Original Article

Role of ^{18}F-Flurodeoxyglucose Positron-Emission Tomography/Computed Tomography in the Evaluation of Early Response to Neoadjuvant Chemotherapy in Patients with Locally Advanced Triple-Negative Breast Cancer

Bina Basnet, Pankaj Goyal[1], Vivek Mahawar[2], Sneha Jatan Bothra[1], Chaturbhuj Agrawal[1], Bikash Bikram Thapa[3], Vineet Talwar[1], Parveen Jain[1], Venkata Pradeep Babu Koyyala[1], Varun Goel[1], Ullas Batra[1], Dinesh Chandra Doval[1]

Departments of Radiology, [1]Medical Oncology, [2]Radiology and [3]Surgical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India

Address for correspondence:
Dr. Vivek Mahawar, Department of Radiology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India. E-mail: drmahawarvivek@gmail.com

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Abstract

Background: Response evaluation in locally advanced breast cancer is done through different methods ranging from clinical examination to magnetic resonance imaging, however evaluation with positron-emission tomography/computed tomography (PET/CT) in now being incorporated for the response evaluation. The aim of the present study is to correlate response to neoadjuvant chemotherapy (NACT) with PET/CT scan. **Materials and Methods:** The present study is a retrospective analysis of 30 locally advanced, triple-negative breast cancer patients. PET/CT scan was done pretreatment and post three and six cycles of NACT and was correlated with pathologic complete response (pCR). Responding disease was considered when there was at least a 50% reduction in the longest diameter. **Results:** The median pretreatment size of the breast lesion in CT scan was 3.9 ± 2.3 cm (2–12 cm) and maximum standardized uptake value (SUVmax) on PET/CT was 8.5 ± 5.5 (2.9–24). Among the responders, the median decrease in size of lesion was 3.2 ± 1.3 cm and median reduction in SUV of the tumor among was −8.1 ± 5.4 and was statistically significant when compared with nonresponders ($P < 0.001$). CT scan has 66% accuracy and PET has 82% accuracy at post three cycles NACT in predicting the pathological response. PET/CT had higher sensitivity and specificity when compared with CT findings alone in response evaluation. **Conclusion:** PET/CT scan can be considered as a sensitive tool for predicting pCRs and further larger trials are required to establish these findings.

Keywords: *18-fluorodeoxyglucose positron-emission tomography/computed tomography, locally advanced breast cancer, neoadjuvant chemotherapy*

Introduction

Breast cancer is the second-most common cancer worldwide after lung cancer in women. Although the incidence has been increasing in recent years, mortality has been declining.[1] According to the American Joint Committee on Cancer the Stage IIb, IIIA and IIIb are referred as locally advanced breast carcinoma which usually have high locoregional recurrence and distant metastasis.[2] Immunohistochemical analysis of the estrogen receptor (ER), the progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) classify breast cancer into luminal type (ER and or PR-positive, HER2-negative), HER2-positive type breast carcinoma, and triple-negative breast carcinoma (TNBC) (ER, PR, and HER2 all negative). The latter two are more aggressive than luminal variety and require timely evaluation of response to treatment.[3]

Neoadjuvant chemotherapy (NACT) for locally advanced breast cancer (LABC) is effective in downstaging the tumor.[4-6] It is important to differentiate between the responders and nonresponders of NACT so that the chemotherapy protocol can be changed for better efficacy or the cost of the treatment and the toxicity can be curtailed in time. Unlike computed tomography (CT) and magnetic resonance imaging (MRI) functional imaging techniques, positron-emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) (^{18}F-FDG PET/CT) have the unique ability to detect subclinical alteration in tumor physiology and biochemistry resulting from efficacious

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therapy.[5] The novel combination of PET/CT has higher accuracy to localize and interpret FDG uptake and has encouraging results in predicting the early response of breast cancer to NACT.[6]

Materials and Methods

Patient population

This is a retrospective analysis of 30 women with histopathology proven locally advanced TNBC. The consort diagram for the study is shown in Figure 1. All patients received six cycles NACT DE (docetaxel 75mg/m^2 and epirubicin 75 mg/m^2) or TAC regime (docetaxel 75 mg/m^2, adriamycin 75 mg/m^2 and cyclophosphamide 750 mg/m^2). Pretreatment 18-FDG PET/CT was done and repeated after three cycles of NACT and then after six cycles of NACT. The results were evaluated with reference to the final histopathology following surgery, which was carried out after completion of six cycles of NACT.

