%) to have HE, and 77 patients (25.5%) to have BL tumors.

Relationship between molecular subtypes and positron emission tomography/computed tomography parameters

The median tumor size in the study population was 4.2 ± 3.1 cm (range 0.7–16.4 cm). Overall median value for SUV_{max} for primary tumor was 14.0 ± 9.6 (range 2.1–64.4) and for axillary nodes was 10.3 ± 7.8 (range 1.1–61.4). Size of the primary, SUV_{max} of primary, and SUV_{max} of the axillary lymph nodes differed significantly between LA and other subtypes (LB, HE, and BL) (*P* value for size of primary for all subtypes <0.001, for SUV max of primary for all subtypes <0.001, for SUV_{max} of LN between LA and LB <0.001, between LA and HE <0.001, and between LA and BE <0.007) [Table 1]. However, there was no difference noted in the same parameters between other groups (LB to HE and BL or between HE and BE). Size of the axillary lymph nodes was not statistically different between any of the groups.

Enlarged and/or FDG avid ipsilateral axillary nodes were found in 273 (90.4%) patients. In LA subtype, 40 patients (76.9%) had positive axillary lymph nodes whereas in rest of the tumor subtypes, the lymph node positivity was found in more than 90% of the patients. The difference between lymph node positivity in LA to

other subtypes was found to be statistically significant as well ($P = 0.002$) [Table 1].

Enlarged and/or FDG avid internal mammary (IM) nodes were seen in 88 (29.1%) patients and supraclavicular (SC) nodes in 75 (24.8%) patients. With respect to molecular subtypes, suspicious IM nodes were identified in 20 (38.5%) patients with LA tumors, 40 (30.5%) patients with LB tumors, 10 (23.8%) patients with HE tumors, and 16 (20.8%) patients with BL tumors. Similarly, SC nodes were found to be suspicious in 16 (30.8%) patients with LA tumors, 34 (26%) patients with LB tumors, 10 (23.8%) patients with HE tumors, and 14 (18.2%) patients with BL type tumors.

FDG avid skin thickening was found in 157 patients (52%). Skin involvement on PET CT was detected in 32 (61.5%) patients with LA tumors, 62 (47.3%) patients with LB type tumors, 19 (45.2%) patients with HE type tumors, and 42 (54.5%) patients in BL type of tumors.

After ^{18}F-FDG PET/CT, 115 patients (38.1%) were upstaged to Stage IV, whereas 187 patients (61.9%) remained as Stage III (LABC). There was a slightly higher incidence of distant metastases observed on ^{18}F-FDG PET/CT in BL tumors when compared to LA, LB, and HE type of tumors [Table 1]. This difference, however, was not found to be statistically significant ($P = 0.749$). In patients who were upstaged to Stage IV, 18 patients had LA tumors, 49 had LB tumors, 15 had HE tumors, and 33 had BL tumors. Fifty-six (48.7%) of these had metastases to bones, 46 (40%) to lungs, 23 (20%) to distant lymph nodes, and 11 (9.6%) to the liver. One patient each (0.9%) had metastases to contralateral breast and omentum. Out of these 115 patients, 93 (80.9%) had metastasis to one site, 16 (13.9%) had metastases to two sites, and only five patients (4.3%) had metastases to 3 or more sites. There was no statistical difference in the location of metastases on the basis of molecular subtypes of tumors.

Relationship of positron emission tomography-computed tomography parameters to estrogen receptor, progesterone receptor, human epidermal growth factor receptor-2, and Ki67

ER and PR positivity were inversely correlated to size of the primary and to SUV_{max} of the primary tumor. The correlation was strong with SUV_{max} ($P < 0.001$), with a median SUV_{max} of ER and PR positive tumors of 10.4 and 9.65 vis-a-vis a median SUV_{max} of 14.2 and 13.9 for ER and PR negative tumors. However, a different trend was noted for HE tumors. HER2 positivity was directly correlated to size of tumor ($P = 0.029$) and SUV_{max} of the lymph node ($P = 0.019$) with little effect on the SUV_{max} of the primary tumor [Table 2].

