Serial MR Imaging of Small Arterially-Enhancing Liver Lesions in Patients with Chronic Liver Disease

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Objective: To determine the significance of small arterially-enhancing liver lesions seen with magnetic resonance imaging (MRI) in patients with chronic liver disease.

Material and Method: Our institutional review board approved this retrospective study, without requiring informed consent. Over a two-year period, 258 consecutive patients with cirrhosis or chronic hepatitis underwent multiphase three-dimensional, gadolinium-enhanced, breath-hold gradient-echo MRI. From this group, 29 patients underwent at least one follow-up MR study. When a small (≤ 20 mm) arterially-enhancing lesion was detected, the maximum diameter, shape, signal intensities (T1-weighted and T2-weighted), and pattern of enhancement were evaluated to assess the associations between the imaging appearance on initial MR exam and subsequent behavior on follow-up imaging. Statistical testing was performed with JMP Statistical Software (SAS, Inc., Cary, NC) and StatXact 7 Statistical Software for Exact Nonparmetric Inference (Cytel, Inc. Cambride, MA).

Results: Sixty-five small (≤ 20 mm) arterially-enhancing lesions were detected in 29 patients. Ten of 65 lesions (15%) in nine patients were subsequently proven to represent hepatocellular carcinoma (HCC), while the remaining lesions either disappeared (46) or remained stable in size (9). Of the 10 lesions subsequently proven to represent HCC, eight lesions converted from hypo- or isointense to hyperintense on subsequent T2-weighted MRI ($p < 0.001$), seven lesions converted from hyper- or isointense to hypointense on subsequent T1-weighted images ($p < 0.001$), seven lesions demonstrated growth on subsequent MRI exam (mean increase in mean diameter = 1.4 cm), and five lesions subsequently developed rim enhancement that was not initially present.

Conclusion: Small, arterially-enhancing lesions detected with MRI have a low likelihood of representing HCC, and MRI follow-up of such lesions is a reasonable approach. Lesions that increase in size, convert to hypointense on subsequent T1W images, convert to hyperintense in T2W images, or develop rim enhancement on follow-up MRI images are concerning and should prompt consideration of intervention.

Keywords: Carcinoma, hepatocellular, Chronic disease, Liver diseases, Magnetic resonance imaging

The most common primary malignant hepatic tumor is hepatocellular carcinoma (HCC), which occurs with increased frequency in patients with chronic hepatitis or cirrhosis[1]. Multiphase, gadolinium-enhanced, MR imaging has an important role in the detection and characterization of benign and malignant hepatic lesions in patients with chronic liver disease[2-5]. Small hepatocellular carcinomas (SHCCs) may manifest as enhancing lesions, during arterial-phase of imaging[6,7]. In cirrhotic patients, small, arterially-enhancing lesions are commonly detected with dynamic gadolinium-enhanced MRI, but not all

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such lesions are HCCs[8,9]. Biopsy of all small arterially-enhancing lesions detected in cirrhotic livers is neither feasible nor advisable. Therefore, such lesions are often followed with periodic imaging to assess interval change. The purpose of the present study was to determine in the studied population of patients with chronic liver disease the significance and natural history of small ($\leq$ 20 mm) arterially-enhancing liver lesions detected with sequential multiphase, gadolinium-enhanced, MRI with attention to distinguishing benign from malignant lesions.

Material and Method
Study population
The institutional review board approved this retrospective study, without requiring informed consent. Over a 2-year period, 258 consecutive patients with cirrhosis or chronic hepatitis underwent multiphase, gadolinium-enhanced liver MRI examination with a 3D, interpolated, gradient-echo technique. From this group, 29 patients were identified as having, a) at least one arterially-enhancing nodule of $\leq$ 20mm; b) one subsequent follow-up MR examination, (range of follow-up = 1-30 months; mean = 12.5 months; and c) a minimum of 18-months follow-up with CT or MRI for cases without histological proof. These 29 patients (21 men, 8 women; age range = 38-78 years; mean age = 54 years) underwent 96 MR examinations and comprised the study population. Sixteen patients had hepatitis C, two patients had hepatitis B, seven patients had alcoholic hepatitis, three patients had cryptogenic cirrhosis, and one patient had methotrexate induced hepatic fibrosis. Sixty-five lesions were seen on the initial MRI examinations. Seven patients (12 lesions) had one follow-up MR study (range of follow-up = 1-12 months; mean = 7 months). Twenty-two patients (53 lesions) had multiple follow-up MR examinations (eleven had two follow-up studies, eight had three follow-up studies, three had four follow-up studies each - range = 6-30 months; mean = 14.3 months). Ten lesions underwent needle biopsy (n = 9) or surgical resection (n = 1) due to increasing size or change in imaging appearance, and all 10 specimens revealed hepatocellular carcinoma.

