Original Article

Role of ^{99m}Tc-sestamibi Scintimammography in Predicting Response to Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer: A Prospective Study

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Abstract

Background: Neoadjuvant chemotherapy (NACT) is the first line of management for locally advanced breast cancer (LABC). However, chemoresistance is prevalent in 18%–50% of the cases. One of the important and most studied causes of chemoresistance is P-glycoprotein (Pgp) expression. ^{99m}Tc-sestamibi scintimammography may serve as a useful imaging tool to predict Pgp expression, thereby response to NACT. **Aim:** The aim was to study the role of ^{99m}Tc-sestamibi scintimammography in predicting response to NACT in treatment-naive, biopsy-proven LABC patients. **Materials and Methods:** ^{99m}Tc-sestamibi scintimammography (early and delayed images) was performed on a total of 34 patients. Eight patients were lost to follow-up, and only 26 (25 females and 1 male) patients were available for final analysis, with a mean age of 49.7 ± 10.7 years. ^{99m}Tc-sestamibi washout rate (WOR) (%) and T/B buildup were calculated. Pre-NACT and Post-NACT tumor sizes were measured clinically, and a % decrease in tumor size was calculated. The WOR and T/B buildup values were correlated with the % decrease in tumor size. **Results:** We found a statistically significant negative correlation between WOR (%) and % decrease in tumor size and a statistically significant positive correlation between T/B buildup and % decrease in tumor size. Furthermore, we found a positive correlation between the early T/B ratio and the Ki-67 index (P = 0.22). **Conclusion:** Early categorization of responders and nonresponders can help in optimal therapy planning. ^{99m}Tc-sestamibi scintimammography can serve as an imaging marker for Pgp expression, thereby predicting clinical response to NACT in LABC patients. Further studies with larger sample sizes are warranted to consolidate the above findings.

Keywords: *Chemoresistance in locally advanced breast cancer, neoadjuvant chemotherapy, scintimammography, sestamibi washout rate*

Introduction

Breast cancer is the most common cancer among women and the second-most common cancer overall.[1] The incidence of breast cancer increased substantially in the last few decades, due to increasing awareness and better screening procedures.[1,2] According to the American Cancer Society data, in spite of increased incidence, the mortality rate decreased from 33.2 in 1989 to 20 in 2016, due to early diagnosis and prompt treatment.[3] However, in developing countries like India, even now, breast cancer presents as locally advanced at the time of diagnosis in 30%–60% of patients, which has higher chances of recurrence and metastasis due to the presence of micrometastases.[4,5]

Locally advanced breast cancer (LABC) includes large breast tumors (>5 cm in longest diameter), tumors that involve the skin or underlying muscles of the chest, tumors that involve one or more axillary or supraclavicular lymph nodes, and inflammatory breast cancer.[6] Neoadjuvant chemotherapy (NACT) is the first line of treatment as it facilitates local disease control, better breast conservation, and progression of survival. It even has the benefit to perform the interim evaluation of tumor sensitivity and response to chemotherapy.[7]

Expression of permeability glycoprotein (Pgp) in solid cancers is associated with more chances of recurrence, fewer remissions, and a poor survival rate. Furthermore, the expression is frequently induced and upregulated following chemotherapy, particularly in breast and gastrointestinal tract cancers.[8] Failure of

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NACT is commonly due to multidrug resistance (MDR) gene coding Pgp, which ensures the resistance to most of the commonly used anthracyclines. Intrinsic chemoresistance is seen in 18%–50% of untreated cancer, whereas resistance is acquired later during the treatment in up to 75% of patients.[8-10]

Clinical and radiological methods to monitor tumor response are not consistent, as they are not able to differentiate between fibrosis and actual residual disease, as long as there is anatomical change.[11,12] Pathological examination is the only way to assess the extent of tumor response after chemotherapy which is an invasive procedure. Therefore, noninvasive imaging with ^{99m}Tc MIBI is a topic that raises interest. ^{99m}Tc MIBI tumor uptake reflects metabolic status and is directly related to the blood flow of the tumor. Retention of ^{99m}Tc MIBI appeared to correlate with chemosensitivity to anthracyclines.[12]

