Prognosis of small hepatocellular nodules detected at only hepatobiliary phase of Gd-EOB-DTPA enhanced MR imaging as hypointensity in cirrhosis or chronic hepatitis

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ABSTRACT

Purpose

To evaluate the prognosis of "strict" high-risk nodules (small hepatocellular nodules detected in only hepatobiliary phase of initial Gd-EOB-DTPA enhanced MR examination) in patients with cirrhosis or chronic hepatitis.

Methods and Materials

Thirty-three patients with 60 "strict" high-risk nodules which showed hypointensity at hepatobiliary phase but could not be detected at vascular phase and other conventional sequences of initial Gd-EOB-DTPA enhanced MR imaging were included. These nodules were observed on the follow-up MR examinations until hypervascular nature was detected in the nodules. The several potential predictive factors for hypervascular transformation were compared between two groups (group A showing hypervascular transformation, and group B not showing hypervascularization).

Results

Ten (16.7%) of 60 "strict" high-risk nodules showed hypervascular transformation during follow-up periods (group A). The growth rate of the nodules in group A (6.3±4.5 mm/year) was significantly higher than that in group B (3.4±7.2 mm/year) (p=0.003). Additionally, the median observation period in group A (177.5±189.5 day) was significantly shorter than that in group B (419±372.2 day) (p=0.045). The other predictive factors were not significantly correlated with hypervascularization.

CONCLUSION

Subsets of "strict" high-risk nodules showed hypervascular transformation during follow-up periods in association with increased growth rate as an important predictive factor.

Key words: magnetic resonance imaging; gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA); hepatocellular carcinoma.

Key points:

・ “Strict” high-risk nodules are defined as hepatocellular nodules detected in only hepatobiliary-phase.

・ Subsets of “strict” high-risk nodules showed hypervascular transformation during follow-up periods.

・ Increased growth rate is an important predictive factor for hypervascular transformation.

・ Management of patients with “strict” high-risk nodules becomes more appropriate.

INTRODUCTION

With the widespread use of Gd-EOB-DTPA-enhanced MR imaging, hepatocellular nodules that showed hypovascularity in the arterial phase and hypointensity in the hepatobiliary phase are increasingly detected in patients with chronic viral hepatitis and/or cirrhosis [1-4]. These nodules could be dysplastic nodules representing borderline lesions or early HCCs [5, 6], but precise differentiation between these two entities without hypervascularity is often difficult. Hence, one study recently proposed the concept of "high-risk nodules" lumping these hypovascular and hypointense nodules, probably including early HCCs and dysplastic nodules, that could have a malignant potential at Gd-EOB-DTPA-enhanced MR imaging, and demonstrated that the presence of intranodular fat was a predictive factor associated with hypervascularization in these "high-risk nodules" during a follow-up MR examinations [7]. The early prediction of hypervascular transformation is clinically important since the detection of arterial hypervascularization can justify treating the nodule as HCCs [8, 9]. Some other studies have also evaluated the evolution or outcome of "high-risk nodules" on Gd-EOB-DTPA-enhanced MR imaging, and suggested that high-risk nodules containing fat or those that were hyperintense on T2-weighted or diffusion-weighted (DW) images were at high risk for development of hypervascularization as the critical change suggesting malignant transformation [10-12]. However, in a sense, these results may be a natural consequence because fatty change of tumor cells as well as hyperintensity on T2-weighted and DW images have been reported to be the characteristic histopathological findings suggestive of HCCs [13-15]. Meanwhile, there are many high-risk nodules which did not have these predictive findings such as fatty metamorphosis or hyperintensity on T2-weighted and DW images,

and it remains unclear whether these high-risk nodules have a nature of hypervascular transformation, whether these high-risk nodules have other predictive findings associated with subsequent hypervascularization or how frequently these high-risk nodules develop to hypervascular HCCs. However, there have been no previous reports evaluating the prognosis of high-risk nodules which were not demonstrated in any other MR images including T1, T2, and diffusion-weighted MR images. We referred to these nodules (hypovascular and hypointense at hepatobiliary phase but not detected at any other MR images) as "strict" high-risk nodules, and investigated the incidence and the predictive factors for hypervascular transformation in "strict" high-risk nodules to evaluate the prognosis of these nodules during follow-up Gd-EOB-DTPA-enhanced MR examinations in patients with cirrhosis or chronic hepatitis.