MR imaging technique
MR imaging was performed on a 1.5 T system (Symphony; Siemens, Erlangen, Germany), using a four-element phased-array multicoil. All patients underwent unenhanced axial T1-weighted spoiled-gradient-echo (TR/TE 160/2.4, 4.8, flip angle 70°, section thickness 8mm; interslice gap 2.5 mm, matrix:128 x 256) and inversion-recovery T2-weighted (turboSTIR, TR/TE 4000/77, flip angle 150°, section thickness 8 mm, interslice gap 2.5 mm, matrix 165x256, inversion time 165 sec) imaging. Multiphase gadolinium-enhanced MR imaging was performed with a fat-suppressed volumetric interpolated-breath-hold sequence (VIBE, TR/TE 4.2/1.9, flip angle15°, matrix 256 x 127, 330-450-mm rectangular field of view, slab thickness 204-230 mm, effective slice thickness 3 mm). For gadolinium enhanced MRI, 0.1 mmol/kg body weight gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) or gadodiamine (Omniscan; Nycomed Amersham, Amersham, United Kingdom) was administered at a rate of 2 ml/s followed by a 20-ml flush of normal saline via an anticubital vein. Scans were acquired at 20, 45, and 90 seconds following contrast administration.

Image interpretation
Initial and subsequent follow-up MR studies were reviewed on a PACS workstation by two abdominal radiologists with additional MRI training for the presence of small ($\leq$ 20 mm) enhancing hepatic lesions on arterial-phase images. The arterial-phase images were characterized by hepatic-artery enhancement with heterogeneous splenic enhancement without significant liver parenchymal or hepatic-vein enhancement. The readers were blinded to pathology results, and imaging studies were viewed in temporal order. When a small, arterially-enhancing lesion was detected, the lesion size was measured in two dimensions with electronic calipers, and lesion shape (round, tubular, wedge-shaped, or irregular) of the lesion was recorded.

The signal intensities of arterially-enhancing lesions on T1-weighted gradient echo and T2-weighted images were recorded as hyperintense, isointense, or hypointense to the liver. Small enhancing lesions were considered to demonstrate delayed wash-out when they remained hyperintense relative to the liver on the portal phase images. Lesions that were isointense or hypointense on subsequent contrast-enhanced images were considered to demonstrate rapid wash-out.

Statistical analysis
For purposes of analysis, lesions that were not visible on subsequent imaging or that remained stable on imaging exams for at least 18 months were considered presumed benign (including lesions that initially showed minimal growth but which were

subsequently stable in size for at least 18 months). Presumed benign and HCC lesion-size data distributions were tested for (1) normality with Shapiro-Wilk W tests, equality of variances with O'Brien, Brown-Forsythe, Levene, and Bartlett tests, and statistically significant differences with a Wilcoxon rank sums test. Differences in location, shape, and second enhancements were tested with Fisher exact tests or chi-square tests. Differences in wash-out and T2- and T1-intensity differences between presumed benign lesions and HCCs were tested with Kruskal-Wallis tests for singly-ordered r x c tables. Differences between baseline and follow up T2- and T1-intensities for benign lesions and for HCCs were tested with McNemar tests, for 2 x 2 comparisons and for tables larger than 2 x 2, with marginal homogeneity tests for doubly-ordered r x c tables. Data permutation was used to calculate exact p-values for chi-square tests, Kruskal-Wallis tests for singly-ordered r x c tables, and marginal homogeneity tests for doubly-ordered r x c tables. Statistical testing was performed with JMP Statistical Software (SAS, Inc., Cary, NC) and StatXact 7 Statistical Software for Exact Nonparmetric Inference (Cytel, Inc. Cambride, MA).

