**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 (PD) 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 Wistar 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 = 192x192, BW = 400 Hz/pixel, TR = 3.3ms, 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 × 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, ET = 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 53 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 145.5±32.6ms, 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±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.

**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.