MATERIALS AND METHODS

Subjects

This retrospective study had institutional review board approval, and the requirement for patient informed consent was waived. A search of our institutional database between January 2008 and January 2012 identified 139 consecutive patients with chronic liver diseases who underwent Gd-EOB-DTPA-enhanced MR imaging more than twice. Among these, patients with "strict" high-risk nodules were selected for this study. "Strict" high-risk nodules were defined as hepatocellular nodules which showed hypovasularity at arterial phase and hypointensity at hepatobiliary phase, but could not be detected at any other MR images including T1, T2, and diffusion-weighted MR sequences. Nodules were excluded if they were depicted in at least one sequence except hepatobiliary phase or if they had non-round configuration suspicious for

pseudolesions. Hepatic cysts and hemangiomas were readily excluded by reviewing T2- and heavily T2-weighted MR images. Finally, a total of 60 "strict" high-risk nodules were identified in 33 patients (21 males and 12 females; mean age, 71 years; range, 53-88 years) in this study. Seventeen patients had one solitary lesion, 9 patients had two lesions, 4 patients had three lesions, 2 patients had four lesions, and 1 patient had five lesions. The presumed causes of chronic liver disease were B viral hepatitis (n=4), C viral hepatitis (n=21), alcohol-induced hepatitis (n=5), nonalcoholic steatohepatitis (n=1), and hepatitis of unknown etiology (n=2). In these 33 patients, 30 patients had liver cirrhosis (Child A=25, Child B=5, Child C=0). The remaining three patients had chronic hepatitis. Liver cirrhosis was confirmed by histological examinations in 8 patients. In the remaining 22 patients, liver cirrhosis was diagnosed on the basis of clinical findings, namely, a combination of physical findings (jaundice, splenomegaly, or ascites), routine biochemical and hematologic blood tests (a decreased platelet count, an increased ratio of aspartate to alanine aminotransferase, or a prolonged prothrombin time), and radiologic imaging features (characteristic morphologic changes of the liver and nodular liver surfaces). Each nodule was followed up until the arterial enhancement was detected in the nodules or until the final MR examination of the study period between January 2008 and January 2012.

MR imaging

All MR examinations were performed with a 1.5-T clinical MR unit (Signa Excite High speed, General Electric, Milwaukee, WI or EXCELART Vantage Powered by Atlas, Toshiba Medical Systems, Tochigi, Japan) using a phased-array body coil.

Imaging was performed in the transverse plane under the fasting condition. MR imaging protocols consisted of in-phase and opposed-phase T1-weighted, breath-hold fat-suppressed fast spin-echo (FSE) T2-weighted, fat-suppressed single shot FSE heavily T2-weighted, and breath-hold single-shot fat-suppressed echo-planar DW (b values=0 and 800 sec/mm^2) sequences, and dynamic contrast-enhanced (DCE)-MR imaging. For DCE-MR imaging, three-dimensional fat-suppressed T1-weighted GRE images (liver acquisition with volume acceleration (LAVA), General Electric or Quick 3D, Toshiba) were obtained before and after the administration of 0.025 mmol/kg of body weight of Gd-EOB-DTPA (Primovist, Bayer HealthCare, Osaka, Japan) with a power injector as a rapid bolus at the rate of 1-3 mL/sec, followed by a 30-mL saline flush at the same rate. The imaging parameters for DCE-MR imaging were as follows: TR/TE, 4.7-4.9/1.9-2.2 msec; flip angle, 12° or 15°; bandwidth, 62.5 kHz; parallel imaging factor, 2; FOV, 35 × 35 cm; slice thickness, 2.2-3.0 mm; matrix, 288-320 × 192; and the acquisition time, 19-20 seconds. Arterial-phase imaging was performed at 25 seconds or with modified scan timing using a fluoroscopic triggering (Fluoro Trigger, General Electric or Visual Prep, Toshiba) or an automated bolus detection algorithm (SmartPrep, General Electric). Portal phase and late phase images were obtained after an imaging delay of 70 seconds and 3 minutes, respectively. The hepatobiliary phase images were obtained at 20 minutes after contrast-material injection.