Resistance to chemotherapy can be due to many reasons; however, one of the most common causes is Pgp expression which ensures the rapid efflux of the chemotherapy drugs.[13-17] The presence of the MDR gene codes for the expression of Pgp, which is a transmembrane protein that effluxes most of the anthracyclines. A similar effect is seen with sestamibi also, which can be studied with ^{99m}Tc-sestamibi scintimammography.[18] ^{99m}Tc sestamibi is a lipophilic cation that concentrates in the cells due to a transmembrane electronegative potential by an energy-requiring transport mechanism and is stored inside the mitochondria. Furthermore, ^{99m}Tc sestamibi is a nonspecific tumor tracer that concentrates more in neoplastic cells than in normal tissue.[19] Moreover, it is a noninvasive method, which gives an idea on tumor cell metabolism and function. It is considered helpful for tracing of MDR pumps *in vivo*.[20-22]

This prospective study aimed at evaluating the role of ^{99m}Tc-sestamibi scintimammography in predicting the response to NACT in LABC patients based on the washout rate (WOR%) of ^{99m}Tc sestamibi from the breast cancer lesions and to correlate the WOR% with clinical response after four cycles of NACT.

Materials and Methods

This prospective study was performed on 34 consecutive patients with histopathologically proven and treatment-naive LABC, satisfying the inclusion criteria from March 2018 to August 2019, after obtaining approval from the Institutional Ethics Committee and after taking written informed consent.

Recently diagnosed LABC patients with age ≥18 years, Karnofsky performance status >50, those who are eligible for NACT, and those who consented to undergo ^{99m}Tc-sestamibi scintimammography before NACT were included in the study. Patients who underwent surgery or received prior radiation or chemotherapy for breast cancer, pregnant women, nursing mothers, and patients not willing to participate in the study were excluded from the study.

Scintimammography procedure

All the patients were explained about the procedure, purpose, benefits, and side effects of the study. A complete history was taken from the patients. Any comorbid conditions, if present, were recorded in the study pro forma. Physical examination of both breasts and axillae was done before the study. Patients were instructed to wear a mammography cape or gown and remove any jewelry if present.

All patients were injected approximately 20 mCi (740MBq) of ^{99m}Tc sestamibi intravenously into the arm contralateral to the side of the breast with the lesion. The radiopharmaceutical was followed by 10 mL of normal saline to flush the vein. A mammopad with lead cutouts was used to allow the breast to be fully dependent so as to get a good view.

A dual-head gamma camera (Siemens), equipped with a low-energy high-resolution collimator, was used for acquiring images. The energy window for image collection was centered 10% above and below, over the 140-keV photopeak of ^{99m}Tc. Planar (anterior and lateral) images were acquired 10 (early) and 120 (delayed) min after injection, each image acquired for 10 min each, using a 256 × 256 matrix. Images were acquired in the anterior view in the supine position and lateral views with the patient in the prone position with the help of scinti-mammopad. The axillae of both breasts were included in the field of view in the anterior image.

Image processing and analysis

Early and delayed images were analyzed both visually and quantitatively, using the tumor-to-normal breast ratio (T/B) of sestamibi uptake. The regions of interest were drawn on the lateral views around the lesion (T) and nearby normal breast tissues (B) in the early image obtained at 10 min and then were translated to the delayed image obtained at 120 min. The tumor-to-normal breast ratio (T/B) was calculated for both early and with decay correction for delayed images. Washout of ^{99m}Tc sestamibi from the tumor (WOR%) and T/B buildup were calculated as, washout rate (WOR)% = Early T/B – Late T/B/Early T/B × 100 and T/B build-up = Early T/B – Late T/B.

