Quantitative Multi-Dimensional PROPELLER MRI of Diethylnitrosamine-Induced Hepatocarcinogenesis in Wistar Rat Model

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INTRODUCTION

Development of hepatocellular carcinoma (HCC) involves a multi-step carcinogenesis process with varying degrees of cellular and structural atypia beginning with a benign regenerative nodule (RN), progressing to a premalignant dysplastic nodule (DN) and finally overt HCC. Multi-dimensional quantitative MRI methods combining T2, proton density (M0) and apparent diffusion coefficient (ADC) measurements have been investigated to provide increased parameterization for accurate tumor tissue characterization (1,2). However, implementation of multi-dimensional quantitative methods for abdominal tumors is challenging. Co-registration between abdominal parametric maps can be difficult given that these maps are typically acquired with different pulse sequences resulting in variable levels of artifacts and distortion. Quantitative PROPELLER MRI (3) methods for abdominal imaging have demonstrated less sensitivity to motion and susceptibility artifacts. A combined PROPELLER acquisition approach providing both T2 (4) and diffusion-weighted (DW) measurements (5) could provide inherently co-registered functional maps. The purpose of this study was to evaluate a quantitative multi-dimensional (T2 and DW) PROPELLER MRI approach for the characterization of the hepatic nodules during hepatocarcinogenesis in the diethylnitrosamine (DEN) rat model.

METHODS

Animal Model Diethylnitrosamine (DEN ISOPAC®, Sigma Chemical Co., USA) is a carcinogen primarily targeting the liver to induce both benign and malignant liver lesions. In 9 Wister rats, oral gavage was performed daily using an 18 gauge gavage needle with a 5mL/kg dose of 0.3% DEN solution for 12 weeks.

MRI All studies were performed using a 1.5T clinical Siemens scanner (Magnetom Espree). Rats were anesthetized with ketamine (120 – 200 mg/kg) and xylazine (4-6mg/kg). The abdomen of each rat was fixed with adhesive tape to limit respiratory motion. Sedated rats were placed within a plastic tube and imaged using clinical carotid coils. DW-PROPELLER and PROPELLER T2 mapping techniques were performed. FOV = 120×120 mm^2, matrix = 192×192, BW= 400 Hz/pixel, TH =3mm, multi-slice (24 slice) acquisition. For DW-PROPELLER: TR/TE = 4950/69 ms, ETL = 15, 168 segments b = 0, 500 and 1000 s/mm^2. For T2 measurement, PROPELLER sequence was modified such that each phase encoding line in each blade segment was sequentially acquired at each echo position along the echo train. The slice thickness ratio between refocusing and excitation RF pulses was adjusted to 3:1 to reduce stimulated echo effects: TR = 4000 ms, TE_i = i × echo spacing (i =1, 2… ETL), ETL = 25, echo-spacing = 8ms, 13 segments, slice gap = 100%. Additionally, T1W PROPELLER images were acquired with TR/TE = 200/8 ms, ETL = 9, 170 segments. After each image acquisition, parametric ADC, T2 and M0 maps were reconstructed.

Histopathology Evaluation Fixed tumor nodules were sectioned into 4μm slices for H&E staining. Using the diagnostic criteria from the International Working Party's Terminology of Nodular Hepatocellular Lesions (6), nodules were classified as cyst, RN, DN or HCC by attending surgical pathologist (>10yrs experience).

RESULTS

DW-PROPELLER, T2W- and T1W-PROPELLER images and resultant parametric maps (i.e. ADC, T2 and M0 maps) clearly delineated liver tumor nodules. No image distortion or motion artifacts were observed on PROPELLER images, allowing co-registration between three parametric maps. Hepatic nodules demonstrated widely variable signal characteristics on T1W and T2W PROPELLER images. Among 33 cirrhosis-associated hepatic nodules in 9 rats, 17 HCC, 7 RN, 4 DN and 5 cysts were identified at histopathology. Mean tumor ADC of HCC, DN, RN and cysts were 1.84±0.36, 2.2±0.92, 1.7±0.45 and 4.0±0.30 (unit: 10^{-3} mm^2/s), respectively. Mean tumor T2 values of HCC, DN, RN and Cysts were 115.8±86.2, 87.6±20.5, 77.2±15.1 and 1455±326.4ms, respectively. There were no significant differences between ADC and T2 values for HCC, DN and RN; however, ADC and T2 values for cysts were significantly higher than those of other three types (independent pair two-tailed *t* test, $p<0.05$). In contrast, mean tumor M0 of HCC (702.4±173) was significantly higher ($p<0.05$) than those of DN (514.5±53.8), RN (505.4±183.6) and cysts (370.5±113); however, no significant difference for M0 was observed between DN, RN and cysts.

