

Digital Breast Tomosynthesis as a Predictor of Pathological Response of Breast Cancer after Neoadjuvant Therapy

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ABSTRACT

Background: Breast cancer is a significant public health concern all over the world. Increasing public knowledge of the disease and development in breast imaging have improved screening and early detection of breast cancer. Neoadjuvant therapy (NAT) is the main treatment for locally advanced breast cancer. Its primary clinical benefit is the reduction of tumor burden and downstage breast cancer so that breast-conservative surgery (BCS) can be performed. Accurate evaluation of response to NAT is essential for surgery planning. **Objectives:** To assess the accuracy of digital breast tomosynthesis (DBT) in predicting the pathological response and assessment of residual tumor size after NAT in patients with locally advanced breast cancer. **Methods:** This prospective study was carried out between April 2023 and September 2024 and included 150 female patients aged between 28 and 75 years old with pathologically confirmed breast cancer who were candidate for NAT. DBT was done before and after NAT and radiological findings were compared with post-operative pathological results. **Results:** There was a statistically significant positive relation between DBT residual tumor size and pathological size (correlation coefficient was found to be 0.951). Sensitivity of DBT size in prediction of pathological response to NAT was 93 %, Area under the curve (ROC) was 0.807.

Conclusions: DBT has good correlation with histopathology for measuring residual tumor size after NAT. It is a sensitive method in predicting pathological response to NAT.

Keywords: Breast Cancer, DBT, Modified radical mastectomy, Neoadjuvant Therapy, Pathological Response.

INTRODUCTION

Breast cancer is the leading cause of cancer-related mortality among women, yet it is curable in 70-80% of individuals with early-stage, non-metastasized illness. Different methods of management are available including surgery, hormonal therapy, radiation therapy, chemotherapy and targeted therapy. Treatment for patients with distant metastases aims to improve survival rate and quality of life ^[1].

NAT is the gold standard treatment for locally advanced breast cancer. It helps tumor downstaging, turns inoperable cases into operable ones thus reduces mastectomy rate and allows more breast conservative surgery (BCS) ^[2].

High sensitivity of digital breast tomosynthesis (DBT) compared to other imaging modalities had made it a popular choice for breast cancer diagnosis in clinical settings ^[3]. Mammography alone is not able to detect mass lesions in dense breasts because the surrounding breast tissue obscures the tumor outline. This major hurdle is eliminated by DBT ^[4]. Despite the high accuracy of MRI imaging, it has limited ability to evaluate the extent of malignant microcalcifications that requires complete excision ^[5].

Accurate assessment of response to neoadjuvant therapy (NAT) is essential for surgery planning. The purpose of this study was to compare DBT with post-operative pathological results in order to determine the accuracy of DBT in predicting the pathological response and assessment of residual tumor size after NAT in breast cancer patients.

PATIENTS AND METHODS

This prospective study was carried out between April 2023 and September 2024 and included 150

female patients aged between 28 and 75 years old with pathologically confirmed breast cancer who were candidate for NAT. Patients were referred from the Outpatient Clinics of Oncology Department to Radiology Department. These patients had baseline imaging evaluation of breast with DBT before starting NAT and follow up was done after completing NAT just before surgery. The radiological findings were compared with histopathology results after surgery.

Inclusion criteria:

- 1) Sex: females with pathologically confirmed breast cancer by true cut biopsy.
- 2) Patients with performance state (0,1,2 groups) according to WHO/ECOG ^[6] with adequate organ function (Performance state 0: fully active, able to carry on all pre-disease performance without restriction. Performance state 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. Performance state 2: capable of only all selfcare but unable to carry out any work activities up and about more than 50 % of waking hours).
- 3) Patients who are candidate for preoperative systemic therapy ^[7]: (a) Patients with inoperable breast cancer (Inflammatory breast cancer, Bulky or mated cN2 or cN3 axillary nodes, cT4 tumors). (b) Patients with: HER2-positive condition and triple negative if $\geq$ cT2 or $\geq$ cN1. (c) Large primary tumor in relation to the size of the breast in a patient who wishes to preserve the breast. (d) Patients for whom definitive surgery may be postponed.