Image Analysis

Two radiologists (20 years and 9 years of experience in abdominal MR imaging) randomly reviewed MR images. They were blinded to any clinical information, clinical MRI interpretations and the final diagnosis to avoid bias. Disagreements in opinions and

measurements were resolved by consensus. All images were evaluated by using a picture archiving and communication system (PACS) workstation monitor (Rapideye Core; Toshiba Medical Systems, Tochigi, Japan), with an adjustment of the optimal window setting in each case. A total of 60 "strict" high-risk nodules were reviewed to evaluate the incidence and the predictive factors for hypervascular transformation during the follow-up Gd-EOB-DTPA-enhanced MR examinations. When arterial enhancement was observed within the nodule during serial MR examinations, the investigation was completed. The following two categories were assessed as potential predictive factors for hypervascular transformation; a) initial MR findings and clinical variables of "strict" high-risk nodules and b) serial changes in MR findings of "strict" high-risk nodules during follow-up MR examinations. The parameters investigated as initial MR findings and clinical variables included the presence of cirrhosis, Child-Pugh classification, initial size of nodules, the presence of multiple high-risk nodules in the liver, the presence of a previous treatment history for HCC (interventional or surgical), and coexistence of hypervascular HCC. Clinical data were obtained by means of review of all available medical records. Additionally, as the serial changes in MR findings of "strict" high-risk nodules during follow-up MR examinations as predictive factors for hypervascular transformation, the growth rate and the observation period were also assessed. The size of a "strict" high-risk nodule was measured as the longest nodule diameter on the hepatobiliary phase images. The growth rate of the nodules was determined by measuring the initial and the most recent size of "strict" high-risk nodules, and then the annual increment of the nodule’s size (mm/year) was calculated. These factors were then compared between two groups (group A showing hypervascular

transformation, and group B not showing hypervascularization) to determine the predictive factors for hypervascular transformation.

Statistical analysis

Statistical analyses were performed using SPSS (version 19.0 for Windows, SPSS, Chicago, IL) software. The MR findings and clinical variables were compared between the two groups using the Mann-Whitney U-test or the Fisher's exact test. Growth rate and initial size of nodules and observation period were assessed using the Mann-Whitney U-test. The presence of a previous treatment history for HCC (interventional or surgical), and the severity of cirrhosis (Child-Pugh classification) and the presence of cirrhosis, hypervascular HCC, and multiple high-risk nodules in the liver were assessed using Fisher's exact test. Multivariate analysis conducted to evaluate the set of factors independently associated with hypervascular transformation among the initial MR findings and clinical variables of "strict" high-risk nodules by using a Cox proportional hazards model developed based on a stepwise algorithm, using a $P<0.10$ criterion for each variable to be added to the model and a $P<0.05$ criterion for the variable to be kept in the model after subsequent variables were added. All tests were two-sided, and P value of less than .05 was considered to indicate statistically significant difference.

