Original Article

Fluorine-18 FDG PET/CT and New NIMS Grading System for Chemotherapy Response in Breast Cancer

Geethika Reddy Vakati, Ranganath Ratnagiri, Madhur Kumar Srivastava[1]

Departments of Surgical Oncology and [1]Nuclear Medicine, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

Abstract

Background: Positron emission tomography with computed tomography (PET-CT) using fluorine 18-fluorodeoxyglucose (F-18 FDG) is increasingly used to stage patients with locally advanced breast cancer and for assessing treatment response after neoadjuvant chemotherapy (NACT). **Aims and Objectives:** The aim of the study was to assess the correlation between PET-CT parameters and pathologic response of breast primary after NACT in breast cancer patients and to devise a grading system called NIMS grading system for response assessment using PET quantitative parameters. **Materials and Methods:** 55 patients who underwent F-18 FDG PET-CT before starting the therapy and again after completion of therapy were identified and included in the study. The clinical data and the histopathologic findings were recorded. All the patients received chemotherapy followed by surgery with axillary lymph node dissection. The PET-CT results were interpreted both qualitatively by visual analysis and quantitatively by estimating maximum Standardized uptake values(SUV_{max}) and other parameters – SUVmean, SUL, SUV_{BSA}, Metabolic tumor volume (MTV) and Total lesion glycolysis (TLG). **Results:** The sensitivity and specificity of F-18 FDG PET-CT to detect the residual disease after neoadjuvant chemotherapy was 75.6% & 92.8% respectively. Differences between complete response and residual disease were significant for ΔSUV_{max}(p=0.005), ΔSUV_{mean}(p=0.006), ΔSUL (0.005) and ΔSUV_{BSA}(0.004), while ΔMTV and ΔTLG were not significantly different between the two groups. The new NIMS grading system included scoring of ΔSUV_{max}, ΔSUV_{BSA}, ΔTLG and ΔMTV on scale of 1 to 4 and correlated well with PERCIST criteria. **Conclusion:** F-18 FDG PET-CT had a good accuracy in the detection of residual disease after completion of NACT. Pre chemotherapy PET-CT is not adequate to predict the response of primary tumour to chemotherapy. However, changes in the values of various PET-CT parameters are a sensitive tool to assess the response to chemotherapy. The new grading system is easy to use and showed good correlation to PERCIST.

Keywords: *Breast cancer, metabolic tumor volume, NIMS grading system, response evaluation, standardized uptake value adjusted to lean body mass, standardized uptake value, standardized uptake value adjusted to body surface area, maximum standardized uptake value, mean standardized uptake value, total lesion glycolysis*

Introduction

Neoadjuvant chemotherapy (NACT) for breast cancer is a widely accepted initial treatment modality for patients with unfavorable tumor characteristics and locally advanced breast cancer. Patients with unicentric, high-grade, human epidermal receptor 2 (HER2)-positive or triple-negative cancers often respond dramatically to chemotherapy. NACT has been shown to be equivalent to adjuvant chemotherapy in terms of overall survival and disease-free survival. Furthermore, it has been shown to improve surgical outcomes and downstage patients with operable breast cancer desiring breast conservation.[1] In addition, NACT is presumed to eliminate micrometastatic distant disease.

Pathological complete response (pCR) is a strong prognostic marker and may be a surrogate for long-term disease-free survival.[1] NSABP-B27 trial defined pCR as no invasive cancer in the breast.[2] von Minckwitz *et al*., in their study, defined pCR as no residual disease (RD) in both breast and axilla and concluded that pCR in the breast and axilla was associated

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Address for correspondence:
Dr. Madhur Kumar Srivastava, Department of Nuclear Medicine, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India. E-mail: drmadhur77@yahoo.co.in

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with a favorable outcome.[3] Achieving pCR after NACT is associated with favorable disease-free and overall survival in early-stage breast cancer. Few studies have suggested that nodal pCR is an excellent prognostic factor and is associated with improved overall survival and relapse-free survival.[4,5] The correlation between pathologic response and long-term outcomes in patients with early-stage breast cancer is strongest for patients with triple-negative breast cancer (TNBC), less so for HER2-positive patients, and least for hormone-positive disease.[6] Randomized trials of patients with operable breast cancer have demonstrated pCR to NACT ranging between 15% and 40%.[7] However, 10%–35% of patients fail to respond to NACT.[7]

Positron emission tomography-computed tomography (PET-CT) using fluorine-18 fluorodeoxyglucose (F-18 FDG) is being increasingly used to stage patients with locally advanced breast cancer and for assessing treatment response after NACT. F-18 FDG PET-CT provides quantitative data on the level of metabolic activity by measuring the degree of F-18 FDG uptake by the tumor, represented by the standardized uptake value (SUV). The measurement of F-18 FDG uptake by PET-CT is a validated technique for assessing tumor responses[1] and is a sensitive and specific tool for the noninvasive assessment of tumor metabolism. The SUV is a widely used quantitative metric for assessing radioactivity concentration in PET images. Multiple variables, such as biological and technological factors, affect SUV, which can over-underestimate the metabolic activity in lesions and tissues. Hence, reliable measurements are essential when evaluating response to therapy. SUV can be normalized to body mass (mean SUV [SUV_{mean}]), SUVs adjusted to lean body mass (SUL), or SUVs adjusted to body surface area (SUV_{BSA}). Hence, in a patient with stable weight, all three SUV normalization methods will give comparable percentage changes with treatment, as the normalization terms cancel out mathematically. Therefore, calculating changes in SUVs may be a potential predictive biomarker of response to NACT.

