The value of gadoxetic acid enhanced hepatospecific phase MR imaging for characterization of hepatocellular nodules in the cirrhotic liver

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Authors: A. Filippone, R. Cianci, F. Sabatino, V. Bianco, E. Pace, A. Tartaro, A. R. Cotroneo; Chieti/IT
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Purpose

In patients with chronic liver disease, HCC develops in a multistep fashion known as hepatocarcinogenesis, that evolves from regenerative nodule through high-grade dysplastic nodule and early HCC, and leads to overt HCC. Dynamic imaging of the liver is one of the most sensitive technique to detect overt HCC, revealing the typical wash-in in the arterial phase and wash-out in the late phase. Unfortunately, there are significant overlaps between the dynamic imaging findings of benign and malignant liver lesions in cirrhotic livers: while early HCC lacks the typical arterial enhancement because of its immature neovascularity, some DN can receive increasing supply from the hepatic artery.

Gadoxetic acid (Gd-EOB-DTPA; Primovist, Bayer Schering Pharma, Berlin, Germany) allows for both dynamic and hepatocyte-specific imaging, which has been reported to be most pronounced at 20 minutes after contrast injection. A recent study showed that a reduced Gd-EOB-DTPA uptake in the hepatospecific phase might be an early event of hepatocarcinogenesis, preceding portal blood flow reduction.

Therefore, the purpose of this study was to retrospectively assess the added value of the hepatospecific phase combined with dynamic Gd-EOB-DTPA-enhanced MR imaging to discriminate HCC and DN in cirrhotic livers.
Methods and Materials

Patients and standard of reference

This retrospective review of MR studies was approved by our Institutional Review Board, which waived requirement for written informed consent.

Between September 2007 and April 2010, thirty-four patients with post-viral infection cirrhosis (27 men and 7 women; mean age 58.7 years) were referred for dynamic and 20 minute Gd-EOB-DTPA-enhanced MR imaging and formed the patient group for this study.

Twenty-one patients had Child-Pugh class A, eight had Child-Pugh class B, and five had Child-Pugh class C cirrhosis.

The final diagnosis of 23 HCCs in 21 patients was confirmed by surgical specimens [surgical resection (n=15) and liver transplantation (n=6)]. Among these 23 nodules, 8 were well-differentiated, 11 were moderately differentiated, and 4 were poorly differentiated HCCs. Conversely, 16 HCCs in 13 patients were diagnosed by a combination of characteristic clinical environments and typical imaging findings including underlying liver cirrhosis, the presence of viral hepatitis B or C, elevated #fetoprotein level, characteristic CT findings of HCC (lesion enhancement in the arterial phase followed by wash-out in the late phases) and lipiodol uptake on lipiodol CT. Eight of these 13 patients underwent radiofrequency ablation of HCC nodules, whereas the remaining 5 underwent transcutaneous arterial chemioembolization. In 9/21 patients who underwent surgery and in 4/8 patients who underwent radiofrequency ablation DNs were also present.

Finally, our study group was represented by 34 patients with 39 HCCs and 15 DNs; these latter were all pathologically confirmed (11 DNs in 9 patients by surgical specimen and 4 DN by core needle biopsy). Fourteen DNs resulted to be low grade DNs (LGDNs) (11 at surgery and 3 at core-needle biopsy) and 1 resulted to be high grade DN (HGDN) (at core-needle biopsy). Non surgically resected DNs were periodically followed by ultrasound (US) for at least 19 months. In the HGDN an increase in size during follow-up period led to carry out a new core-needle biopsy which showed progression to HCC. Radiofrequency ablation was therefore performed.

The diameter of the 39 HCCs ranged from 0.8 to 7.5 cm (mean, 3.2 cm); the diameter of the 15 DNs ranged from 1 to 2.2 cm (mean, 1.3 cm).

MR Imaging
This study was performed using a 1.5 T MR system (Achieva; Philips Medical System, Best, the Netherlands) equipped with a 16 elements phased array body coil (SENSE XL Torso).

The liver was imaged in the axial plane and the baseline MR included the following sequences: a respiratory-triggered T2 weighted turbo spin-echo (TSE) with fat-suppression sequence, a breath-hold Half-Fourier acquired Single-Shot turbo Spin-Echo (HASTE) sequence and a double-echo T1 weighted gradient echo sequence (in-phase and opposed-phase images).

Contrast-enhanced MRI was performed after intravenous administration of Gd-EOB-DTPA at a dose of 0.25 µmol/kg of body weight with a 1 ml/s flow rate, followed by a 20-mL saline flush at the same flow rate using a power injector (MEDRAD Spectris).

A three-dimensional spoiled gradient-recalled-echo sequence with fat suppression was performed during arterial (bolus tracking + 10 s), portal-venous (70 s), and equilibrium (180 s) Gd-EOB-DTPA enhanced MR phases. Additional hepatospecific phase images were obtained at 20 minutes after contrast agent administration.

All pulse sequence parameters are listed in Table 1 on page

Image analysis

Two radiologists with 15 and 4 years of experience in interpreting liver imaging independently reviewed the MR examinations. The observers were aware that all patients had a history of cirrhosis but they were blinded to the results of surgery, biopsy, or other imaging studies.

