Diffusion-Weighted Magnetic Resonance Imaging of Focal Hepatic Nodules in an Experimental Hepatocellular Carcinoma Rat Model[1]

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Rationale and Objectives. We sought to investigate the value of diffusion-weighted MR imaging in evaluating focal hepatic nodules in an experimental hepatocellular carcinoma (HCC) rat model.

Materials and Methods. Forty rats with chemically induced primary hepatic nodules ranging pathologically from regenerative nodules (RNs) to dysplastic nodules (DNs) to HCC were examined with diffusion-weighted imaging. The apparent diffusion coefficient (ADC) values of hepatic nodular lesions were calculated. Tukey's HSD post hoc test was used to compare the difference in ADC values between different hepatic nodular lesions.

Results. Eight RNs, 16 DNs, 7 well-differentiated HCCs (HCC_{well}), 11 moderately differentiated HCCs (HCC_{mod}), and 14 poorly differentiated HCCs (HCC_{poor}) were evaluated. There was no significant difference between RNs and DNs ($P > 0.05$). Although the ADC values of HCC_{well} were slightly lower than those of DNs, there was no significant difference between them ($P > 0.05$). The ADC values of HCC_{mod} and HCC_{poor} were significantly higher ($P < 0.05$) than those of other nodules, and no significant difference was seen between HCC_{mod} and HCC_{poor} ($P > 0.05$).

Conclusion. Diffusion-weighted magnetic resonance imaging can be useful in characterizing focal hepatic nodular lesions, but ADC values cannot be used efficiently to distinguish HCC_{well} from DNs.

Key words. Magnetic resonance imaging; diffusion; hepatocellular carcinoma; dysplastic nodules

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver, with highest incidences occurring in Africa, Southeast Asia, and China (1–3). A cirrhotic liver is often the background from which HCC arises. One pathway to the development of HCC in patients with cirrhosis is a multistep carcinogenesis process from benign regenerative nodule (RN) to dysplastic nodule (DN) to a dysplastic nodule with microscopic foci of HCC, which may enlarge and replace the nodule giving rise to a small HCC, and finally to the overt HCC (4–7). DNs are considered precancerous lesions of HCC (8, 9). Therefore, it is clinically important to detect DNs and HCC at an early stage for prompt surgical resection, transplantation, or local ablation therapy to ensure a better chance of survival.

Diffusion-weighted (DW) MRI is an imaging technique used to show microscopic motion in biologic tissues (10, 11). The apparent diffusion coefficient (ADC), a quantity calculated from the DW MR images, combines the effects of capillary perfusion and water diffusion in the extracellular extravascular space (10, 11). Thus, DW MRI is currently the only imaging method for assessing

Acad Radiol 2007; 14:279–286

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doi:10.1016/j.acra.2006.12.005

in vivo perfusion and diffusion simultaneously within the same organ (10–12).

DW MRI has recently been used to characterize abdominal organs and hepatic lesions (13–16). Results of these studies showed principally that DW MRI, by means of ADC measurement, can be used to characterize focal hepatic lesions (13–16). Benign lesions, such as hepatic cysts and hemangiomas, showed higher ADCs than those of malignant lesions (HCC and metastases). To our knowledge, very few studies have reported the ADCs of RNs and DNs in cirrhotic liver.

The purpose of this study was to investigate the value of DW MRI in the evaluation of RNs, DNs, and HCC in an experimental rat model. This model was induced by diethylnitrosamine (DEN), which results in hepatic nodules with histological features similar to the type of lesions observed in human cirrhotic liver carcinogenesis (17–19).

MATERIALS AND METHODS

Animal Model

The experiment was performed in accordance with the *Guide for the Care and Use of Laboratory Animals* (National Institutes of Health publication No. 85-23, revised 1996), with the approval of the local ethical committee for animal care and use. Six-week-old male rats (n = 40) of the Sprague-Dawley strain, weighing 120−150 g, were supplied by the Department of Laboratory Animal Science, Peking University, Beijing, China. The animals were acclimated for 1 week and maintained under specific pathogen-free environmental conditions with lighting from 9:00 [scap]am[r] to 9:00 [scap]pm[r], temperature of 22 ± 2°C, and relative humidity of 45−60% and were fed chow pellets and solution ad libitum during the entire study period. HCC was induced with 70 mg/kg DEN (0.95 g/ml; Sigma Chemical Co., St. Louis, MO) intragastrically once a week for 10 weeks.

MR Imaging

From week 10 to week 20 after induction of HCC by DEN, three or four treated animals were randomly scanned every week. After fasting for 12 hours, each rat was anaesthetized with 40 mg/kg pentobarbital sodium (Nembutal; Beijing Chemical Co., Beijing, China) intraperitoneally before imaging.

The rats were examined with a 1.5-T whole-body MR system (Sonata; Siemens, Erlangen, Germany) with a maximum gradient capability of 40 mT/m. A two-channel phased-array coil (50 mm in diameter; Chen Guang Medical Science Co., Shanghai, China) specially designed for rats was used to obtain all MR images. The rats were placed in a supine position inside the coil with the liver region located in the center of the coil and the abdomen fixed with adhesive tape to reduce respiratory movement.

To detect the hepatic nodules, a conventional liver MRI protocol was used as follows: T2-weighted turbo spin-echo (TSE) transverse, sagittal, and coronal orientation sequences with fat saturation (TR = 3,000 ms, TE = 79 ms, a flip angle of 150°, echo train length of 7, field of view 90 mm × 65 mm, matrix 192 × 135, slice thickness 3 mm), transverse two-dimensional T1-weighted fast low-angle shot (FLASH) sequence with fat saturation (TR = 250 ms, TE = 3.53 ms, a flip angle of 70°, field of view 90 mm × 55 mm, matrix 192 × 135, slice thickness 3 mm).

Transverse diffusion-weighted multisection echo-planar MRI was performed with two groups of diffusion gradient b values: b = 0, 600 sec/mm^2 and b = 0, 1,000 sec/mm^2. In the sequence, a unidirectional diffusion gradient was applied along the section-select direction (z axis). The following parameters were used for this sequence: TR = 3,000 ms; TE = 79 ms (b = 0, 600 sec/mm^2) or TE = 88 ms (b = 0, 1,000 sec/mm^2); field of view 90 × 68 mm; matrix 64 × 64; section thickness 3 mm. Fat saturation was used to avoid chemical shift artifacts.

Histology

The animal was killed after completion of MRI. The liver was removed and cut sequentially into 3-mm sections in the transverse plane that corresponded as closely as possible to the MRI plane. We identified the nodule that corresponded to DW MRI; then the tissue was fixed in 4% buffered formalin and embedded in paraffin, and thinner sections of 5 μm were cut and stained with hematoxylin-eosin for histological examination. Histological examination was conducted by two experienced hepatopathologists. By using the diagnostic criteria from the International Working Party's *Terminology of Nodular Hepatocellular Lesions* (4), nodules were classified as RN, DN, well-differentiated HCC (HCC_{well}), moderately differentiated HCC (HCC_{mod}), and poorly differentiated HCC (HCC_{poor}).

Image Analysis

Quantitative ADC maps were calculated automatically on a voxel-by-voxel basis with the MR system. The ADC