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# Is gadoxetic acid-enhanced MRI limited in tumor characterization for patients with chronic liver disease?☆

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ABSTRACT

*Purpose:* There are pros and cons to the use of gadoxetic acid in hepatocellular carcinoma (HCC) workup due to the potential for high false positive diagnosis. This study was conducted to investigate the preoperative diagnostic performance of gadoxetic acid-enhanced MRI protocol including diffusion-weighted imaging (DWI) with emphasis on tumor characterization developed in high risk HCC patients.
*Materials and methods:* We included 144 patients (102 men, 42 women; age range 33–74 years) with chronic viral hepatitis or cirrhosis and 183 focal hepatic tumors (size range, 0.4–11.0 cm; mean, 3.2 cm), including 148 HCCs, 13 cholangiocarcinomas, 12 hemangiomas, three hepatocellular adenomas, two focal nodular hyperplasias, and five other tumors. All patients underwent gadoxetic acid-enhanced MRI protocol with DWI. MRIs were independently interpreted by three observers for the detection and characterization of hepatic tumors.
*Results:* Sensitivities for detecting all 183 liver tumors were 98.4%, 97.8%, and 96.2% for each observer, respectively, with a 97.5% for pooled data. Among 183 hepatic tumors, 91.3% (n = 167), 87.4% (n = 160), and 86.9% (n = 159) were correctly characterized according to their reference standard by each observer, respectively. In 13 cholangiocarcinomas, one to three were misinterpreted as HCC, and the remaining tumors were correctly characterized by each observer. The accuracies (Az) of MRI for HCC diagnosis were 0.952 for observer 1, 0.906 for observer 2, and 0.910 for observer 3, with 0.922 for pooled data. There was good inter-observer agreement.
*Conclusion:* The gadoxetic acid-enhanced MRI including DWI showed a reasonable performance for tumor characterization with high sensitivity for tumor detection in patients with chronic liver disease, despite concerns of high false positive diagnosis of hypervascular tumors.


## 1. Introduction

The goal of liver imaging for patients with chronic liver disease is the early detection and accurate characterization of hepatocellular carcinoma (HCC) by differentiating it from benign cirrhosis-associated hepatocellular nodules as well as other hepatic tumors. This increases the success rate of curative treatment and leads to a better outcome [1,2]. Magnetic resonance imaging (MRI) has the potential to better fulfill these imaging requirements than other liver imaging modalities since it not only offers excellent soft tissue contrast resolution, but also provides multiparametric information by using a variety of contrast agents, such as tissue-targeted agents, as well as baseline imaging and novel sequences, such as diffusion-weighted imaging (DWI).

Gadoxetic acid is a novel dual-acting MR contrast agent for liver imaging that offers the combined properties of an extracellular fluid (ECF) contrast agent during the early vascular–interstitial phases and a liver-specific agent during the hepatobiliary phase (HBP) [3–6]. Inclusion of an HBP benefits clinicians in the diagnosis of HCC, since HCCs are more frequently hypointense during HBP than during the portal venous phase or delayed phase of conventional dynamic CT or MRI [7–11]. However, this benefit might be offset by the fact that other focal liver lesions besides HCC, particularly intrahepatic cholangiocarcinoma (ICC), might show a similar enhancement pattern to HCC due to a short-acting duration of gadoxetic acid as an ECF agent and its early hepatocyte uptake [12–15]. In addition, it is challenging to differentiate HCCs showing iso- or hyperintensity on HBP due to increased uptake of the contrast media (i.e. well- or moderately differentiated HCC) from focal nodular hyperplasia (FNH) [16]. Thus, there is controversy regarding whether gadoxetic acid-enhanced imaging should be introduced into the noninvasive

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diagnostic criteria for HCC. Due to recent tremendous advances in image quality, DWI is routinely used as a standard clinical liver MR protocol [17–19]. Given that hepatocarcinogenesis is related to increased cellular density, diffusion restriction in the hepatocarcinogenetic pathway is highly indicative of HCC development. In that sense, previous researchers have shown benefit in combining gadoxetic acid and DWI in the detection and characterization of small HCCs that do not fit to HCC criteria on conventional dynamic imaging, as well as the differentiation between HCC and other liver tumors based on signal intensity pattern on HBP or DWI [14,19,20].

To the best of our knowledge, limited research has been conducted to assess the diagnostic performance of gadoxetic acid-enhanced MRI protocol including DWI in the diagnosis of focal liver lesions with emphasis on lesion characterization in patients who are at high risk of developing HCC. Since there are pros and cons with regard to the use of gadoxetic acid in HCC workup, assessing the performance of a state of the art MRI protocol using gadoxetic acid in the characterization of focal liver lesions has clinical impact. Therefore, we conducted this study to investigate the preoperative diagnostic performance of a gadoxetic acid-enhanced MRI protocol including DWI with an emphasis on the characterization of hepatic tumors in high-risk HCC patients with chronic liver disease.

## 2. Materials and methods

### 2.1. Patients

Our institutional review board approved this retrospective study, and informed patient consent was waived. We searched our hospital's surgical database in the date range between January 2013 and December 2013. This search identified 258 patients who had undergone surgery for hepatic tumors. The inclusion criteria were as follows: (a) patients with chronic hepatitis or cirrhosis who had surgically proven hepatic tumors and (b) patients who underwent liver MRI before surgery. Of the 258 patients, 114 were excluded because of lack of underlying chronic hepatitis or cirrhosis ($n = 110$) or treatment for HCC prior to an MR examination ($n = 4$).