Results

Initially, 65 arterially enhancing lesions $\leq$ 20 mm in maximum dimension were detected in 29

patients. The distribution of initial signal intensities for presumed benign lesions and hepatocellular carcinoma are presented in Table 1. There was no statistically significant difference between presumed benign lesions and HCC based on initial T1-weighted or T2-weighted signal intensity. Washout characteristics of the lesions also did not distinguish between presumed benign lesions and HCC. 78% of presumed benign and 70% of HCCs demonstrated immediate wash-out (p = 0.69)

Table 2 shows the distribution of lesions based on initial shape and Table 3 shows the distribution of lesions based on location on the initial MRI examination. The differences between presumed benign lesions and HCC did not reach statistical significance in either the case of shape (p = 0.22) or location (p = 0.74). Fig. 1 shows the size distribution of lesions at baseline separated into presumed benign lesions and HCC. None of the proven HCC lesions was less than 5 mm at baseline.

On follow-up examinations, 46 lesions were not visualized on subsequent MRI examinations (mean follow-up interval, 10 months). Of the 10 lesions subsequently proven to represent HCC, eight converted from hypo- or isointense to hyperintense on subsequent T2-weighted MRI (p < 0.001). Of the 10 lesions proven to represent HCC, seven lesions converted from hyper- or isointense to hypointense

Table 1. Initial signal intensity of 65 lesions in 29 patients with chronic liver disease

Signal intensity	T1-weighted		T2-weighted	
	Presumed benign	HCC	Presumed benign	HCC
Hypointense	1 (2)	2 (20)	6 (11)	2 (20)
Isointense	42 (76)	5 (50)	49 (89)	7 (70)
Hyperintense	12 (22)	3 (30)	0	1 (10)
Total	55 (100)	10 (100)	55 (100)	10 (100)

Numbers in parentheses are percentages

**Table 2.** Initial shape and location of 65 lesions in 29 patients with chronic liver disease

	Irregular	Round	Tubular	Wedge
Presumed benign	0	45	3	7
HCC	1	8	0	1

Differences were not statistically significant

Table 3. Initial location of 65 lesions in 29 patients with chronic liver disease

	Subcapsula	Parenchymal
Presumed benign	26	29
HCC	4	6

Differences were not statistically significant
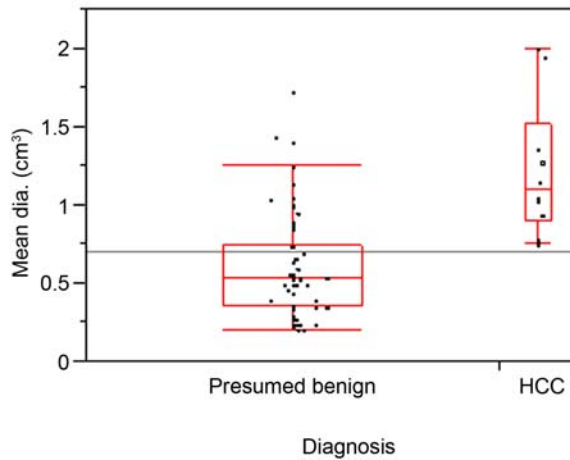
Fig. 1 Initial lesion sizes for HCCs and presumed benign lesions. To better illustrate the distribution of the data points; they are spread horizontally to minimize their overlapping one another. The ends of the boxes are the 25th and 75th quantiles (quartiles). The lines across the middles of the boxes are the medians. The interquartile range is the difference between the quartiles. The lines (whiskers) extend from the boxes to the outermost points that fall within the distance computed as 1.5 (interquartile range)

on subsequent follow-up T1-weighted images (p < 0.001) (Table 4). Seven proven HCCs demonstrated growth on subsequent MRI exam (mean increase in mean diameter = 1.4 cm), and five subsequently developed rim enhancement that was not initially present (Fig. 2, 3, Tables 4, 5). Nine lesions demonstrated stability in size over the course of at least 18 months and did not change imaging appearance with the exception of one lesion that converted from isointense to hypointense on T2-weighted images (Fig. 4).

