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Correlation of Pathological Complete Response with Radiological Evaluation after Neoadjuvant Chemotherapy of Breast Carcinoma

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Abstract

Introduction: Neoadjuvant chemotherapy is the standard treatment modality in locally advanced breast cancer, and accepted as an alternate modality in operable breast cancer. Pathological Complete Response (pCR) is a surrogate for better outcome. The identification of the most sensitive clinical and radiological method to pCR will be helpful in patient's management.

Patients and methods: Multicenterprospective study assessed the correlation between (pCR) and radiological Complete Response (rCR) using different radiological modalities. 125 female with primary measurable stage II or III non inflammatory breast cancer, were enrolled in the study after pathological confirmation using image guided core biopsy. Pathological assessment was done. All eligible cases received neoadjuvant chemotherapy (FEC) IV every 3 weeks for three cycles followed by Docetaxel IV every 3 weeks for three cycles. Trastuzumab was added in Her2neu positive patients concomitantly with docetaxel. Radiological evaluation was done before chemotherapy and prior to definitive surgery. pCR was defined as complete disappearance of invasive tumor cells in both breast surgical specimen and lymph nodes. Patients who achieved pCR were correlated with truly positive rCR by different modalities. The results were statistically analyzed using the Kappa method for agreement.

Results: 20% of the patients achieved pCR 25/125. All these patients received 6 cycles of chemotherapy, only 4 patients received Trastuzumab. Conservative surgery was performed in 80% of cases and MRM in 5/25 of them. True radiological Complete Response (rCR) was achieved in 56% of patients by mammography, 17/25 (68%) of patients by ultrasonography who showed complete disappearance of the mass. 23/25 (92%) achieved rCR morphologically by Dynamic MR-Mammography and in 24/25 (96%) of cases using the kinetic data. MR Spectroscopy showed rCR in (92%) cases. In our study, predictions made on the basis of MRI showed a better correlation with the pathological response after neoadjuvant chemotherapy than did estimations made on the basis of mammography or sonography. The sensitivity, specificity, PPV and NPV for Dynamic MRI in predicting complete pathological response were 96%, 94%, 89% and 99% respectively. The sensitivity, specificity, PPV and NPV for MRS were 92%, 92%, 85% and 97% respectively while the sensitivity, specificity, PPV and NPV for Mammography were 44%, 87%, 61% and 87% respectively and the sensitivity, specificity, PPV and NPV for ultrasonography were 68%, 90%, 77% and 92% respectively.

Conclusion: The most sensitive radiological methods correlated with pCR were dynamic MR mammography and MR Spectroscopy, further studies using new modalities and larger number of patients is required to confirm our results.

Keywords: pathological Complete Response (pCR); Neoadjuvant chemotherapy; Dynamic MR-mammography

Abbreviations: pCR: pathological Complete Response; rCR: radiological Complete Response; NAC: Neoadjuvant Chemotherapy; MX: Mammography; MRM: Magnetic Resonance Mammography; MRS: Magnetic Resonance Spectroscopy

Introduction

Neoadjuvant chemotherapy is the standard treatment modality in locally advanced and inflammatory breast cancer, and accepted as a treatment option in operable breast cancer [1]. Advantages of primary systemic therapy or the neoadjuvant chemotherapy include: decreasing tumor size, consequently, allowing the surgeon to preserve the breast, in vivo testing to tumor response to specific drug treatment and future potential response to further treatment and finally, it may be informative about the biology of the carcinoma under treatment. Many studies assessed the efficacy of neoadjuvant systemic therapy and comparing it to adjuvant therapy. The results of the recently published

meta-analysis revealed no difference between neoadjuvant therapy and adjuvant therapy in terms of survival and overall disease progression. Accordingly, neoadjuvant chemotherapy can be considered as an alternative option to patients in whom the chemotherapy is a part of their treatment plan [2]. Moreover, patients who achieved pathological complete response are expected to do better in the terms of disease free

and overall survival [3,4]. Based on that, there were many efforts to clinically detect, predict and also assess the sensitivity of clinical and radiological modalities to evaluate pCR. Complete disappearance of the tumor clinically or radiologically is not an indication of pCR, between 60-80% of patients who achieved rCR, residual tumor cells were found in the excised tumor bed, while we may find complete pathological responders in those patients who did not achieve complete response clinically [5].