Metabolic tumor volume (MTV) measures the metabolically active tumor volume, and total lesion glycolysis (TLG) is obtained by multiplying SUV_{mean} by MTV.[8] MTV and TLG are reported to correlate better with histopathological response than do maximum SUV (SUV_{max}).[9] PERCIST criteria are the most common method used for response assessment after NACT with PET-CT. This criterion is based on the percentage change in SUL and does not include TLG.[10] In this study, we aimed to assess the ability of PET-CT to predict response to chemotherapy in patients with breast cancer, to study the correlation between PET-CT parameters and pathologic response of breast primary after NACT in breast cancer patients and to devise a new grading system for the clinical assessment of tumor response after NACT in breast cancer.

Materials and Methods

Patients

This prospective study was conducted in a tertiary care hospital in South India between May 2019 and September 2022. Seventy-three women with breast cancer were enrolled. Of these, 55 patients completed the study in all aspects and were included in the final analysis. Patients with bilateral breast cancer and those who underwent excision biopsy before receiving NACT were excluded from the study. The study was approved by the institutional ethics committee.

The clinical data of each patient were recorded, and the histopathologic findings were noted. All patients underwent diagnostic mammograms, including ultrasonography, where the primary tumor and axillary nodes were assessed. Core biopsy samples were used to evaluate the expression of estrogen receptor, progesterone receptor, human epidermal growth factor receptor, and Ki67. Immunohistochemistry staining with appropriate antibodies was performed to assess the receptor status. Allred score, which is the sum of the proportion score and intensity score, was used to score the estrogen receptor and progesterone receptor. The results were positive when the total score was ≥3. For HER2 receptor assessment, membranous staining was graded as 0, 1, 2, or 3. A tumor with a score of 3 was considered positive and equivocal results were further tested by fluorescent *in situ* hybridization to confirm HER2 amplification.

Neoadjuvant chemotherapy regimens

All patients were clinically staged using TNM classification of AJCC Staging, Eighth Edition, before initiating NACT. Patients with unfavorable tumor characteristics and/or lymph node metastasis were offered NACT. Seven patients were identified to have oligometastases on PET-CT. All of them had a single lesion in either bone (n = 5) or lung (n = 2) (not proven histologically). With curative intent, they were planned for NACT. The type of chemotherapy regimen administered was as per the standard guidelines. Majority of the patients received anthracycline-based regimens, followed by 3-weekly or weekly taxanes. Anti-HER2 therapy was added to patients with HER-2 neu-enriched subtype of breast cancer. The sequential chemotherapy regimen consisted of four cycles of 3-weekly adriamycin and cyclophosphamide, followed by either four 3-weekly or 12-weekly cycles of taxanes. All patients underwent either breast conservation surgery or mastectomy with axillary lymph node dissection, 3 weeks after completion of NACT. Following surgery, patients received either anti-HER2 therapy, endocrine therapy, or radiotherapy according to the standard protocol.

Pathological assessment

The surgical specimens were assessed for any RD and pathologic responses. pCR was defined as no evidence of residual invasive or *in situ* cancer in the breast and axillary nodes. Histopathological response was evaluated as pCR or RD. Based on clinical and histopathological assessment, patients were divided into four categories – complete response (CR), partial response (PR), no response (stable disease [SD]), and progressive disease (PD).

Fluorodeoxyglucose positron emission tomography scanning and analysis

All patients had undergone staging PET-CT before receiving NACT and 3 weeks after completion of NACT. All patients were fasting for at least 6 h before the F-18 FDG injection. Their blood glucose was checked and they were considered fit for the study if it was <140 mg/dl. Patients having blood glucose levels >140 mg/dl were rescheduled. The patients were injected intravenously through a previously secured intravenous catheter with F-18 FDG in the dosage of 5–7 MBq/kg body weight with a minimum dose of 185 MBq. The scan was performed 45–60 min after injection on GE Discovery® 710 whole-body PET scanner with 128 slices of CT. The height and weight of the patients, their blood glucose levels, pre- and postsyringe counts, and the time of injection were filled in the PET-CT scanner at the required place before starting the scan. The institute PET imaging protocol consists of acquiring a high-resolution CT chest image, followed by CT imaging from the base of the skull to mid-thigh after intravenous administration of iodinated contrast in the dosage of 1 ml/kg body weight injection, given after checking serum creatinine level which was ensured to be in normal range. In cases having raised serum creatinine, noncontrast CT imaging was performed. Then, PET imaging was performed in multiple bed positions, typically requiring 4–6 beds to cover the imaging area and acquisition of 1.5 min per bed position.