RESULTS

The median observation period of 60 "strict" high-risk nodules was 372.5±356.1 days (range, 47 to 1366 days). The average number of MR examinations was 3.7±2.1 times (range, 2 to 10 times). The median interval between follow-up MR

examinations was 124.0±137.1 days. The range of follow-up intervals was 44 to 770 days, based on clinical decision by our hepatologists. Sixty "strict" high-risk nodules were categorized into two groups according to the development of hypervascular nature during follow-up MR examinations. Hypervascular transformation was observed in 10 of 60 "strict" high-risk nodules (16.7%) during follow-up studies (group A) while 50 of 60 "strict" high-risk nodules (83.3%) did not show arterial hypervascularization at the final MR examination (group B). The cumulative rates of strict high-risk nodules that showed hypervascularization at 1, 2 and 3 years were 14%, 26%, and 26%, respectively. Table 1 summarized the relationships between possible predictive factors and hypervascularization on univariate analysis. In the serial changes in MR findings of "strict" high-risk nodules during follow-up MR examinations, the growth rate of nodule in group A (6.3±4.5 mm/year) was significantly higher than that in group B (3.4±7.2 mm/year) (p=0.003), indicating that a higher growth rate of nodule was a positive predictive factor for hypervascular transformation. Additionally, the median observation period in group A (177.5±189.5 day) was significantly shorter than that in group B (419.5±372.2 day) (p=0.039). In 7 (70%) of 10 "strict" high-risk nodules in group A, hypervascular transformation was developed within 6 months with a mean growth rate of nodules of 8.0±4.3 mm/year. Regarding the initial MR findings and clinical variables of "strict" high-risk nodules, there was not the significant correlation between hypervascularization and all predictive factors such as, the presence of cirrhosis, Child-Pugh classification (limited to class A and B cirrhosis), initial size of nodules, the presence of multiple high-risk nodules, the presence of a previous treatment history for HCC, and coexistence of hypervascular HCC as the results of both univariate analysis and the multivariate analysis.

DISCUSSION

In this study, we defined hepatocellular nodules which showed hypovascularity and hypointensity at hepatobiliary phase and were not detected at any other MR images (including T1, T2, and diffusion-weighted MR images), as “strict” high-risk nodules, and assessed the incidence and the predictive factors for hypervascular transformation of these "strict" high-risk nodules. Our results showed that these “strict” high-risk nodules still have a nature of hypervascular transformation although the incidence of hypervascularization was relatively low (16.7%) compared with previously reported incidence in “conventional” high-risk nodules (26-32%) [7, 12, 16]. Some studies reported that the presence of fat, hyperintensity on T2-weighted images or hyperintensity on DW images were strong risk factors for subsequent hypervascularization in “conventional” high-risk nodules, potentially including dysplastic nodules and early HCCs [7, 10-12]. These findings would be reasonable because fatty change within the nodule has been reported to be one of the characteristic pathological finding of early HCC [13, 14, 17], and because most of hyperintense nodules on T2-weighted images or DW images have been reported to be HCCs in the characterization of dysplastic nodules and HCCs [11, 18, 19]. However, there were substantial number of “conventional” high-risk nodules which did not have fatty metamorphosis or hyperintensity on T2-weighted images or DW images, and in which hypointensity on hepatobiliary phase images was the only visible finding in the initial MR examination. In these nodules which we call "strict" high-risk nodules (i.e., hypointense at hepatobiliary phase but were not detected at any other MR images), there were no useful initial MR findings and clinical variables (the presence of cirrhosis,

Child-Pugh classification (limited to class A and B cirrhosis), initial size of nodules, the presence of multiple high-risk nodules, the presence of a previous treatment history for HCC, and coexistence of hypervascular HCC) to predict hypervascularization of "strict" high-risk nodules in this study. This fact indicated that it is not possible to predict hypervascular transformation of "strict" high-risk nodules based on clinical variables and any findings of the initial MR examination.

Conversely, our study showed that a higher growth rate of nodule was a positive predictive factor for hypervascular transformation of "strict" high-risk nodules. Therefore, it is indispensable to carefully observe the serial change of the size of "strict" high-risk nodules during follow-up MR examinations. In this study, a median observation period to hypervascularization of "strict" high-risk nodules in group A was 177.5±189.5 day, and the shortest period of hypervascularization was 91 days. Therefore, in the case that a "strict" high-risk nodule was detected on the initial Gd-EOB-DTPA enhanced MR images, the nodule should be reexamined after 3 months for checking the development of hypervascular nature. Afterwards, if the nodule was still hypovascular, follow-up MR examination at every 6 months will be recommended for the assessment of increase in size and changes in vascular patterns.