Until now, many studies have shown that physical examinations, mammography and sonography provide suboptimal evaluations of lesion extent that do not allow accurate assessments of pathological response or residual tumor size. In the case of LABC, physical examination, mammography or sonography had higher sensitivity to detect large lesions, but the sensitivity was lower in smaller residual lesions [6]. For mammography, calcifications is not an indication of residual disease, it may persist or even increase in patients responding to neoadjuvant chemotherapy [7].

Recent studies have shown that MRI is the most reliable technique for evaluating residual tumor after neoadjuvant chemotherapy, although false-negatives with smaller-volume tumors were reported.

The sensitivity of MRI, with the new protocols and the use of kinetic assessment minimize the underestimation of residual disease. It is still difficult, however, to distinguish residual scarring, necrosis and fibrosis from viable residual malignancy and to predict accurate response after neoadjuvant chemotherapy, especially in responders [8].

Based on that, the identification of the most sensitive clinical and radiological method to pCR will be helpful in patient's management.

Patients and Methods

Study population

Women eligible for the study were between 18 and 65 years old after pathological confirmation of being breast cancer using image guided core biopsy from both the primary tumor and lymph nodes. Stage II and III were only included in this study, while Patients with inflammatory breast cancer were excluded. Pathological evaluation and assessment of ER, PR, Her2neu and Ki 67 were done. Main eligibility criteria included WHO performance status less than 2; adequate hematologic (Hemoglobin more than 10 gm/dl, granulocyte count $\geq$ 2×10^9/L, platelet count $\geq 100 \times 109$/L) and hepatic (liver enzymes $\leq$ $1.5 \times$ the Upper Limit Of Normal [ULN], alkaline phosphatases $\leq 2.5 \times$ ULN, and bilirubin $\leq$ ULN) tests; and normal cardiac function.

Exclusion criteria included pregnancy, documented history of cardiac disease contraindication of any of the medications in the protocol previous cancer (except treated basal cell and squamous cell carcinoma of the skin).

Metastatic work up was performed in potentially eligible patients including chest x-ray, abdominal ultrasound and bone scan. Informed consent was obtained before inclusion in the study.

Study design and treatment

Multicenter prospective study assessed the correlation between pathological Complete Response (pCR) and radiological Complete Response (rCR) using different radiological modalities. This study was approved by the institutional review board and ethical committee of all participated centers. Informed written consents from participants were obtained before starting of the study. 125 female with primary measurable stage II or III non inflammatory breast cancer, based on Tumor-Nodes-Metastases (TNM) Criteria as detailed in Handbook for Staging of Cancer, American Joint Committee on Cancer, 7th Edition, were enrolled in the study after pathological confirmation using image guided core biopsy from both the primary tumor and lymph nodes. Pathological evaluation and assessment of ER, PR, Her2neu and Ki 67 were done. All eligible cases received neoadjuvant chemotherapy in the form of fluorouracil 500 mg/m², epirubicin 100 mg/m², and cyclophosphamide 500 mg/m² (FEC) intravenously on day 1 every 21 days for three cycles followed by Docetaxel 100 mg/m² intravenously on day 1 every 21 days for three cycles. Trastuzumab 8 mg/kg as loading dose followed by 6 mg/kg every 21 days was added in Her2neu positive patients started concomitantly with docetaxel and planned to continue after for a total of 17 injections. Radiological evaluation was done before chemotherapy was initiated and evaluation of response was done one month after the end of chemotherapy, prior to definitive surgery. Radiologist analyzes each image set blinded to other imaging modalities and histopathology. pCR was defined as complete disappearance of invasive tumor cells in both breast surgical specimen and lymph nodes. rCR was defined according to the modality as mentioned in Table 1.

The Patients enrolled in the study who achieved pCR were correlated with truly positive (truly identified) rCR by different modalities. The results were statistically analyzed using the Kappa method for agreement.

Definitions, calculations and accuracy measures of different imaging modalities as regards the prediction of pCR in patients receiving NAC were mentioned in Table 6. Treatment discontinuation was required for patients with disease progression, unacceptable toxicity, WHO grade 3 to 4 cardiac event. Further management was discussed for each case individually.

In patients with single mass lesion, clip marks were inserted into the tumor before starting the systemic therapy (Figure 1).

Post-chemotherapy surgical management

Each case was discussed again in investigators multidisciplinary tumor board, and final recommendations for mastectomy versus breast preservation were made. Results of the imaging studies were available to the clinicians and were used to make the surgical decision. Preoperative wire localization (Figure 2) was done to 20/25 of cases.