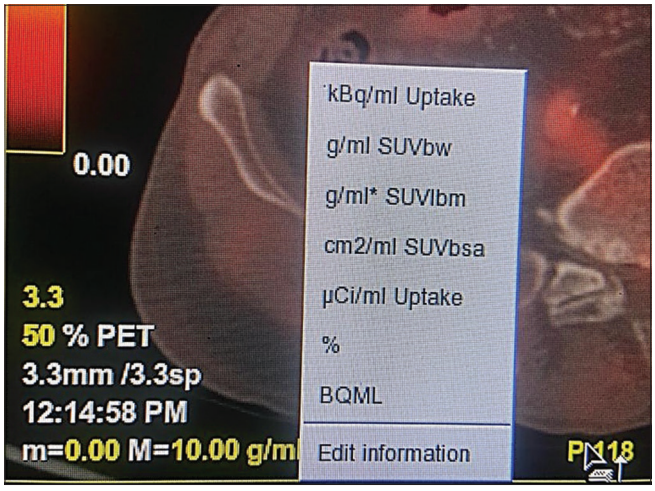

Figure 1: Calculation of various standardized uptake value parameters on Advantage Workstation®

Post acquisition, the PET-CT images were processed on Advantage Workstation® (ADW) of GE Healthcare Limited. The images were reconstructed into axial, coronal, and sagittal cross-sections for interpretation. The results were interpreted both qualitatively by visual analysis and quantitatively by estimating the SUV_{max} after drawing a three-dimensional adjustable region of interest (ROI) on the area showing maximum FDG uptake on visual analysis. The SUV_{max} represents the maximum value of FDG uptake seen in any pixel in the ROI. Using the patient data filled in the PET-CT system, other quantitative parameters such as SUV_{mean}, SUL, SUV_{BSA}, MTV, and TLG were generated. With advancements in technology, these parameters are computer generated on ADW in less than a minute by simply choosing the value of SUV from g/ml to cm^2/ml for SUV_{BSA} and so on [Figure 1].

The percentage reduction in SUV_{max} (ΔSUV_{max}) after the completion of chemotherapy was calculated as (100× [baseline SUV_{max} − postchemotherapy SUV_{max}])/ baseline SUV_{max}. Similarly, the percentage reductions of other PET-CT parameters were also calculated and represented as ΔSUV_{mean}, ΔSUL, ΔSUV_{BSA}, ΔMTV, and ΔTLG. Response to chemotherapy was evaluated as CR, PR, SD, and PD as described in PERCIST criteria.[10] Their histopathological parameters, including pathologic response, hormone receptor status, HER2 neu status, and Ki67 values, were correlated with the PET CT parameters.

Statistical analysis

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the F-18 FDG PET-CT in the identification of CR to chemotherapy compared to the histopathology report. The receiver operating characteristic (ROC) curve analysis was utilized to obtain cutoffs for each of the PET-CT parameters in their prediction of the clinical outcome of tumors. For the before–after comparisons, a series of paired Student's *t*-tests were performed, where $P < 0.05$ was considered statistically significant.

NIMS grading system for chemotherapy response in breast cancer

Based on the previous studies and area under the curve (AUC) as described later, the author selected ΔSUV_{max}, ΔSUV_{BSA}, ΔMTV, and ΔTLG for the NIMS grading system for chemotherapy response in breast cancer.[8-10] According to the clinical and histopathological responses, cutoff values for ΔSUV_{max}, ΔSUV_{BSA}, ΔMTV, and ΔTLG were categorized into four groups. A score of 1–4 was assigned for each parameter, where 1 represents the complete resolution of metabolic activity of all lesions, 2 represents PR, 3 represents SD, and 4 represents an increase in the metabolic activity of any lesion. The final score ranged between 4 and 16. The new grading system

was then correlated with the conventional PERCIST criteria and $P < 0.05$ was considered statistically significant.

Results

A total of 55 patients were included in the study. The characteristics of the 55 patients included in the study are summarized in Table 1. The median age at the time of diagnosis of breast cancer was 45 years. Thirty (54.5%) patients were premenopausal at the time of diagnosis. Most (92.7%) patients had invasive ductal carcinoma, no special type (NST). Clinical Stage II was observed in 9 (16.3%) patients and Stage III in 40 (72.7%) patients. Clinical subgroups were Luminal A in 2 (3.6%), Luminal B in 20 (36.4%), HER-2 enriched in 10 (18.2%), and TNBC in 23 (41.8%).

