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Signal Intensity Characteristics of Liver Masses at Hepatobiliary Phase Images of Gadoxetate-Enhanced MR (EOB-MR): Qualitative Assessment

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1. Introduction

Gadolinium ethoxybenzyl diethylenetriamineoentacetic acid (gadoteric acid disodium, or Gd-EOB-DTPA, Primovist, BayerSchering, Germany) is a liver cell specific contrast agent, with which dynamic phase images can be obtained to assess arterial blood supply or arterial flow to the liver tumors, in addition to hepatobiliary phase (HBP) images that yields high accuracy in the detection of liver lesions [1-3]. In other words, Gd-EOB-DTPA behaves as non-specific extracellular contrast agent in the early dynamic phase, and as a tissue-specific contrast agent in later phases. Evaluation of vascularity helps in part differentiate various liver lesions, applying our previous experience of Gd-based extracellular contrast medium [4-6]. It is sometimes difficult, however, to make differentiation only from findings of Gd-EOB-DTPA-enhanced MR (EOB-MR) images, because of insufficient arterial enhancement due to small dose of Gd-EOB-DTPA used ($25 \mu\text{mol/kg}$), and lack of "equilibrium phase images" in the conventional sense of the word [1].

On HBP images, because most of the liver lesions, except for some hepatocellular lesions, uptake little Gd-EOB-DTPA, they are uniformly considered to present as hypointense areas in contrast to the well-enhanced normal surrounding liver parenchyma [1-6]. However, it has already been reported that most of the liver tumors do enhance on the HBP images [1,5,6] possibly through several different mechanisms. Both liver metastasis and hepatocellular carcinoma (HCC) exhibit 20-30% higher signal intensity on HBP as compared to precontrast images [1,6]; the presumed mechanism for the former is contrast accumulation in the abundant fibrous interstitium or stroma, by similar mechanism as that of conventional extracellular Gd-based contrast medium [7], and that for the latter is either cellular uptake of Gd-EOB-DTPA by the neoplastic cells or interstitial accumulation, or both. Focal nodular hyperplasia (FNH) is well known to show 150% higher signal [1,6] because of

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the characteristic cellular uptake of Gd-EOB-DTPA by the tumor. Hemangioma becomes 50% higher in signal on HBP [1,6] possibly due to contrast retention in the blood pool in the sinusoidal space in the tumor.

We therefore hypothesized that patterns of signal intensity on HBP images, when assessed in detail, may vary according to the types of liver masses and also that it may be of some help in the characterization of each entity. Thus, we conducted this study to elucidate whether qualitative assessment of signal intensity on HBP of Gd-EOB-DTPA-enhanced MR (EOB-MR) is useful in differential diagnosis of liver masses, in addition to the assessment of patterns of blood supply on the dynamic phase images.

2. Materials and methods

2.1 Patients

Between June 2008 and November 2008, 65 patients underwent Gd-EOB-DTPA enhanced MR in our institute. Medical charts and radiological images, including MR and CT images, were retrospectively reviewed, and liver lesions were recruited according to the inclusion criteria as shown below. Our institutional review board approved this study without requiring specific informed consent for this study because of its retrospective nature.

Inclusion criteria of the lesions are as follows: 1) image quality is not degraded due to any artifacts, 2) confirmation of the etiology of the lesions is obtained either pathologically or clinicoradiologically. Exclusion criteria were: 1) poor image quality due to artifacts, such as motion, respiratory, or susceptibility artifacts (lesions visualized in the edge slices of the imaging slab where considerable signal drop was noted were also excluded) 2) lack of final confirmation according to our definition as shown below. Clinicoradiological criteria of the liver masses were as follows: hypovascular hepatocellular nodules (group 1) were defined as those nodules which were detected on ultrasonography (US) in patients with hepatitis or cirrhosis, and showed no hypervascularity on dynamic MDCT which were obtained within four weeks from EOB-MR, or on dynamic phase of EOB-MR. Hypervascular hepatocellular carcinoma (HCC) (group 2) were defined as lesions which exhibited typical early enhancement and subsequent washout (lower density than the surrounding hepatic tissue on portal venous or equilibrium phase images) [8] on MDCT in patients with hepatitis or cirrhosis, or those which accumulated lipiodol after transcatheter treatment in patients who had previously had pathologically proven HCC. Hemangiomas (groups 3) were defined as those for which conventional MR or dynamic CT had shown typical findings [8,9], and remained unchanged over one year. Metastases (group 4) were defined as those nodules which progressed on the follow-up imaging studies including CT/US in patients with pathologically proven primary malignancies. FNH (group 5) were defined as those nodules which strongly enhances on the arterial phase and becomes similar density on the equilibrium phase images of MDCT, and also associated with at least partial uptake of superparamagnetic ironoxide (SPIO) confirmed on T2- or T2*-weighted MR images [8].

2.2 MR and CT technique

MR examination was performed in a 1.5 T clinical unit (Achieva Nova Dual, Philips Medical Systems, Netherland). T1-weighted chemical-shift gradient-echo images (CSI) were initially obtained under breath-holding using the following parameters; repetition time (TR) 165

msec, echo-time (TE) 2.3 and 4.6 msec, flip angle (FA) 75 degrees, 256 matrix and slice thickness/gap=7-8/1 mm. Then dynamic scan was performed using three-dimensional (3D) T1-weighted field-echo images with fat suppression (T1-high resolution isotropic volumetric excitation: THRIVE) (TR/TE/FA=4.7 msec/2.3 msec/15 degrees, 4 mm thickness with gap - 2 mm, 224 matrix) and test injection method. First, the injection rate was determined according to each patient as the whole amount of contrast (0.025mmol/kg) was injected at 3 sec (fixed injection time), and additional 0.5 mL Gd-EOB-DTPA was injected at that rate for test injection, followed by an injection of 20 mL saline. Single-level, sequential, axial, turbo field-echo (repetition time/echo time = 13.4/1.47, 60° flip angle) were performed every 1 second for 60 seconds at the level of the center of the aorta at the level of celiac artery using as large a region of interest as possible. A time-signal intensity curve was generated using the software package on the MR imaging system. The time delay from the commencement of the test injection to the arrival of Gd at the abdominal aorta was recorded as arrival time of the aorta (Tao). According to the previous literature [10,11] and to our personal experience, the optimal arterial dominant phase (T) was roughly calculated using the following formula: $T = T_{ao} + 9 - 1/2$ (acquisition time). Dynamic MR scanning was performed with THRIVE before and at T, T + 30, 90, and 240 seconds after the beginning of bolus administration of Gd-EOB-DTPA.

Subsequently, two types of T2-weighted images are obtained. First, turbo-spin-echo sequence with breath-holding (TR/TE/echo-train=10000/120/59, slice thickness/gap=7-8/1 mm) and then, 3D T2-weighted imaging with fat saturation (VISTA; TR/TE/echo-train=2000/99/79) was performed with respiratory navigation; slice thickness and gap=3 and -1.5mm, scan time approximately 8 min). Then, diffusion-weighted images were obtained with TR/TE/FA=1500/72/90 degree, b factors 0 and 1000, 3NEX, and respiratory navigation. In 15 minutes, hepatocellular phase images were obtained with THRIVE in the axial and coronal direction, the same sequence as one used for the dynamic study.

CT was obtained with a 64-row multidetector CT (Aquilion 64, Toshiba, Tokyo, Japan) with the following parameters; 120kVp, auto-mAs, 0.5 mmx64, pitch 53, reconstruction 2 mm thickness. After unenhanced scanning of the upper abdomen, 600 mgI/kg iodinated contrast medium (Iopamiron 370, Bayer-Schering, Germany) was injected in 30 sec via superficial venous branches of the upper extremities, and arterial dominant phase (40 sec delay or delay determined by bolus tracking method), portal phase (70 sec delay), and equilibrium phase (240 sec delay) imaged were obtained.