At two different sessions separated by 4 weeks MR images were reviewed for the possibility of HCC or DN according to a four-point confidence rating scale: a score of 1, probably HCC; a score of 2: certainly HCC; a score of 3: probably DN; a score of 4: certainly DN. For each reading session, each observer recorded the presence and the segment location of lesions according to the classification scheme of Couinaud.

The two sessions included in a random order two sets of MR images: set A, unenhanced (T1- and T2-weighted images) and Gd-EOB-DTPA enhanced dynamic images (arterial, portal-venous and equilibrium phases); set B, unenhanced, Gd-EOB-DTPA-enhanced dynamic and hepatospecific images.

The criteria for diagnosis of HCC were as follows: a) a nodule with wash-in at arterial phase and wash-out at portal or/and equilibrium phase; b) a nodule with wash-in at arterial phase and hyperintensity on T2 weighted images; c) a nodule with definite hypointensity on hepatospecific phase images.
The criteria for diagnosis of DN were as follows: a) a nodule with iso or hypointensity on T2 weighted images, hyperintensity on T1 weighted images, with no contrast enhancement at arterial phase; b) a nodule with iso or hypointensity on T2 weighted images, hyperintensity on T1 weighted images with contrast enhancement at arterial phase, no wash-out at portal-venous or/and equilibrium phase; c) a nodule with uptake of contrast agent on hepatospecific phase images similar or higher than that of the adjacent liver parenchyma.

**Statistical Analysis**

Receiver operating characteristic (ROC) curves for each observer and each reading session were calculated. The area under ROC curve (Az) was used to indicate the overall performance of the observers for the diagnosis of HCC.

The sensitivity and specificity of each set of MR images to characterize HCC were also measured for each observer considering the total number of lesions, lesions ≤ 2 cm and lesions > 2 cm. Lesions with score 1-2 were considered positive results and lesions with score 3-4 were considered negative results for the diagnosis of HCC. The significance of any difference was assessed using McNemar test (p< 0.05).

Kappa statistics were used to assess interobserver agreement in the detection of HCC. The degree of agreement was categorized as follows: Kappa values of 0.00-0.20 were considered to indicate poor agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, good agreement; and 0.81-1.00, excellent agreement.
Results

Table 2 on page summarizes Az values for each observer and each reading session. For diagnosis of HCC, both observers achieved higher diagnostic accuracy when the hepatospecific phase was added to unenhanced and Gd-EOB-DTPA enhanced dynamic study (Figure 1 on page and Figure 2 on page). The increase of Az value during the reading session including hepatospecific phase images resulted to be superior for the less experienced observer [observer 2: from 0.881 in set A to 0.945 in set B (p=.045)].

Table 3 on page shows the sensitivities and specificities of the two reading sessions for each observer considering the overall HCC lesions. All observers had higher sensitivity when hepatospecific phase images were available and the differences between the two reading sessions for each observer were statistically significant [observer 1: from 0.82 in set A to 0.92 in set B (p=.044); observer 2: from 0.77 in set A to 0.92 in set B (p=.025)].

Table 4 on page shows the sensitivities of the two reading sessions for each observer according to HCC size. For diagnosis of HCC larger than 2 cm, the two reading sessions achieved the same results for both observers (p=.201). Conversely, for diagnosis of small HCC (# 2 cm) both observers significantly improved the sensitivity with the addition of hepatospecific phase images (Figure 3 on page and Figure 4 on page).

When considering the overall HCC nodules and set A of MR images, observer 1 evaluated 7/39 HCCs as DNs (false negative cases); similarly, observer 2 considered 9/39 HCCs as DNs. Among these 9 false negative cases, 7 were the same lesions considered as DNs by observer 1. Therefore, at the reading session including set A of MR images, the two observers agreed in 37/39 (94%) HCCs (k=0.86). On the other hand, when assessing set B of MR images, the two observers judged the same 3/39 HCCs as DNs and, therefore, they agreed in 39/39 (100%) HCCs (k=1.00).

When considering the specificity, both observers interpreted one DN as HCC (false positive case) at session including hepatospecific phase images.
Conclusion

The present study demonstrated that adding the hepatospecific phase to unenhanced and dynamic Gd-EOB-DTPA enhanced MR images helps to differentiate HCC from DN. Moreover, it confirms the literature data revealing that the feature of hypointensity on hepatospecific phase occurred at an early stage of hepatocarcinogenesis, preceding the typical feature of arterial vascularisation appreciable on dynamic phase.

The clinical impact of preoperative diagnosis of early HCC or high grade DN allows a well-timed therapeutic decision for these patients who can obtain a higher chance for curative treatment and a lower risk of recurrence. Therefore, we recommend a more rigorous follow-up or biopsy of high-risk nodules; otherwise, when these nodules coexist with overt HCC eligible for surgical treatment, we suggest resection.
References


Personal Information

Antonella Filippone, MD

Department of Clinical Sciences and Bioimages, Section of Radiological Sciences, "G. d'Annunzio" University of Chieti, via dei Vestini, 66013, Chieti, Italy.

phone and fax number: +39 0871 358237

e-mail: a.filippone@rad.unich.it