Overall, the median value for Ki67 was 29.5 ± 18 (range 2–90). It was 8.7 ± 2.2 (range 5–10) for LA tumors, 30.3 ± 13.6 (range 2–90) for LB, 31.8 ± 15.6 (range 10–80) for HE, and 40.8 ± 19.9 (range 5–80) for BL tumors. There was positive correlation observed between Ki67 and size of the tumor (Pearson Coefficient 0.321, $P < 0.001$), SUV_{max} of tumor (0.408, $P < 0.001$), size of lymph nodes (0.134, $P = 0.028$), and SUV_{max} of lymph nodes (0.235, $P < 0.001$). Out of all these parameters, Ki67 was found to have the strongest association with SUV_{max} of tumor (0.408).

On sorting Ki67 as high or low based on the 14% cutoff, a median SUV_{max} of the primary was 7.7 (interquartile

Table 1: Clinical and positron emission tomography - computed tomography profile of the patients

	Luminal A (*n*=52)	Luminal B (*n*=131)	HE (*n*=42)	Basal like (*n*=77)
Age mean±SD (range), in years	49.0±11.9 (27-75)	48.3±11.5 (24-74)	50.8±8.5 (33-68)	47.5±10.8 (26-75)
Size of primary tumor* (cm)	3.0	4.6	4.6	4.4
Axillary node involvement on PET-CT (%)	76.9	91.6	97.6	93.5
Size of axillary nodes* (cm)	1.3	1.5	1.6	1.7
SUV_{max} of primary tumor*	7.4	11.7	13.5	15.4
SUV_{max} of axillary nodes*	4.9	9.2	9.2	8.4
Upgrade to Stage IV on PET-CT (%)	34.6	37.4	35.7	42.9

*Median values. PET-CT: Positron emission tomography - computed tomography, SUV_{max}: Maximum standardized uptake value, HE: Human epidermal growth factor receptor-2 enriched

Table 2: Correlation of estrogen receptors, progesterone receptor and human epidermal growth factor receptor-2 positivity with Positron emission tomography - computed tomography parameters

	ER		PR		HER2	
	Positive	Negative	Positive	Negative	Positive	Negative
Size of primary tumor* (cm)	3.9	4.6	3.6	4.6	4.7	3.9
Size of axillary nodes* (cm)	1.5	1.6	1.5	1.6	1.6	1.4
SUV_{max} of primary tumor*	10.4	14.2	9.6	13.9	12.7	11.6
SUV_{max} of axillary nodes*	8.5	8.6	8.5	8.7	9.4	7.9

*Median values. PR: Progesterone receptor, ER: Estrogen receptors, SUV_{max}: Maximum standardized uptake value, HER2: Human epidermal growth factor receptor-2

range [IQR] 6.5, range 2.1–21.0) for tumors with low Ki67 and 13.1 (IQR 9.1, range 2.1–64.4) for tumors with high Ki67. This difference was again found to be statistically significant ($P < 0.001$).

Cutoff value of maximum standardized uptake value to differentiate between Luminal A other subtypes

On the basis of ROC curve, a SUV_{max} value of 9.65 was determined as a cutoff to differentiate between LA and other subtypes [Figure 1]. The sensitivity and specificity of SUV_{max} value of 9.65 as a cutoff value was 72.3% and 70.6%, respectively.

Discussion

Breast cancer is the most common cancer among women, yet is still incompletely understood because of the heterogeneity associated with it. Classic pathologic markers of prognosis often fail to provide an answer for prognostic predictions, especially in an individual patient. The last 15 years have seen a change in the understanding of breast cancer and tumor biology has been better defined as a result of the development of molecular subtypes of breast cancer. These subtypes have shown significant differences in terms of natural history, risk factors, prognosis, and therapeutic options.[12,13] In daily clinical practice, the classification of these molecular subtypes is based on surrogate markers tested by IHC. However, there is a variable concordance between the subtypes defined by IHC and those defined by gene expression profiling.[7]

