Diffusion-weighted imaging to quantify the residual tumour post-neoadjuvant chemotherapy in locally advanced breast cancer: in comparison with dynamic contrast-enhanced MRI

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Purpose

Locally advanced breast cancer (LABC) represents a stage in which the tumour is most aggressive and non-metastatic. Neoadjuvant chemo/hormone therapy (NACT/HT) was pioneered in the setting of locally advanced breast cancer.

- For patients with inoperable LABC, NACT/HT has become standard treatment, despite limited supporting data from randomized controlled trials conducted specifically in these patients [1, 2]. The goal is to induce tumour response, to facilitate local control through surgical resection and radiation therapy, and to improve disease-free and overall survival.

- For patients with operable LABC, NACT/HT has improved breast conservation rates. Clinical trials, individually and in meta-analysis, have demonstrated that for these patients, NACT/HT results in long-term disease-free survival and overall survival comparable to that achieved with adjuvant (postoperative) systemic therapy [1,3].

The extent of residual disease post NACT/HT has a direct bearing on the choice of surgical strategy. Prediction of the extent of residual tumour accurately prior to surgery will spare patients having pathological complete response (pCR) from having an extensive disfiguring surgery and also identifies candidates for breast conservation surgery (BCS) in patients with residual tumour, thereby decreasing the number of lumpectomies with positive margin. Numerous studies have demonstrated that the burden of pathologically detected residual disease after NACT/HT correlates with long-term prognosis [4]. It becomes imperative, therefore, that the residual tumour is accurately measured preoperatively.

Contrast enhanced MRI has been shown to be more accurate than physical examination, mammography, or ultrasonography in predicting the amount of residual disease after NACT/HT [8]. However, several studies have noted that conventional breast MR imaging is limited in terms of specificity in the assessment of breast tumours [5-7, 9].

Diffusion-weighted imaging is a modality that makes use of MRI to depict the diffusivity of water molecules in a defined voxel by means of the application of motion-probing gradients. Signal intensity at diffusion-weighted MRI is inversely proportional to the degree of water molecule diffusion. The degree of water diffusion in tissue is inversely correlated with tissue cellularity and the integrity of cell membranes. A tumour, which has a high cellular burden, appears bright on DWI and this acts as a natural contrast to delineate the extent of the tumour. Diffusion is quantified by measuring what is known as the apparent diffusion coefficient (ADC) value in square millimetres per second.
The signal intensity at diffusion-weighted imaging consists of T2-weighted signal and diffusion-weighted signal. The latter is emphasized with the application of higher motion-probing gradients. In addition, the signal intensity at DWI will decrease as \( b \) value increases; thus, an SNR that is sufficient for lesion detection must be provided while emphasizing the contribution from the diffusion coefficient alone because of their "trade-off" relationship [10]. The signal of the mammary gland might not be suppressed at \( b = 1000 \text{ sec/mm}^2 \) in cases of severe fibrocystic disease [6], and recent studies have documented the usefulness of a \( b \) value of 1500 sec/mm\(^2\) [12,13].

There are limited published data probing the role of DW MRI in prediction of response of LABC to NACT/HT. In all but one, it was the role of ADCs which was investigated in prediction of tumour response. To our knowledge, there has been only one study which investigated the visual assessment at DW MRI post NACT/HT [13]. This study was undertaken to compare the accuracies of Diffusion-weighted MR Imaging and Dynamic Contrast Enhanced MRI with Pathological assessment in measuring the residual tumour post Neoadjuvant Chemo/Hormone-Therapy in Locally Advanced Breast Cancer and to assess the reliability of ADCs in tumour response prediction.
Methods and materials

Subjects:

This study is a prospective comparative trial in patients diagnosed with LABC between November 2010 and June 2012 in a tertiary care centre in South India.

Fifty one patients were included for the study. MRI of the bilateral breasts was performed before, and after the completion of Neoadjuvant chemo/hormone therapy.

The Neoadjuvant systemic therapy consisted of either chemotherapy or hormone therapy. The chemotherapeutic regimen used was either FAC (5-fluorouracil, doxorubicin, and cyclophosphamide) or FEC (5-fluorouracil, epirubicin and cyclophosphamide) given 3-weekly for 3 or 4 cycles prior to surgery. The hormone therapy consisted of Letrozole 2.5 mg daily for 16 weeks prior to surgery.