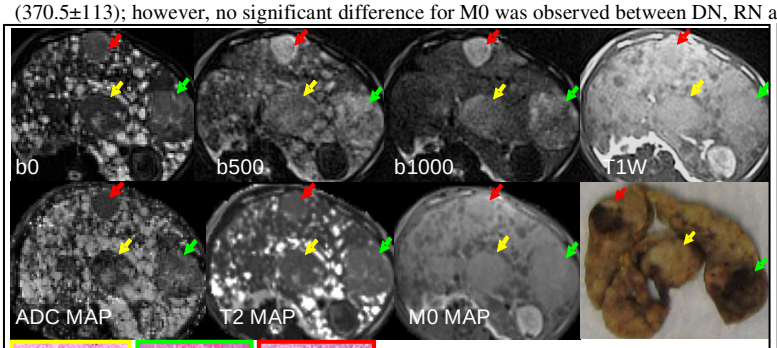

Figure 1. DW-PROPELLER images with resultant ADC map, along with T2 map, M0 map and T1W PROPELLER image of three large HCC tumors (HCC-1: yellow, HCC-2, green and HCC-3: red). These HCC tumors showed hypo-intense in b0 DW-PROPELLER image. With increasing b-value, HCC demonstrated less signal suppression than surrounding liver tissues. All HCC demonstrated relatively lower ADC values at the viable tumor periphery but elevated ADC values within necrotic tumor tissues. On T2 map, these HCC tumors demonstrated slightly higher T2 values compared to surrounding cirrhotic liver tissues. On M0 map, HCC regions demonstrated more homogeneous iso-intensity compared to surrounding cirrhotic liver tissues. On T1W image, HCC1 and HCC2 were iso-intense but HCC3 was slightly hypo-intense. The tumor positions depicted in MR images were well correlated to gross images of the sliced liver specimen at necropsy. H&E cell morphology of tumors tissues within these three nodules were characterized as HCC.

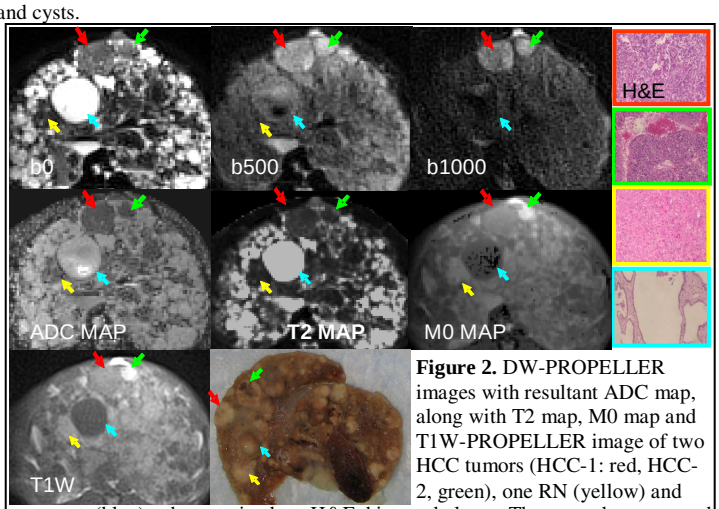

Figure 2. DW-PROPELLER images with resultant ADC map, along with T2 map, M0 map and T1W-PROPELLER image of two HCC tumors (HCC-1: red, HCC-2, green), one RN (yellow) and one cyst (blue), characterized at H&E histopathology. The cyst demonstrated distinctly higher ADC value and T2 value but was hypo-intense on the M0 map and T1W image. Both two HCC and the RN demonstrated hypo-intense on the b0 DW-PROPELLER image; however RN showed lower signal intensity compared with HCC. Two HCC demonstrated decreased ADC values but higher T2 values compared with the RN. Two HCC demonstrated different image contrasts on M0 map and T1W image with hypo-intensity in the larger HCC (red) and the hyper-intensity in the smaller HCC (green). The tumor positions depicted in MR images were well correlated to the gross image of the sliced liver specimen at necropsy.

CONCLUSIONS

In this preclinical study, we demonstrated the feasibility of using quantitative multi-dimensional analysis for characterization of a spectrum of hepatic nodules developed during hepatocarcinogenesis in the rat DEN HCC model. Multiple parametric maps of ADC, T2 and M0 acquired with the multi-shot PROPELLER technique were inherently co-registered providing increased parameterization for parallel assessment of tumor tissue properties. This multi-dimensional PROPELLER approach may also prove effective for serial non-invasive assessment of liver tumor therapy response.

Reference: [1] Henning EC, MRM 2007;57:501-512. [2] Carano RA, MRM, 2004;51:542-551. [3] Pipe JG, MRM 1999;42:963-969 [4] Deng J, Proc. ISMRM 2008, #238. [5 Deng J, Invest Radiol 2006;41(10):769-775. [6] Hepatology 1995;22(3):983-993