The final cohort included 144 patients (102 men, 42 women; age range 33–74 years; mean age 57 years) who had a total of 148 HCCs, 13 ICCs, 12 hemangiomas, three hepatocellular adenomas (HCAs), two FNH, one high-grade dysplastic nodule (HGDN), one low-grade dysplastic nodule (LGDN), one large regenerative nodule (RN), one reactive lymphoid hyperplasia (RLH), and one bile duct adenoma (BDA). The causes of chronic liver disease were liver cirrhosis ($n = 95$) or chronic hepatitis ($n = 8$) associated with viral hepatitis B, liver cirrhosis ($n = 34$) or chronic hepatitis ($n = 2$) associated with viral hepatitis C, and liver cirrhosis associated with both viral hepatitis B and viral hepatitis C ($n = 5$). Based on the Child–Pugh classification, 140 patients were classified as Child–Pugh class A and four as class B. The diagnosis of all solid hepatic tumors and five hemangiomas was based on a histopathological examination of the surgical specimens. The mean time interval between the MR examination and the surgery was 16 days (range 1–27 days). The operations included segmentectomy ($n = 97$), lobectomy ($n = 45$), and liver transplantation ($n = 2$). The remaining seven hemangiomas were diagnosed based on typical findings, including nodular or globular enhancement with centripetal enhancement patterns on dynamic CT or MRI, very high signal intensity on both moderate and heavily T2-weighted images (T2WI), and stability for at least 12 months of follow-up.

### 2.2. MR examination

MRIs were acquired using a 3.0-T MR system (Intera Achieva 3.0-T, Philips Healthcare, Best, The Netherlands) equipped with a dual-source parallel radiofrequency transmission system and a quadrature body coil. The baseline MRIs included a T1-weighted turbo field-echo in-phase and opposed sequence (TR/first echo TE, second echo TE, 10/2.3 [in-phase], 3.45 [opposed-phase]; flip angle, 15°; matrix size, 256 × 194; bandwidth, 434.3 Hz/ pixel), a breath-hold multishot T2WI with an acceleration factor of 2 (1796/70; flip angle, 90°; matrix size, 324 × 235; bandwidth, 258.4 Hz/pixel), a respiratory-triggered single-shot heavily T2WI with an acceleration factor of 2 (1802/160; flip angle, 90°; matrix size, 252 × 254; bandwidth, 420.9 Hz/pixel) and a 5 mm section thickness, and a field of view of 32–38 cm.

Diffusion-weighted single-shot echo planar imaging with the simultaneous use of respiratory triggering was performed using a TR/TE of 1600/70. The scanning parameters were as follows: b-values of 0, 100 and 800 s/mm$^2$; spectral presaturation with inversion recovery for fat suppression; matrix size, 124 × 124; SENSE acceleration factor, 4.0; field of view, 35 × 35 cm; number of excitations, 3; slice thickness, 5 mm; and slice gap, 1 mm. The apparent diffusion coefficient (ADC) was calculated using a mono-exponential function at b-values of 100 and 800 s/m$^2$. Acquisition time for this sequence was 2–3 min depending on the respiratory efficiency of the patient. Thus, total image acquisition time for precontrast MRI including DWI was 6–7 min.

Unenhanced, arterial-phase (20–35 s), portal-phase (60 s), 3 min late-phase, and 20-min hepatobiliary phase (HBP) were obtained for gadoxetic acid-enhanced imaging using a T1-weighted 3D turbo-field-echo sequence (enhanced T1 high-resolution isotropic volume examination, eTHRIVE, Philips Healthcare) (3.1/1.5; flip angle, 10°; matrix size, 256 × 256; bandwidth, 724.1 Hz/pixel) with the spectral attenuated inversion recovery fat suppression technique, a 2-mm section thickness, and a field of view of 32–38 cm. The time for the arterial phase imaging was determined using the MR fluoroscopic bolus detection technique. The contrast agent was administered intravenously using a power injector at a rate of 1 mL/s for a dose of 0.025 mmol/kg body weight, followed by a 20-mL saline flush.

### 2.3. Image analysis

Two on-site (observer 1 and 3) and one off-site (observer 2) gastrointestinal radiologists (with 13, five and three years of experience in liver MRI interpretation, respectively) retrospectively reviewed MRIs independently on a picture archiving and communication system (Centricity 3.0, General Electric Medical Systems, Milwaukee, WI). They knew that the patients were at risk for HCC but were blinded to the initial MRI report and pathologic diagnosis of hepatic tumors. Each observer documented the presence of hepatic tumor using a four-point confidence scale (1: probably not a lesion. 2: possibly a lesion, 3: probably a lesion, 4: definitely a lesion) and the possibility of HCC using a four-point confidence scale (1: probably not HCC. 2: possibly HCC, 3: probably HCC, 4: definitely HCC). As for classifying as HCC or not HCC, hepatic nodule considered as DN or hepatic tumors other than HCC was assigned as a confidence level of 1 or 2. Missed lesions were given a rating of 0. Observers were also asked to make a specific diagnosis of detected lesions as HCC, ICC, or other benign lesion such as hemangioma, FNH, or HCA. Observers made a diagnosis of liver tumors based on subjective features of the lesions (including the size, margin, shape, homogeneity, signal intensity, presence of fat, central scar, capsule, and mosaic pattern) and the major features used as diagnostic criteria for HCC (nodule showing enhancement foci during the arterial phases and early washout on portal phase and/or 3 min-late phase, and/or hypointensity on HBP with/without ancillary findings such as hyperintensity on T2WI, mosaic appearance, and tumor capsule), for ICC (nodule showing early peripheral enhancement with a centrally enhanced area and peripheral hypointense rim on 3 min-late phase and or 10 min- and 20 min HBP), for hepatic hemangioma (centripetal enhancement during dynamic MRI and bright hyperintensity similar