2.3 Assessment

Signal intensity of the liver lesion on HBP was qualitatively graded into five categories using surrounding non-tumorous liver parenchyma and the inferior vena cava (IVC) as reference tissue; H (higher than the surrounding liver), I (similar to the liver), L1 (lower than the liver, and higher than IVC), L2 (similar to IVC), and L3 (lower than IVC). Visual comparison of the mass to IVC was made primarily within the same slice as the target mass is located, but when IVC is too small in size and hard to evaluate its signal intensity at visual inspection, the adjacent slices available were referred to. Two radiologists (SK, KY) interpreted the axial HBP images of 54 patients, and disagreement was resolved by consensus. Signal pattern was compared between the groups using ANOVA with post-hoc test.

In the early stages of multistep hepatocarcinogenesis [12,13], some hepatocellular nodules including regenerative nodules (RN), dysplastic nodules (DN), early hepatocellular carcinomas (eHCC) or well differentiated hepatocellular carcinomas (wHCC), have been known to exhibit high signal intensity on T1WI, either related or unrelated to fatty metamorphosis [14-17]. Therefore, there could be a hypothesis that signal intensity before contrast administration may influence signal intensity on the postcontrast image. To test this hypothesis, we correlated SI on HBP in groups 1 and 2, namely hypo- and hypervascular hepatocellular nodules, to the incidence of lesions exhibiting high signal intensity (H) on the precontrast THRIVE image using Spearman's rank correlation. Because fat suppression is applied to THRIVE, high signal on precontrast THRIVE indicates non-fatty component with short T1 characteristics, such as copper or iron accumulation [14-16]. Also correlated was to the presence of fat on CSI, namely presence of signal loss on out-of-phase images [17] as compared to in-phase images.

3. Results

Among the 65 patients, 10 patients were excluded because these did not meet the inclusion criteria. In one patient, there were a combined-hepatocellular and cholangiocellular carcinoma that were surgically resected and pathologically confirmed, but this was excluded because of its too small number that would not tolerate statistical evaluation. Finally 154 liver nodules in 54 patients consisted the study population for this study. There were 41 men and 13 women, with age ranging from 32 to 92 years old (mean 67). The details of the recruited 154 liver masses are as follows: group 1 (n=45) 9 were pathologically proven by biopsy (4 dysplastic nodules, 2 well-differentiated carcinoma, 1 well to moderately differentiated carcinoma) and remaining 37 were clinicoradiologically proven: group 2 (n=78) 10 were pathologically proven either by biopsy or surgery (3 well differentiated carcinoma and 7 moderately differentiated carcinoma) and remaining 68 were clinicoradiologically proven: group 3 (n=13) all lesions were proven clinicoradiologically: group 4 (n=17) all were clinicoradiologically proven (primary lesion for 7 masses was colorectal carcinoma, that for 4 was gastrointestinal stromal tumor, that for 3 was breast carcinoma, and that for another 3 was renal cell carcinoma): group 5 (n=2) all FNH nodules were confirmed clinicoradiologically.

The details of signal pattern of the four groups are shown in Table 1. There was significant difference between the groups ($p < 0.05$, Kruskal-Wallis test). The difference was significant between group 5 and other 4 groups ($p < 0.005$, ANOVA with Bonferroni-Dunn's post-hoc test). Namely, the lesions showing high signal intensity on HBP are considered to suggest the diagnosis of FNH. None of the FNH nodules in this series had typical central scar. Using high signal intensity on HBP as a sign of FNH, 100% sensitivity, 97% specificity, 33% positive predictive value, and 100% negative predictive value, were obtained. There were one and two lesions that showed high signal intensity on HBP in groups 1 and 2, respectively. There was no such lesion in groups 3 and 4. Among these nodules, hypovascular hepatic nodule (n=1) can be discriminated from FNH by its hypovascular nature (Fig.2). The two lesions in group 2 (hypervascular HCC) can be discriminated from FNH by the presence of its fibrous capsule and/or nodule-in-nodule appearance (Figs.3 and 4). Thus, combining all findings of EOB-MRI, 100% sensitivity, 100% specificity, 100% positive and negative predictive values, were achieved.

	Group 1 (n=56)	Group 2 (n=78)	Group 3 (n=13)	Group 4 (n=17)	Group 5 (n=2)
H	1	2	0	0	2
I	5	5	3	0	0
L1	19	21	2	9	0
L2	16	31	4	0	0
L3	5	19	4	8	0

Group 1: hypovascular hepatocellular nodules,

Group 2: hypervascular hepatocellular carcinoma, Group 3: hemangioma,

Group 4: metastasis, Group 5: focal nodular hyperplasia

H: higher signal than that of the surrounding liver tissue,

I: similar signal intensity as that of the liver,

L1: lower than the liver, but higher than the signal of inferior vena cava (IVC)

L2: similar signal as that of IVC

L3: lower signal than that of IVC

Differences were significant between group5 and groups 1, 2, 3, and 4. ($p < 0.005$, ANOVA with Bonferroni-Dunn's post-hoc test)

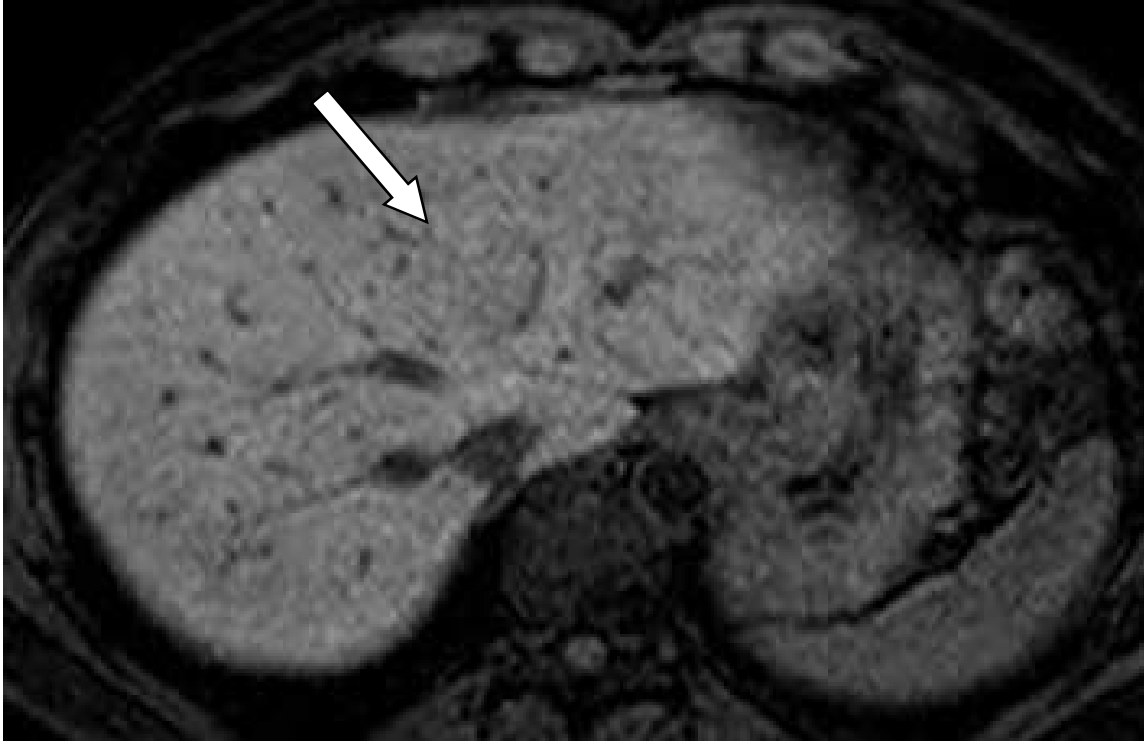
Table 1. Signal intensity of various liver lesions on hepatobiliary phase images

