Monitoring of therapeutic response of tumor in locally advanced breast cancer by diffusion weighted MRI

U. Sharma1, K. A. Danishad1, V. Seeenu2, and N. R. Jagannathan1

1Department of NMR, All India Institute of Medical Sciences, New Delhi, Delhi, India, 2Department of Surgery, All India Institute of Medical Sciences, New Delhi, Delhi, India

Objective
To evaluate the sensitivity and specificity of diffusion weighted imaging (DWI) in assessing the response of breast cancer to neo-adjuvant chemotherapy (NACT) and to compare the results with clinical/histopathological assessment.

Introduction
NACT is the most preferred treatment option in patients with locally advanced breast cancer (LABC), in terms of the possibility of breast conservation surgery. However close monitoring of the response of breast cancer to NACT is necessary to avoid unnecessary toxicity and to change the chemotherapy regimen in non-responders. Conventional methods of assessing the response are based on changes in tumor volume that occurs at the latter stage of the therapy. DWI can be used to predict and assess the response of tumors to NACT. In this study, sequential diffusion weighted MRI measurements were carried out using DWI to evaluate the potential of DWI in monitoring and for predicting the tumor response to therapy.

Methods
A total of 68 women, including 15 normal subjects (Group I) were recruited for the study. MR examinations were carried out on LABC patients at 4 time periods namely, prior to therapy (Tp0), after 1st cycle (Tp1), after 2nd cycle (Tp2), and after 3rd cycle (Tp3). Out of 42 patients, sequential ADC data at Tp0 followed by Tp1 was obtained for 7 patients. 19 patients were serially monitored at Tp0 and Tp3 and among these 12 were also scanned at Tp2. In total 39 patients were monitored at Tp0 (Group II), 9 at Tp1 (Group III), 20 at Tp2 (Group IV) and 22 at Tp3 (Group V). DW images were acquired in the transverse plane using a single shot echo planar imaging (EPI) sequence (TR = 5000 ms; TE= 87 ms; FOV = 250 – 350 mm; NS = 1; b = 0, 500 and 1000; matrix= 128 x 128 with 5mm slice thickness with out any inter slice gap) with the diffusion gradients applied along orthogonal directions concurrently to reduce motion artifacts. ADC values were calculated from the ADC map by drawing circular ROIs of five pixels from the hypo-intense area of the tumor for all patients. The largest diameter of the tumor was calculated from MR images while the tumor volume was calculated by perimeter method using the formula Volume = ST (A1+A2+ ... An) where ST is the slice thickness and An is the area of the tumor of nth slice. Patients with more than 50% reduction in tumor volume measured clinically were categorized as clinical responders while the patients with less than 50% reduction in tumor volume and/or increase in tumor volume were grouped as non-responders. This criterion was applied to the classification of patients based on diameter and volume determined by MRI after III NACT. Patients were classified as responders, if the ADC obtained after III NACT showed an increase by two times the SD of the mean pre-therapy ADC value, while patients with ADC value less than this value were classified as non-responders.

Results
Pre-therapy (Gp II) mean ADC of tumor was [0.93 ± 0.12 x 10⁻³ mm²/s; p < 0.005] is significantly lower compared to the value obtained for normal breast tissue (Gp I; 1.88 ± 0.20 x 10⁻³ mm²/s). ADC measured after NACT showed a gradual increase in its value after each cycle. The pre-therapy ADC [0.93 ± 0.12 x 10⁻³ mm²/s; Group II] was significantly lower compared to that observed after I NACT [Group I; 1.08 ± 0.19 x 10⁻³ mm²/s; p = 0.03]. The ADC value showed further increase after II NACT [1.22 ± 0.25 x 10⁻³ mm²/s; Group IV] and III NACT [1.34 ± 0.15 x 10⁻³ mm²/s]. Among the nineteen sequentially monitored patients, 11 were clinical responders while 8 were non-responders. In clinical responders, the percentage change in mean ADC, longest diameter and volume after III 59 ± 30%, 42 ± 18% and 91 ± 4%, respectively compared to pre-therapy. In clinical non-responders, the relative percentage change was lower than the clinical responders, the values being 17 ± 14, 27 ± 19, 56 ± 22 for ADC, diameter and volume, respectively. The sensitivity to assess tumor response was found to be 91%, 45% and 73% for volume, diameter and ADC methods, respectively while the accuracy of these methods was found to be 84% for ADC, 68% for volume and 63% for diameter.

Discussion
ADC was found to be increasing in LABC patients after each cycle of NACT. This increase may be attributed to the fact that therapeutic interventions cause cell damage there by affecting the integrity of cell membranes which increase the fractional volume of the interstitial space. Decrease in cellularity of breast cancer tissues after NACT has also been documented compared to pre-therapy and many clinical and pre-clinical studies point out that NACT induces apoptosis in breast cancer which can further increase the fractional volume there by increasing the diffusion of water1-2. Among the three methods of determining the response status, it was found that diameter method was in poor agreement with the clinical results. In this study, the total change in ADC after III NACT is only 60% while tumor volume changed over 91% but the accuracy of determination of responders and non-responders using ADC is higher compared to volume. Another important finding of the present study is the significant increase in ADC after I NACT, indicating changes in water diffusion occur early during the course of treatment3.

Conclusion
DWI can be used to monitor the therapeutic response in breast cancer patients. The accuracy of differentiating responders from non-responders was high for ADC compared to volume and diameter method of assessing the response. This technique may be used in a clinical setting and the protocol is less time consuming and has high sensitivity and accuracy in determining the response status.

References
3. Pickles MD et al., Magn Reson Imaging 2006; 24:843-847