^{18}F-flurodeoxyglucose positron-emission tomography/computed tomography

Patients were kept fasting for 6 h (blood glucose level <200 mg/dl). ^{18}F-FDG (5–10 MBq/kg) was administered into the arm opposite to the breast tumor using a venous line. Imaging was started 40–60 min after injection and was performed from mid-thigh level to the vertex with the arms raised. PET and CT data were acquired with the Biograph true point PET/CT scanner with 40-slice Sensation CT scanner (Siemens). CT data were acquired first (120 kV, 100 mAs, no contrast enhancement). PET emission data were acquired in a three-dimensional mode, with 2 min/bed position, and reconstructed using a three-dimensional row-action maximum likelihood algorithm. The attenuation-corrected images were normalized for injected dose and body weight and converted into standardized uptake values (SUVs). The SUV was defined as (tracer concentration [kBq/mL])/(injected activity [kBq]/patient body weight [g]). PET/CT images were interpreted by 2 nuclear medicine specialists masked to the patient's record. Images were displayed on the syngovia workstation (Siemens). The SUV was measured by manually marking a circular region of interest in the three planes (coronal, sagittal, and axial) around the tumor (three-dimensional region of interest). The maximum SUV (SUVmax within the region of interest) was used for the study analysis.

Response evaluation included clinical examination, PET/CT, and postsurgery final histopathological response. Clinical examination and PET/CT were performed in all patients after the third cycle of NACT and after the completion of six cycles before the surgery. The CT part of PET/CT was considered for baseline as well as for NACT response evaluation. On CT, maximum diameter in one plane was used and on PET/CT SUVmax of CT assigned lesion was used. For clinical and CT analysis, the cutoff

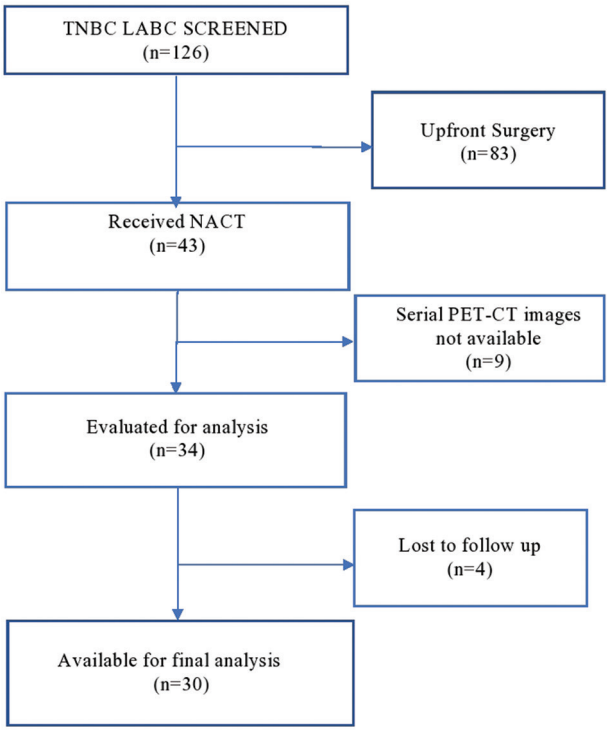

Figure 1: Consort diagram

value of 50% was taken as cutoff value to classify the study population as responder (reduction in >50%) and nonresponders (reduction <50%).

A single pathologist validated all histopathological report. Maximum diameter in one plane was taken for reporting. Patients were considered as responders when the tumor was entirely replaced by fibrosis/necrosis or when the pathological tumor size is ≤25% of the pretreatment size. Patients were nonresponders when the pathological tumor size is more than 25% of the pretreatment size.

The data were analyzed using SPSS version 16 (IBM, USA). Comparison of response on PET/CT response was done using sensitivity, specificity, and accuracy, which were determined at the end of the study considering pathological response as the gold standard. The mean difference of SUVmax between responders and nonresponders was compared using Mann–Whitney U-test. A value of $P < 0.05$ was considered statistically significant.

Results

The mean age of patients was 47.8 ± 14.0 (range 29–69 years). Among them stage IIb is 8 (26.7%), stage IIIA is 13 (43.3%), and stage IIIB 9 (30%). All patients had invasive ductal carcinoma in tru-cut biopsy. Among NACT, DE was given in 19 (63.3%) and 11 (36.7%) patients received TAC.