Discussion

Although MR imaging has been reported to be relatively insensitive for the diagnosis of small hepatocellular carcinoma (< 20 mm) in the setting of chronic liver disease[5,10-13], it appears to have better potential than other imaging techniques for early diagnosis[14-16]. Currently, breath-hold multiphase gadolinium-enhanced MR imaging using three-dimensional interpolated techniques has been shown to be the most sensitive method for detecting small enhancing tumors[12,17-19]. Classically, HCC manifests on MR images as a mass demonstrating increased signal intensity on T2-weigthed images, decreased signal intensity on T1-weighted images, and arterial

phase enhancement that subsequently "washes out" on portal phase images[14-16,20]. As MRI techniques become more sensitive for the detection of HCC, the rate of detection of lesions other than HCC has also increased. In particular, small arterially enhancing lesions are particularly common in patients with chronic liver disease who are also at risk for HCC, although only a minority of these lesions are subsequently shown to represent HCC[8,9,21-24]. Distinguishing between HCC and benign hypervascular lesions remains a major challenge in management of patients at risk for developing hepatocellular carcinoma.

Several investigators have reported that HCCs can be distinguished from small benign hypervascular lesions based on high signal intensity on T2W images, coronal enhancement surrounding the lesion on dynamic MRI, the presence of delayed hypointensity of small arterially-enhancing lesion, and rapid central wash-out after early enhancement with contrast CT[21,25-27]. However, many small HCCs (< 1.5 cm.) have no specific imaging features, exhibiting variable signal intensity on unenhanced T1- and T2-weighted images[8,20,28].

The present study confirms that the majority of small hypervascular lesions detected with multiphase gadolinium-enhanced MRI are likely benign[8,9,22,29]. In the present study, 85% (55/65) of small arterially enhancing lesions either disappeared on subsequent imaging studies using similar technique or remained

Table 4. Change in imaging appearance over time of 65 lesions in 29 patients with chronic liver disease

	Presumed benign	HCC
Converted to hyperintense on T2-weighted images	0/55	8/10
Converted to hypointense on T1-weighted images	0/55	7/10
Developed rim enhancement	0/55	5/10