Patients, who chose breast preservation, fulfilled the criteria of breast conservation with no absolute or relative contraindication to undergo breast conserving surgery. The area of concern, where the wire

	Pathologic	Mammography	Ultrasound	D-MRI	MRS
Complete Response	No viable invasive tumour cells in both breast surgical specimen and lymph nodes	Residual asymmetric density with or without microcalcifications by mammography	Complete disappearance of the lesion	*Morphological changes*: complete disappearance of an image evidence of a mass.	Complete disappearance of the choline peak
				Kinetic data: complete change in the kinetics of the lesions from type 3 to type 1 and type 2a curves	

Table1: Definition of Pathologic and Radiologic complete response.
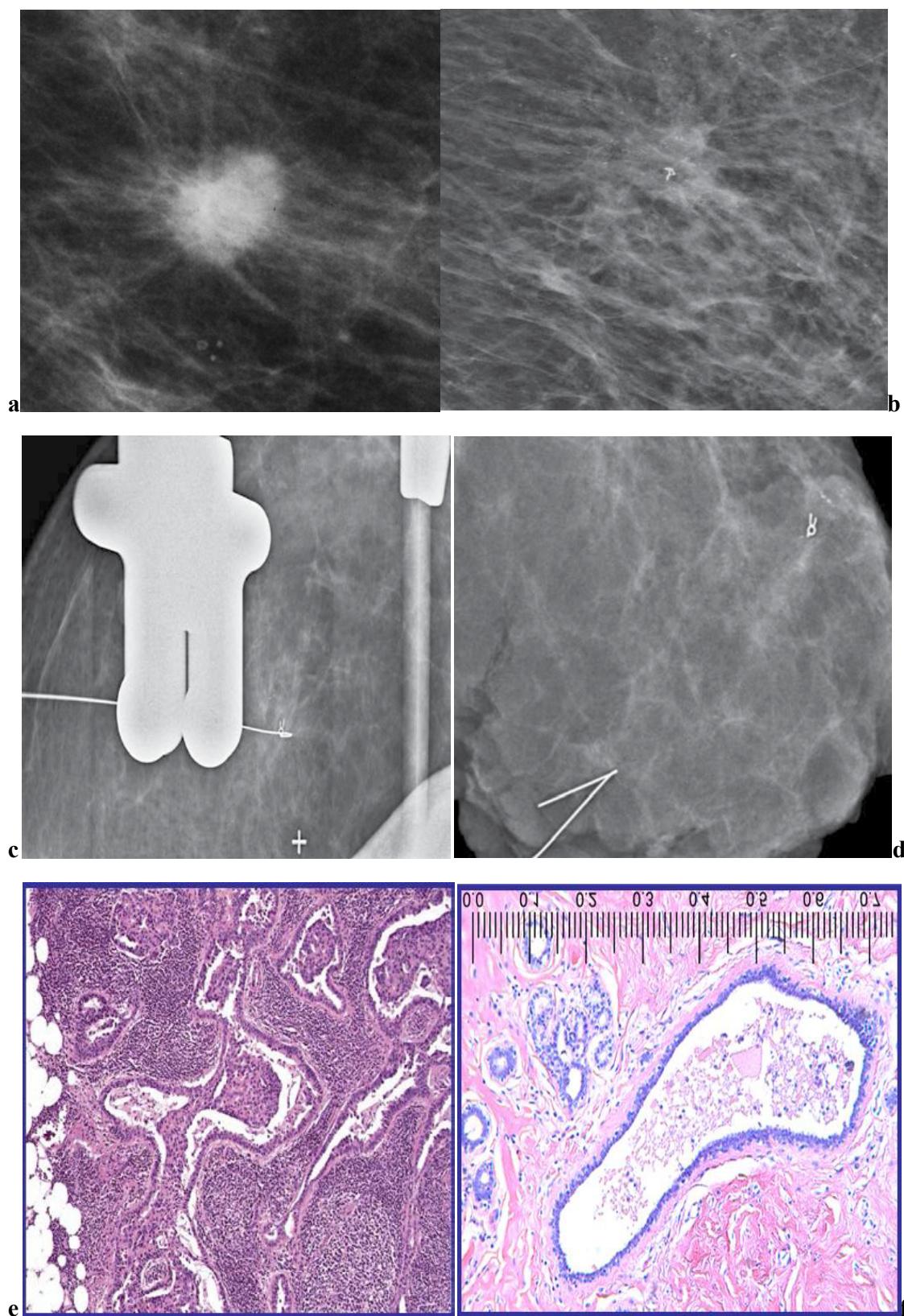
Figure 1: (a) Mamography showing speculated carcinoma before starting NCA. (b) A metallic clip mark is inserted within the tumor. (c) Sterotactic wire localization of the clip mark after complete NAC (6 cycles) and Mammography detected rCR. (d) Specimen radiography after conserving surgery showing the clip and the wire. (e) Histopathology before treatment showing IDC. (f) Complete pathological response evidenced by absence of tumor cells.