Exclusion criteria:

- 4) Patients with stage IV disease.
- 5) Patients with contraindication for preoperative systemic therapy or surgery.
- 6) Patients with recurrent breast cancer.
- 7) Patient with previous breast surgery.
- 8) Male patients.

METHODS

Comprehensive personal and family history were collected from each patient includes: age, complaint, history of hormonal pills, previous mammograms or previous breast surgeries and family history of breast cancer. For patients eligible for BCS, clips were inserted under ultrasound guidance.

The X-ray machine used for the examination was a full field digital mammography (FFDM) with 3D digital breast tomosynthesis (DBT), done by (AMULET Innovality "FDR MS 3500") manufactured by FUGIFILM Corp., Japan. During acquisition, the breast was compressed between breast plates, the routine views of FFDM were taken (craniocaudal and mediolateral oblique). For DBT, the x-ray tube swept in an arc of 25° around the compressed breast. Low dose 11-15 projection 2D images were acquired with 2° increment per image. Images were obtained in the same standard mediolateral oblique and craniocaudal views.

Data from the low dose projection 2D images were reconstructed to produce 1-mm-thick sections separated by 1 mm space to form the 3D images of the compressed breast in the form of a series of images that varied according to the thickness of the compressed breast. All data acquired were transferred to AMULET BELLUS II workstation.

Base line image analysis

Two breast imaging specialists with 15 years' experience in breast imaging, interpreted the DM and DBT images for:

- (a) Breast composition according to ACR classification (i- entirely fatty, ii- scanty fibroglandular densities, iii- heterogeneously dense, iv- extremely dense).
- (b) Mass lesions as regard shape (rounded, oval, irregular), margins (circumscribed, indistinct, obscured, spiculated, microlobulated), density (low, equal, high), size (largest three-dimensional diameters in cranio-caudal and oblique views).
- (c) Breast calcifications as regard morphology and distribution.
- (d) Associated findings as skin thickening and nipple retraction.

The patients received 8 cycles of chemotherapy; Anthracycline based chemotherapy for 3-4cycles (Doxorubicin or epirubicin plus Cyclophosphamide) followed by 12 weeks of paclitaxel or 4 cycles docitaxel plus or minus anti her 2 nue according to molecular subtype (total of 8 cycles)^[7].

Follow up image analysis: DBT was done after finishing 8 cycles of NAT, at the same week of the planned operative treatment. The same baseline

imaging technique and image analysis was used. The radiological response to NAT therapy was classified into the following using the measurement obtained from DBT: 1- Complete response (CR): no evidence of residual tumor. 2- Partial response (PR): reduction of tumor size by more than 30%. 3- No response: reduction of tumor size less than 30%. For each patient, the maximum dimensions of the residual tumor were measured. These findings were subsequently compared with the final histopathology results after surgery. All Patients underwent surgery either BCS or mastectomy based on their response to NAT and the residual tumor measured by DBT. Pathological response was also classified into: 1- Pathological complete response (pCR): complete disappearance of invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement. 2- Partial response. 3- No response.

Ethical approval: The study was done according to the regulations of the Ethical Committee; IRB approval number and date (5/2023 RAD 24) and patients were well-informed in details about the examination. Written consent was taken. The study adhered to the Helsinki Declaration throughout its execution.

Statistical analysis

The data was tabulated and analyzed using SPSS, version 26, NY, USA. We encountered multiple descriptive statistics data which were expressed as number and percentage (Number, percentages, mean, SD, and range for quantitative data) and analytical statistics like the Fisher exact test was employed to investigate the association between the two qualitative variables. Wilcoxon signed rank test was used to compare different interpretations of the same non-normally distributed data set. A plot of ROC curve: The X-axis shows the relationship between sensitivity (TP) and specificity (FP) at different cut off values. The diagnostic efficacy of the test was shown by area under the curve (AUC). For statistical purposes, a p-value less than 0.05 was considered significant.

