# Sensitivity to tumor micro-vasculature without contrast agents in high spectral and spatial resolution MR images

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**Introduction:** Dynamic contrast enhanced MRI (DCEMRI), detects dense vasculature associated with aggressive cancers. However, DCEMRI has some disadvantages including adverse reactions to contrast agents (1) and 'blooming' artifacts (2). Therefore, we propose that high spectral and spatial resolution imaging (HiSS) can reliably detect tumor vasculature, due to local magnetic susceptibility gradients caused by dense, deoxygenated tumor blood. Here we compare results obtained with HiSS MRI to those obtained with conventional contrast enhanced imaging.

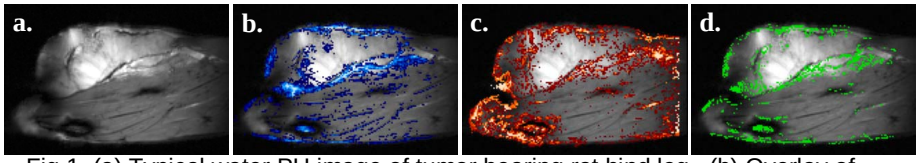

Fig 1. (a) Typical water PH image of tumor bearing rat hind leg. (b) Overlay of largest absolute differences (blue scale) in GRE difference images. (c) Overlay of largest signal intensities (red scale) in FCI-MIP. (d) Overlay of correlated voxels between b and c (green).

**Methods:** HiSS datasets (n = 8) from AT6.1 tumors inoculated in the hind limbs of Copenhagen rats were collected using respiratory-gated EPSI (TR = 1200ms, in-plane resolution = 136-195 microns, spectral resolution = 3.1Hz). Gradient echo (GRE) images collected before and after injection of a blood pool contrast agent (iron-oxide particles) were used as the 'gold standard' for detection of tumor vasculature. Spectral asymmetry in HiSS datasets was measured as the difference in the intensities of the higher frequency and lower frequency halves of the normalized water spectrum.

To identify regions of dense vasculature, images of the various Fourier components of the water resonance were calculated for frequencies ranging from –30 Hz to +30 Hz about the peak of the water resonance. We tested the hypothesis that regions of dense vasculature appear in FCI's as small groups of pixels that have sharp contrast relative to surrounding pixels. To maximize sensitivity to vasculature we synthesized images in which intensity at each pixel was determined by the FCI with the greatest image contrast at that position (3). These images can be thought of as maximum intensity projection images along the spectral direction (referred to as FCI-MIPs).

ROIs were manually selected at the tumor rim and center, and normal muscle. Sensitivity, specificity, and 'positive predictive values' (PPV) were calculated for FCI-MIPs using GRE difference images (post-contrast images minus pre-contrast images) as the "gold standard" for vasculature detection.

**Results:** Statistically significant spectral asymmetry [greater than 4*sqrt(2) times the noise level] was detected in 82 ± 6% of voxels at the tumor rims, 91 ± 2% of voxels in the tumor centers, and 59 ± 29% of voxels in normal muscle (pooled data from all experiments). Mean asymmetry (as a percentage of the water resonance integral) pre-contrast injection was 19 ± 4% at the tumor rim, 8.0 ± 1.5% at the tumor center, and 4.8 ± 0.6% in muscle. The asymmetry at the tumor rim was significantly higher than in the other two ROIs ($p < 0.003$, ANOVA). This was consistent with the contrast enhanced images, which showed highest vascular density at the tumor rim.

Compared with the gold standard, the sensitivity of FCI-MIPS for tumor vasculature at the tumor rim, tumor center, and normal muscle was found to be 75 ± 13% and 45 ± 17%, 3 ± 8%, respectively. Specificity was 74 ± 10%, 95 ± 4% and 99 ± 1% for these three regions. The sensitivity of HiSS MRI at the tumor rim was significantly larger than that at the tumor center or normal muscle ($p < 0.0004$, ANOVA). The PPV was 91 ± 4% at the tumor rim. Figure 1 shows the excellent correlation between vasculature identified with FCI-MIPs and GRE-difference images.

**Discussion:** Regions with high contrast in FCI-MIPs correlated strongly with dense vasculature identified in GRE difference images. High contrast in FCI-MIPs was usually associated with shoulders or partially resolved components of the water resonance, likely due to deoxyhemoglobin in dense tumor neo-vasculature. The FCI-MIPs provided high sensitivity, specificity, and positive predictive value for tumor vasculature in the tumor rim. Even better sensitivity and specificity can be achieved as methods for acquisition and analysis of HiSS data are improved. Asymmetry analysis was less effective for detecting vasculature in normal muscle. This may be because blood in normal tissue contains less deoxyhemoglobin than tumor vasculature, and therefore has decreased variation in magnetic susceptibility.

HiSS could be used clinically to **1)** detect tumor vasculature in patients with renal insufficiency; **2)** evaluate the 'native' morphology of tumors before contrast agent is injected **3)** prescribe subsequent DCEMRI scans to provide the highest spatial and temporal resolution in suspicious areas, with more modest resolution elsewhere..

**References:**

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