In this study, initial size of the nodule was not a significant predictor of hypervascularization, which is inconsistent with previous study evaluating "conventional" high-risk nodules [10, 16]. The probable reasons for this were that our study was limited to patients having "strict" high-risk nodules, and thus, the mean size of the nodule was less than 10mm in both group A and B.

Several limitations of this study should be noted. First, the number of patients was small, and there was no pathologic proof for "strict" high-risk nodules evaluated in this

study. However, our purpose was not to characterize “strict” high-risk nodules (dysplastic nodules versus early HCCs), but to evaluate the incidence and predictive factors associated with subsequent hypervascularization in “strict” high-risk nodules detected on the hepatobiliary phase of initial Gd-EOB-DTPA-enhanced MR imaging in the absence of biopsy data. It would not be practical to perform liver biopsy for “strict” high-risk nodules because most of these nodules cannot be visualized on ultrasound or CT. The data obtained in this study are believed to be sufficient to propose this concept. Second, owing to the retrospective study design, the intervals between the follow-up examinations were not consistent among the study patients although the follow-up intervals were based on usual practice in patients at high risk of HCC. Prospective, clinical studies of Gd-EOB-DTPA-enhanced MR imaging performed at constant intervals are required to resolve this limitation. Third, because of our retrospective study design, different infusion rates (1–3 mL/s) of contrast materials were used as a trial in our early study to determine the optimal infusion rate. After August 2009, the infusion rate was fixed at 1mL/s in our study protocol, and future studies should be performed under this condition. Fourth, in the analysis of the growth rate of nodules, measurement errors associated with manual evaluation may have led to bias. Although all measurements were performed in the same manner on the magnified image by using electronic calipers to improve accuracy, a large-scale study would be necessary to validate the reproducibility of our results. Finally, regarding lesion detection, hepatic parenchymal enhancement at hepatobiliary phase may be reduced according to decreased liver function in cases of Child C cirrhosis. If we had many cases with Child C cirrhosis, nodules might not have been clearly identified and followed, and this point might become a limitation of the current study. However, as no patients with

Child-Pugh class C cirrhosis were included in the current study, the abovementioned situation regarding the inability to follow nodules was not experienced.

In conclusion, subsets (16.7%) of "strict" high-risk nodules (small hepatocellular nodules detected at only hepatobiliary phase of initial Gd-EOB-DTPA enhanced MR examination) showed hypervascular transformation during follow-up periods. An increased growth rate of nodule, which represents a serial change in MR findings of "strict" high-risk nodules during follow-up MR examinations, was an important predictive factor for hypervascular transformation. Therefore, follow-up MR examination at every 6 months will be recommended for the assessment of increase in size and changes in vascular patterns of "strict" high-risk nodules.

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TABLE LEGEND.

Table 1: The relationships between possible risk factors and hypervascularization.

- HCC = hepatocellular carcinoma
- SD = standard deviation
- group A = "strict" high-risk nodules showing hypervascular transformation
- group B = "strict" high-risk nodules not showing hypervascularization