Response evaluation

Tumor size was measured clinically with the help of measuring tape, and surface area was calculated as the product of two measurable perpendicular diameters. The tumor size was determined both before and after four cycles of chemotherapy with an AC regimen clinically. The % reduction in the size of the tumor was calculated. ≥50% reduction in tumor size in response to NACT was taken as "clinical response." Patients who showed ≥50%

reduction in tumor size are categorized as responders, and the patients who showed <50% reduction in tumor size or increase in size are categorized as nonresponders.

Statistical tests

Statistical analysis was performed using International Business Machines Corporation (IBM), New York, USA, Statistical Package for Social Sciences (SPSS) software version 22.0. All the quantitative variables were expressed as mean ± standard deviation. Different parameters of the two groups (responders and nonresponders) were compared (quantitative variables using the Students' *T*-test and Mann–Whitney test and categorical variables using the Chi-square test). The Pearson correlation analysis between the ki-67 index and early T/B ratio, WOR and % decrease in tumor size, and between T/B buildup and % decrease in tumor size were performed, and their correlation coefficients were obtained. Receiver operating characteristics curve analysis was performed to obtain a cutoff of WOR (%) and T/B buildup values. $P < 0.05$ was considered statistically significant.

Results

A total of 34 patients who presented with LABC, referred for ^{99m}Tc-sestamibi scintimammography from March 2018 to August 2019, were included in the study. Out of them, eight patients deferred from follow-up (one patient expired after two cycles of NACT, and seven patients were lost from the follow-up after three cycles of NACT). Therefore, only 26 patients were considered for analysis.

25/26 (96.1%) were female and 1/26 (3.9%) was male (male breast carcinoma). The mean age of the patients was 49.7 ± 10.7 years, with a median age of 50 years, ranging from 30 to 73 years. 14/26 (54%) patients had the primary lesion in the right breast, whereas 12/26 (46%) patients had the primary lesion in the left breast. No patient had bilateral breast involvement. On HPE, all (100%) of the patients showed infiltrating duct cell carcinoma. 12/25 (48%) were premenopausal and 13/25 (52%) were postmenopausal. Out of 26 patients, 3/26 (11.5%) were stage IIB, 8/26 (30.7%) were stage IIIA, 10/26 (38.4%) were stage IIIB, and 5/26 (19.2%) were stage IIIC. 12/26 (46.2%) were hormone receptor (ER, PR) positive and 14/26 (53.8%) were hormone receptor (ER, PR) negative. In the hormone receptor-positive patients, 7/26 (27%) were Luminal-A, and 5/26 (19.2%) were Luminal-B type. In the hormone receptor-negative patients, 4/26 (15.4%) were HER2-enriched type and 10/26 (38.4%) were triple negative/basal like. Table 1 shows the demographic data of the study population.

All the patients were examined clinically for the primary tumor and axillary lymph nodes. 18/26 (46.1%) patients have a primary tumor size of >5 cm, 2/26 (7.69%) patients have multifocality, 6/26 (23%) have skin infiltration, 8/26 (30.7%) have chest wall infiltration, and 2/26 (7.69%) had ipsilateral axillary lymph nodes as per clinical examination [Table 2].

Quantitative analysis

Quantitative parameters of tumor WOR% and T/B ratio buildup derived from all the patients individually for all patients. The mean WOR (%) of all the patients is 10.1 ± 21.4%. The median WOR (%) is 10.17%, with an interquartile range of −9.4–44.2%. The mean T/B ratio buildup of all the patients is −0.265 ± 0.618. The median T/B ratio buildup is −0.27, with an interquartile range of −0.8–1.25. Table 3 shows different quantitative parameters obtained in scintimammography.

In addition to IHC, the Ki-67 index was available for all patients which was correlated with early image T/B ratio. A positive correlation is observed between the Ki-67 index and the early T/B ratio. The Pearson correlation coefficient is found to be 0.244, with $P = 0.22$ as described in the scatter plot [Figure 1].