Table 5. Initial, follow-up, and change in sizes for HCCs

	n	Median (range)
Initial size (cc)	10	1.1 (0.8-2.0)
Follow-up time (days)	10	183 (32.0-453.0)
Follow-up size (cc)	10	2.1 (1.0-4.2)
Change in size (cc)	10	0.6 (0.0-3.4)
Percent change in size	10	58.4 (0.0-345.7)
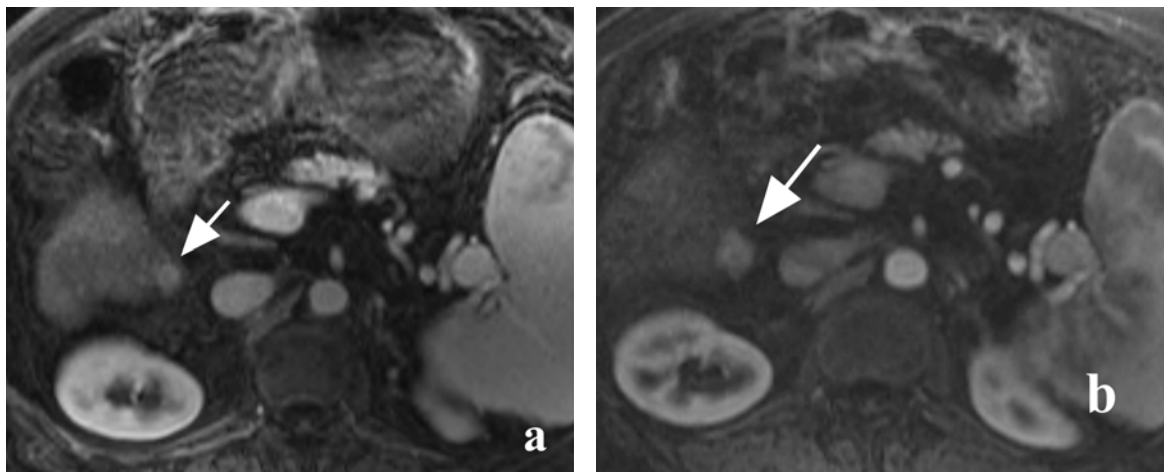
Fig. 2 MR images of a growing enhancing lesion in 62-year-old women with cirrhosis subsequently proven to be HCC: (a) Baseline lesion (arrow) showed small arterially-enhancing lesion, (b) Six-month follow-up of lesion (arrow) showed only increased size, indicating growing of tumor
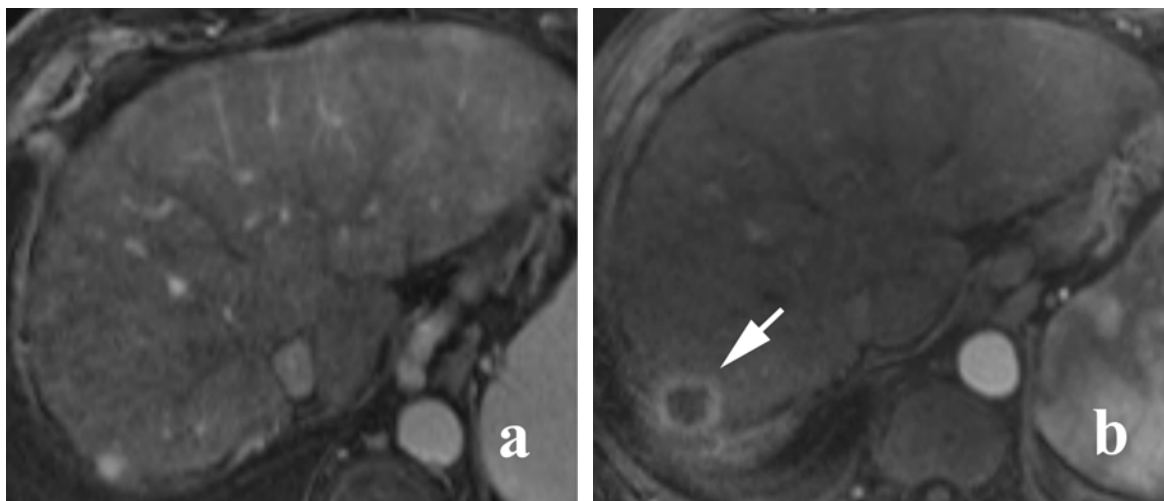

Fig. 3 MR images of a small early enhancing hepatic lesion that increased in size and also developed rim enhancment by the 6-month follow up in a 61-year-old man with cirrhosis: (a) Arterial-phase contrast-enhanced dynamic VIBE image (4.2/1.9) obtained at the initial MR examination shows a round early enhancing lesion (arrow) in the right posterior segment of the liver, (b) Arterial-phase contrast-enhanced dynamic VIBE MR image (4.2/1.9) obtained 6 months later shows that the lesion (arrow) has increased in size and became a rim enhancement, which is highly suggestive of HCC

stable for at least 18 months. In the presented population, lesion shape, location, and initial signal intensity were not reliable indicators of malignancy.

Because signal intensity characteristics on a single examination alone cannot reliably distinguish between benign and malignant arterially enhancing lesions, another method of distinguishing malignant lesions is needed. Biopsy of all small arterially enhancing lesions detected with MRI in the setting of chronic liver disease would be extremely difficult, if not impossible, and likely to be of low yield. It is possible that alternate techniques such as diffusion-weighted imaging will improve the specificity of MRI for distinguishing between benign and malignant
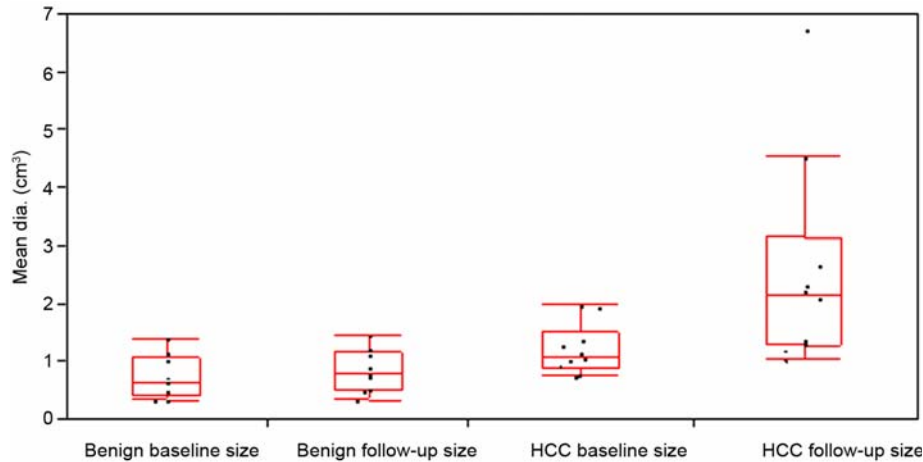
Fig. 4 Lesion sizes for 10 HCCs and 9 benign lesions at baseline and follow up. To better illustrate the distribution of the data points; they are spread horizontally to minimize their overlapping one another. The ends of the boxes are the 25th and 75th quantiles (quartiles). The lines across the middles of the boxes are the medians. The interquartile range is the difference between the quartiles. The lines (whiskers) extend from the boxes to the outermost points that fall within the distance computed as 1.5 (interquartile range)