Figure 2: (a) Ultrasound image of a locally advanced breast carcinoma before starting NCA seen as indistinct outline large solid hypoechoic mass lesion. (b) After complete 6 cycles of NCA there is an evidence of rCR evidenced by disappearance of the already seen breast mass.
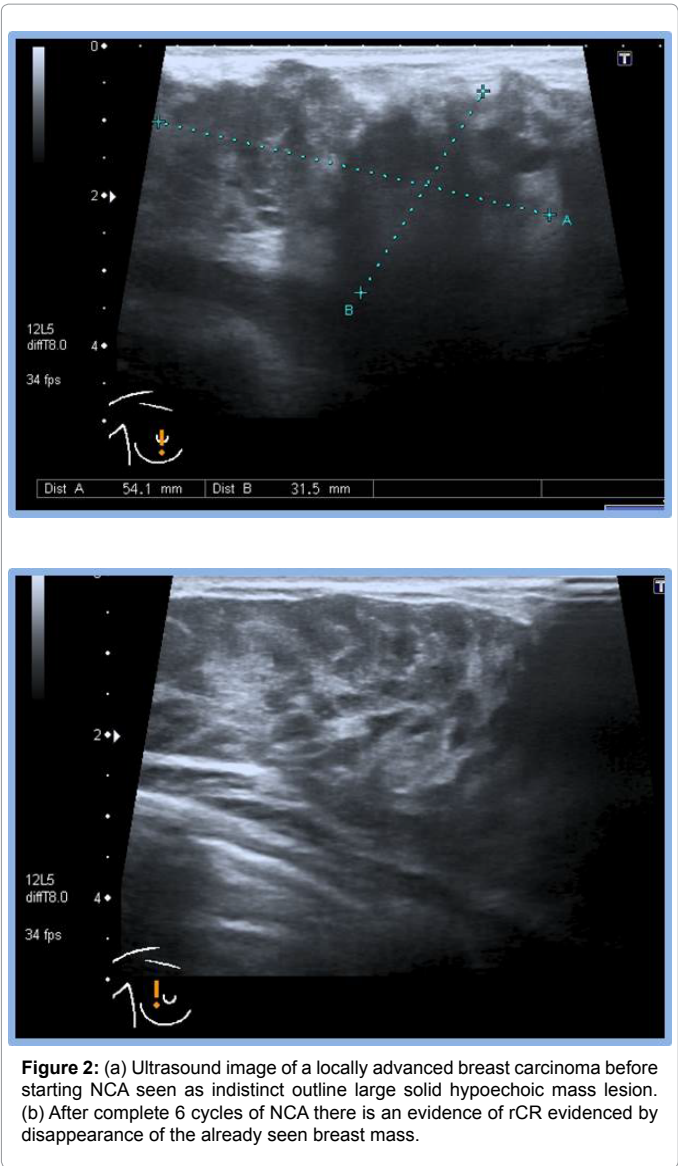
was hooked was completely and widely excised down to the pectoral fascia. Then the specimen was oriented and sent for pathological examination. Metallic clips were inserted in the tumor bed and around the margins of the excision, in order to be identified for postoperative radiation therapy.

Breast reshaping was done by glandular remodeling to close the surgical defect. All patients underwent level I and II axillary lymph node dissection at the time of surgery after completion of chemotherapy. Modified radical mastectomy was done in 4 patients due to the initial multicentricity and in one patient due to her preference.

pathologic Complete Response (pCR)

We defined pathologic Complete Response (pCR) as complete disappearance of any invasive cancer cells in the excised breast tissue and lymph nodes after the end of the neo adjuvant systemic therapy (ypT_0, ypN_0). The presence of residual DCIS or LCIS did not affect our definition of pCR [9]. We consider this definition as the most informative to the patient outcome and surrogate for his survival [10,6].