Table 1: Patient characteristics

	Number of patients (%)
Age at diagnosis, median (range)	45 (30–75)
Age group (years)	
30–44	25 (45.5)
45–59	19 (34.5)
60 or>60	11 (20)
Menopausal status	
Premenopausal	30 (54.5)
Postmenopausal	25 (45.5)
Clinical tumor classification	
T2	13 (23.6)
T3	26 (47.3)
T4	16 (29.1)
Multicentric disease	3 (5.4)
Clinical node classification	
N1	39 (70.9)
N2	11 (20)
N3	5 (9.1)
M1 - oligometastases on PET CT (not proven histologically)	7 (12.7)
AJCC clinical stage	
IIB	10 (18.1)
IIIA	26 (47.2)
IIIB	14 (25.4)
IIIC	5 (9.1)
Surgery	
BCS + ALND	20 (36.3)
MRM	28 (50.9)
MRM + immediate LD reconstruction	7 (12.7)
Histology	
Ductal, NST	51 (92.7)
Mucinous	1 (1.8)
Metaplastic	1 (1.8)
Neuroendocrine differentiation	2 (3.6)
Molecular subtype	
Luminal A	2 (3.6)
Luminal B	20 (36.4)
HER2 enriched	10 (18.2)
TNBC	23 (41.8)

PET CT: Positron emission tomography-computed tomography, BCS: Breast-conserving surgery, ALND: Axillary lymph node dissection, MRM: Modified radical mastectomy, LD: Latissimus dorsi, HER2: Human epidermal receptor 2, TNBC: Triple-negative breast cancers, NST: No special type, AJCC: American joint committee on cancer

Forty-six patients were treated with four 3-weekly cycles of adriamycin and cyclophosphamide followed by four cycles of 3-weekly docetaxel or 12 cycles of weekly paclitaxel. Out of 14 patients with HER-2 receptor-positive tumors, eight patients received six cycles of 3-weekly paclitaxel, carboplatin, and trastuzumab. The remaining six patients received trastuzumab in combination with paclitaxel in a sequential chemotherapy regimen. Only one patient received pertuzumab in combination with the TCH regimen. One patient with invasive carcinoma with neuroendocrine differentiation received six cycles of 3-weekly carboplatin and etoposide.

The patients who had oligometastases had complete resolution of the metastatic lesions postchemotherapy and, hence, were taken up for surgery. Thirty-five patients underwent modified radical mastectomy, of which seven patients underwent immediate latissimus dorsi reconstruction following mastectomy. The remaining 20 patients underwent breast conservation surgery, including oncoplastic procedures. In our study, the pCR rate was found to be 25.5%. Histopathological response to chemotherapy is summarized in Tables 2 and 3.

Fluorodeoxyglucose positron emission tomography-computed tomography result analysis

The sensitivity and specificity of the F-18 FDG PET-CT to detect the RD after NACT was 75.6% and 92.8%, respectively. The accuracy, PPV, and NPV were 80%, 96.8%, and 56.5%, respectively [Table 4]. The accuracy of PET-CT to detect RD was 80%.

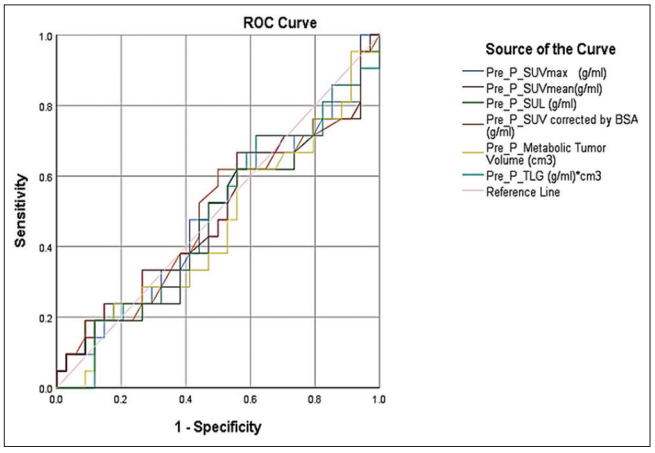

Figure 2: Receiver operating characteristic analysis of prechemotherapy positron emission tomography-computed tomography parameters in the prediction of pathological complete response. SUV: Standardized uptake value, SUV_{max}: Maximum SUV, SUV_{mean}: Mean SUV, SUL: SUV adjusted to lean body mass, BSA: Body surface area, TLG: Total lesion glycolysis, ROC: Receiver operating characteristic

Table 2: Histopathological response to chemotherapy

	All patients (*n*=55)	Luminal A (*n*=2)	Luminal B (*n*=20)	HER2 enriched (10)	TNBC (23)
pCR, *n* (%)	14 (25.4)	1 (7.14)	1 (7.14)	3 (21.4)	9 (64.2)
Residual disease, *n* (%)	41 (74.5)	1 (2.43)	19 (46.3)	7 (17.07)	14 (34.14)

pCR: Pathological complete response, HER2: Human epidermal receptor 2, TNBC: Triple-negative breast cancers

Table 3: Response to chemotherapy as assessed by positron emission tomography-computed tomography

	All patients (*n*=55)	Luminal A (*n*=2)	Luminal B (*n*=20)	HER2 enriched (10)	TNBC (23)
Complete response, *n* (%)	23 (41.8)	1 (4.34)	8 (34.7)	5 (21.7)	9 (39.1)
Residual metabolic disease, *n* (%)	32 (58.2)	1 (3.12)	12 (37.5)	5 (15.6)	14 (43.7)