4. Discussion

Qualitative diagnosis on EOB-MR is usually achieved by combining information obtained from precontrast conventional MR images (signal intensities on T1WI and T2WI, chemical shift imaging, and diffusion-weighted images), and enhancement pattern on the dynamic phase images [1,2,4-6]. It is sometimes challenging, however, because of insufficient arterial enhancement secondary to the small dose of Gd-EOB-DTPA used ($25 \mu\text{mol/kg}$) in contrast to conventional Gd-based extracellular contrast medium (0.1mmol/kg). In addition, since hepatocellular uptake of Gd-EOB-DTPA occurs shortly after Gd-EOB-DTPA administration [1], there is no "equilibrium phase" images on EOB-MR in its strict sense of the word, which precludes simple application of our previous diagnostic experience based on Gd-based extracellular contrast medium. Our results suggested SI on HBP images may help differentiate FNH from other liver nodules, particularly combining findings on other pulse sequences.

High signal intensity on HBP was suggested to be characteristic to FNH, which is concordant to the previous reports [1,6] (Fig.1). Although few, however, there were several non-FNH nodules that showed high signal intensity on HBP. High signal intensity of one hypovascular hepatocellular nodule may be attributable to high signal intensity on precontrast T1-weighted image, which are sometimes observed in dysplastic nodules or early HCC, due to copper or iron deposition [12-14] (Fig.2) or fatty metamorphosis [15]. Because EOB uptake have been reported to be almost constant regardless of the grade of HCC, if the precontrast signal intensity is high, that would be directly reflected on the SI on HBP [16]. The differentiation of this nodule from FNH was easy, because of its hypovascular nature as seen on the arterial phase of dynamic study. High SI of two hypervascular HCCs (group 2) on HBP may be attributable to its cellular function of Gd-EOB-DTPA uptake, typically

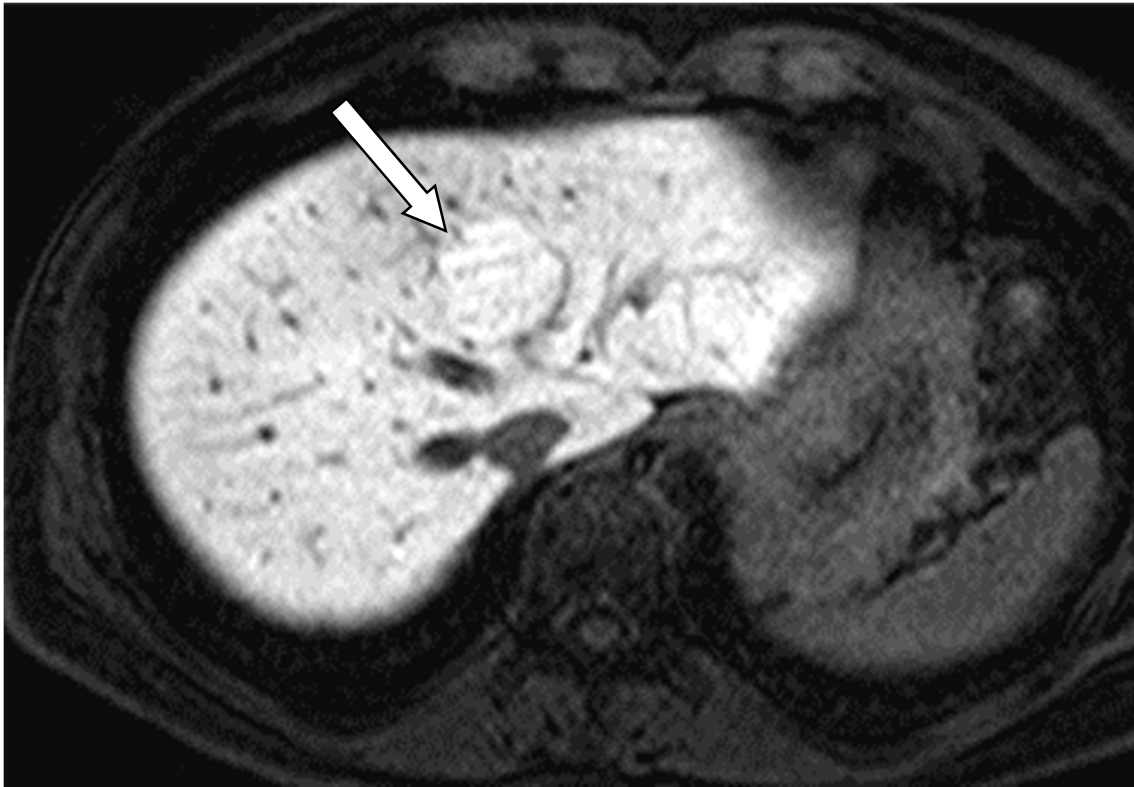
known as green hepatoma [17, 18]. One of these two was easily discriminated from FNH by the presence of fibrous capsule seen as hypointense rim on the arterial phase image or on HBP (Fig.3). The other one was associated with a typical nodule-in-nodule appearance [8], which also helped differentiate this from FNH (Fig.4).