Results

From the period between January 2012 till March 2013, 125 female patients were enrolled in the study. 20% of the patients achieved pCR 25/125. Those patients who achieved pathological complete response were evaluated in this study. Patients who achieved pCR were correlated with truly positive (truly identified) rCR by different modalities. Table 2 shows the demographic data, tumor biology and treatment regime of the responders (pCR) (N=25 cases). The age of patients ranged from 22-64 years with the median age 46 years. ER positive were recorded in 64% of the patients, while only 5 patients were Her2neu positive. Multicentricity was encountered in 4 patients (16%). All patients received 6 cycles of chemotherapy while only 4 patients received Trastuzumab and one patient did not receive Trastuzumab due to financial reason. Conservative surgery was performed in 80% of cases and MRM in the remaining 5 patients (20%) Table 4 shows the correlation between the rCR (vanishing carcinoma) by different imaging modalities as regards the sensitivity and the pCR after complete NAC. Chart 1 is an illustration of the overall accuracy of the different imaging modalities in diagnosis of pCR. True radiological complete response rCR was achieved in 56% of patients by mammography, 17/25, 68% of patients by ultrasonography who showed complete disappearance of the mass. 23/25 (92%) achieved rCR morphologically by Dynamic MR-Mammography and in 24/25 (96%) of cases using the kinetic data. MR Spectroscopy showed rCR in (92%) cases (Figures 3-5).

	No=25	20%
Age		
median	46	
Range	22-64	
Pre chemotherapy		
Tumor size	Between 2.5-6 cm diameters with average size 3.5 ± 0.6cm	
	25/25	-100%
Axillary nodes +ve	25-Dec	-48%
Multifocal	25-Apr	-16%
Multicentric disease		
ER		
*ve	18/25	72%
-ve	7/25	28%
PR		
+ve	16/25	64%
-ve	25-Sep	36%
HER 2		
+ve	25-May	20%
-ve	20/25	80%
ki67		
<14	25-Jan	4%
>14	24/25	96%
Histopathology		
IDC	21/25	84%
ILC	25-Apr	16%
NAC		
3 cycles FEC 3cycles docetaxale .	25/25	100%
Herceptine	25-Apr	16%
Operative data :		
Conservation surgery	20/25	80%
Mastectomy	25-May	20%

Table 2: Demographic data, tumor biology and treatment regime of the complete pathologic responders (pCR) 25 cases.

	No =100	**80%**
Age		
median	49	
Range	22-68	
Pre chemotherapy		
Tumor size	Between 2.5-6 cm diameters with average size 3.5 ± 0.6 cm	
Axillary nodes +ve	100/100	-100%
Multifocal	25/100	-25%
Multicentric disease	11/100	-11%
ER		
*ve	55/100	55%
-ve	45/100	45%
PR		
+ve	52/100	52%
-ve	48/100	48%
HER 2		
+ve	25/100	25%
-ve	75/100	75%
ki67		
<14	36/100	36%
>14	64/25	64%
Histopathology		
IDC	81/100	81%
ILC	19/100	19%
NAC		
3 Cycles FEC 3cycles docetaxale	100/100	100%
Herceptine	23/100	23%
Operative data		
Conservation surgery	77/100	77%
Mastectomy	23/100	23%

Table 3: Demographic data, tumor biology and treatment regime of the cases with residual disease, incomplete and non-responders (non-pCR) 100 cases.

Modality	DM	US	D-MRI	MRS
rCR	11	17	24	23
sensitivity	-44%	-68%	-96%	-92%
pCR	25	25	25	25
Agreement value by Kappa method	0.43	0.46	0.83	0.81

Table 4: Correlation between the rCR (vanishing carcinoma) by different imaging modalities as regards the sensitivity and the PCR after complete NAC.

The patients who did not achieve pCR and residual lesion was found after surgery were also evaluated as regards the incidence of rCR by different imaging modalities in this group of those patients. Table 3 shows the demographic data; tumor biology and treatment regime of the patients and Table 5 shows the correlation between the rCR (vanishing carcinoma) by different imaging modalities as in cases that did not achieve pCR after complete NAC.

Table 6 shows the accuracy measures of different imaging modalities as regards the prediction of pCR in patients receiving NAC.