RESULTS

This prospective study included 150 patients with mean age 45.72 ± 9.67 year. Fifty two percent of the patients were postmenopausal and 45% had positive family history of breast cancer. The most common breast composition was ACR category B (55 %). Our study showed that most common histological type of breast cancer was IDC (86%). Eighty percent was grade 2. Molecular subtype ER and PR positive was found in 88% of the patients while HER2 was positive in 20 % and 12 % was triple negative. In our study the density of mass (at base line image analysis) was higher than breast tissue in 96 %, the margin was spiculated in 76 %, and the shape was irregular in 84 %. Mean width of the mass was 2.87 ± 1.28 cm and mean length was 3.33 ± 1.26 cm (**Table 1**).

Table (1): Pre and post-treatment characteristics of mass by DBT among studied patients:

Parameter		Pre		Post		Test of significance	P value
		No.	%	No.	%		
Density	No mass	0	0	14	28	MH=1.72	0.085 (NS)
	Equal	2	4	2	4		
	High	48	96	20	40		
	Less dense	0	0	14	28		
Margin	No mass	0	0	14	28	MH=3.50	<0.001*
	Indistinct	2	4	2	4		
	Lobulated	10	20	6	12		
	Spiculated	38	76	28	56		
Shape	No mass	0	0	14	28	MH=4.22	<0.001*
	Irregular	42	84	36	72		
	Oval	4	8	0	0		
	Rounded	4	8	0	0		
Width (cm)	Mean ±SD	2.87 ±1.28		1.64 ±1.83		W=5.15	<0.001*
	Range	1.5-6.2		0-7.4			
Length (cm)	Mean ±SD	3.33 ±1.26		2.02 ±2.22		W=4.59	<0.001*
	Range	1.6-6.2		0-7.8			

*: Statistically significant, NS: Non-significant, MH: Marginal homogeneity test, W: Wilcoxon signed rank test.

Microcalcifications was found in 16% of the lesions. Most common shape was fine pleomorphic (50%) and most common distribution was regional (50%). Lymph nodes involvement was found in 48% of patients, nipple retraction in 12%, skin thickening in 52% and 40 % had inserted clips. After NAT radiological complete response was found in 28% of the patients, partial response was found in 64% (Figure 1) and no response in 8 % (Figure 2).

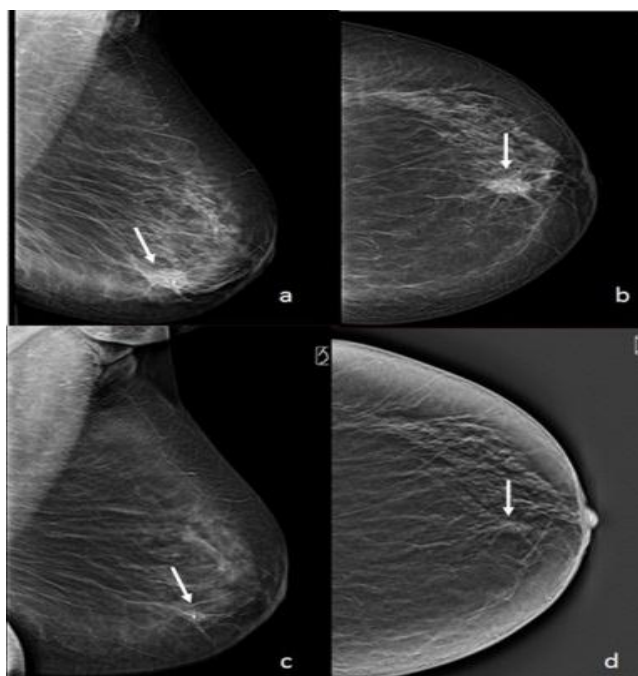


Figure (1): 55 years old female patient with left breast IDC grade 2 (ER +ve, PR +ve, HER2neu -ve) (a) Mediolateral oblique (MLO) and (b) CC tomogram before NAT show spiculated mass lesion at lower inner quadrant measuring about 2.3x2.2 cm. (c) MLO and (d) CC tomogram after NAT show residual spiculated mass lesion measuring about 1.5 x0.9 cm with inserted metallic clip (Partial radiological response). Final Pathological results after left BCS (partial pathological response; residual invasive ductal carcinoma 1.5 cm).