Table 1: Demographic data of the study population

Characteristics of the study population	Number of patients, *n* (%)
Females	25/26 (96.1)
Males (male breast carcinoma)	1/26 (3.9)
Mean age of the study population (years)	49.7±10.7
Right breast	14/26 (54)
Left breast	12/26 (46)
Premenopausal	12/25 (48)
Postmenopausal	13/25 (52)
Luminal-A	7/26 (27)
Luminal-B	5/26 (19.2)
HER2 enriched	4/26 (15.4)
Triple negative	10/26 (38.4)
Stage IIB (3)	3/26 (11.5)
Stage IIIA (8)	8/26 (30.7)
Stage IIIB (10)	10/26 (38.4)
Stage IIIC (5)	5/26 (19.2)

Table 2: Clinical examination findings

Clinical examination findings	Number of patients, *n* (%)
Primary tumor size (>5 cm)	18/26 (69.2)
Multifocality	2/26 (7.69)
Skin infiltration	6/26 (23)
Chest wall infiltration	8/26 (30.7)
Ipsilateral lymph nodes	2/26 (7.69)

Table 3: Quantitative parameters assessed in scintimammography

	Mean	Median	IQR
WOR (%)	10.1±21.4	10.17	−9.4*–44.2
T/B ratio buildup	−0.265±0.618	−0.27*	−0.8*–1.25

IQR: Interquartile range, WOR: Washout rate, T/B: Tumor-to-normal breast ratio

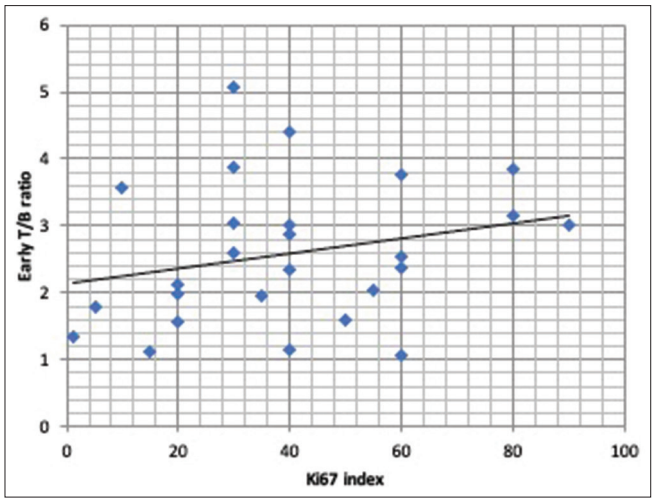

Figure 1: Scatter plot showing a correlation between the Ki-67 index and early T/B ratio

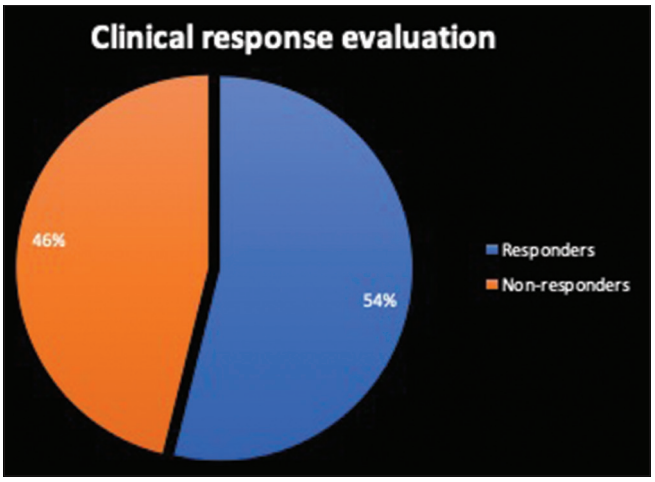

Figure 2: Pie diagram showing the clinical response across the study population

Clinical response evaluation

All 26 patients received NACT with four cycles of AC (600 mg/m^2 of adriamycin, and 60 mg/m^2 of cyclophosphamide) regimen. No untoward event was noted in any patient, and all the patients tolerated the treatment well. Clinical response was assessed by measuring the tumor size clinically (product of two longest diameters) before and after four cycles of NACT. Out of the 26 patients, 14/26 (54%) were responders and 12/26 (46%) were nonresponders, which is represented as a pie diagram [Figure 2].