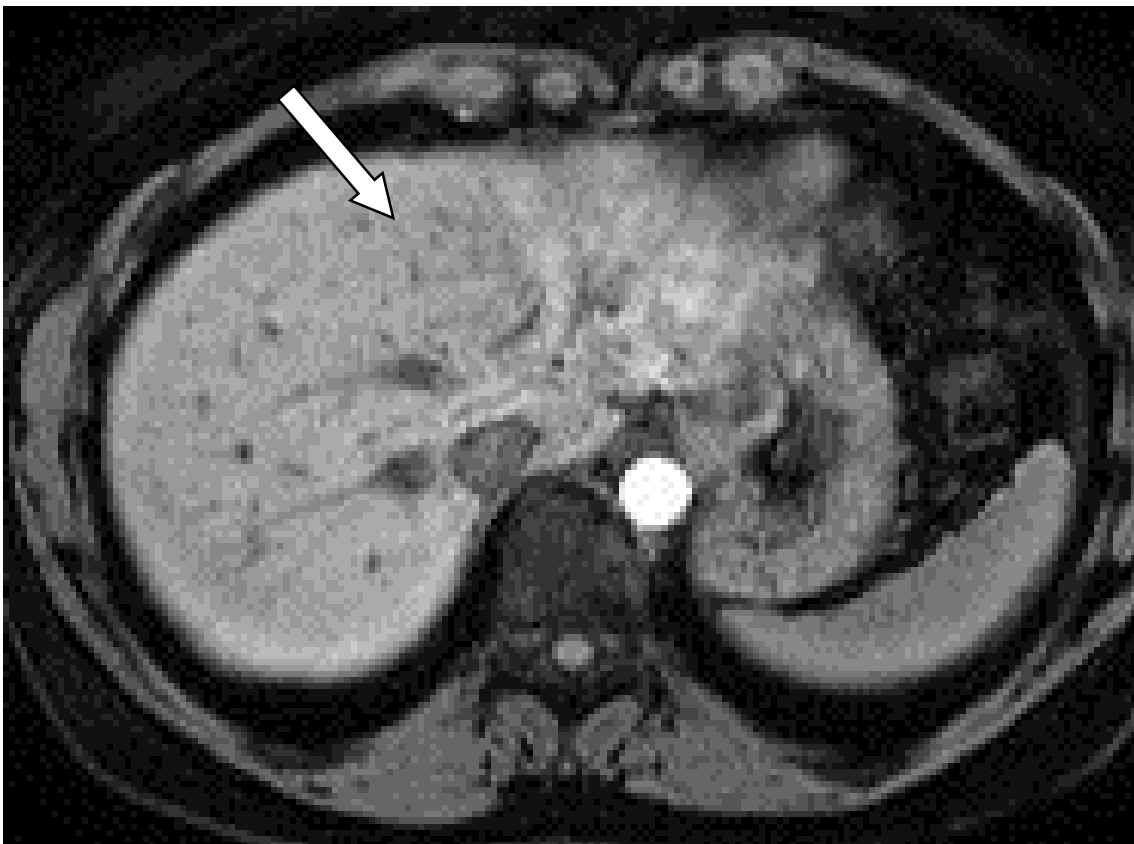
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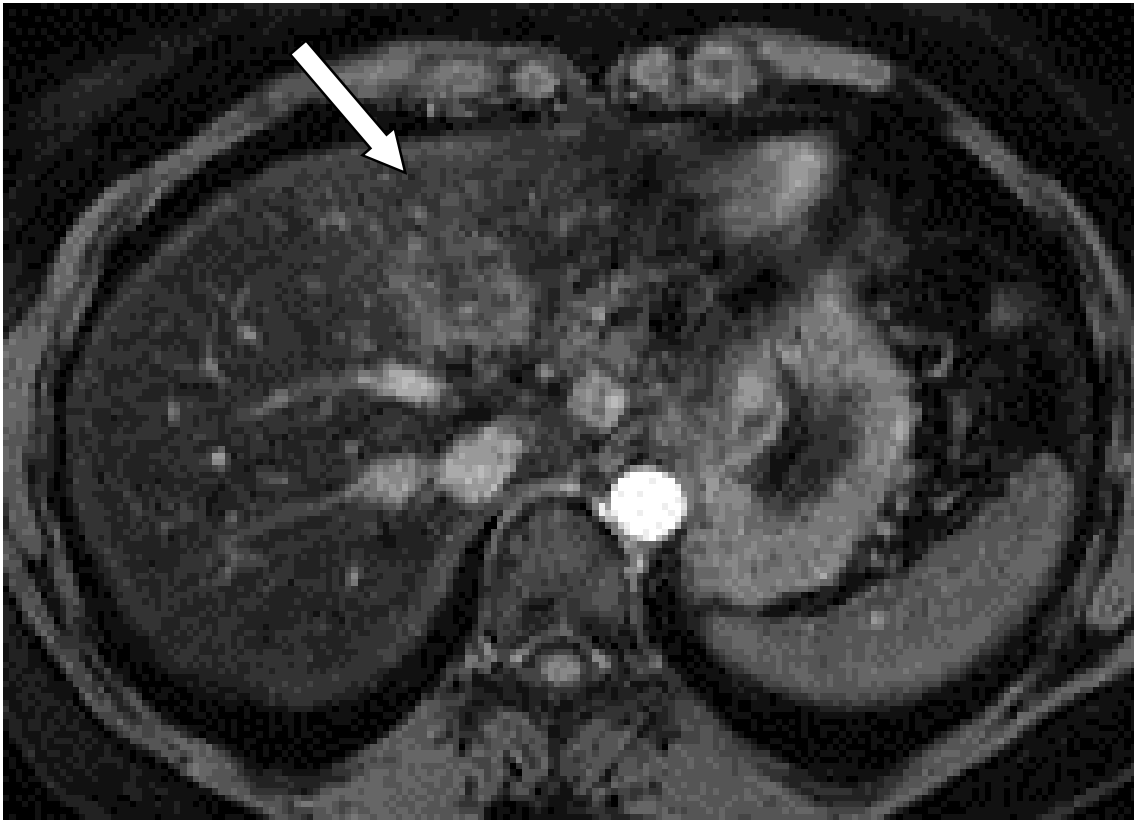
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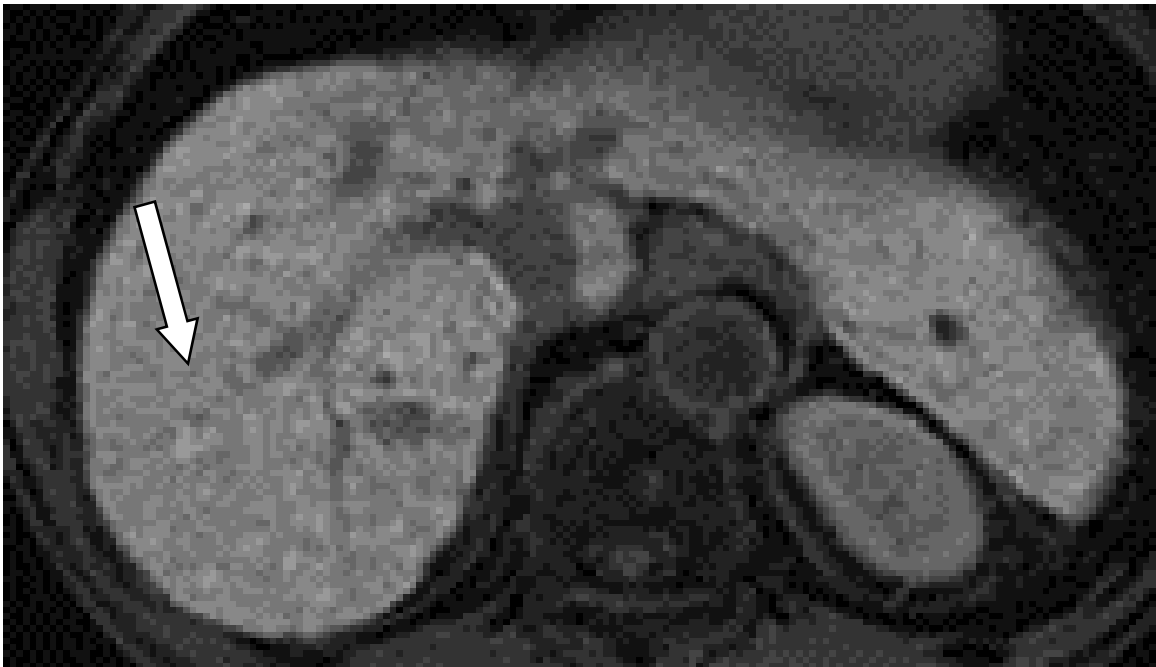
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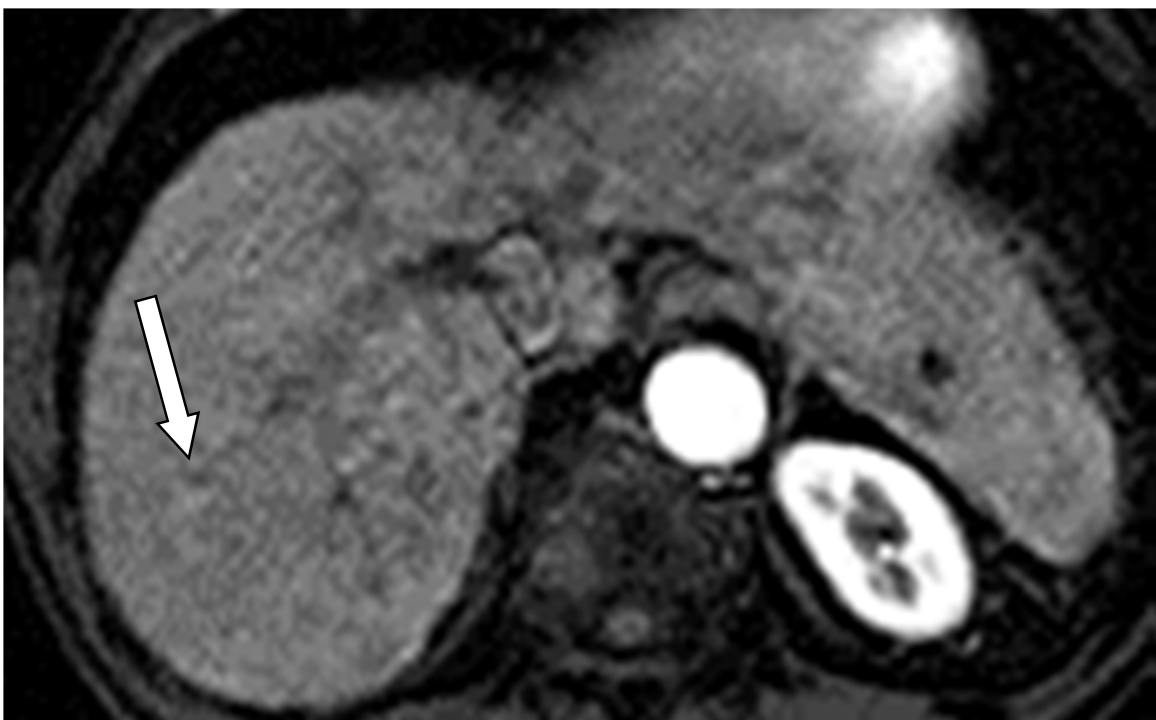
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Fig. 1. 43-year-old asymptomatic woman with minimal liver dysfunction. The mass in the left hepatic lobe has remained unchanged for over three years and clinical diagnosis of focal nodular hyperplasia (group 5) is made.