HER 2: Human epidermal receptor 2, TNBC: Triple-negative breast cancers

Table 4: Correlated histopathological response with positron emission tomography-computed tomography response

	Complete response on PET CT (*n*=23)	Residual disease on PET CT (*n*=32)
pCR on HPE	13	1
Residual disease on HPE	10	31

PET-CT: Positron emission tomography-computed tomography, pCR: Pathological complete response, HPE: Histopathological examination

Table 5: Association between positron emission tomography-computed tomography parameters and histopathological response after completion of neoadjuvant chemotherapy

Prechemotherapy parameters	Median		*P*
	Complete response (*n*=14)	Residual disease (*n*=41)	
SUV_{max}	7.8	5.9	0.921
SUV_{mean}	4.4	3.6	0.992
SUL	5.3	3.9	0.820
SUV_{BSA}	2.1	1.5	0.753
MTV	2.7	2.4	0.515
TLG	10.6	8.7	0.924

SUV: Standardized uptake values, SUL: SUV normalized by lean body mass, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, BSA: Body surface area

The ROC curve analysis showed the largest AUC for SUV_{max} (AUC = 0.494) followed by TLG (AUC = 0.482). A cutoff at 53.65 for TLG had sensitivity and specificity of 71.4% and 38.2% respectively, while a cutoff at 3.5 for SUV_{BSA} had sensitivity and specificity of 61.9% and 50.0%, respectively [Figure 2]. There was no correlation between the prechemotherapy PET parameters and the histopathological response of the primary tumor in the CR group versus RD group [Table 5].

There was a strong correlation between the percentage reduction in PET parameters and histopathological response in the CR group versus the residual group. Differences between CR and RD were significant for ΔSUV_{max} (P = 0.005), ΔSUV_{mean} (P = 0.006),

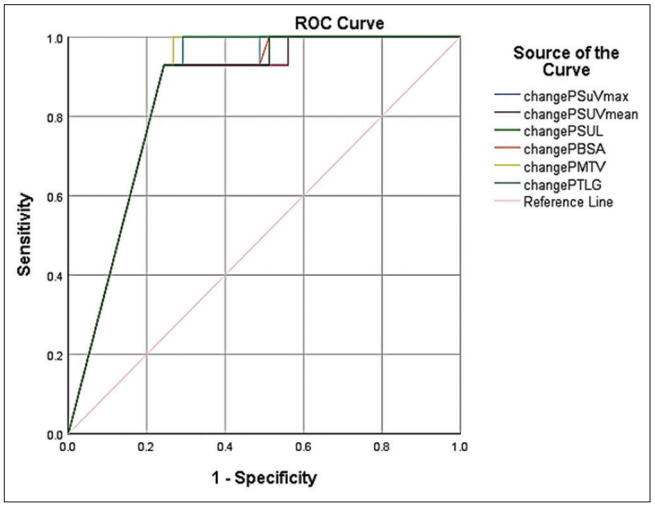

Figure 3: Receiver operating characteristic analysis of percentage reduction in positron emission tomography-computed tomography parameters in the prediction of pathological complete response. SUV_{max}: Maximum standardized uptake value, SUV_{mean}: Mean standardized uptake value, SUL: Standardized uptake value adjusted to lean body mass, BSA: Body surface area, TLG: Total lesion glycolysis, ROC: Receiver operating characteristic, MTV: Metabolic tumor volume

ΔSUL (P = 0.005), and ΔSUV_{BSA} (P = 0.004), while ΔMTV and ΔTLG were not significantly different between the two groups [Table 6]. All PET parameters had similar sensitivity and specificity in predicting pCR. ROC analysis showed the largest AUC for ΔTLG (AUC = 0.866), followed by ΔMTV (AUC = 0.858), ΔSUV_{max} (AUC = 0.852), and ΔSUV_{BSA} (AUC = 0.851). A cutoff of 99.7% for ΔTLG in the primary tumor had a sensitivity of 92.9% and specificity of 75.6% in predicting pCR. ROC analysis of percentage reduction of all parameters is depicted in Figure 3.

As per the proposed new grading system called "NIMS grading system for Chemotherapy Response in Breast Cancer" patients were divided into four groups [Table 7] - complete metabolic response (CMR) [Figure 4] with a score equal to 4, partial metabolic response (PMR) [Figure 5] with a score between 5 and 8, SD with a score between 9 and 12, and progressive metabolic disease [Figure 6] with a score between 13 and

16. There was no significant difference between the two grading systems and its response categories since the $P > 0.05$, so both the grading systems are the same or equally distributed ($\chi^2 = 0.088$, $P = 0.994$) [Table 8].