Characteristics of responders and nonresponders

All 26 patients' ^{99m}Tc scans were analyzed for obtaining the quantitative parameters. These include WOR (%), T/B buildup ratio, and results correlated with the clinical performance of the patients in the response groups. Figure 3a shows that nonresponders show relatively high WOR (%) compared to responders. A box and whisker plot is drawn for the WOR (%) among the responders and nonresponders, as shown in Figure 3b.

The responder and nonresponder groups were analyzed for different characteristics. The quantitative variables are compared using the Students' *T*-test and Mann–Whitney U test, whereas the categorical variables using the Chi-square test [Table 4]. A few representative images of the patients are illustrated in Figure 4.

Correlation of washout rate (%) with % decrease in tumor size after neoadjuvant chemotherapy

A scatter plot is drawn using WOR on the X-axis and % reduction in tumor size on the Y-axis. The scatter plot shows a statistically significant negative correlation between WOR and % reduction in tumor size, with a Pearson correlation coefficient of −0.445, with P = 0.023. [Figure 5a]. This shows that with an increase in WOR (%), there is a decrease in response to NACT. With the increase in retention of MIBI, there is increased retention of the chemotherapy agents, resulting in better response.

Table 4: Characteristics of responders and nonresponders

Parameter	Responders (n=14)	Nonresponders (n=12)	P
Mean age	49.5±8.8	50.1±13	0.9115
Mean WOR (%)	4.37±21.22	16.7±20.47	0.143
Mean T/B buildup	−0.12±0.65	−0.43±0.55	0.199
Mean Ki-67 index	35.8±20.6	42.5±22.5	0.438
Mean % decrease in tumor size	84.8±15.6	−20.4±52.8	0.0001
Group I (9)	6 (43)	3 (25)	0.136
Group II (17)	8 (57)	9 (75)	
Luminal-A (7)	4 (28.5)	3 (25)	0.078
Luminal-B (5)	4 (28.5)	1 (8.3)	
HER2 enriched (4)	1 (7.1)	3 (25)	
Triple negative (10)	5 (35.7)	5 (41.7)	
IIB (3)	1 (7.1)	2 (16.6)	0.424
IIIA (8)	6 (42.8)	2 (16.6)	
IIIB (10)	4 (28.5)	6 (50)	
IIIC (5)	3 (21.4)	2 (16.6)	

WOR: Washout rate, T/B: Tumor-to-normal breast ratio

A scatter plot is drawn using T/B buildup on the X-axis and % reduction in tumor size on the Y-axis. The scatter plot shows a weak positive correlation between T/B buildup and % reduction in tumor size, with a Pearson correlation coefficient of 0.364, with P = 0.06 (>0.05) [Figure 5b]. This shows that the more the T/B buildup, the more the response to NACT. The T/B ratio was calculated both in initial (10 min) and delayed (120 min) images. The increase in the T/B ratio in delayed images compared to initial images was considered a "T/B buildup."

