Apparent Diffusion Coefficient of Breast Cancer Metastases in Bone as a Predictor of Therapeutic Response

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Introduction

The apparent diffusion coefficient of water (ADC_w) as measured by diffusion-weighted MRI is sensitive to changes in the cellular environment of tissues. Increases in the ADC_w have been ascribed to microscopic cell lysis, cell shrinkage, and increased cell membrane permeability. The ADC_w has been shown to be valuable for predicting early response to therapies in a variety of cancers (1,2). Because breast cancer commonly metastasizes to bone, a study was undertaken to examine the use of ADC_w as an early predictor of therapeutic response of breast cancer metastases in bone. Changes in ADC pre and post treatment were compared to TTP (time to progression), a robust and clinically relevant measure of therapeutic response.

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 using CT, conventional MRI, radiographs and/or bone scans prior to initiation of the study protocol. Imaging sessions were carried out on a GE Signa scanner (Milwaukee, WI) at a field of 1.5 T with 33 mT/m shielded gradients. Conventional T1 and T2 weighted imaging was performed, along with isotropic diffusion-weighted radial fast spin echo imaging (3) using b-values of 0, 100, 300 and 600 s/mm^2. With no diffusion weighting, lesions appeared bright with a corresponding signal attenuation at higher b-values. 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. ADC_w maps were calculated by fitting the decay of signal with increasing b-value to a single exponential decay. Representative ADC_w maps are shown in **Fig. 1**. Time to progression (TTP) was determined by the treating oncologist who was blinded to the diffusion weighted MRI data. TTP was the primary endpoint of the study and was defined as the time from initiation of therapy (day 0) to documented disease progression. Six patients have completed the study for which TTP data have been obtained. MRI data have been acquired for 12 additional patients, which will be included in the analysis as TTP data become available.

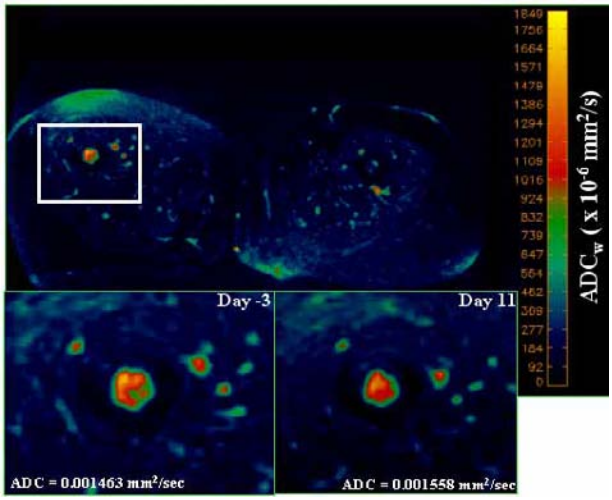

Figure 1. Representative pre-treatment (day –3) and post treatment (day 11) ADC_w maps of a lesion in the femur.

Results

A summary of the results is shown in **Table 1, Fig. 2,** and **Fig. 3** for 3 responding and 2 non-responding patients. Patients were classified as 'Responders' if their TTP was 12 weeks or longer. Patients were classified as 'Non-responders' if their TTP was shorter than 12 weeks. In responding patients the ADC_w is significantly increased at day 11 compared to pretreatment levels while it decreased in non-responding patients. Day 11 was used as it provided the earliest and most robust timepoint for early evaluation. The pretreatment ADC_w values in responding patients was lower than in non-responders but the difference was not significant in the initial sample.

Conclusions

These results, although preliminary, provide evidence that the ADC_w as measured by diffusion-weighted MRI may be predictive of response in breast cancer metastases in bone. With the analysis of data from additional patients, a more thorough assessment of the predictive value of the ADC_w for TTP will be possible.

Patients	Day –3 pretreatment	Day 11	ΔDay 11	TTP (weeks)
Responders				
1	.0017309	.001889	1.09	27
2	.0013069	.001343	1.03	60
3	.0014431	.001549	1.07	52
Non-Responders				
1	.0017078	.001442	0.85	7
2	.0017516	.001516	0.88	6

Table 1. Initial data for lesion ADC_w of responding and non-responding patients. ADC_w values have units of mm^2/sec.

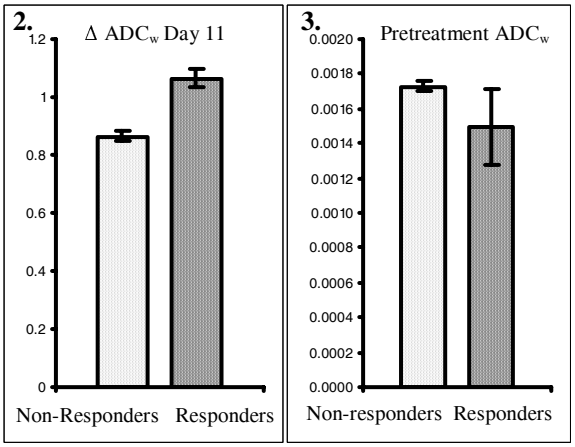

Figure 2. Data shown (above left) as Δ ADC_w ± S.D., (Δ ADC_w = ADC_w at Day 11 divided by pretreatment ADC_w). Non-responders have a smaller Δ ADC than responders (P = 0.0047).

Figure 3. Data shown (above right) as ADC_w ± S.D., Day –3 pretreatment for TTP responders and non-responders. Non-responders are expected to have greater pretreatment ADC_w than responders (P = 0.2415). ADC_w has units mm^2/sec.

References

1. Chenevert TL et al., 2002, Mol Imaging, 1, 336.
2. Theilmann et al, 2004, Neoplasia, 6, 831.
3. Sarlls JE et al., 2005, Mag Res Med, 53, 1347.