

Early assessment of sequential combined therapy with radiation and sorafenib for hepatocellular carcinoma using quantitative perfusion and diffusion weighted magnetic resonance imaging: a pilot study

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Purpose: To measure the early response of hepatocellular carcinomas (HCCs) to sequential combined therapy with x-ray radiation and sorafenib using diffusion-weighted (DW) and dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) in a clinical pilot study.

Materials and Methods: Five patients having newly diagnosed, biopsy-proven HCCs were accrued, and received radiation therapy delivered using an individualized dose prescription in 6 fractions completed within 2 weeks (dose 40.5-54.0 Gy), followed by sorafenib given by mouth at 400 mg for one week, increased to 400 mg twice a day for the next 5 weeks. MRI was performed prior to radiation therapy (baseline imaging; week 0), at approximately one week after completion of radiation therapy (week 4), and after completing sorafenib therapy (week 10). All subjects were examined on a single 3T clinical MR system using a torso phased array coil. Respiratory-gating DW single-shot echo-planar imaging (DW-SS-EPI) was performed with three b values of 0, 50, and 700 s/mm² in one direction with following parameters: repetition time/echo time (TR/TE) = 1586/55 ms, field of view (FOV) = 42x42 cm, number of excitation (NEX) = 4, thickness/gap = 7/1 mm, matrix size = 140/140 (interpolated to 288/288), and number of slices = 30-40. DCE-MR images were obtained by a breath-hold 3D fast field echo T1 weighted axial sequence with following parameters: TR/TE = 5/2.3 ms, FOV = 40x40 cm, NEX=1, thickness/gap = 6/0 mm, matrix = 192/154 (interpolated to 256x256), flip angle = 15°, and sensitivity encoding (SENSE) factor = 2. A total of 10 slices covering the central region of a tumor were obtained at each time (longitudinal FOV: 6 cm), and a total of 91-120 images per slice were continuously acquired with temporal resolution of 2.1 seconds after intravenous injection of 0.1 mmol/kg of gadoteridol followed by a 20-ml saline flush at the rate of 2 ml/s. During DCE-MRI, patients were instructed to perform breath-hold in maximal end inspiration for as long as possible, and then repeat similar breath-holds as feasible for the duration of the acquisition. T1 maps were created before contrast injection using T1W images obtained with the same imaging sequence and parameters as above, but with different three flip angles (5°, 10°, 15°). For correcting motion in DCE-MR images, three post image-processing techniques were employed: unwarping, median filtering, and curve fitting. For unwarping, the boundary of a patient's body above the paravertebral muscle and abdominal aorta was determined in each DCE-MR image, then the boundary in each DCE-MR image was unwarped to match with the boundary in the baseline image. All pixels within the boundary were relocated accordingly. Thereafter, median filtering and curve fitting were applied. T1 maps were also unwarped as described above, and co-registered with DCE-MR images. A two-compartment pharmacokinetic model was employed to calculate volume transfer constant (K^{trans}) and reverse reflux rate constant (k_{ep}). In DWI analysis, the ADC value was calculated by finding the best fitting curve to the equation, $S = S_0 e^{-bD}$, where S is the intensity of DW images, S_0 is a constant, and D is ADC value.

Results: Figure 1A shows motion-corrected DCE-MR images (gray-scale) of a 77-year-old woman with a HCC at 30 seconds after initiating gadoteridol injection superimposed with K^{trans} and k_{ep} maps (color-scale) in the tumor regions, and DW images ($b=0$, gray-scale) superimposed with tumor ADC maps (color-scale). The same color-scale was applied for the three maps of each physiological parameter (K^{trans} , k_{ep} , or ADC) acquired before (baseline) and after therapy initiation. The initial mean tumor volume, K^{trans} , k_{ep} , and ADC values were 98 ± 71 cm³, 0.022 ± 0.009 min⁻¹, 0.062 ± 0.018 min⁻¹, and $1.29 \pm 0.09 \times 10^{-3}$ mm²/s, respectively. After completing radiation therapy (week 4), the averaged tumor volume, K^{trans} , k_{ep} , and ADC values were 65 ± 42 cm³, 0.017 ± 0.009 min⁻¹, 0.053 ± 0.013 min⁻¹, and $1.55 \pm 0.13 \times 10^{-3}$ mm²/s, respectively, and, after completing sorafenib therapy (week 10), values were 22 ± 8 cm³, 0.014 ± 0.006 min⁻¹, 0.050 ± 0.014 min⁻¹, and $1.65 \pm 0.18 \times 10^{-3}$ mm²/s, respectively. Figure 1B shows the changes (%) of HCC variables (volume, K^{trans} , k_{ep} , and ADC) following therapies, relative to the baseline values. Statistical significance was represented with either asterisks ($p \leq 0.05$) or hash marks ($p \leq 0.01$). Significant correlation was only found between the change in tumor volume and K^{trans} value after radiation therapy ($p=0.05$).

