Monitoring of the Hepatocellular Carcinoma Growth by ^{1}H and ^{23}Na MRI

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Introduction

Hepatocellular carcinoma (HCC) is an increasing problem worldwide with an estimated incidence of 1 million new cases a year (1). The recently developed HCC rat model reflects many characteristics of human hepatoma (2). The rat HCC growth and efficiency of chemotherapy have been estimated using T_1 and T_2 ^{1}H MRI and diffusion weighted ^{1}H MRI (DWI) (3, 4). However, HCC growth has never been examined by single-quantum (SQ) and triple-quantum-filtered (TQF) ^{23}Na MRI that allow estimation of total tissue and intracellular Na^+, respectively. It has been shown that changes in water apparent diffusion coefficient (ADC) and total tissue Na^+ depend on the tumor cell line and the tumor location (5, 6). In this study, the relationship between water ADC, SQ, and TQF ^{23}Na MRI SI in growing HCC rat tumors and surrounding normal liver tissue was examined.

Methods

SQ and TQF ^{23}Na MRI, and ^{1}H diffusion imaging were performed on Sprague-Dawley (SD) rats with intra-hepatic HCC tumors. MR images were acquired with a Varian 9.4 Tesla, 31-cm horizontal bore system. Each animal (n = 7) was examined every 7 days after injection of 10^7 N1S1 cells into the left liver lobe. Water ADCs in the tumor and nearby liver tissue were measured with a 63-mm birdcage coil tuned to 400 MHz using a multi-slice DWI sequence. The following imaging parameters were used: 1,100 ms repetition time (TR), 21 ms echo time (TE), 256 x 128 data points over a 80 x 80 field of view (FOV), 0.5 mm slice thickness, 1.5 mm slice gap, 7 min total imaging time. Two diffusion gradient pulses of δ = 6 ms duration separated by a Δ = 11 ms period were applied along all three axes. Four interleaved *b*-factors (*b* = 0, 256, 945 and 1,679 s/mm^2) were used. 3D trans-axial ^{23}Na MR images were obtained with a loop-gap volume resonator (inner diameter = 60 mm, depth = 25 mm) tuned to 105 MHz using a gradient-echo imaging sequence. The following imaging parameters were used: ~ 240 µs non-selective excitation RF pulse, 50 ms TR, 4.6 ms TE, 64 x 64 x 16 data points over a 60 x 60 x 36 mm FOV, 10 min total data collection time. TQF ^{23}Na MRI were collected employing the same parameters as used for SQ ^{23}Na MRI except a TR of 100 ms and a data size of 64 x 32 x 8 were used. Total data collection time for a TQF ^{23}Na MRI was 52 min.

Results and Discussions

Seven days after N1S1 cell injection into the liver, the tumors grew to 0.24 ± 0.07 cm^3 in volume. Tumors of this size were visible not only on the T_2-weighted ^{1}H MRI, but also on the SQ and TQF ^{23}Na MRI (Fig.1). At this time point the ADCs of water in HCC and the adjacent normal liver were (in $\times 10^{-3}$ mm^2/s) 1.3 ± 0.1 and 0.9 ± 0.1 ($p \leq 0.05$), respectively (Fig.2). On days 14, 21, and 28 after cell inoculation the tumors showed a doubling time of ~2.2 days while the tumor and liver water ADCs remained unchanged. Thus, during the four weeks the rats were monitored, the ratio of water ADC in tumor to nearby liver was always 1.5 – 1.6 (Fig.2). The HCC growth was associated with an increase in both SQ and TQF ^{23}Na MR SI compared to the surrounding liver tissue. The most intense tumor ^{23}Na signals were observed on day 28 after the cell inoculation (Fig.1).

An increase in necrotic area is expected in large HCCs (7). However, water ADC would have to show an increase during tumor growth to indicate necrosis, while in our experiments the tumor ADC remained unchanged. Preliminary histological analysis of the HCCs after the last MRI experiments did not show big necrotic areas inside the tumors. The distribution of ^{1}H SI on the ADC map also did not indicate significant separation of signals coming from the viable and necrotic areas. Because we used different MR coils to collect ^{1}H and ^{23}Na signals, co-registration between water ADC and tumor ^{23}Na images was difficult. However, SQ and TQF ^{23}Na MR images were collected using the same volume coil. In growing HCCs, a correlated increase in both total tumor tissue and intracellular Na^+ MR SI was observed. This data suggests that the increase in SQ ^{23}Na SI was not a result of edema and/or increase in extracellular space but rather it was due to an increase in intracellular Na^+ as a result of the developing ischemia/hypoxia, a decrease in Na^+/K^+-ATPase activity, an increase in Na^+/H^+ exchanger activity, and/or an increase in apoptotic and pre-necrotic cells. Additional histological and destructive chemical analyses need to be done to understand the exact mechanism for the observed changes in SQ and TQF ^{23}Na MRI in the growing HCC.

Conclusion

The growth of the HCC is characterized by an increase in both SQ and TQF ^{23}Na MRI SI due to changes in cellular function. On the other hand changes in water ADC and cellular necrosis were not observed even in relatively large intra-hepatic tumors.

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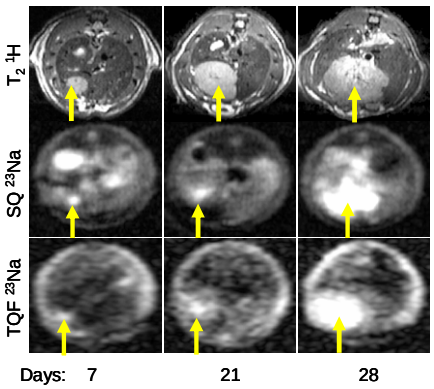

Fig. 1. T_2 weighted ^{1}H, SQ ^{23}Na, and TQF ^{23}Na MRIs of the HCC tumor in the rat liver 7, 21, and 28 days after N1S1 cell injection. HCC location marked by arrow.

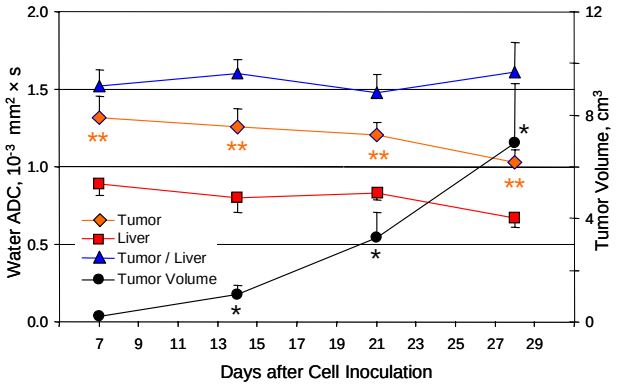

Fig. 2. Water ADC in the growing HCC tumors and in the surrounding liver tissue. M ± SE, N=7. Significance: * $p \leq 0.05$ - vs. day 7, ** $p \leq 0.05$ - ADC in tumor *vs.* ADC in liver.