Discussion

A sensitive and specific method to identify tumor response to neoadjuvant chemotherapy is needed because early recognition of non-responders facilitates an earlier change of treatment plan to a more effective regime, hence minimizing toxicity and optimizing timing of surgery. In addition, lack of response to a particular regime in vivo may guide additional chemotherapy after surgery [11,12]. In this study we explored the sensitivity of radiological modalities to accurately determine pathologic complete response in the breast after NAC. In previous studies, correlation with the pathologically assessed residual tumor size ranged from 0.42 to 0.68 for tumor sizes assessed by clinical examination, from 0.33 to 0.84 for tumor sizes assessed by mammography and from 0.29 to 0.89 for tumor sizes assessed by sonography [13].

Dense breast tissue and the infiltrating nature of the growth of locally advanced or inflammatory breast cancer are two major factors that might make it difficult to evaluate exact tumor size and response rate after neoadjuvant chemotherapy on mammography [14]. Dense breast tissue often obscures the tumor margin on mammography, thus making size determination difficult. In our study, we determined the extent of the tumor by evaluating a combination of findings such
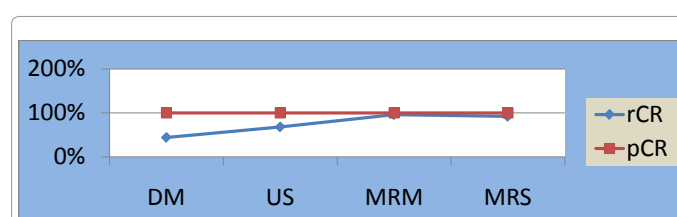

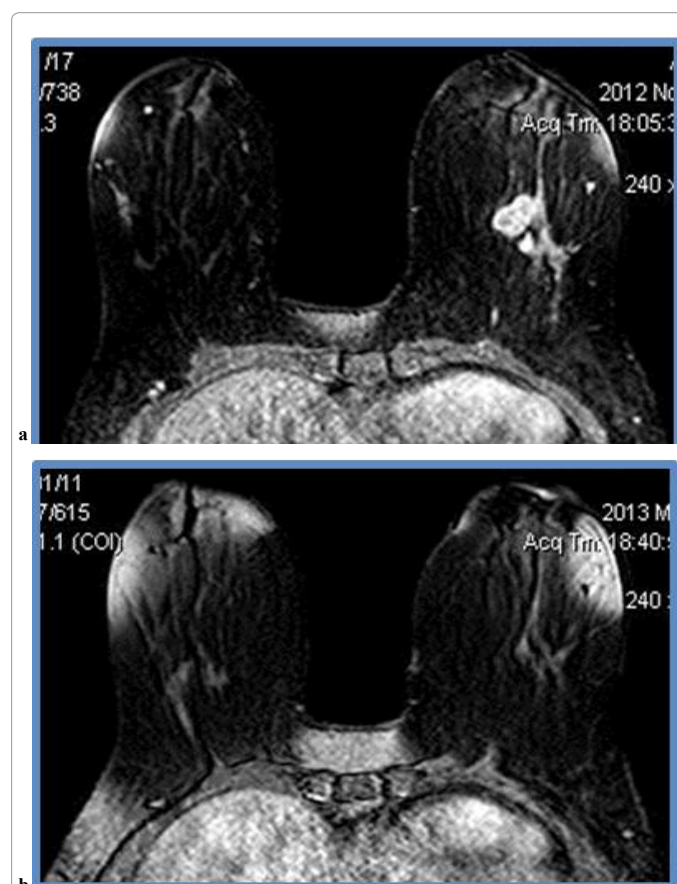**Chart 1:** Showing the overall accuracy of the different imaging modalities in diagnosis of CPR.

