Early Detection of Response to Antiangiogenic Therapy in Metastatic Clear-cell Renal Cell Carcinoma with ASL MRI

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Introduction: Arterial spin labeling (ASL) MRI uses magnetic fields to label the water protons in arterial blood and measures blood flow into tissue; quantitative images of blood flow can be generated without exogenous contrast media. In contrast to other imaging techniques for measuring perfusion (i.e. DCE-CT, DCE-MR), ASL measurements of blood flow are not affected by vascular permeability. The feasibility of ASL to monitor response to antiangiogenic therapy in metastatic renal cell carcinoma (RCC) has been previously reported (1). Our goal was to assess the ability of ASL MRI to depict early changes in the vascularity of RCC metastases treated with an antiangiogenic regimen and to evaluate the correlation between decreased vascularity, as measured by ASL MRI, and tumor response.

Material and Methods: This HIPAA compliant study was approved by the Institutional Review Board of the Dana-Farber/Harvard Cancer Center and a signed informed consent was obtained from all patients prior to enrollment. Six patients (5 male, 1 female; average age 57 years, range 44-66) with metastatic clear-cell RCC enrolled in a Phase II trial for evaluation of response to therapy with sorafenib and bevacizumab were included in this study. All patients underwent imaging with computed tomography (CT) prior to initiation of therapy. Patients were imaged with ASL MRI prior to and 1 week after initiation of therapy. Changes in tumor perfusion at 1 week were measured and correlated to changes in tumor size at 1 week (by MRI) and at 4 months on CT imaging. Patients received sorafenib (200 mg) po each day and bevacizumab (5 mg/kg) IV every 2 weeks, the established phase II dose for this combination (2).

ASL Technique: ASL was performed using a single slice through the center of the target lesion in the axial plane (1 lesion in 1 patient), two orthogonal planes (axial, coronal, and/or sagittal plane) (5 lesions in 4 patients), or 3 orthogonal planes (2 lesions in 1 patient). Imaging planes were selected depending on the location of the mass. A maximum of 2 lesions were evaluated in each patient. Perfusion imaging was achieved with a pulsed-continuous labeling, optimized background suppression, and a SSFSE acquisition. The labeling was performed in an axial plane 8-10 cm superior to (for abdominal lesions) or inferior to (for upper thoracic lesions) the center of the target lesion for 1500 ms followed by a 1500 ms post-labeling delay. SSFSE parameters: 40 cm field of view, 128x128 matrix, slice thickness 10 mm. A repetition time of 6 s was used to allow for recovery of blood signal and the subjects were instructed to breathe in the quiet period between the image acquisitions. Sixteen averages of label and control were acquired for a total acquisition time of 3.5 minutes per anatomic location. The ASL acquisitions are reconstructed to provide a T2-weighted reference image, and a difference image (labeled minus control). For tumor perfusion measurements, the ASL data were reconstructed and quantified assuming the labeled water spends most of the time after labeling within the blood of arteries and microvasculature (3) and perfusion measurements were calculated in ml/100 g/min.

Image Analysis: All target lesions were measured on CT or MRI at baseline, and 1 week and 4 months after initiation of therapy. Bi-dimensional measurements of up to 2 metastases per patient were obtained and tumor response was analyzed using RECIST criteria. Tumor perfusion at baseline and 1 week after initiation of therapy were measured by region-of-interest (ROI) analysis with ROIs drawn around the outer contour of the target lesions using the open-source DICOM viewer Osirix (Osirix X, v3.1 32-bit). Changes in tumor perfusion at 1 week were correlated to changes in tumor size by RECIST criteria at 1 week and 4 months.

Results: Eight metastatic tumors were analyzed in 6 patients. Metastatic tumors were located in the left kidney (n=1), right nephrectomy bed (n=1), retroperitoneal lymph nodes (n=2), liver (n=1), left flank (n=1), lung (n=1), and mediastinal lymph nodes (n=1). At 4 months, 3 patients had a partial response (>30% reduction in longest diameter) and 3 patients had stable disease by RECIST criteria. None of the patients had progressive disease. Mean tumor perfusion at one week after initiation of therapy (80 ± 64 ml/100 g/min) was significantly lower than tumor perfusion at baseline (176 ± 107 ml/100 g/min)(mean reduction of 45%, p=0.02, paired t-test) (Figure 1). In contrast, there was no significant decrease in measured tumor size at 1 week (mean reduction of 3%, p=0.06, paired t-test) (Figure 1).
A relationship between fractional decrease in perfusion and size change at 4 months was hypothesized based on a similar finding with PTK/ZK (1). No significant relationship was observed. Similarly, there was no statistical correlation between changes in tumor size at 1 week and changes in tumor size at 4 months by RECIST criteria. Though tumors with higher baseline perfusion tended to exhibit larger decreases in perfusion at 1 week, these results were not statistically significant (p>0.05).

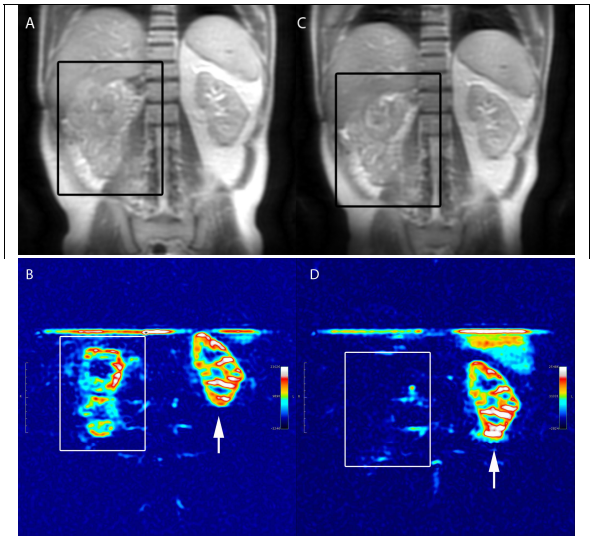

Figure 1: Coronal T2-weighted (A) and perfusion (B) images prior to therapy in a patient with history of right nephrectomy for RCC and local recurrence in the nephrectomy bed (box). ASL MRI shows high levels of perfusion within the mass, similar to those of the renal cortex in the left kidney (arrow). Coronal T2-weighted (C) and perfusion (D) images of the same patient obtained 1 week after initiation of antiangiogenic therapy with sorafenib and bevacizumab show minimal decrease in size of the lesion but marked decrease in the tumor vascularity.

Discussion: Changes in tumor perfusion in RCC metastases can be detected by ASL MRI as soon as 1 week after initiation of antiangiogenic therapy with sorafenib and bevacizumab. The mean tumor perfusion at one week after initiation of therapy was significantly lower than the tumor perfusion at baseline. The traditional assessment of tumor response using the RECIST criteria however failed to demonstrate significant changes in tumor size at 1 week. The fact that all patients had a partial response (n=3) or stable disease (n=3) at 4 months after initiation of therapy suggests that the early changes in tumor perfusion on ASL are indicative of effective targeting of tumor vascularity with the combination of sorafenib and bevacizumab. The lack of correlation between changes in perfusion on ASL at 1 week and changes in tumor size at 4 months is likely caused by the small sample size and the high stable disease and response rate in this study.

Conclusion: ASL MR imaging allows for detection of significant decreases in tumor perfusion as soon as 1 week after initiation of antiangiogenic therapy with the combination of sorafenib and bevacizumab in patients with metastatic RCC.

References:

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