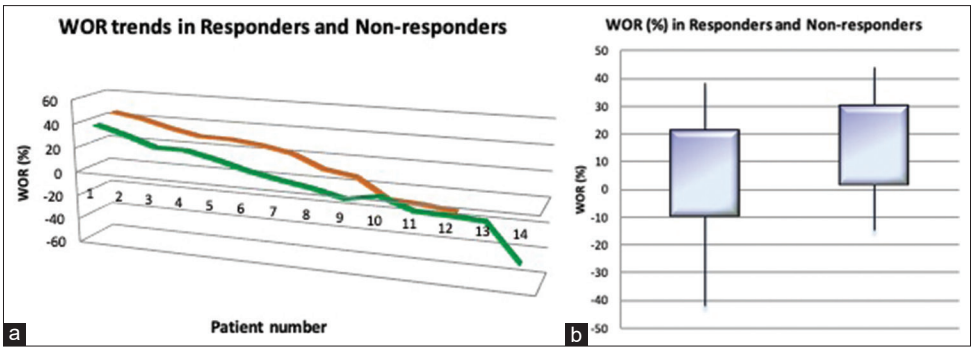

Figure 3: (a) Washout rate (WOR [%)]) among the responders and nonresponders. The green line represents responders, the red line represents the nonresponders. (b) Box and whisker plot drawn for WOR (%) among the responders and nonresponders