Figure 3: (a) Dynamic MR Mammography of a large left breast carcinoma before starting NCA showing intense enhancing mass lesion (b) after complete 6 cycles of NAC there is complete disappearance of the image evidence of a mass.
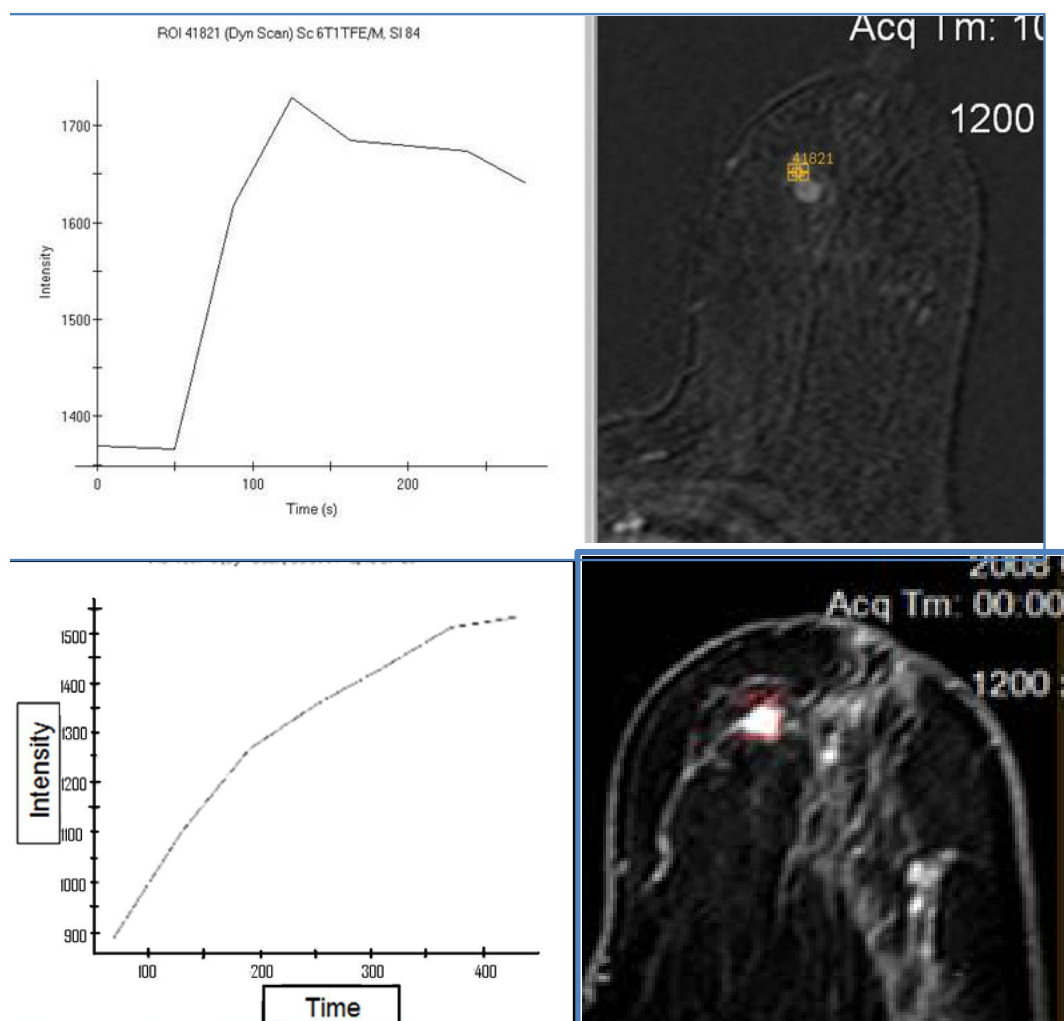
Figure 4: (a) Left UIQ carcinoma before NCA showing type 3 curve. (b) After complete NAC still there is an enhancing small nodule however there is shift of the Kinetic data from type 3 to type 1 curve.

as asymmetric increased density, bulging contour and associated calcifications. In cases where the whole breast parenchyma is involved on initial mammography, however, it was difficult to evaluate the exact extent of the residual tumor after neoadjuvant chemotherapy.

The incidence of pCR in our study was 20% (25 cases out of 125) cases of breast carcinoma given NAC before surgery, which is comparable to other neoadjuvant trials [10,11] and may be lower than those trials of patients receiving trastuzumab in addition to chemotherapy. This may be explained by the smaller number of patients with the consequent smaller HER2 positive patient number beside the financial restrictions that affected administration of the drug to one of the patients in the group who achieved pCR.

In their study of 162 patients, Peintinger et al. [15] showed that the combination of mammography and sonography provided a high accuracy in predicting pCR and a moderate agreement in predicting pathological residual tumour size after neoadjuvant chemotherapy. In their study, the accuracies of mammography and sonography were reduced for the invasive lobular histological tumor type, which was associated with an underestimation of residual tumor size.

In our study, predictions made on the basis of MRI showed a better correlation with the pathological response after neoadjuvant chemotherapy than did estimations made on the basis of mammography or sonography. The sensitivity, specificity, PPV and NPV for Dynamic MRI in predicting complete pathological response were 96%, 94%, 89% and 99% respectively. The sensitivity, specificity, PPV and NPV for MRS were 92%, 92%, 85% and 97% respectively while The sensitivity, specificity, PPV and NPV for Mammography were 44%, 87%, 61% and 87% respectively and the sensitivity, specificity, PPV and NPV for ultrasonography were 68%, 90%, 77% and 92% respectively.