arterially enhancing lesions, but published data are lacking. As a result, repeat imaging with MRI seems a reasonable alternative[30]. None of the arterially enhancing lesions encountered in the present study that subsequently were shown to represent HCC progressed to unresectable disease or disease that would have precluded liver transplantation[30].

The present results suggest that lesions developing certain imaging features on follow-up MRI have a high likelihood of representing HCC. These features include interval growth or development of ring enhancement. The present results agree with those of Jeong et al. who demonstrated that interval growth is a useful indicator for diagnosis of small HCCs[8]. Lesions that develop new hyperintensity on T2-weighted images or hypointensity on T1-weighted images relative to background liver are also of concern.

The present study has some limitations. Presumed benign lesions in the present study were not proved by histology. In addition, multiple lesions per patient were included in the present analysis. For purposes of statistical analysis, including one lesion per patient would have been ideal, although such a situation does not reflect clinical practice.

In conclusion, the present study provides further evidence to suggest that small arterially-enhancing lesions encountered in the liver of patients with chronic liver disease on dynamic gadolinium-enhanced MRI images can be safely followed. The

majority of such lesions will either not be visible on subsequent exams performed with similar technique or will remain stable. Features that should prompt consideration of biopsy or other intervention include interval growth, development of ring enhancement, conversion from hyper- or isointense to hypointense on T1-weighted images, or conversion from hypo- or isointense to hyperintense on T2-weighted images.

Acknowledgments

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ลักษณะรอยโรคขนาดเล็ก (≤ 20 mm) ที่มีการติดสีเพิ่มขึ้นในภาพMRIของผู้ป่วยโรคตับ

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วัตถุประสงค์: เพื่อศึกษาความสำคัญของลักษณะรอยโรคขนาดเล็ก (≤ 20 มิลลิเมตร) ของผู้ป่วยโรคตับที่มีการติดสีเพิ่มขึ้นในภาพ MRI

วัสดุและวิธีการ: เก็บข้อมูลภาพลักษณะรอยโรค ที่มีการติดสีเพิ่มขึ้น ในผู้ป่วยโรคตับ 258 คน เพื่อเปรียบเทียบลักษณะรอยโรคที่มีภาพการเปลี่ยนแปลง ในเวลาต่อมา

ผลการศึกษา: จากการศึกษาพบว่า มี 65 รอยโรคที่มีการติดสีเพิ่มขึ้น, 10 รอยโรคเป็นมะเร็งตับ ที่เหลือนั้นไม่มีการเปลี่ยนแปลง หรือ ตรวจไม่พบรอยโรคในการตรวจ MRI ถัดไป สำหรับรอยโรคที่เป็นมะเร็งตับ พบว่า อาจมีการเปลี่ยนแปลงเป็นสี ขนาด หรือ ลักษณะการติดสีจากภาพการตรวจในเวลาต่อมา

สรุป: ลักษณะรอยโรคขนาดเล็กจากภาพ MRI ที่มีการติดสีเพิ่มขึ้นในผู้ป่วยโรคตับ โดยส่วนใหญ่ไม่ใช่มะเร็งตับ