The final pathological examination was performed after surgical excision following the last cycle of chemo/hormone therapy. The presence of any residual disease evaluated by using DW Imaging and Dynamic contrast enhanced MR imaging were compared with postoperative histological findings.

MR Imaging:

Each patient underwent contrast-enhanced MRI of the breast before and after Neoadjuvant chemo/hormone therapy administration. MRI was performed immediately before the administration of the first cycle of chemotherapy, 1-2 weeks after the completion of adjuvant chemotherapy, and within 2 weeks of planned definitive surgery. All patients had previously undergone percutaneous core needle breast biopsy 1-4 weeks before the initial MRI examination. Specific contraindications for MRI or MR contrast medium were sought for and excluded.

Breast MR imaging was performed by using a 1.5-T MR imaging system with a dedicated breast coil. Patients were examined in prone position. The details of the MR sequences are presented in table 1:

Table 1: Summary of MR sequences
<table>
<thead>
<tr>
<th>Sequence</th>
<th>Repetition Time/Echo Time (msec)</th>
<th>Flip Angle (°)</th>
<th>Field of View (mm)</th>
<th>Section Thickness (mm)</th>
<th>No. of Sections</th>
<th>Receiver Bandwidth (kHz)</th>
<th>Imaging Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>STIR</td>
<td>4500/56</td>
<td>-</td>
<td>340</td>
<td>4</td>
<td>34</td>
<td>252</td>
<td>4min 41sec</td>
</tr>
<tr>
<td>T2 Turbo Spin-echo FS</td>
<td>6000/108</td>
<td>-</td>
<td>180</td>
<td>4</td>
<td>23</td>
<td>150</td>
<td>1min 56 sec</td>
</tr>
<tr>
<td>DW single-shot echo-planar imaging (b value of 0, 500, 1000, 1500 sec/mm²).</td>
<td>4800/1.34</td>
<td>-</td>
<td>230</td>
<td>5.5</td>
<td>20</td>
<td>1240</td>
<td>3 min 18 sec</td>
</tr>
<tr>
<td>Three-dimensional T1 FLASH Dynamic</td>
<td>4.27/1.45</td>
<td>6</td>
<td>340</td>
<td>0.9</td>
<td>160</td>
<td>320</td>
<td>6 min 22 sec</td>
</tr>
</tbody>
</table>

In the Dynamic contrast enhanced MRI sequence, the image depicting the maximum tumour size was selected, and the lesion was measured using electronic callipers. The maximum dimension of the abnormally enhancing lesion or lesions corresponding to the known malignancy was measured (see Fig. 1 on page ). This maximum
dimension was chosen to represent the extent of disease present in the breast. Thus, if the tumour bed consisted of multiple adjacent lesions, the maximum dimension was a single measurement encompassing the lesions farthest apart, with a goal to determine the extent of malignancy in the affected breast.

The distribution of tumour in the breast was also characterized as focal (single discrete mass) or nonfocal (segmental, regional, or diffuse). Interval change was assessed by directly comparing similar images from studies performed before and after NACT/HT and comparing measurements obtained from these similar images.

In the index breast, the area or areas with higher signal intensity than that of healthy breast parenchyma were identified as lesion(s) on DW images with a b value of 1500 sec/mm². On the DW images after Neoadjuvant chemo/hormone therapy, the presence of high signal intensity lesions (higher than that of healthy breast parenchyma) was considered positive for residual disease. At both instances, the longest diameter of the high signal intensity lesion(s) was measured using the same algorithm as for DCE MRI. ADCs from those lesions positive on DW images were analysed by using an ADC map on a workstation. The region-of-interest placement for the tumours was undertaken on three separate foci within the lesion, and ADCs were averaged.

Histopathological Examination:

After Neoadjuvant systemic therapy, 29 patients underwent Modified Radical Mastectomy and 7 underwent Breast conservation surgery. Breast specimens were evaluated by gross and microscopic pathologic examination. The specimens were processed by serial gross sectioning at approximately 5 mm intervals. The largest grossly identifiable tumour mass was measured, and representative H and E-stained slides were examined to confirm the presence of carcinoma. Representative sections of grossly normal breast tissue were examined from quadrants distant from the largest tumour mass. Any other suspicious masses in the breast that were detected by gross examination were also sampled for histologic examination.