Discussion

Breast cancer is the most frequently diagnosed cancer and the leading cause of death among women worldwide**.** According to Globocan 2020, the cumulative risk of women developing breast cancer is 1 in 29 in India[11] with the majority of the patients being diagnosed at a locally advanced stage (57%).[11] NACT is the initial treatment modality for patients with locally advanced breast cancer. NACT has shown to improve surgical outcomes and downstage patients with operable breast cancer desiring breast conservation.

pCR is a strong prognostic marker and may be a surrogate for long-term disease-free survival, especially in aggressive tumor subtypes.[1] Randomized trials of patients with operable breast cancer have demonstrated pCR to NACT ranging between 15% and 40%.[7] Thus, early prediction of pathologic response would be of great clinical significance to identify nonresponders and offer alternative therapeutic regimens with potentially better responses. In addition, 3% of patients have disease progression while receiving NACT.[12] This is indicative of resistance to the NACT regimen and the aggressive nature of the disease. In our study, the pCR rate was found to be 25.4%. The majority of the patients who achieved pCR belonged to the TNBC subtype (64.2%), and the luminal subtype was found to have the lowest pCR rate (7.14%).

Table 6: Association between percentage reduction in positron emission tomography-computed tomography parameters and histopathological response after completion of neoadjuvant chemotherapy

Percentage reduction in PET parameters	Median		*P*
	Complete response (*n*=14)	Residual disease (*n*=41)	
ΔSUV_{max}	100	74.2	**0.005**
ΔSUV_{mean}	100	75.3	**0.006**
ΔSUL	100	75.6	**0.005**
ΔSUV_{BSA}	100	74.6	**0.004**
ΔMTV	100	85.5	0.164
ΔTLG	100	96.9	0.311

Numerical in bold is indicative of a significant *P*-value.
SUV: Standardized uptake values, SUL: SUV normalized by lean body mass, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, BSA: Body surface area, PET: Positron emission tomography

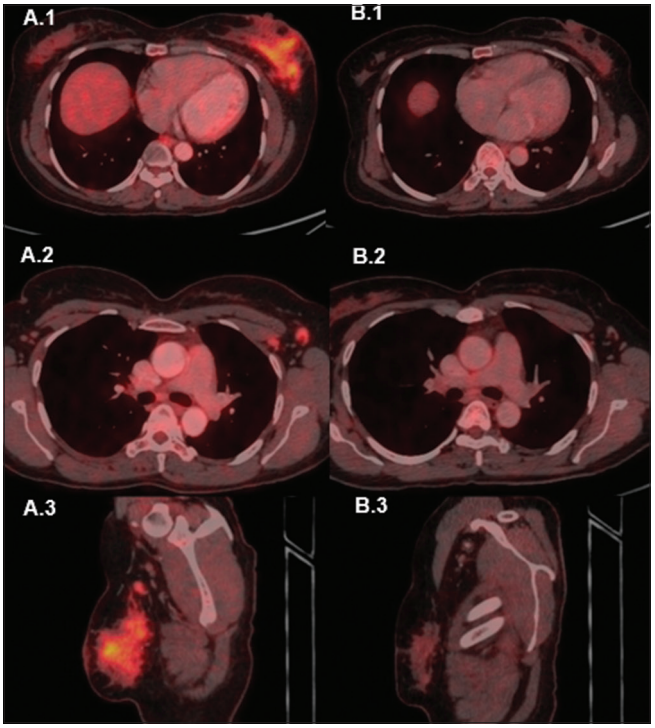

Figure 4: A 39-year-old female was diagnosed with carcinoma left breast – cT3N1M0, estrogen receptor-negative, progesterone receptor-negative, and human epidermal receptor 2 neu positive (HER2neu enriched type). She was planned for neoadjuvant chemotherapy and received six cycles of 3-weekly paclitaxel, cyclophosphamide, and trastuzumab. The initial staging positron emission tomography-computed tomography (PET-CT) images show fluorine-18 fluorodeoxyglucose accumulation in the primary lesion in the left breast (A.1) and left axillary nodal disease (A.2). Similar findings are depicted in the sagittal section (A.3). The postchemotherapy PET-CT showed complete resolution of metabolic activity in the primary lesion (B.1) and left axillary nodes (B.2) and also depicted in sagittal images (B.3]). The PERCIST grading and NIMS grading system (Grade 4) both are suggestive of complete metabolic response

Table 7: NIMS grading system for chemotherapy response in breast cancer (values assigned to each variable)

	ΔSUV_{max}	ΔSUV_{bsa}	ΔTLG	ΔMTV
Complete metabolic resolution of all lesions	1	1	1	1
Up to 50% decrease in the metabolic activity of all lesions	2	2	2	2
<50% decrease in the metabolic activity of all lesions	3	3	3	3
Increase in the metabolic activity of any lesion	4	4	4	4
Total score				
CMR	4			
PMR	5–8			
SD	9–12			
Progressive disease	13–16			

MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, BSA: Body surface area, SUV: Standardized uptake values, CMR: Complete metabolic response, PMR: Partial metabolic response, SD: Stable disease, NIMS: Nizam's institute of medical sciences