The median pretreatment size of the breast lesion in CT scan was 3.9 ± 2.3 cm (2–12 cm) and SUVmax on PET/

CT was 8.5 ± 5.5 (2.9–24). Twenty-four of 30 patients had positive lymph nodes on PET/CT showing FDG uptake. The size of lymph nodes ranged from 0.9 to 4.5 cm and the SUVmax of the axillary lymph node ranges from 1.4 to 17.0 cm. The average reduction in size and SUV of the primary tumor after three cycles of NACT was mentioned in Table 1. Among the responders, the median decrease in size of lesion was 3.2 ± 1.3 cm and median reduction in SUV of the tumor among was −8.1 ± 5.4 and was statistically significant when compared with nonresponders $P < 0.001$. Response evaluation in one of the patients is shown in Figure 2.

Five patients had a complete metabolic response in the primary tumor after three cycles NACT. Of 26 lymph node positive patients, 9 (34.6%) was metabolically inactive in PET/CT after three cycles of NACT.

All patients underwent surgery, 26 patients underwent MRM and 4 underwent BCS. At cutoff of 25% baseline value, 18 patients were pathological responders and 12 patients were pathological nonresponders. The reduction in metabolic activities (SUVmax) of tumors among responders and nonresponders post-NACT were 70.0% ±26.0% and 34.5% ±37.0%, respectively [Table 2]. CT has 66% accuracy and PET has 82% accuracy at post three cycles NACT in predicting the pathological response. PET/CT had higher sensitivity and specificity when compared with CT findings alone in response evaluation [Table 3].

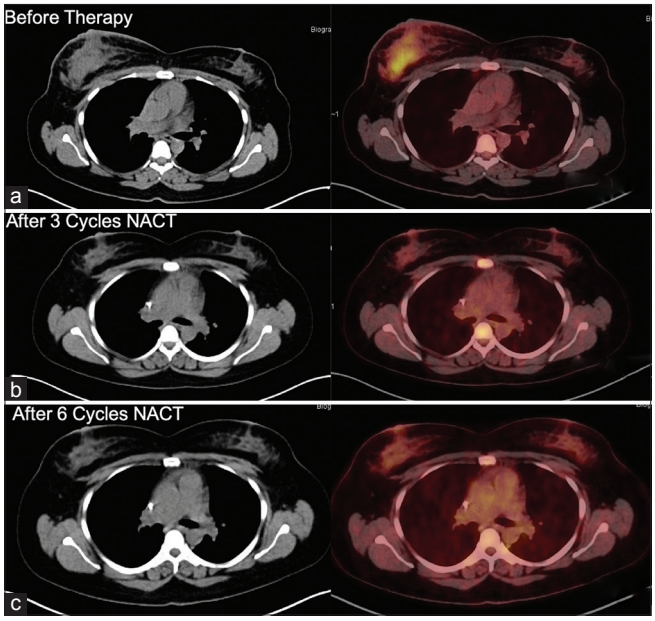

Figure 2: (a) Right breast shows metabolically active confluent lobulated nodular ill-defined soft tissue mass (6.8 cm × 3.0 cm, maximum standardized uptake value 7.5) predominantly in lower half. (b) Right breast shows mildly metabolically active lobulated nodular ill-defined soft-tissue lesion (2.0 cm × 1.7 cm, maximum standardized uptake value 1.8) at 6–8 o'clock position. (c) Right breast shows mildly metabolically active lobulated nodular ill-defined soft-tissue lesion (2.0 cm × 1.1 cm, maximum standardized uptake value 1.5) at 6–8 o'clock position

Discussion

Locally advanced breast cancer that includes Stage IIB and Stage III necessitates multidisciplinary approach for the optimal outcome. LABC of any subtype is candidate for NACT to achieve complete pathological resection, breast conservation, and minimize the risk of distant recurrence.[7-9] Patients undergoing neoadjuvant treatment for breast cancer require periodic evaluations during treatment to assess the response. There are no formal guidelines regarding response evaluation. The general approaches are clinical examination and imaging studies including ultrasound and/or MRI. The correlation between tumor measurements by physical examination, imaging (mammography, ultrasonography, or MRI), and tumor size on final pathologic analysis is modest at best.[10] Meta-analysis shows contrast-enhanced MRI has high specificity (91%), but low sensitivity (63%) to predict pathologic complete response (pCR).[11]