Statistical analysis:

Comparison of imaging measurement by DW MRI and DCE MRI with pathologically determined tumour size was done using Pearson correlation coefficient. Their correlation coefficients were compared using Fischer r-to-z transformation. Measures of diagnostic accuracy for DW MRI and DCE MRI in detection of residual tumour were obtained with 95% CI. Change in tumour size, ADC values between
pre and post NACT/HT and between pCR and non-pCR groups were analyzed using *unpaired-t test*. 
Fig. 1: 55 yr old female with a diagnosis of Invasive Ductal carcinoma. A. Axial STIR image of bilateral breasts shows a heterogeneously hyperintense mass in lateral and posterior right breast. B. Axial subtracted image of the dynamic contrast enhanced T1 FASH 3D sequence shows a 43.7 mm sized enhancing mass in the lateral and posterior right breast. C. Axial Diffusion Weighted Imaging with a b value of 1500 sec/mm² shows a 39.6 mm hyperintense mass in the same region. D. ADC map of bilateral breasts shows a hypointense area corresponding to the hyperintensity at DWI, suggesting diffusion restriction.

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Results

Of the 51 patients included in the study, 36 were eligible for final analysis. Seven patients were lost to follow up after the first MRI. Six patients did not undergo MRI prior to Neoadjuvant systemic therapy. Two patients had motion related artefacts on MR imaging precluding their accurate analysis.

The study cohort consisted of patients of various ages ranging from 29 to 75 yrs. (mean age - 50 yrs.). Of the 36 patients, 22 (61%) were postmenopausal and 14 (39%) were premenopausal. Among the study patients, 30 (83%) underwent Neoadjuvant chemotherapy with either FAC or FEC regimen before definitive surgery. 6 patients (17%) underwent Neoadjuvant Hormone therapy with Letrozole before surgery. Twenty patients (5%) had 'focal' lesions whereas in 16 patients (44%) the distribution was 'nonfocal'. Five patients (14%) showed complete response on final histopathological evaluation (pCR). Rest of the patients (86%) had pathologically measured residual tumour in the post-surgical specimens. No patient had positive margins after breast conservation surgery.

Table 2: Extent of Response on pathology:

<table>
<thead>
<tr>
<th>Extent of Response on pathology</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR*</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Residual disease</td>
<td>31</td>
<td>86</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>100</td>
</tr>
</tbody>
</table>

*pCR - pathological complete response

Among the pCR group, the mean initial ADC was 0.79 x10^{-3} mm²/s and in the non-pCR group it was 0.75 x10^{-3} mm²/s, but the difference was not found to be statistically significant (P value is 0.5527) [see ]. In patients with residual disease, the mean ADC before NACT/HT was 0.75 x10^{-3} mm²/s and that after NACT/HT was 0.68 x10^{-3} mm²/s. There was no significant change in ADCs (P value is 0.1325) before and after Neoadjuvant systemic therapy [see Fig. 3 on page 13].

The mean initial tumour size in the pCR group was 39.82 mm and in the non-pCR group was 43.87 mm. Statistically, there was no significant difference in the initial tumour sizes between the pCR and the non-pCR groups (P value is 0.5737).
Clinical examination predicted tumour size to within 1 cm in 25 cases (70%), whereas DWI and DCE MRI predicted the same in 31 cases (86%) each. Clinical examination underestimated the tumour size by more than 1 cm in 3 cases (9%) whereas DWI and DCE MRI did the same for 1 case (3%) each. Clinical examination overestimated the tumour size by more than 1 cm in 8 cases (21%) whereas DWI and DCE MRI did the same for 4 cases (11%) each [see Fig. 4 on page 14].

The change in ADC from before to after Neoadjuvant systemic therapy did not correlate with the size change measured at DCE MRI in the non-PCR group (Pearson correlation coefficient $r = 0.1182$, $P = 0.5267$).

For the detection of Residual tumour post NACT/HT, Clinical Examination showed a sensitivity of 83.87% (95% CI from 66.26 to 94.55%) and a specificity of 80% (95% CI from 28.35 to 99.49%). The sensitivities and specificities of DW MRI and DCE MRI for the detection of residual tumour were similar and were 100% (95% CI from 88.78 to 100%) and 80% (95% CI from 28.35 to 99.49%) respectively. There were 5 false negative cases and 1 false positive case on clinical examination. There was one false positive case on DWI and DCE MRI. It was observed as a focus of haemorrhage on histopathology [see Fig. 5 on page 15]. There were no false negatives.

Comparison of pathological data with the diagnostic modalities showed strong correlation for measurement of residual tumour size by DW MRI ($r=0.94$, $p < 0.001$) and DCE MRI ($r=0.93$, $p < 0.001$) [see Fig. 6 on page 16, Fig. 7 on page 17].