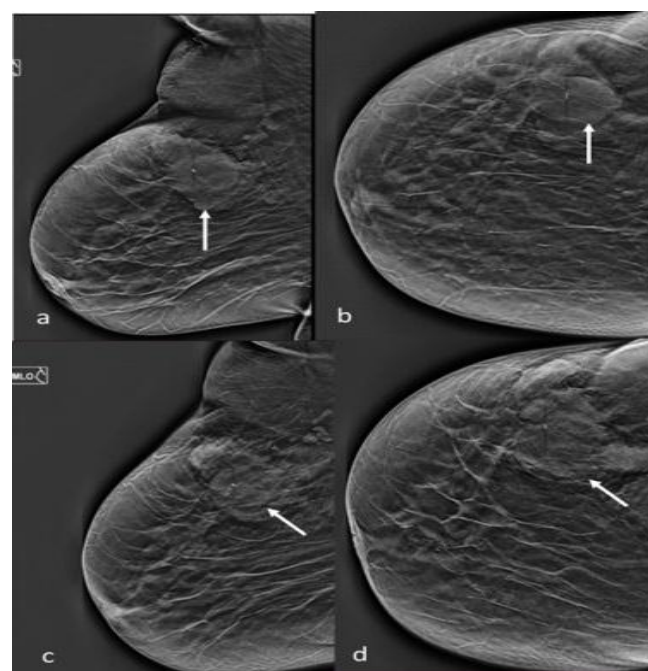


Figure (2): 64 years old female patient with right breast IDC grade 3 (ER -VE, PR -ve, HER2neu -ve) (a) MLO and (b) CC tomogram before NAT show microlobulated mass lesion at upper outer quadrant measuring about 4.2x3.8 cm. (c) MLO and (d) CC tomogram after NAT show residual microlobulated mass lesion measuring about 4 x3 cm with inserted metallic clip (no radiological response). Final Pathological results after right modified radical mastectomy (no response; residual invasive ductal carcinoma 4.5 cm).

Residual mass was found in 72% of the patients. The expected changes after NAT on DBT include the mass size, shape, margin and density (**Table 1**). In our study there was no statistically significant difference between pre and post treatment mass density, but there was statistically significant difference between pre and post treatment margin, shape and size (**Figure 3**).