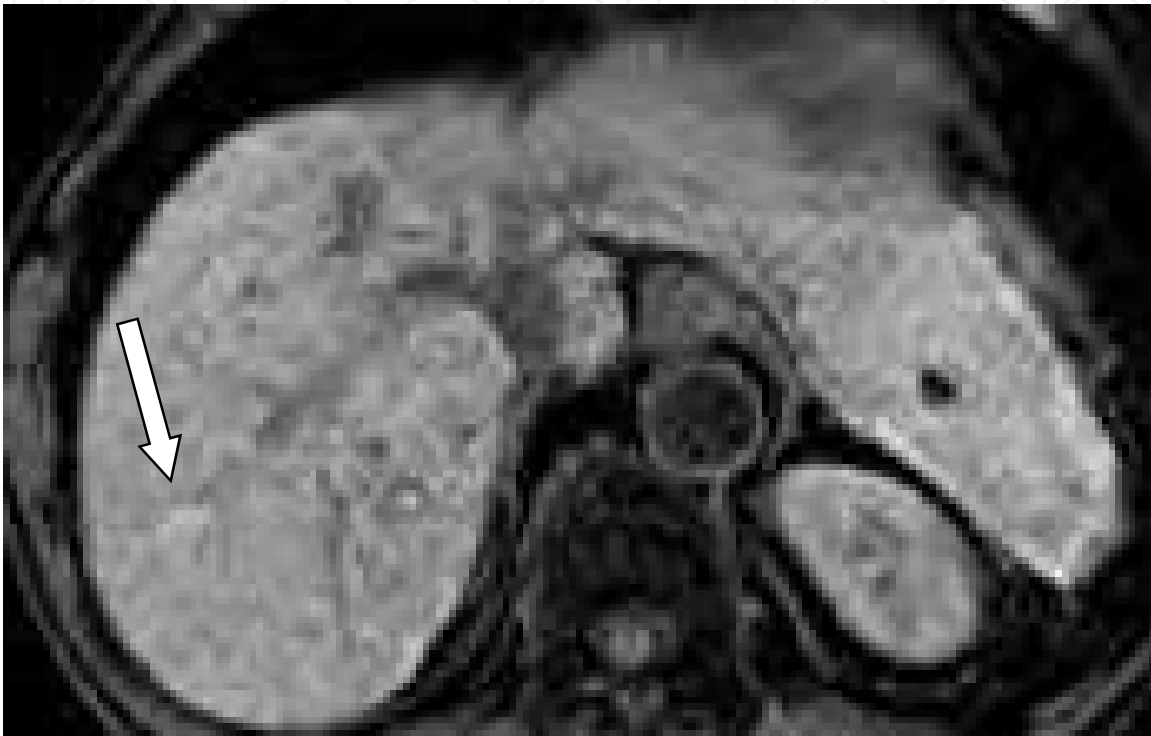
- A. Precontrast image of the dynamic study. The lesion exhibited similar or slightly lower signal intensity as compared to the surrounding liver tissue (arrow).
- B. Arterial phase image of the dynamic study of gadoxetate (EOB) enhanced MR. The lesion is strongly enhanced (arrow).
- C. Hepatobiliary phase image shows homogeneous uptake of EOB within the mass.
- D. Precontrast T2*weighted images (TR/ TE/ FA=266msec /9.2msec /30 degrees) revealed an almost isointense or slightly hypointense mass (arrow).
- E. T2* weighted images after administration of superparamagnetic iron oxide (SPIO). The signal intensity of the lesion is partially reduced (arrow) suggesting uptake of SPIO.



A.



B.