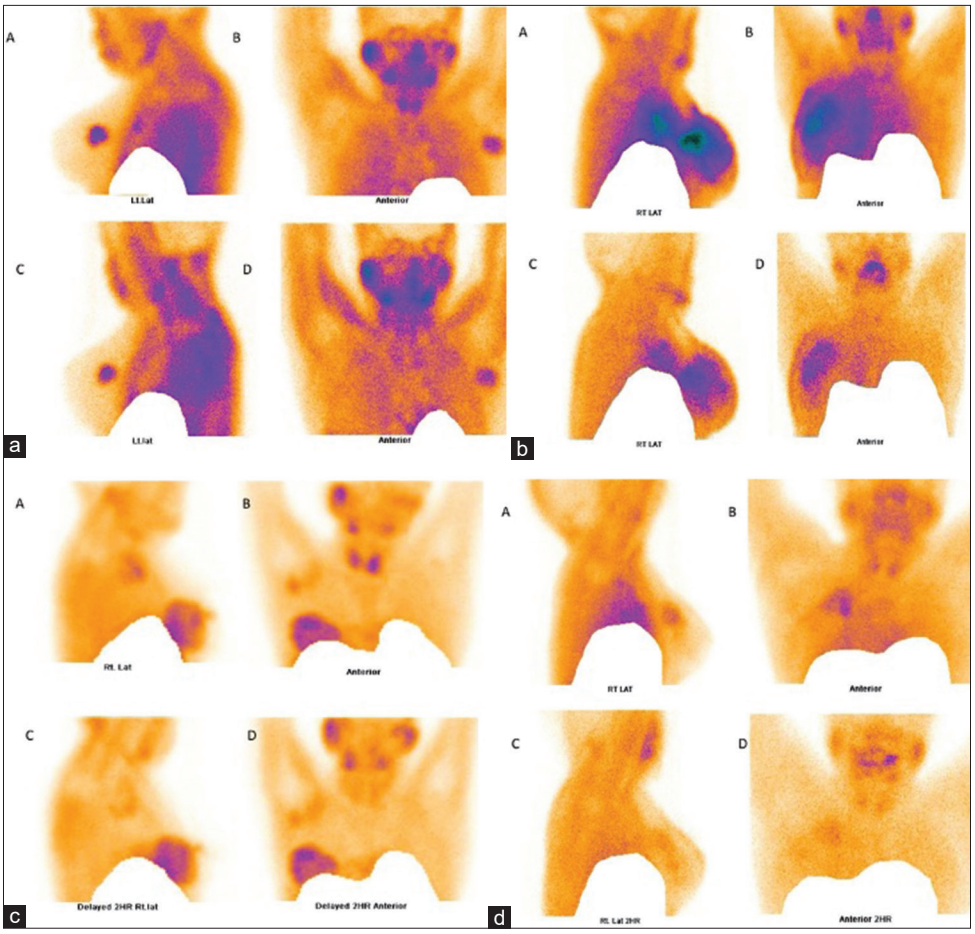

Figure 4: (a) Representative image of a responder with less washout rate (WOR [%]) and high T/B buildup: A 42-year-old female patient presented with locally advanced breast cancer (LABC) of the left breast. On ^{99m}Tc-sestamibi scintimammography (A and B: 10-min images, C and D: 120-min images), increased radiotracer uptake noted in the left breast upper outer quadrant, which shows retention of tracer in corresponding 120-min images. WOR% is −41.8%, T/B buildup is 1.26, and the patient had a 100% decrease in the tumor after four cycles of chemotherapy. (b) Representative image of a nonresponder with high WOR (%) and less T/B buildup: A 39-year-old female patient presented with LABC of the right breast. On ^{99m}Tc-sestamibi scintimammography (A and B: 10-min images, C and D: 120-min images), increased radiotracer uptake noted in the right breast, which shows washout of tracer in corresponding 120-min images. WOR% is 44.2%, T/B buildup is −1.27, and the patient had a 50% increase in tumor after four cycles of chemotherapy. (c) Representative image of a nonresponder with less WOR (%) and high T/B buildup: A 50-year-old female patient presented with LABC of the right breast. On ^{99m}Tc-sestamibi scintimammography (A and B: 10-min images, C and D: 120-min images), increased radiotracer uptake noted in the right breast, which shows retention of tracer in corresponding 120-min images. However, on follow-up postneoadjuvant chemotherapy, tumor size increased. WOR% is −14.6%, T/B buildup is 0.36, and had a 28.6% increase in the tumor after four cycles of, (d) representative image of a responder with high WOR (%) and low T/B buildup: A 30-year-old female patient presented with LABC of the right breast. On ^{99m}Tc sestamibi scintimammography (A and B: 10-min images, C and D: 120-min images), increased radiotracer uptake noted in the right breast upper inner quadrant, which shows washout of tracer in corresponding 120-min images. WOR% is 38.2%, T/B buildup is −0.909, and the patient had a 64% decrease in the tumor after four cycles of chemotherapy

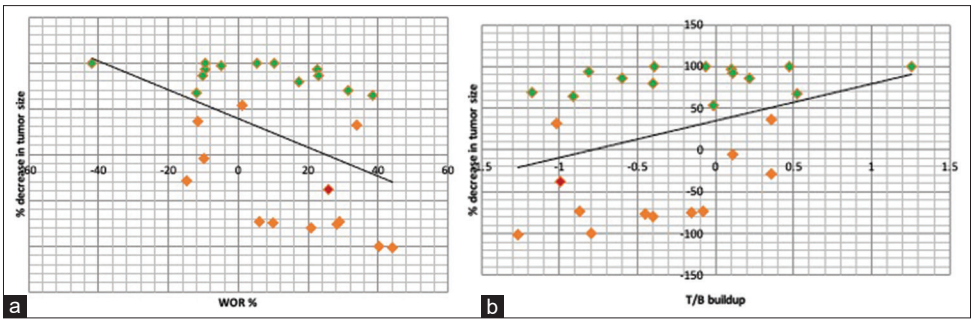

Figure 5: (a) Scatter plot showing the negative correlation between the % washout rate (WOR) and % decrease in tumor size. The green dots represent responders, and the red dots represent nonresponders, (b) scatter plot showing a weak positive correlation between the T/B buildup and % decrease in tumor size. The green dots represent responders, and the red dots represent nonresponders

Discussion

^{99m}Tc sestamibi (hexakis 2-methoxy isobutyl isonitrile) is a lipophilic radiopharmaceutical that localizes inside the cell by means of negative transmembrane potential and is trapped inside mitochondria. The uptake is linearly related to both perfusion and the number of mitochondria, which indirectly indicates cell proliferation. Furthermore, the uptake relates to the aggressiveness of the tumor. Pgp expression results in efflux of sestamibi, as in the case of many anthracyclines.[23,24]

In 2001, Takamura *et al*. evaluated 46 patients with LABC and recurrent breast cancer, with ^{99m}Tc-MIBI scintigraphy. The results were comparable to immunohistochemical examination for the determination of Pgp expression. Furthermore, ^{99m}Tc-MIBI scintigraphy can not only determine Pgp but also all the proteins involved in the extrusion of these chemotherapeutic agents like MDR-related proteins. Thus, it has an important role in the prediction of response to chemotherapy in patients with locally advanced or recurrent breast cancer.[18] In our study, we could not perform IHC for Pgp expression due to unavailability. However, we correlated MIBI scintigraphy findings with clinical response.