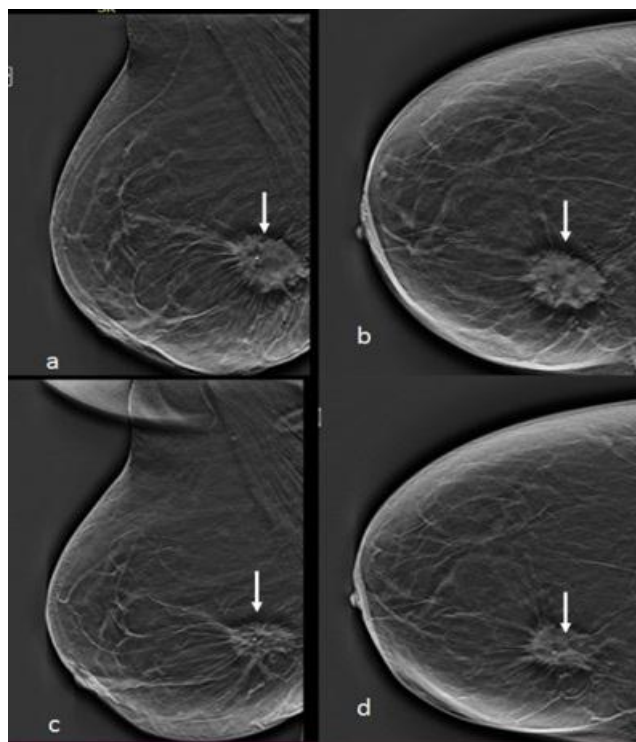


Figure (3): 32 years old female patient with right breast IDC grade 2 (ER +ve, PR +ve, HER2neu +ve) (a) MLO and (b) CC tomogram before NAT show spiculated mass lesion at upper inner quadrant measuring about 4 x 4 cm. (c) MLO and (d) CC tomogram after NAT show residual spiculated mass lesion about 2 x 1.5 cm with inserted metallic clip (Partial radiological response). Final Pathological results after right modified radical mastectomy (partial pathological response, residual invasive ductal carcinoma 1.5 cm).

Most of the patients underwent MRM (72 %) while 28 % underwent BCS. pCR was found in 24 % of the patients, 66 % had partial response (**Figure 4**), and 10 % had no response to NAT. There was significant correlation between DBT and post-surgical pathological results with Accuracy 94 % (**Table 2**).

There was also significant correlation between residual tumor size measured by DPT and pathological size (**Figure 5**). We found that at cut off point (mass size ≤ 4.1 cm), the sensitivity of DBT in predicting pathological response to NAT was 93 %, specificity was 75 %, accuracy was 88 % (**Figure 6**).

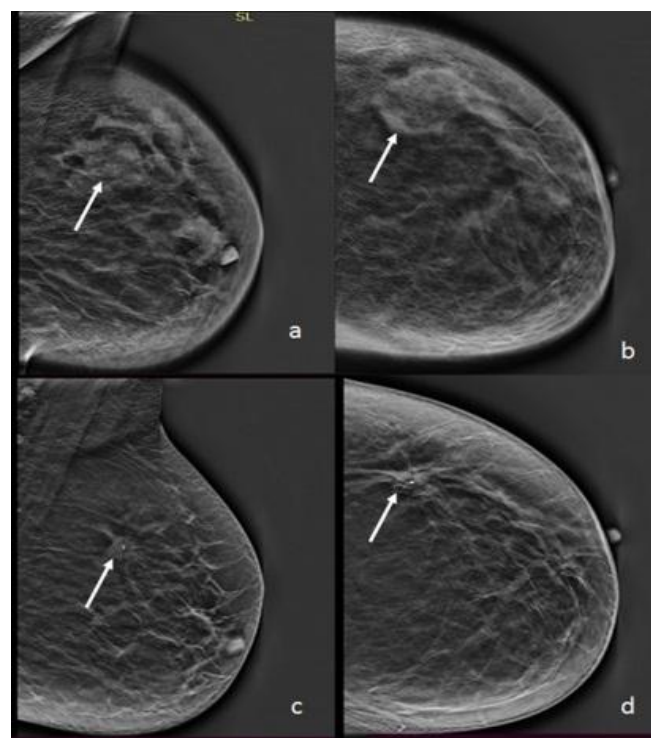


Figure (4): 32 years old female patient with left breast IDC grade 2 (ER +ve, PR +ve, HER2neu -ve) (a) MLO and (b) CC tomogram show lobulated mass lesion at upper outer quadrant measuring about 4.9 x 4.6 cm. (c) MLO and (d) CC tomogram after NAT show residual spiculated mass lesion about 2.2 x 2 cm with inserted metallic clip (Partial radiological response). Final Pathological results after left modified radical mastectomy (Partial pathological response, residual invasive ductal carcinoma 2.5 cm).

Table (2): Accuracy of digital breast tomosynthesis (DBT) in relation to pathology (n=50)

DBT	Pathology			
	Response (n=135)		No response (n=15)	
	No.	%	No.	%
Response (n= 138)	132	97.7	6	40
No response (n=12)	3	2.3	9	60
Test of significance	FE=66.0			
P value	<0.002*			
Sensitivity	97.8%			
Specificity	60%			
Accuracy	94%			
PPV	95.7%			
NPV	75%			

*: Statistically significant, FE: Fisher exact test, PPV: Positive predictive value, NPV: Negative predictive value.