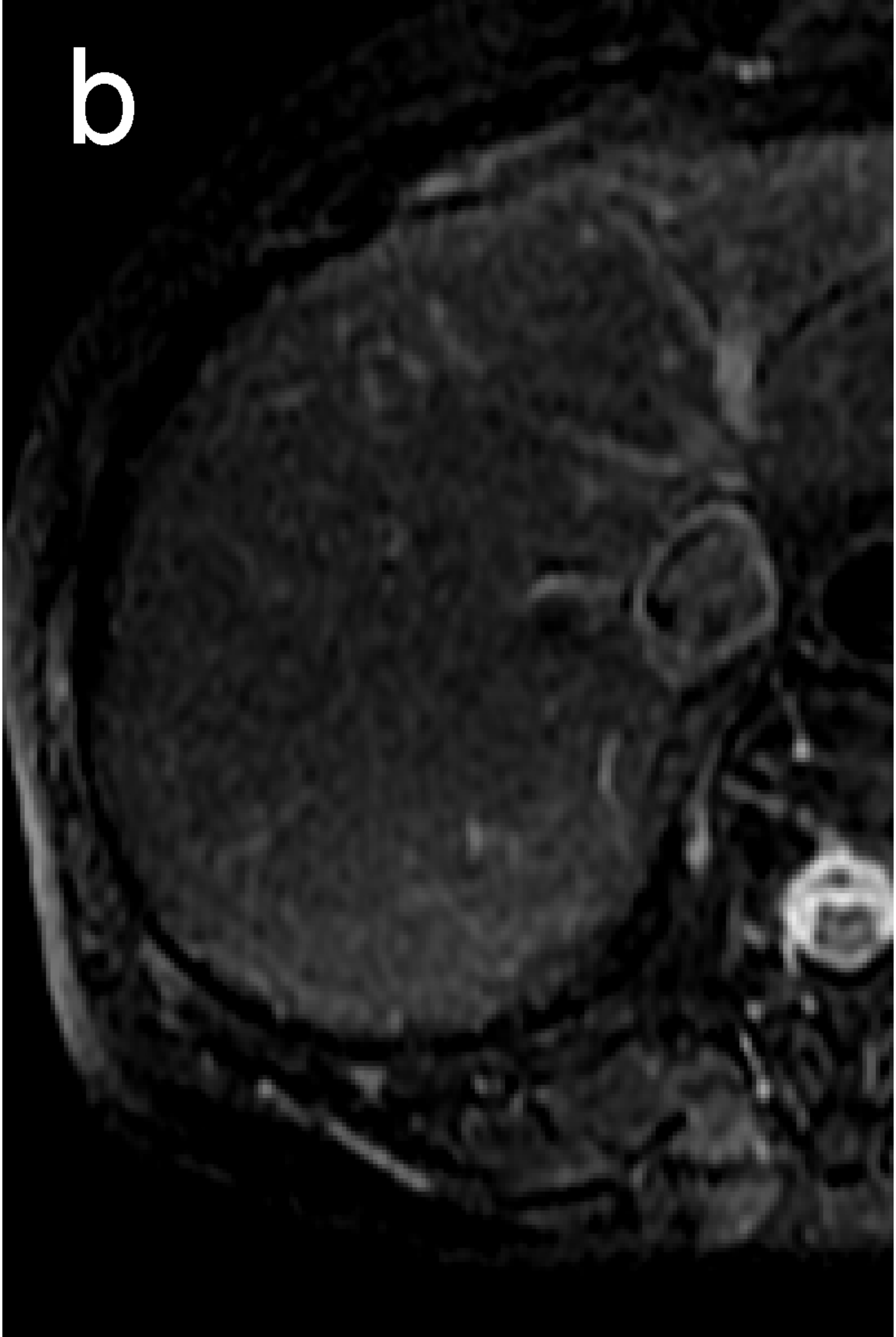
FIGURE LEGEND

Figure 1: A strict high-risk nodule that showed hypervascular transformation during 10 months of follow-up in an 84-year-old woman with hepatitis C–related cirrhosis.

a)-f) Initial MR images.
a, b and c) No lesions are shown on T1 (a), T2 (b), and diffusion-weighted MR images (c).
d) Precontrast MR image shows no nodules.
e) Arterial-phase gadoxetic acid-enhanced MR image shows no enhancing nodules.
f) Hepatocyte-phase gadoxetic acid-enhanced MR image shows the hypointense nodule measuring 8.4 mm (arrow), indicating a strict high-risk nodule.

g)-i) Follow-up MR images obtained 10 months after the initial MR examination.
g) Precontrast MR image shows a slightly hypointense nodule (arrow).
h) Arterial-phase gadoxetic acid-enhanced MR image shows hypervascular foci in the nodule (arrow).
i) Hepatocyte-phase gadoxetic acid-enhanced MR image shows a hypointense nodule measuring 15.8 mm (arrow). The nodule appears markedly enlarged 10 months after the initial MR examination.