Discussion: DCE-MRI/DWI was successfully applied for patients with HCCs to quantitate the perfusion and diffusion parameters of tumors. Significant decreases of K^{trans} and k_{ep} values were observed after sequential combination therapy with radiation and sorafenib, while tumor ADC values were significantly increased. Tumor K^{trans} change was significantly correlated with tumor-volume change, and therefore it may serve as an effective surrogate biomarker, especially when applied at earlier time points, to assess the therapeutic efficacy of radiation therapy alone or in combination with sorafenib. The credibility of the data in this study, however, would be strengthened with larger sample size.

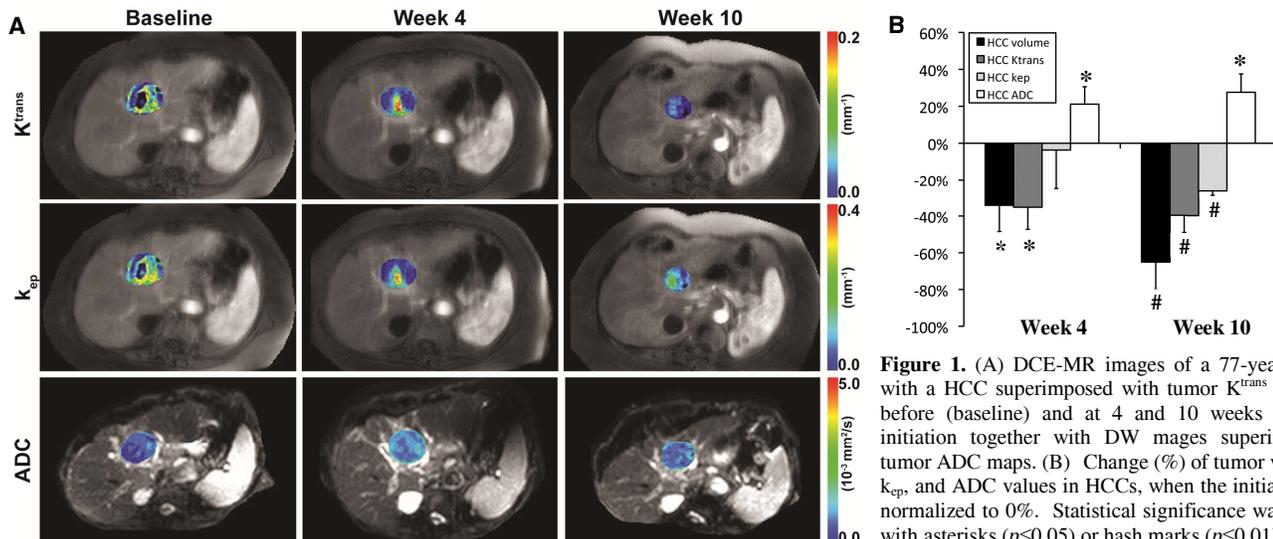


Figure 1. (A) DCE-MR images of a 77-year-old woman with a HCC superimposed with tumor K^{trans} and k_{ep} maps before (baseline) and at 4 and 10 weeks after therapy initiation together with DW images superimposed with tumor ADC maps. (B) Change (%) of tumor volume, K^{trans} , k_{ep} , and ADC values in HCCs, when the initial values were normalized to 0%. Statistical significance was represented with asterisks ($p \leq 0.05$) or hash marks ($p \leq 0.01$).