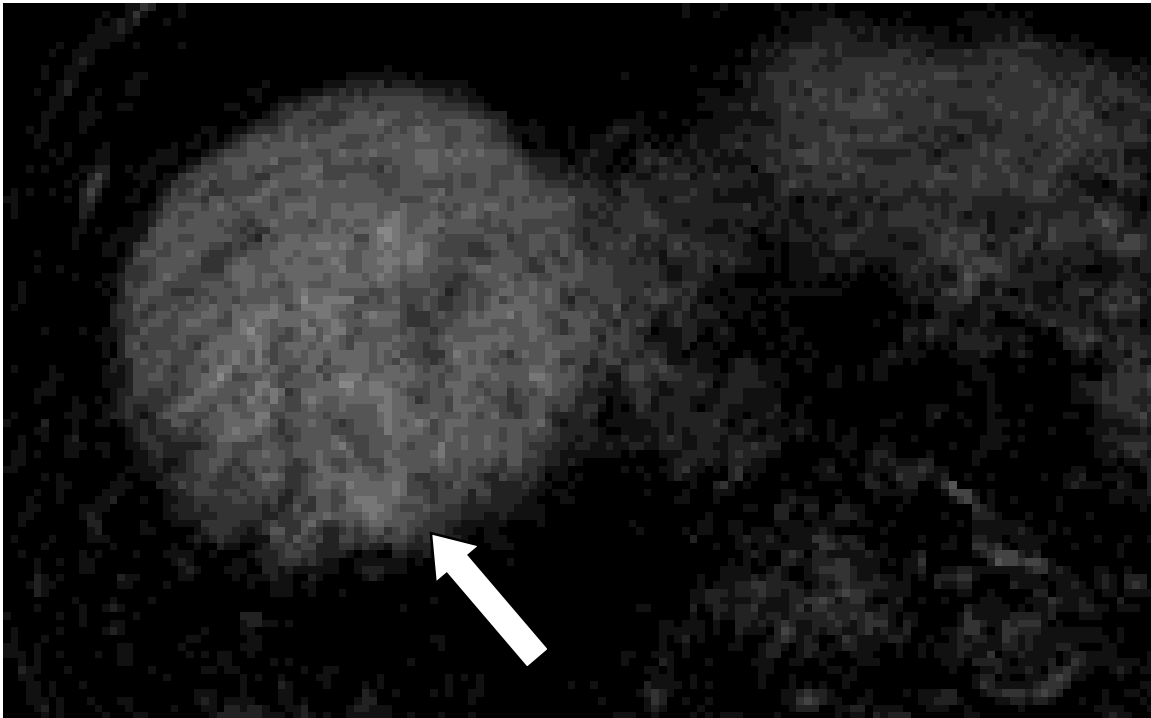


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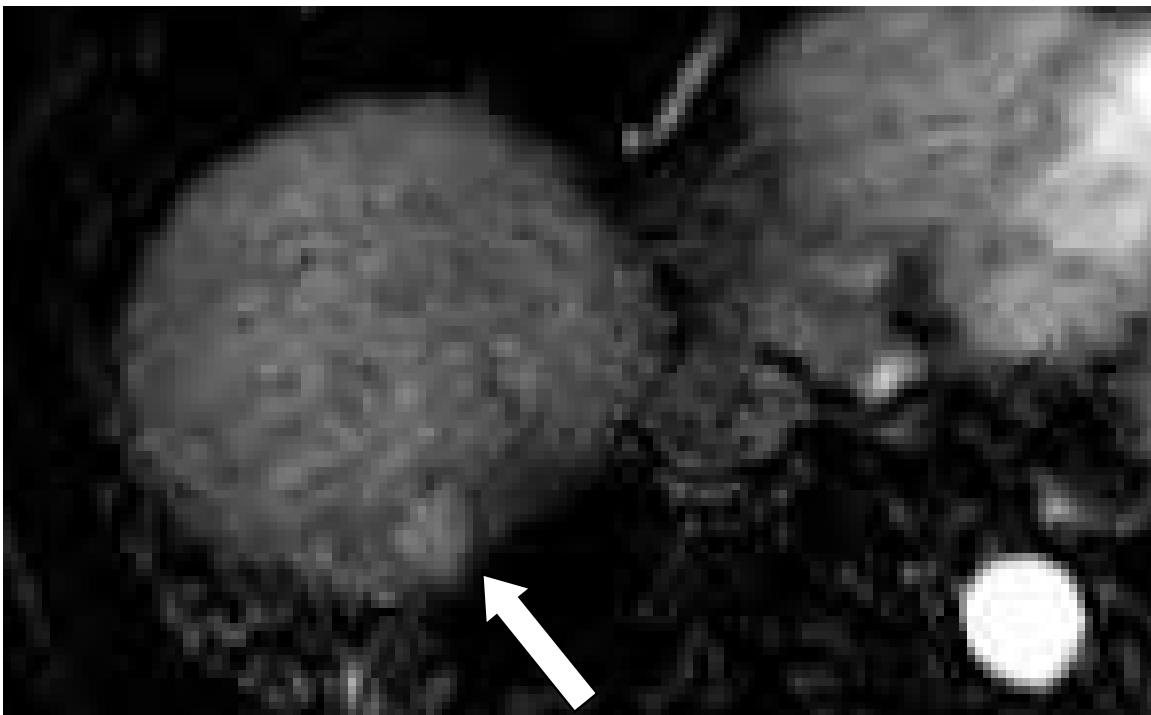
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Fig. 2. 58-year-old woman with a histology-proven early hepatocellular carcinoma (group 1) who had been followed up for chronic hepatitis C.

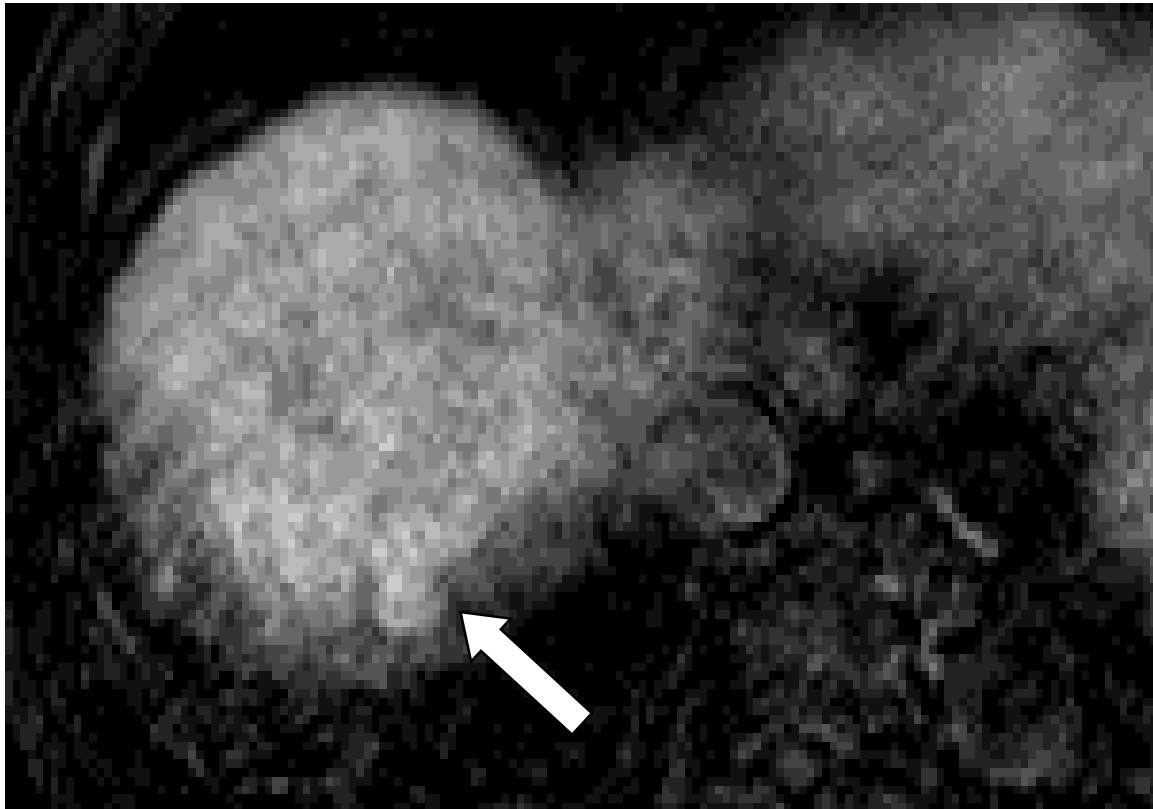
- A. Precontrast THRIVE image. A nodule with similar or slightly higher signal as compared to the surrounding liver tissue is seen (arrow).
- B. Arterial dominant phase THRIVE image after injection of Gd-EOB-DTPA. No significant enhancement is observed (arrow). MDCT obtained at the same period also fail to show arterial vascularity (not shown).
- C. Hepatobiliary phase image of THRIVE image. The nodule exhibit almost similar or slightly lower signal intensity as compared to the surrounding liver tissue (arrow) (I-L1).



A.



B.