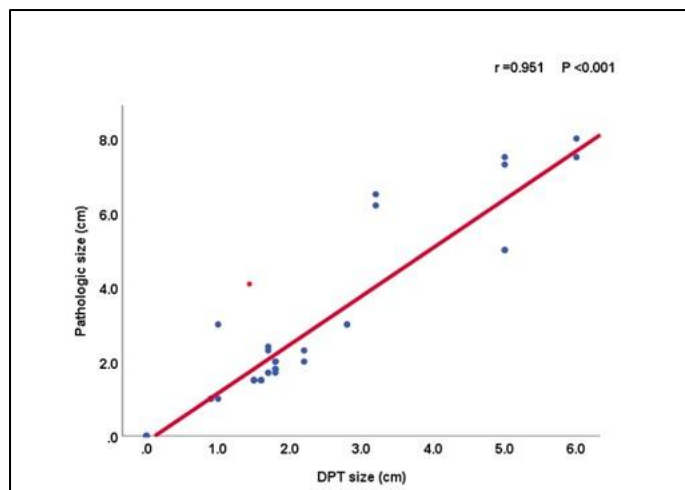


Figure (5): Scatter plot of DPT residual tumor size in relation to pathology shows that there was statistically significant positive relation between DPT size and pathological size.

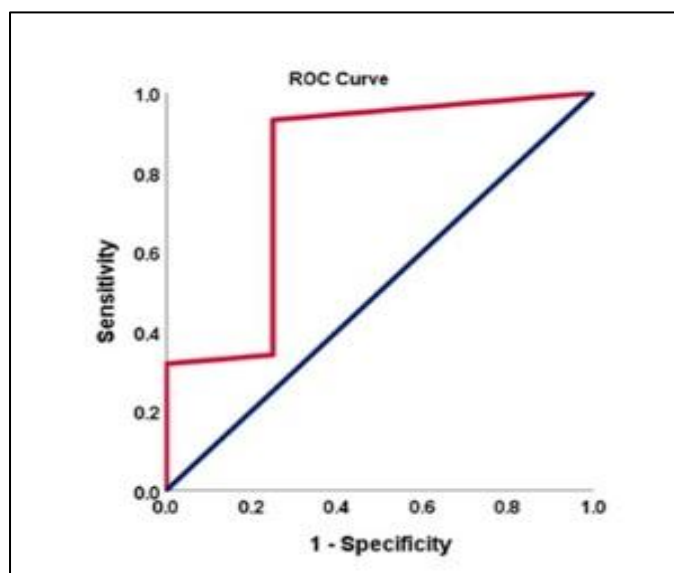


Figure (6): ROC curve showed that at cut off point (mass size ≤ 4.1 cm), the sensitivity of DBT in predicting pathological response to NAT was 93%, specificity was 75%, accuracy was 88%.

DISCUSSION

Neoadjuvant therapy (NAT) is the standard treatment for locally advanced breast cancer. It is used to decrease mastectomy rates in patients with loco-regional disease^[12].

Most of our patients were postmenopausal (52%), this agreed with **Skarping et al.**^[8] who had more post-menopausal patients (52.5 %). The histological subtypes of breast cancer were IDC in 86% and ILC in 14 %. This was also found in **Peintinger et al.** study^[9] who reported IDC in 84 % and ILC in 8 % of their patients and in **Fattacciu et al.**^[10] study who reported that 76.8 % of their patients had IDC.

In our study most prevalent molecular subtype of breast cancer was ER and PR positive (88 % each) and 12 % was triple negative. That agreed with **Murakami et al.**^[11] who found ER and PR positive the most common (65.3%) while triple negative

represented (18.9 %) of their patients. **Peintinger et al.**^[9] also reported that ER and PR Positive was found in 73.5%. **Fattacciu et al.**^[10] found ER and PR positive the most common 55.2%. However, **Shin et al.**^[12] reported that estrogen receptor negative was most common molecular subtype between their patients (60%).