Triple-negative breast cancers (TNBC)[12] are those without hormone receptor and HER2 expression and account for 15% of breast tumors. TNBC has aggressive biology and has a poorer outcome compared with other subtypes. However, they have high responsiveness to NACT, called the "triple-negative paradox."[13] Due to its elevated risk of distant recurrence and death,[8] it is extremely important to identify the clinic-biologic, molecular, or imaging biomarkers that may predict early response to NACT.[14] Accurate response evaluation of NACT allows for response-adjusted sequential chemotherapy. It gives an opportunity for independent evaluation of different drug regimens and the possibility to individualize therapy based on a patient's tumor response.[15,16]

Table 1: Response evaluation in PET/CT

CT response	Reduction in size of lesion	Reduction in SUV_{max}
Responders	-3.2±1.3 cm, (75.0±20.0%) (*n*=16)	-8.1±5.4, (70.3±33.8%) (*n*=19)
Non-responders	-0.6±1.5 cm, (15.0±24.6%) (*n*=14)	-2.5±2.7, (27.2±15.7%) (*n*=11)
P	<0.001	<0.001

Table 2: Change in metabolic activity among pathological responders and non-responders

	Mean±SD	*P*
SUV_{max} Basline		
pResponders (*n*=18)	10.0±4.6	0.8
pNon-Responders (*n*=12)	10.6±6.8	
SUV_{max} reduction post NACT		0.06
pResponders	-7.8±5.0	
pNon-responsers	-4.0±5.3	
SUV_{max} % reduciton post NACT		0.01
pResponders	-70.0±26.0	
pNon-Responders	-34.5±37.0	

Table 3: Prediction of pathological response

	Pathological Response		Prediction of PET/CT		
	Responders	Non-Responders	Sensitivity	Specificity	Accuracy
CT Response					
Responders	12	4	66%	67%	66%
Non-Responders	6	8			
PET Response					
Responders	16	3	89%	75%	82%
Non-Responders	2	9			

^{18}F-FDG-PET/CT, a gold standard for *in vivo* evaluation of tumor cell activity is superior to other morphological imaging modalities. The use of PET/CT to monitor early tumor response to NACT have showed higher efficacy in predicting the pathological response whatever the tumor subtype.[6,17] In an evaluation[6] to determine optimal imaging time for predicting pathologic chemotherapy response, it was found that the best discrimination was measured for mean SUV at the midpoint of therapy, which identified 77% of low responding tumors and 100% of high responding tumors and had a receiver operating characteristic area of 0.93.[18]

The variation in sensitivity (39%–100%) and specificity (39%–100%) in literature is probably due to differences in inclusion and exclusion criteria. There is significantly different (P = 0.04) reduction rate in SUVmax between patients who are pathologically responsive and nonresponsive to NACT with higher (>80%) sensitivity and specificity.[19,20] The difference in response rate is also significant in our study with P = 0.01. Different studies showed different values of sensitivity, specificity at the different cutoff values. Evaluation after second-course NACT[6] with SUVmax reduction rate cutoff value of 40% showed the sensitivity, specificity of 89% and 95%. Higher the cutoff range lower the sensitivity and specificity has been observed.[17]

In univariate logistic analysis, negative HER2 status (P = 0.042), high metabolic response (cutoff = 50%; P = 0.002), and low tumor SUV_2-max (cutoff = 6.9; P = 0.013) correlated with complete pathological response.[21] Huober demonstrated in multivariate analysis the most accurate and strongest independent predictor of pCR was tumor difference in SUVmax: with the cutoff at 50%.[15,21] Beside FDG, 11-C methionine and 15 O-water have also been used in different studies and revealed promising results regarding the prediction of pathological response rate. Magnetic resonance spectroscopy, another functional imaging modalities is also being used in response evaluation of NACT in LABC.[20]

Major limitations of this study are its retrospective nature and heterogenous NACT regimens. However, robust prospective design with a large sample size would be required to confirm these results.

Conclusion

PET-CT scan can be considered as an important imaging modality for response evaluation to NACT and can also predict pathologic CR. Thus, further trials should be conducted to solidify the findings of the current study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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