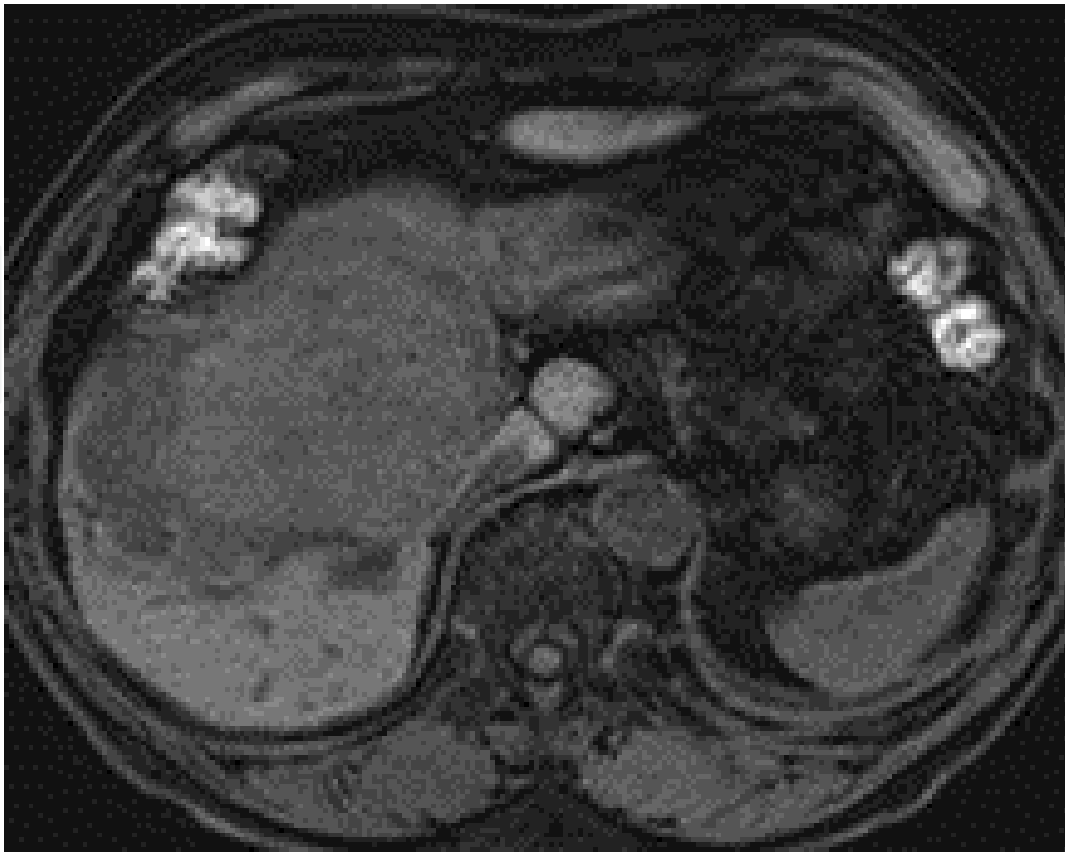


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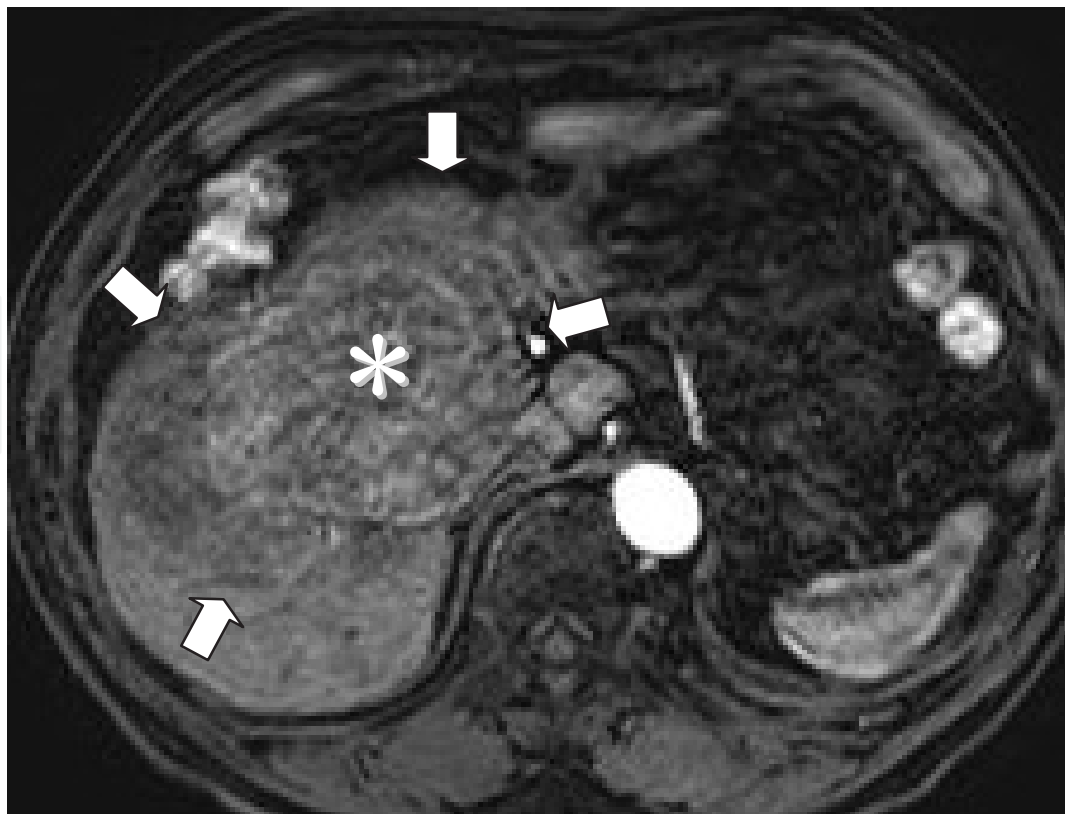
Fig. 3. 54-year-old man with a clinicoradiologically proven hypervascular hepatocellular carcinoma (group 2) which was treated with transarterial chemoembolization.

- A. Precontrast THRIVE image. A nodule with similar or slightly higher signal as compared to the surrounding liver tissue is seen (arrow).
- B. Arterial dominant phase THRIVE image after injection of Gd-EOB-DTPA. Significant enhancement is observed (arrow). MDCT obtained at the same period also showed arterial enhancement (not shown). Note hypointense fibrous capsule.
- C. Hepatobiliary phase image of THRIVE image. The nodule exhibit higher signal intensity than the surrounding liver tissue (arrow) (H). The fibrous capsule is partially seen.

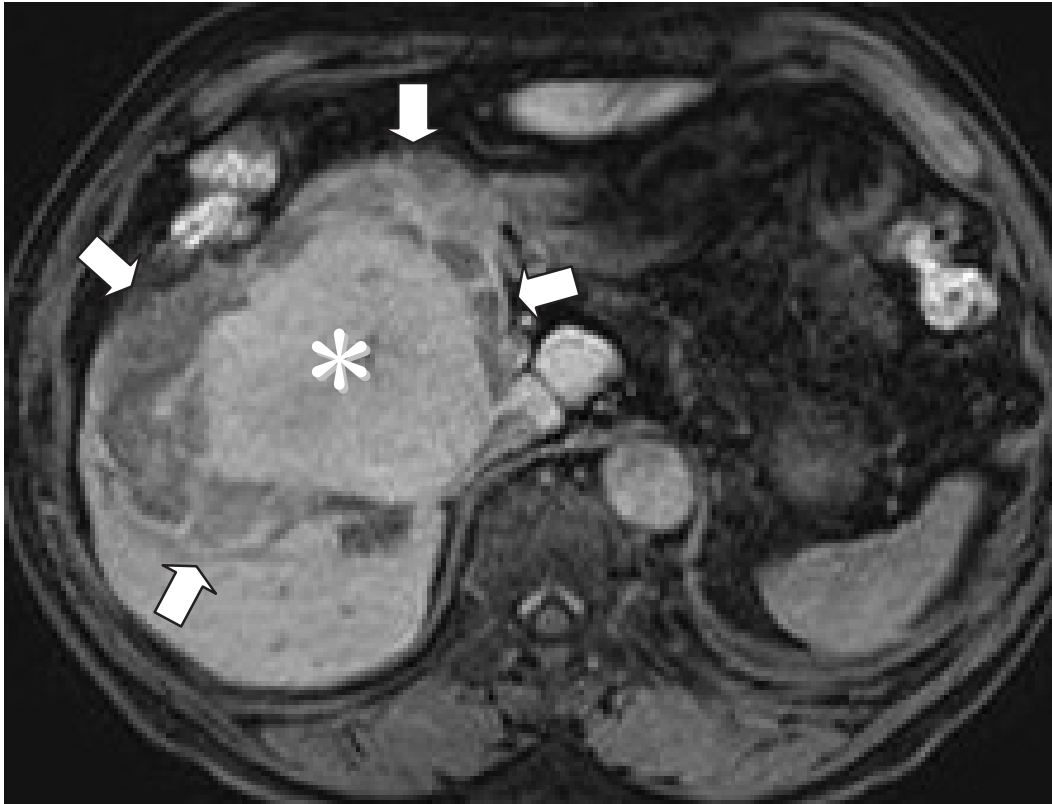
Thus, using combined all findings on EOB-MRI, we could achieve 100% sensitivity, 100% specificity, 100% positive predictive value, and 100% negative predictive value, in discriminating FNH from other lesions. Our results, however, suggest the difficulty in differentiation among other 4 categories using SI on HBP, namely hypovascular hepatocellular lesions, hyper vascular HCC, hemangiomas, and metastasis. For the differentiation among these entities, findings on other sequences, including dynamic phase images, T2-weighted images, diffusion-weighted images, and chemical shift images, may be important.