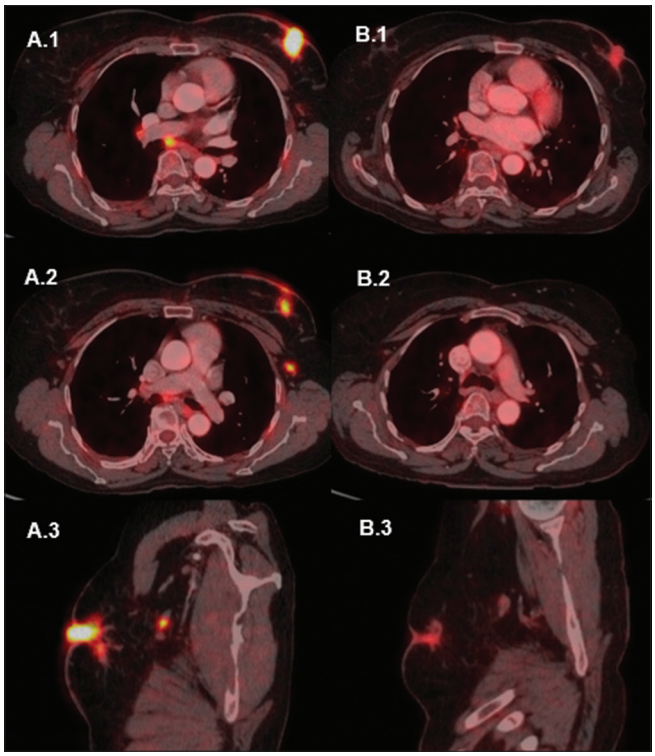

Figure 5: A 60-year-old female was diagnosed with carcinoma left breast - cT4bN1M0, estrogen receptor-positive, progesterone receptor-negative, human epidermal receptor 2 neu negative, and Ki67 25% (Luminal B type). She was planned for neoadjuvant chemotherapy and received four cycles of 3-weekly adriamycin and cyclophosphamide followed by 12 cycles of weekly paclitaxel. The initial staging positron emission tomography-computed tomography (PET-CT) images show fluorine-18 fluorodeoxyglucose accumulation in the primary lesion in the left breast infiltrating the nipple-areola complex with mildly thickened adjoining skin (A.1) and left axillary nodal disease (A.2), also seen in sagittal section (A.3). The postchemotherapy PET-CT showed partial resolution of metabolic activity in the primary lesion (B.1) and left axillary nodes (B.2), also depicted in sagittal images (B.3). The PERCIST grading is suggestive of partial metabolic disease, whereas the NIMS grading system (Grade 9) is suggestive of stable disease

Table 8: Correlating the new grading system with conventional positron emission tomography response criteria in solid tumors criteria

Response	PERCIST criteria (*n*=55)	New grading system (*n*=55)
CMR	26	27
PMR	13	13
SD	8	7
PMD	8	8

PERCIST: Positron emission tomography response criteria in solid tumors, CMR: Complete metabolic response, PMR: Partial metabolic response, SD: Stable disease, PMD: Progressive metabolic disease

F-18 FDG PET-CT is the most common imaging modality used to assess tumor response after NACT, especially in locally advanced diseases. Our study reported sensitivity, specificity, PPV, and NPV of 75.6%, 92.8%, 96.8%, and 56.5%, respectively, to detect the RD after NACT. The accuracy to detect the RD was 80%. The study by Goktas Aydin *et al*.[13] reported the overall