In a similar study done by Bonazzi *et al*.,[25] they observed a positive correlation between the cellular proliferation index (Ki-67 index) and early tumor uptake ratio. In our study, similar findings were found. We found a positive correlation between the early T/B ratio and Ki-67 index that represents the amount of cell proliferation and aggressiveness of the tumor. However, the *P*-value was not statistically significant ($P = 0.22$), probably due to the small sample size.

In a study done by Del Viechio *et al*.,[26] they performed a tracer kinetic analysis over a 4-h period in 30 patients with ^{99m}Tc-MIBI avid breast cancer and found a statistically significant positive correlation between tracer efflux and Pgp levels. The authors further tested whether the tracer clearance could predict response to subsequent treatment in patients with LABC who were candidates for NACT. They showed that rapid clearance of ^{99m}Tc MIBI from tumors was significantly associated with a highly cellular macroscopic residual tumor at the pathological examination of surgical specimens, indicating a lack of tumor response to NACT. Furthermore, prolonged retention of the tracer was associated with an effective pathological tumor response to treatment in two-thirds of the patients.[27] Similarly, in our study, dual-point imaging is done, i.e., imaging is done at 10 min and at 120 min, to calculate the WOR. As evident from Figure 5a, there is a statistically significant negative correlation between the % decrease in tumor size and WOR (%) with a Pearson correlation coefficient of −0.445 with $P = 0.023$ (<0.05).

In 2014, Trehan *et al*.,[21] in PGIMER, Chandigarh, performed a similar study and evaluated the clinical response. They observed a statistically significant negative correlation between the WOR and % decrease in tumor size. In our study, similar findings are observed. We found a statistically significant negative correlation ($P = 0.023$) between WOR (%) and % decrease in size.

Mubashar *et al*. analyzed early and delayed uptake ratios in 20 patients with breast carcinoma before and after treatment with toremifene. An inverse correlation between the delayed uptake ratio and Pgp expression in tumors was confirmed before treatment. They stated that analysis of the change between the early and the delayed scan appeared to be a better predictor of Pgp status. The change in the delayed compared to early images correlated negatively with Pgp status, thereby positively with clinical response.[28]

In our study, we calculated a similar parameter, T/B buildup values, in all the patients. The mean T/B buildup value is − 0.26 ± 0.62, and the mean % decrease in tumor size is 23.3 ± 75.7. T/B buildup was observed in 9/26 (34.6%) patients. Among them, six patients were responders and three were nonresponders (2/3 showed progressive disease, and 1/3 showed stable disease). However, the *P* value is not significant, probably due to the small sample size. T/B buildup values showed a positive correlation with a % decrease in tumor size, with a Pearson correlation coefficient of + 0.364 and $P = 0.06$ [Figure 4b]. It implies that if there is a building up of the T/B ratio with time (on delayed images), there is a better response to NACT. This parameter needs validation in further studies with larger sample sizes.

Limitations of the study

- Small sample size
- Posttherapy scintimammography could not be done, in view of radiation exposure to the patient
- Only clinical response was assessed. Pathological response could not be assessed
- Pgp expression of the tumors could not be assessed histopathologically.

Conclusion

^{99m}Tc-sestamibi scintimammography findings can be utilized as an imaging marker to detect the Pgp expression, thereby the presence of chemoresistance to NACT. Tumor WOR (%) and T/B ratio buildup are the two parameters that can help in the interpretation of scintimammography for predicting post-NACT responders and nonresponders. Further studies with larger sample sizes are warranted to obtain a cutoff of WOR (%) to differentiate between responders and nonresponders.

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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Nil.

Conflicts of interest

There are no conflicts of interest.

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