Kwong et al. [16] reported that MRI frequently overestimated residual disease in responders to chemotherapy treatment. In our study, MRI overestimated residual disease in 19% and underestimated residual disease in 7% of our study patients.

Based on our results, MRI proton spectroscopy and Dynamic MRI are the most sensitive tools to detect pCR, comparison with other new and expensive modalities like PET-CT scan is recommended. Also, confirmation of our results in larger prospective studies to include higher pCR numbers is highly recommended.
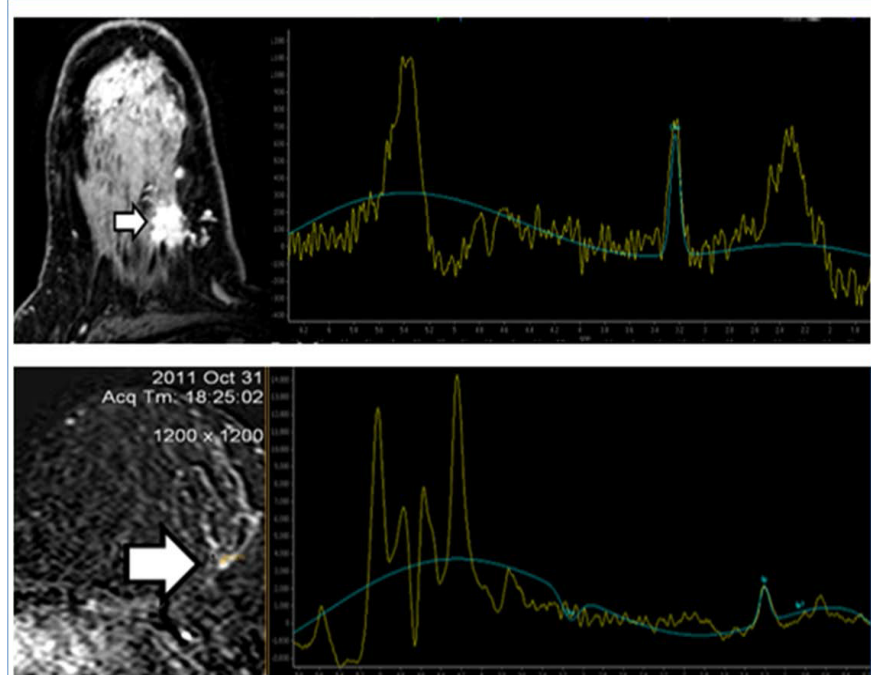
Figure 5: (a) Left breast upper outer quadrant infiltrative mass lesion showing intense enhancement with evidence of high Choline peak in the MR Spectroscopy. (b) After complete NAC there is evidence of small residual enhancing focus with absence of Choline peak in the spectrum.

Modality	DM	US	D-MRI	MRS
rCR false negative	7	5	3	4
No pCR (residual disease)	100	100	100	100
Agreement value by Kappa method	0.54	0.58	0.91	0.87

Table 5: Correlation between the rCR (vanishing carcinoma) by different imaging modalities as regards the sensitivity in patients who did not achieve PCR after complete NAC (100 patients).

True positive(TP); Truly identified	pCR correctly identified as rCR
False positive (FP)	Non-pCR incorrectly identified as rCR
True negative(TN)	Non-pCR correctly identified as non rCR
False negative(FN)	False negative(FN): pCR incorrectly identified as non rCR
Sensitivity	$\dfrac{TP}{TP + FN}$
Specificity	$\dfrac{TN}{TN + FP}$
Positive Predictive Value (PPV)	$\dfrac{TP}{TP + FP}$
Negative Predictive Value (NPV)	$\dfrac{TP}{TP + FP}$

Modality	DM	US	D-MRI	MRS
TP	11	17	24	23
FP	7	5	3	4
TN	93	95	97	96
FN	14	8	1	2

MRS	D-MRI	US	DM	Accuracy markers
92%	96%	68%	44%	Sensitivity
92%	94%	90%	87%	Specificity
85%	89%	77%	61%	PPV
97%	99%	92%	87%	NPV

Table 6: Definitions, calculations and accuracy measures of different imaging modalities as regards the prediction of pCR in patients receiving NAC.

Conclusion

Based on our results, the most sensitive radiological methods correlated with pCR after neoadjuvant chemotherapy were dynamic MR mammography and MR Spectroscopy. Larger prospective studies are encouraged to confirm our results.

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