Clinical Utility of Sequential DWI in Studying Tumor Margins as an aid to Breast Conservation Surgery

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Introduction: Breast conservation surgery (BCS) is the preferred choice for long-term disease control and for minimizing local morbidity and is a well-established alternative to mastectomy (1). It is important to define clear tumor margin (free of cancer cells) to reduce the recurrence after BCS. Large-sized tumors like locally advanced breast cancer (LABC) have been shown to undergo central necrosis (2) and show poor prognosis. Gilchrist et al. documented the presence of tumor necrosis to be an independent predictor of tumor recurrence in breast cancer (3). Generally, pathologic examination of peri-tumor tissue is performed after surgery to define the clear tumor margin. Molecular studies demonstrated hypermethylation as an indicator of cancer positive tumor margins (4). Since, resected tissue specimens after surgery are used for these examinations; there is a need for a non-invasive method which may provide information on cellular extent of tumor in peri-tumor area. Diffusion weighted imaging (DWI) probes the variation in cellular properties of tissues through the measurement of apparent diffusion coefficient (ADC) of water molecules in tissues. We hypothesize that DWI may have the potential to provide an insight into the tumor extent along the tumor margins as well as on tumor necrosis. Thus, the aim of the present study was to measure the ADC in LABC patients sequentially i.e., prior to (Tp0), after I (Tp1) and III (Tp3) neoadjuvant chemotherapy (NACT). ADC was calculated in a layer-wise manner consisting of five geographical zones defined as inside tumor margin (IM), tumor margin (TM), three layers outside tumor margin (OM1, OM2 & OM3). In addition, ADC of whole tumor (WT), and from intra-tumoral necrotic domains (Nec) was determined and data was analyzed to understand the role of ADC in defining cancer free margins.

Patients and Methods: DWI at 1.5 T (Avanto, Siemens) was carried out in axial plane covering both the breasts in 36 women with cytologically proven infiltrating ductal carcinoma (IDC; mean age = 41.2 ± 9.2 yrs). The parameters used were: b = 0, 500, and 1000 mm^2/s; TR = 5000 ms; TE = 87 ms; field of view (FOV) = 250-350 mm; NSA = 1; EPI factor = 128 and acquisition matrix = 128 × 128; and slice thickness = 5 mm without any inter-slice gap with a total acquisition time = 42 s. Response to NACT was assessed clinically (21 clinical responders and 15 non-responders) at the end of III NACT. ADC was calculated by drawing small circular ROIs of 5 pixel (0.49 cm^2) in layer-wise manner from different regions of tumor on ADC map (see Figure 1 & Table). Each layer has a thickness of 7.9 mm. Written informed consent was obtained and Institutional ethical committee approved the study.

Results: In clinical responders an increase in whole tumor ADC was seen as early as first cycle (Tp1) of NACT (1.23 ± 0.21) × 10^{-3} mm^2/s, which further increased significantly at Tp3 (1.41 ± 0.31) × 10^{-3} mm^2/s compared to that at Tp0 (1.03 ± 0.08) × 10^{-3} mm^2/s. ADC of inside margin showed a significant increase compared to the value at Tp0 which significantly increased at Tp3 in responders. The outer margins of the tumor showed gradual increase in ADC, but ADC at OM1 in responders after therapy was lower than the ADC at OM2 and OM3, while no such change was evident in non-responders. Pearson correlation analysis showed a significant positive correlation (r=0.8) between the changes in ADC of whole tumor (ΔADC_{WT}; Tp0 vs Tp3) and the changes in necrotic ADC (ΔADCnec; Tp0 vs Tp3) in responders.