A.



B.



C.

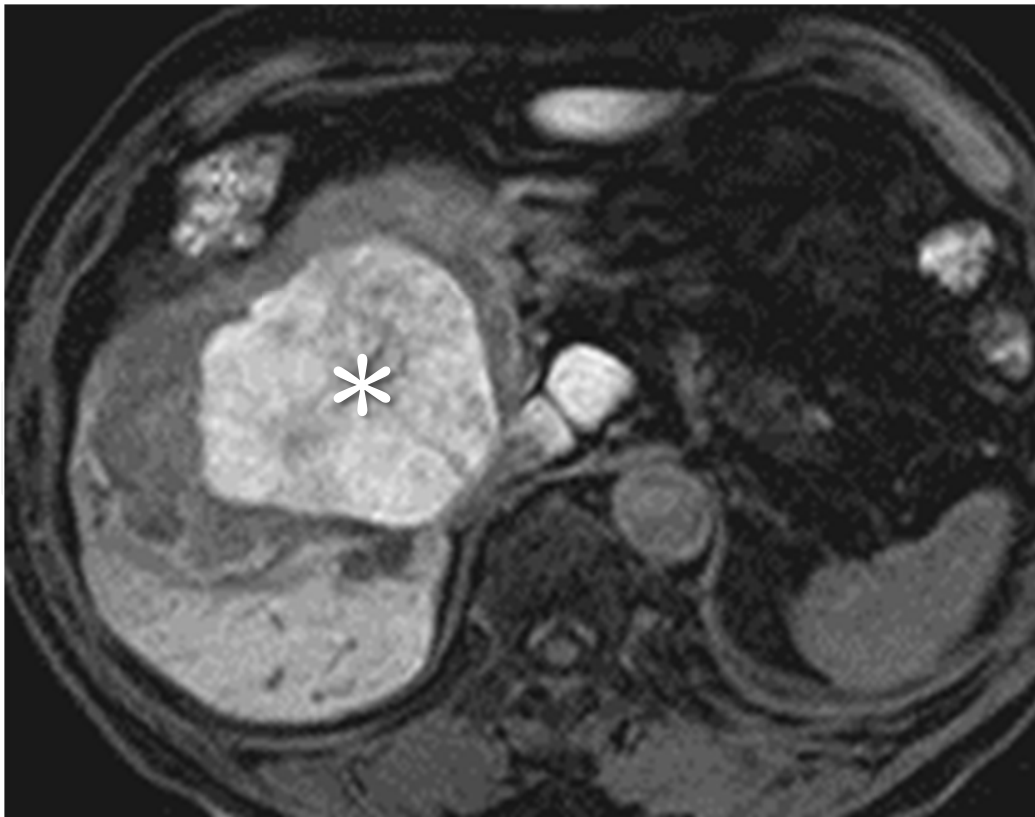


Fig. 4. 75-year-old man with a pathologically proven hypervascular hepatocellular carcinoma (group 2).

- A. Precontrast image. A large heterogeneous mass is seen in the right hepatic lobe.
- B. Arterial dominant phase image after injection of Gd-EOB-DTPA. Significant enhancement is observed in the central component of the mass (star), whereas peripheral components shows only faint enhancement (arrows).
- C. Late phase image of the dynamic phase. Each component of the mass shows various enhancement pattern, resulting in so-called nodule-in-nodule appearance (star and arrows).
- D. Hepatobiliary phase image. The predominant central part shows apparent high signal (star) (H).

There are several limitations in our study, in addition to its retrospective nature. First, the biggest limitation is the lack of pathological proof in the majority of the liver masses enrolled in this study. Particularly, lesions in groups 1 and 2 are considered quite heterogeneous: nodules in group 1 may include DN, eHCC, wHCC, and some RNs and mHCC; lesions in group 2 may include wHCC, mHCC, and pHCC. The results could have been different if only histology-proven lesions are recruited. Another limitation may be the adequacy of the use of signal intensity of IVC as a reference tissue to assess the relative signal intensity of the liver masses. Because of the possible flow effect, signal intensity of IVC could be inconsistent. We therefore measured SI of IVC in the first several patients and confirmed there are less than 10% signal difference in IVC between the slices except for the edge slices of the scanning slab. This may partly be attributable to the sufficient saturation pulse used in THRIVE sequence we used in this study. One needs to be careful of this issue, therefore, when other sequence is used for HBP images of EOB-MR, in which spatial saturation pulse is insufficient. Other reason for the usage of IVC as reference tissue is that it is almost always visualized in the images of the liver and therefore easy to be used for direct comparison. Ideally speaking, quantitative measurement of enhancement ratio of HBP image vs precotrast images would have been performed, but we preferred practical method to evaluate the HPB images which would help differentiate liver nodules in daily practice. Third, the time delay of 15 minutes for HBP imaging may be somewhat short as compared to the previous reports [1-6]. Because it has been reported that HBP persist from about 10 to 40 minutes after injection of Gd-EOB-DTPA [1,6], and our preliminary assessment revealed no significant difference in the lesion detection between 15 and 20 minutes delay images (unpublished data), we adopted 15 minutes delay for HBP in our institute for clinical demand in terms of patient through-put. It is still possible, however, that different results may be obtained if HBP images were obtained in 20 minutes or even later.

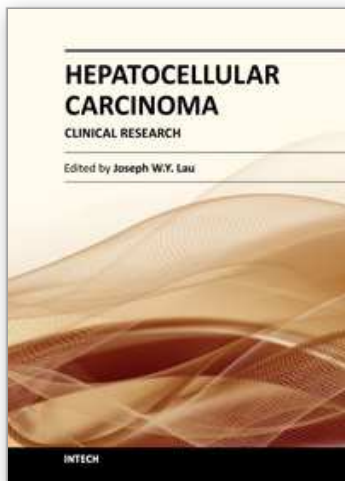
In conclusion, signal patterns on 15-minute-delay HBP images are different between FNH and other liver nodules, including hypovascular hepatocellular nodules, hypervascular HCC, hemangiomas, and metastases, and are useful in differentiating these nodules. Combining all EOB-MR findings, 100% sensitivity, specificity, positive and negative predictive values were achieved in differentiating FNH from non-FNH.

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