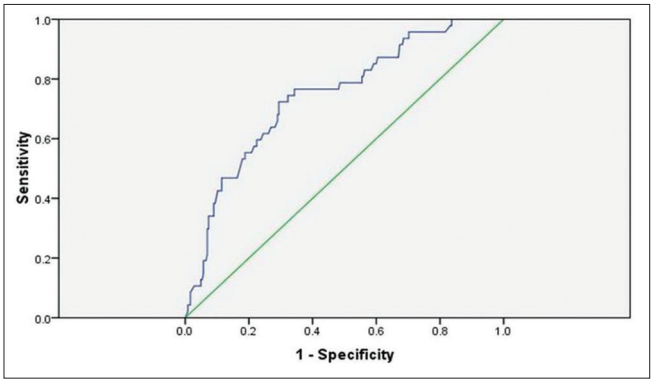

Figure 1: Receiver operating characteristic curve of maximum standardized uptake value values for Luminal A tumors

The imaging findings on ^{18}F-FDG PET/CT in patients with breast cancer have been correlated to tumor type, size, grade, receptor expression, and nodal metastases with variable success.[14,15] The present study aimed to see if the changes in ^{18}F-FDG PET/CT could reflect the tumor biology as represented by the molecular subtype. The study population was fairly uniform that all patients had locally advanced infiltrating duct breast cancer. LA tumors had smaller primary tumors, and lower SUV_{max} values in both the primary and the axillary nodes. This reflects the biology of LA tumors, which are relatively slow growing as compared to the other subtypes. A reverse analysis showed that ER/PR-positive tumors were associated with smaller tumors and lower SUV_{max} values. Ki67 values were lowest in LA tumors.

^{18}F-FDG PET/CT findings have been correlated to different clinical and pathological prognostic factors in breast cancer, but the number of studies that have analyzed the ^{18}F-FDG PET/CT findings according to the molecular subtype are few [Table 3]. All the studies reveal similar findings with Luminal tumors showing lower SUV_{max} values as compared to HE and BL tumors. However, there is significant overlap in the range of values in the various molecular subtypes. Similarly, an attempt to deduce a SUV_{max} value to characterize LA tumors could do so only with a sensitivity and specificity of 72.3% and 70.6%, respectively.

These findings depict the futility of trying to characterize the molecular subtypes on the basis of ^{18}F-FDG PET/CT findings. There is considerable variation in the clinical outcome of patients within each molecular subtype. It would be interesting to correlate the long-term clinical behavior of individual patients to their ^{18}F-FDG PET/CT findings and see if the ^{18}F-FDG PET/CT could predict prognostic subgroups within each molecular subtype.

Conclusions

There were significant differences observed between LA and other subgroups in terms of size of primary,

Table 3: Review of studies using molecular subtypes for analyzing positron emission tomography - computed tomography findings

Reference	Number of patients	SUV_{max} values				
		Luminal A	Luminal B HER-	Luminal B HER+	HER2+	TNBC
Koolen *et al*., 2012[16]	57	5.5			6.2	10.8
Garcia Vicente *et al*., 2013[17]	168	6.01	7.09	8.6	9.38	11.67
Koo *et al*., 2014[18]	548	4.69	6.51		7.44	9.83
Miyake *et al*., 2014[19]	89	4.4	7.7	7.3	11.8	9.1
Kitajima *et al*., 2015[20]	306	3.41	5.17	6.57	7.55	6.97
Higuchi *et al*., 2016[21]	387	2.9	5.15		4.36	6.3
Lee *et al*., 2017[22]	183	4.5	7.2	7.2	10.2	8.8
Present study	302	7.4	11.7		13.5	15.4

SUV_{max}: Maximum standardized uptake value, TNBC: Triple negative breast cancer, HER2: Human epidermal growth factor receptor-2

SUV_{max} of primary, presence of axillary lymph nodes, and SUV_{max} of lymph nodes. These parameters, especially SUV_{max} of primary, cannot be used in the clinical setting to classify the molecular subtypes. The clinical behavior of individual patients needs to be correlated with their imaging parameters to see if ^{18}F-FDGPET/CT can identify prognostic subgroups within each molecular subtype.

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Conflicts of interest

There are no conflicts of interest.

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