Using the Fisher r-to-z transformation, z values were calculated for determining the significance of the difference in correlations of clinical examination, DWI and DCE MRI with pathology. The details are presented in Table 3. The strength of correlation with pathology for DW MRI was significantly better than that of clinical examination ($z = 2.07$, $p = 0.0385$). The strength of correlation between DWI and Pathology was not statistically different from that between DCE MRI and Pathology ($p = 0.9045$).

**Table 3: Significance of the difference in correlations of clinical examination, DWI and DCE MRI with pathology:**

<table>
<thead>
<tr>
<th>Value</th>
<th>Clinical examination vs. DWI</th>
<th>Clinical examination vs. DCE MRI</th>
<th>DWI vs. DCE MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$z$</td>
<td>2.07</td>
<td>1.95</td>
<td>0.12</td>
</tr>
<tr>
<td>P value</td>
<td>0.0385</td>
<td>0.0512</td>
<td>0.9045</td>
</tr>
</tbody>
</table>

There was no significant difference between the correlation coefficients of DW MRI ($z=0.797$, $p=0.425$) and DCE MRI ($z=0.88$, $p=0.379$) with pathology, among focal and nonfocal lesions.
Fig. 1: 55 yr old female with a diagnosis of Invasive Ductal carcinoma. A. Axial STIR image of bilateral breasts shows a heterogeneously hyperintense mass in lateral and posterior right breast. B. Axial subtracted image of the dynamic contrast enhanced T1 FASH 3D sequence shows a 43.7 mm sized enhancing mass in the lateral and posterior right breast. C. Axial Diffusion Weighted Imaging with a b value of 1500 sec/mm² shows a 39.6 mm hyperintense mass in the same region. D. ADC map of bilateral breasts shows a hypointense area corresponding to the hyperintensity at DWI, suggesting diffusion restriction.

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**Fig. 2:** Initial ADC in pCR and non-pCR groups

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Fig. 3: Mean ADC values in the non pCR group, pre and post NACT/HT

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Fig. 4: Extent of errors in prediction in Tumour size by clinical examination, DWI and DCE MRI

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**Fig. 5:** False positive case on MRI: 48 yr old female with Invasive ductal carcinoma after NACT/HT. A. Axial image of the dynamic contrast enhanced T1 FASH 3D sequence shows a 7 mm enhancing focus in the left breast. B: Axial Diffusion Weighted Imaging with a b value of 1500 sec/mm² shows a 5 mm sized focus of restricted diffusion in the left breast. C: ADC map of bilateral breasts shows a hypointense focus corresponding to the hyperintensity at DWI, confirming diffusion restriction. It was shown to be a focus of haemorrhage at pathology. D: Axial non-contrast T1 TSE sequence of bilateral breasts shows that the focus is mildly hyperintense than the surrounding parenchyma, suggesting haemorrhage.

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**Fig. 6:** Correlation between residual tumour sizes by DW Imaging and pathology

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Fig. 7: Correlation between residual tumour sizes by DCE MRI and pathology

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Conclusion

Studies evaluating the efficacy of Neoadjuvant chemo/hormone therapy suggest that accurate assessment of tumour response to chemotherapy and the maximum size of the primary tumour after therapy are important predictors of local recurrence [14-16].

The utility of DWI in measuring the size of the residual tumour is yet to be explored. One previous study documented the same accuracy for diffusion-weighted imaging and contrast-enhanced MR imaging in the detection of residual tumour [13]. In this study, diffusion-weighted imaging helped detect residual cancers that contrast-enhanced MR imaging did not help detect. Therefore, diffusion-weighted imaging may increase diagnostic accuracy in the evaluation of chemotherapy effect and the detection of residual disease.

In our single centre prospective study, we evaluated 36 patients who were diagnosed with Locally Advanced Breast Cancer with two MRIs timed before and after the Neoadjuvant systemic therapy. The MR Imaging protocol involved Diffusion weighted Imaging and Dynamic contrast enhanced MR Imaging in each of the sittings.

The visual analysis at DWI was performed at a b value of 1500 sec/mm² to keep the T2 shine through effect to a minimum. To our knowledge this is the first study to use Dynamic contrast enhanced MRI for comparing with the sizes obtained at DWI. Several studies in the past have shown that there is a decrease in peak tumour enhancement with alteration of the enhancement kinetics post Neoadjuvant systemic therapy. Hence, a Dynamic sequence was considered as part of this study to measure the tumour size in the sequence with the maximum enhancement, and to avoid excluding areas with altered enhancement pattern. To the best of our knowledge, this is the first study to include patients who underwent primary hormone therapy.