ADC (× 10^{-3} mm^2/s)	Responders (R)			Non-responders (NR)		
	Tp0 (n=21)	Tp1 (n=18)	Tp3 (n=21)	Tp0 (n=15)	Tp1 (n=15)	Tp3 (n=15)
WT	1.03 ± 0.08	1.23 ± 0.21*	1.41 ± 0.31*	1.08 ± 0.30	1.18 ± 0.08	1.15 ± 0.14
IM	0.98 ± 0.14	1.04 ± 0.14	1.14 ± 0.23*	1.00 ± 0.17	1.19 ± 0.23	1.07 ± 0.14
TM	1.45 ± 0.45	1.48 ± 0.18	1.39 ± 0.25	1.47 ± 0.24	1.53 ± 0.15	1.50 ± 0.16
OM1	1.70 ± 0.25	1.79 ± 0.32	1.56 ± 0.27*	1.79 ± 0.27	1.90 ± 0.19	1.73 ± 0.22
OM2	1.73 ± 0.31	1.78 ± 0.30	1.62 ± 0.37	1.92 ± 0.65	1.90 ± 0.26	1.73 ± 0.28
OM3	1.72 ± 0.31	1.73 ± 0.39	1.63 ± 0.38	1.80 ± 0.42	1.86 ± 0.26	1.71 ± 0.29
Nec	1.22 ± 0.10	1.26 ± 0.65	1.75 ± 0.44*	1.26 ± 0.54	1.26 ± 0.37	1.35 ± 0.19
Here * denotes p < 0.05; correlation coefficient (r)= 0.8 for ΔADC_{WT} and ΔADCnec in responders						

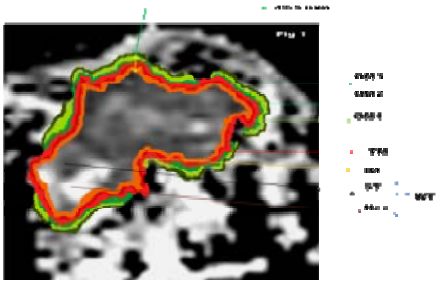

Figure 1: Representative ADC map with outlines for different geographical zones is shown. OM1, OM2, OM3=Outside tumor margins 1, 2 &3; IM = Inside margin; TM= tumor margin; ST = solid tumor; Nec = intra-tumoral necrosis & WT= whole tumor area.

Discussion: Present study demonstrated variations in mean ADC values of five different geographical zones IM, TM, OM1, OM2 & OM3, and of the WT and intra-tumoral necrotic domains (ADCnec) in LABC patients at three different time points (Tp0, Tp1 & Tp3). In responders, the mean ADC at Tp0 was similar for IM and WT that showed a significant increase at Tp1 and Tp3 which might be attributed to the cytotoxic effects of chemotherapy drugs. In non-responders, the mean ADC of IM and WT was similar at Tp0 and Tp3. In both responders and non-responders mean ADC of TM at Tp0 was significantly higher compared to the mean ADC of WT and IM at Tp0 and did not show any significant variation at Tp3 indicating no change in cellularity following NACT. In responders, mean ADC at OM1 showed a significant decrease at Tp3 compared to its value at Tp0, while no such change has been observed in non-responders. In responders, as tumor size shrinks after therapy, the layer OM1 at Tp3 is not the same as it was at Tp0. Hence, it is possible that OM1 contains some viable cancer cells that may be proliferating leading to increased cellularity and thereby decreased ADC. However, regions OM2 and OM3 showed higher ADC values in both responders and non-responders indicating that these regions are similar to the normal tissue. This is in agreement with the study of Yilli et al., wherein a gradual increase from tumor to peri-tumor to normal breast tissue has been reported (5).

Interestingly, our data also showed that in responders ADCnec at Tp0 showed a significant increase at Tp3. While in non-responders, ADCnec at Tp3 was similar to that observed at Tp0, however it is significantly lower compared to the ADCnec of responders at Tp3. Further, the changes in ADC (ΔADC_{WT}) of WT and ΔADCnec showed a strong correlation in responders, however, no such correlation was observed in non-responders. This indicated cytotoxic effects of drugs on intermingling viable cells that may be present in intratumoral necrotic domains in responders. The presence of cancer cells in outside tumor margin and intra-tumoral necrosis is reported as predictor of tumor recurrence in breast cancer (3). Our study demonstrated that the layer OM1 in responders contains proliferating tumor cells and defining of tumor margins using DWI may aid surgeons in the management of breast cancer patients especially, while planning breast conservation surgery.

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