In our study Her2 status was positive in 20% of our patients. This was in line with **Skarping et al.**^[8] who found Her2 positive in 24.3%. However, **Fattacciu et al.**^[10] reported higher incidence of Her2 status positive as it was found in 50.4% of studied patients.

In our study the most common histological grade was grade 2 (represented 80%). This was consistent with **Fattacciu et al.**^[10] who reported grade 2 in 47.2% of their patients. That was discordant with results of **Peintinger et al.**^[9] who reported that most common histological grade was grade 3 by 49.4% and **Murakami et al.**^[11] who reported most common histological grade was grade 3 (38 %).

In our study most common radiological response to NAT in DBT was partial response in 64% of patients, 28% achieved complete response and 8% had no response. This was close to the results of **Uchiyama et al.**^[4] who found the most radiological response to NAT in combined mammogram and tomogram was partial response in (77%), complete response in (19.2%) and progressive disease in 3.8%).

In our study 72% underwent MRM, and 28% underwent BCS. This was close to results of **Murakami et al.**^[11] who reported that 64.2% underwent MRM and 35.7% of the patients underwent BCS. Also, the study done by **Giani et al.**^[2] reported that 56% of their patients underwent MRM and 44% underwent BCS, also **Fattacciu et al.**^[10] reported that 55.2 % of their patients underwent MRM and 49.6% underwent BCS. However, the study by **Telegrafo et al.**^[13] reported that most of study population underwent BCS (81%) and the least underwent mastectomy (19%).

In our study sensitivity of DBT in comparison to pathology after surgery was 97.8%, specificity 60%, Accuracy 94%, PPV 95.7%, NPV 75%. In comparison with pathology after surgery three patients that achieved radiological complete response was found to had residual invasive breast carcinoma in pathology and one patient that had no response in DBT was found to had partial response in pathology. In a study done by **Uchiyama et al.**^[4] they reported that at combined DBT and FFDM one of 21 patient that achieved radiological partial response was found to had pCR and 4 of 4 patients that achieved radiological complete response was found to had pCR.

In our study there was statistically significant positive relation between DBT residual tumor size and pathological size and the correlation coefficient of DBT according to the pathology was found to be high (0.951). That was consistent with **Murakami et al.**^[11]

who stated that DBT improved diagnostic accuracy following NAT as they found DBT and MRI had a stronger correlation with pathology than FFDM and US with correlation coefficients values 0.85, 0.87, 0.74, and 0.77.

Park et al. ^[14] also reported that MRI and DBT size correlated better with pathology than mammography and US size (correlation coefficient was 0.83, 0.63, 0.56, 0.55 respectively). Also, that was consistent with **Uchiyama et al.** ^[4] who reported that adjunction of DBT to FFDM, correlate better with pathology and showed statistically significant difference (p value 0.04).

In our study sensitivity of DBT tumor size in prediction pathological response to NAT was 93%, specificity was 75%, accuracy was 88%. That was in discordance with a study done by **Skarping et al.** ^[8] they reported that sensitivity of DBT in predicting pCR was 50% and specificity was 91%. This may be attributed to their larger patient number.

For predicting pCR, area under the ROC curve was 0.807 in our study (**Figure 5**). That was in agreement with **Murakami et al.** ^[11] that reported area under the ROC curve for DBT was 0.79, and also **Park et al.** ^[14] who stated that for predicting pCR, MRI and DBT had a better performance compared to MG and US area under the ROC curve for DBT in their study was 0.84.

Our study has some limitations as we enrolled a limited number of patients due to single centre study. The study population included 21 patients with invasive lobular carcinoma, which is known to be more difficult to evaluate on imaging and is usually less responsive to NAT compared with IDC. Further studies with a larger number of patients, multicentre validation, comparative studies with other imaging modalities are recommended.

CONCLUSIONS

DBT has good correlation with histopathology for measuring residual tumor size after NAT. It is sensitive in predicting pathological response to NAT.

No funding.

No conflict of interest.

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