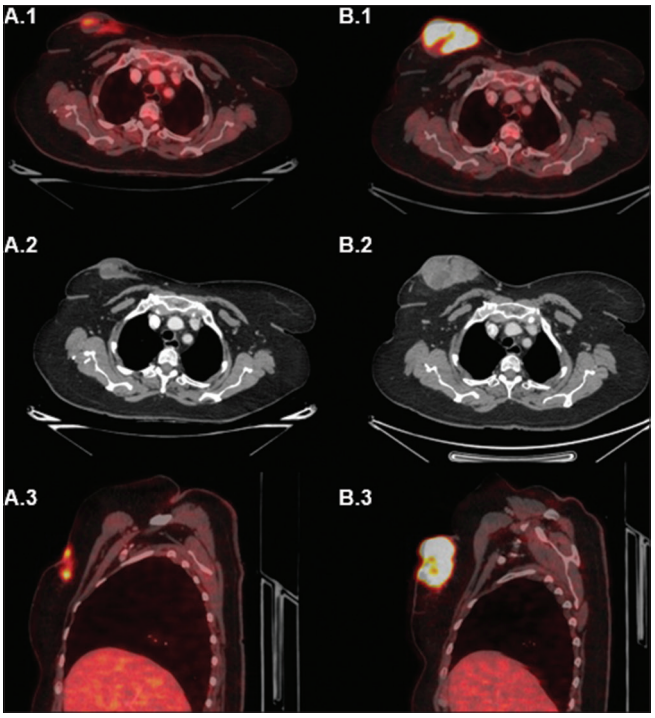

Figure 6: A 65-year-old female was diagnosed with carcinoma left breast - cT4bN1M0, estrogen receptor-positive, progesterone receptor-negative, human epidermal receptor 2 neu negative, and Ki67 33% (Luminal B type). She was planned for neoadjuvant chemotherapy and received four cycles of 3-weekly adriamycin and cyclophosphamide followed by 12 cycles of weekly paclitaxel. The initial staging positron emission tomography-computed tomography (PET-CT) fused images show fluorine-18 fluorodeoxyglucose accumulation in the primary lobulated lesion with the cystic component in the left breast infiltrating the skin (A.1), also seen on CT images (A.2), and in PET-CT fused sagittal images (A.3). The postchemotherapy PET-CT fused images showed an increase in size and metabolic activity of the primary left breast lesion (B.1), also seen in CT images (B.2), and in PET-CT fused sagittal images (B.3). The PERCIST grading and NIMS grading system (Grade 16) are suggestive of progressive disease

sensitivity, specificity, accuracy, PPV, and NPV of F-18 FDG PET-CT to determine the pCR after NACT to be 100%, 72.2%, 85%, 75.2%, and 100%, respectively. Tian *et al*.,[1] in their meta-analyses, concluded that the sensitivity of F-18 FDG PET-CT to predict therapy response in primary cancer ranged from 63% to 100% and specificity from 38% to 97%. Such difference was reportedly to be due to considerable heterogeneity in the studies.

In our study, the prechemotherapy PET-CT parameters were not effective in predicting pCR (AUC for all PET parameters was <0.5). In a study by Kiyoto *et al*.,[14] there was no correlation between baseline SUV_{max} of the primary tumor and the pathological response between the pCR group and non-pCR group. Similar results were reported by Başoğlu *et al*. in their study.[15] Another study reported that an SUV_{max} cutoff of 7.9 showed a sensitivity of 79% and specificity of 69% in the prediction of NACT response.[16] Later, several studies were performed to determine the efficacy of interim PET parameters as a

predictor for extensive residual cancer burden. In the present study, F-18 FDG PET-CT was done before and after the completion of NACT, and no interim PET-CT was performed. In our institute, it is not a routine practice to do PET-CT between chemotherapy cycles in breast cancer patients unless there is clinical suspicion of progression of the disease, although interim F-18 FDG PET-CT is routinely done in other malignancies like lymphoma.

Previous authors have concluded that PET after NACT was a significant predictor of pathological outcome, and the decrease in FDG uptake on PET after NACT was a good predictor of pCR.[14] The median ΔSUV_{max} measured in the primary tumor was 100% in patients who achieved pCR versus 74.2% in patients who did not (P = 0.005). Similar statistically significant results were noted with ΔSUV_{mean}, ΔSUL, and ΔSUV_{BSA}. However, similar correlation was not noted with ΔMTV and ΔTLG. In a study conducted by Im *et al*.,[17] a significant correlation was noted between the MTV and TLG reduction rates and tumor size reduction rate and they concluded that MTV and TLG could be robust indices in discriminating pathologic responders as SUV_{max}, after NACT. Another study by Garcia-Vicente *et al*.[16] concluded that volume-based metabolic variables were good predictors of NACT response.

The results from the present study showed that a cutoff of 95.7%, 96.6%, 95.8%, and 96.8% decrease in ΔSUV_{max}, ΔSUV_{mean}, ΔSUL, and ΔSUV_{BSA}, respectively, offered similar sensitivity (92.9%) and specificity (75.6%) in predicting pathological response. Kiyoto *et al*.,[14] in their study, concluded that a cutoff of 81.3% decrease in SUV_{max} offered a sensitivity of 100% and specificity of 64% in predicting pathological response. In another study, a cutoff Δ SUV_{max} value of 52% differentiated responders from nonresponders with a sensitivity of 86% and a specificity of 90%.[18]

Our study results show that a decrease in the FDG uptake on PET after NACT was a significant predictor of pathological outcome. The most commonly used criterium in routine reporting is $SUV_{max,}$ which has its own flaws and for clinical assessment of chemotherapy response, we use PERCIST criteria which use SUL, but that is not routinely measured. However, no previous study has proposed a grading system that takes other PET parameters into consideration. In this study, we propose a new grading system – "NIMS grading system for Chemotherapy Response in Breast Cancer" based on ΔSUV_{max}, ΔSUV_{BSA}, ΔMTV, and ΔTLG. Using this grading, the response can be divided into CMR, PMR, SD, and PD. The new grading system correlated well with the conventional PERCIST criteria. However, the P value was not significant, probably due to the small sample size, and warrants a multi-institutional study.

Conclusion

F-18 FDG PET-CT had moderate accuracy in the detection of RD after completion of NACT. Prechemotherapy PET-CT parameters were not adequate to predict the response of the primary tumor to chemotherapy. However, changes in the values of various PET-CT parameters are a sensitive tool to assess the response to chemotherapy. Our new grading system is easy to use and correlates well with the conventional grading system.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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