Early therapeutic response of bone metastases in breast cancer patients using diffusion-weighted MRI

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Introduction

Breast cancer commonly metastasizes to bone. Bone scintigrapy, CT and MRI/MRS are useful and sensitive means by which to attain anatomic quantitation of the extent of bone lesions (1). These methods are frequently used in combination for the detection and surveillance of therapy-induced changes in bone metastases. However, these methods lack high specificity in reporting response to therapy. Diffusion MRI is an alternative method for therapy response evaluation, as it has been shown to change early in response to a variety of therapies in a variety of cancers (2). Increases in the apparent diffusion coefficient of water (ADC_w) have been ascribed to microscopic cell lysis, cell shrinkage and increased cell membrane permeability. Recent clinical studies have shown that the ADC_w increases early following effective anti-tumor therapy of breast cancer patients with liver metastases (3). Because of the prevalence and morbidity associated with bone metastases, the current study was undertaken to (a) determine if ADC_w could be measured reliably and reproducibly in bone lesions, (b) determine if ADC_w could be calculated for all voxels in a lesion, and (c) to obtain preliminary data regarding changes in ADC_w with therapy. The ADC_w was measured using an isotropic diffusion-weighted radial-FSE acquisition technique (4) at three b-values.

Methods and Materials

All subjects were recruited from the Arizona Cancer Center voluntarily and provided informed consent. Metastatic lesions were initially identified by a radiologist (M.T.) using CT, conventional MRI, radiographs and/or bone scans prior to initiation of the protocol. Imaging sessions were conducted on a GE Signa scanner at a field of 1.5 T (Milwaukee, WI) equipped with 33 mT/m shielded gradients. Conventional T1 and T2 weighted imaging was performed, along with diffusion-weighted imaging using b-values of 0, 100, 300 and 600 s/mm^2 (5). Without diffusion weighting, lesions appeared bright with a corresponding signal attenuation at higher b-values (**Fig. 1**). Each patient was imaged 3 days prior to the initiation of treatment (Day –3) and on days 4, 11 and 39 following the commencement of cytotoxic therapy. The ADC_w map was calculated by fitting the signal decay pixel-by-pixel from the diffusion-weighted images. Histograms were generated for lesion regions of interest and plotted as the sum of the pixels against its corresponding ADC_w value. The calculated mean and median values provided information about changes in the ADC_w of the lesion and the distribution of values within the histogram were used for statistical comparisons. Clinical responses were determined by the treating oncologist who was blinded to the DWMRI data and were based on repeat radiographic testing, history and physical exam findings and tumor marker results when available.

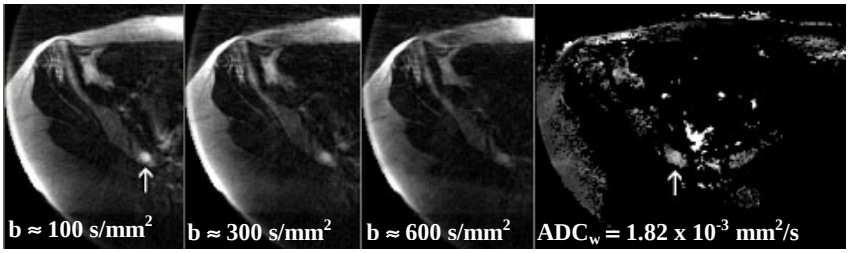

Figure 1. Diffusion-weighted images and representative ADC_w map.

Results

Results presented herein are from 8 responding and 4 non-responding tumors. At presentation, most ADC_w values were between 1.23 and 1.92 x 10^{-3} mm^2/sec. Patients with stable disease or a positive clinical response to therapy were grouped as "responders", and for seven of the eight lesions that were analyzed, a significant increase in the ADC_w was observed by day 11 ($P < 0.005$, **Table 1**). Conversely, a decrease or no change in the ADC_w was observed in all four lesions from patients with progressive disease. Increases in the ADC_w following therapy for two of the four lesions (see table) contributed to the variability in the day 4 time point for non-responder data (**Fig. 2**). However, the ADC_w decreased by day 11, consistent with a non-responding lesion in these patients (**Fig. 2**). Except for day 4 non-responders, the data exhibited low variation (standard deviation) in both groups pre- and post-therapy, resulting in clear differences between responders and non-responders.

Lesions	Δ Day 4	Δ Day 11	Δ Day 39
Responders			
1	1.21	1.36*	1.04
2	1.04	1.21*	0.42*
3	1.01	1.07*	1.08*
4	1.10	1.11*	1.16*
5	1.11	1.00	1.04
6	0.90	1.05*	1.15*
7	0.92	1.06*	1.12*
8	1.06	1.08*	1.05*
Non-Responders			
1	1.77	0.74*	0.82*
2	1.63	0.96	0.79*
3	0.92	1.03	0.99
4	0.70	0.73*	0.86*

Table 1. *Significant difference ($P < 0.05$) between the means. Data were shown as changes in mean ADC_w relative to baseline (Day -3). Chi-Squared statistic: $[\mu_{post\text{-}tx} - \mu_{pre\text{-}tx}]/[\sigma/\sqrt{n}]$ (5).

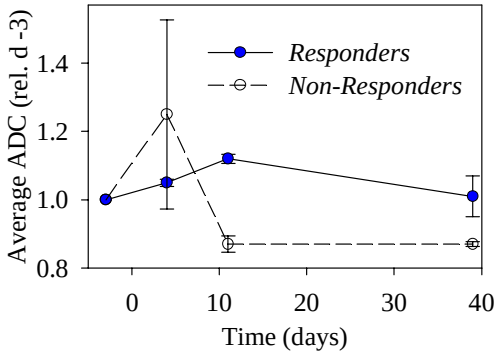

Figure 2. Data shown as $ADC_w \pm$ S.D., normalized to individual pre-treatment baselines

Conclusions

Results from the study indicate that the diffusion-weighted radial-FSE scans provide high-resolution images with low sensitivity to field inhomogeneity in bone. The results also provide preliminary evidence that changes in the ADC_w as measured by DWMRI may be predictive of subsequent clinical responses, and that diffusion MRI holds promise as a response biomarker for bone meastases in breast cancer. With the accrual of additional patients, an assessment of the positive and negative predictive value of the ADC_w will be determined. Future directions will include expanding this approach to predict responses of bone lesions to novel therapies in patients with metastatic breast cancer and in other common malignancies that metastasize to bone.

References

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