There was no significant difference in the prechemotherapy ADCs between the pathological complete response cases and residual disease cases.

There was no significant change in the ADC values in the residual disease cases, before and after Neoadjuvant systemic therapy. Further, the ADC change observed did not correlate with the tumour size change observed at DCE MRI. Our result concurs with the previous study by Woodhams et al [13]. There are a few studies in the past showing a correlation between the ADC change and the chemotherapy effect [18,19]. However, in one of these studies, the final ADC after the whole course of Neoadjuvant chemotherapy was not analysed. In the other study, the size of the residual tumour after chemotherapy
was not shown. Therefore, the reliability of the ADC measurement after chemotherapy remains uncertain.

The residual tumour size has to be accurately measured in order to plan an optimal surgical strategy. In our study, Diffusion weighted imaging and Dynamic contrast enhanced MR imaging correctly depicted the diagnosis in 35 of the 36 cases. The diagnostic accuracies were similar for both the modalities, at 100% and 80% respectively. The diagnostic accuracies for clinical examination in depicting the presence of residual tumour were 84% and 80% respectively. The results show that Diffusion weighted imaging proved to be equivalent in diagnostic accuracy to Dynamic contrast enhanced MR imaging, whereas both these modalities were slightly better than clinical examination in detecting the residual tumour post Neoadjuvant systemic therapy.

There was significant correlation between the sizes measured at clinical examination, Diffusion weighted imaging and dynamic contrast enhanced MR imaging with size determined at pathology, but the size prediction by DWI had a stronger correlation with pathology than that by clinical examination. There was no statistically significant difference in the size prediction by DWI and DCE MRI.

The strengths of correlation of DW MRI and DCE MRI with pathology did not significantly vary between focal and nonfocal lesion distributions, suggesting that there is no significant influence of lesion distribution on diagnostic accuracy of these MR imaging modalities.

Other investigators [4-7, 9] have demonstrated false positive and false negative incidents with contrast enhanced MRI for detection of residual tumour after Neoadjuvant chemotherapy. There is a higher rate of false negatives reported in few studies with contrast enhanced MRI. In our study, there was only one false positive case for both DWI and DCE MRI. There were no false negatives. We used a dynamic contrast enhanced MRI sequence which might have improved our results.

The single false positive case was shown to be a focus of granulation tissue with coexisting haemorrhage at pathology. Areas of haemorrhage have been variably characterised by DW MRI in literature. Hematomas containing intracellular components (intracellular oxyhemoglobin, deoxyhemoglobin, or methemoglobin) show significantly reduced diffusion compared with hematomas containing lysed red blood cells (extracellular methemoglobin) [20]. Some hematomas have high signal intensity on precontrast T1-weighted images, as was the case in our situation. Therefore, T1-weighted images should be evaluated together with diffusion-weighted images to avoid misdiagnosis. The residual tumour size was grossly underestimated in two cases in which diffuse carcinomatous infiltration of fat was present surrounding the gross tumour at
pathology, which was not visualised by MR imaging. Size discrepancies can also be due to distortion of the specimens during histological processing.

**Limitations:**

First, the sample size was relatively small. This may be due to temporal, technical, protocol related issues or related to feasibility of MRI within the tight schedule of surgical planning in the Neoadjuvant setting. Attrition was also a factor. Further studies with larger sample are needed to prove the role of DWI beyond doubt. Second, the proportion of cases that had pathological complete response was low and this limits the ability to demonstrate statistical significance among the pathological response groups. Third, image guided wire localisation was not performed for BCS candidates, compromising the identification of a residual tumour focus at surgery that was missed by MR imaging.

To conclude, Diffusion Weighted MR Imaging is as accurate as Dynamic contrast enhanced imaging in assessing the presurgical residual disease in patients with locally advanced breast cancer who undergo Neoadjuvant systemic therapy. This modality can be of use in patients with end stage renal disease in whom Gadolinium based contrast agents are contraindicated, due to the dreaded complication of Nephrogenic systemic fibrosis. Further studies with larger sample size and a multi-centre setting are needed to establish the role of Diffusion weighted imaging in this group of patients, particularly the reliability of ADC values for tumour response assessment.
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