a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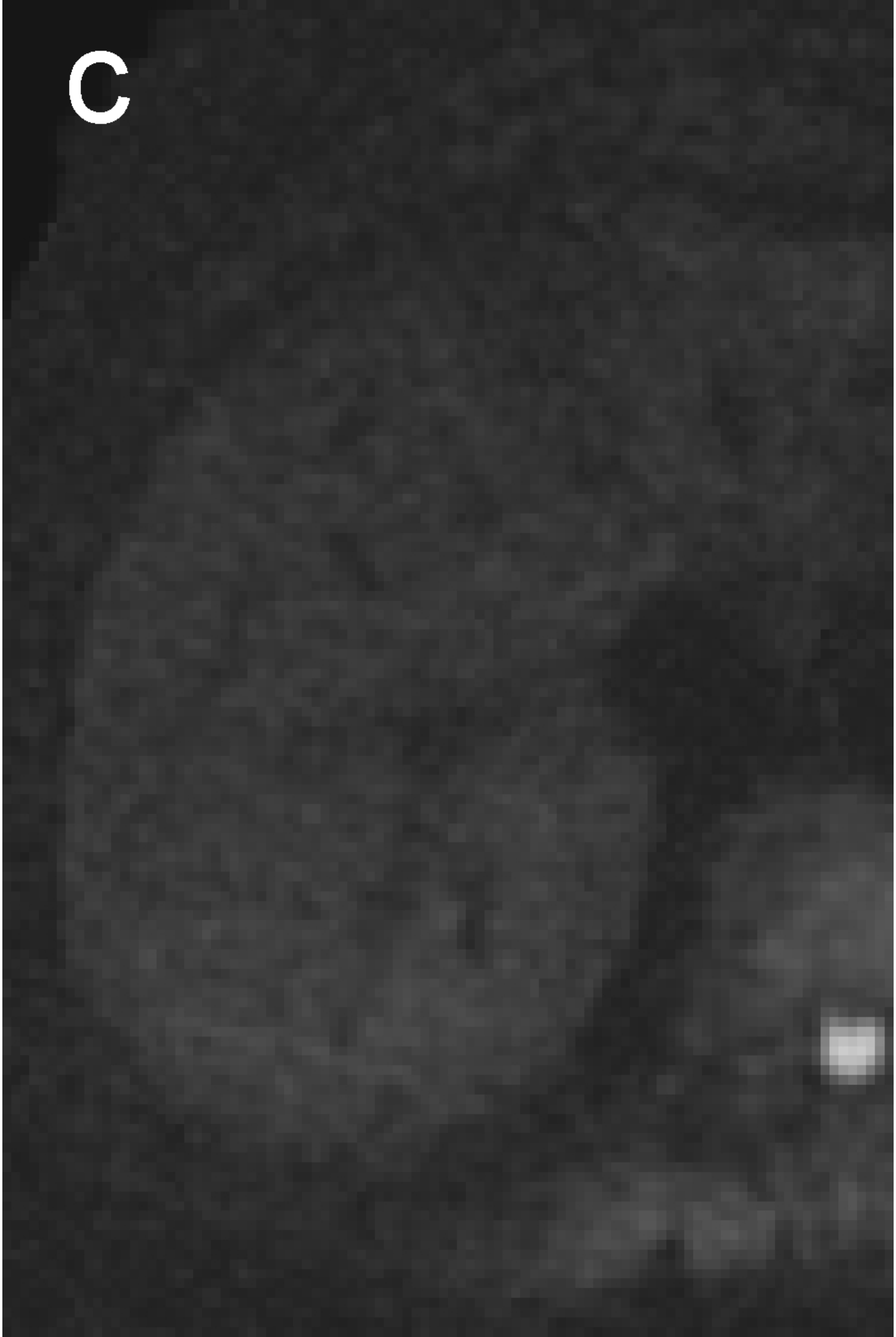
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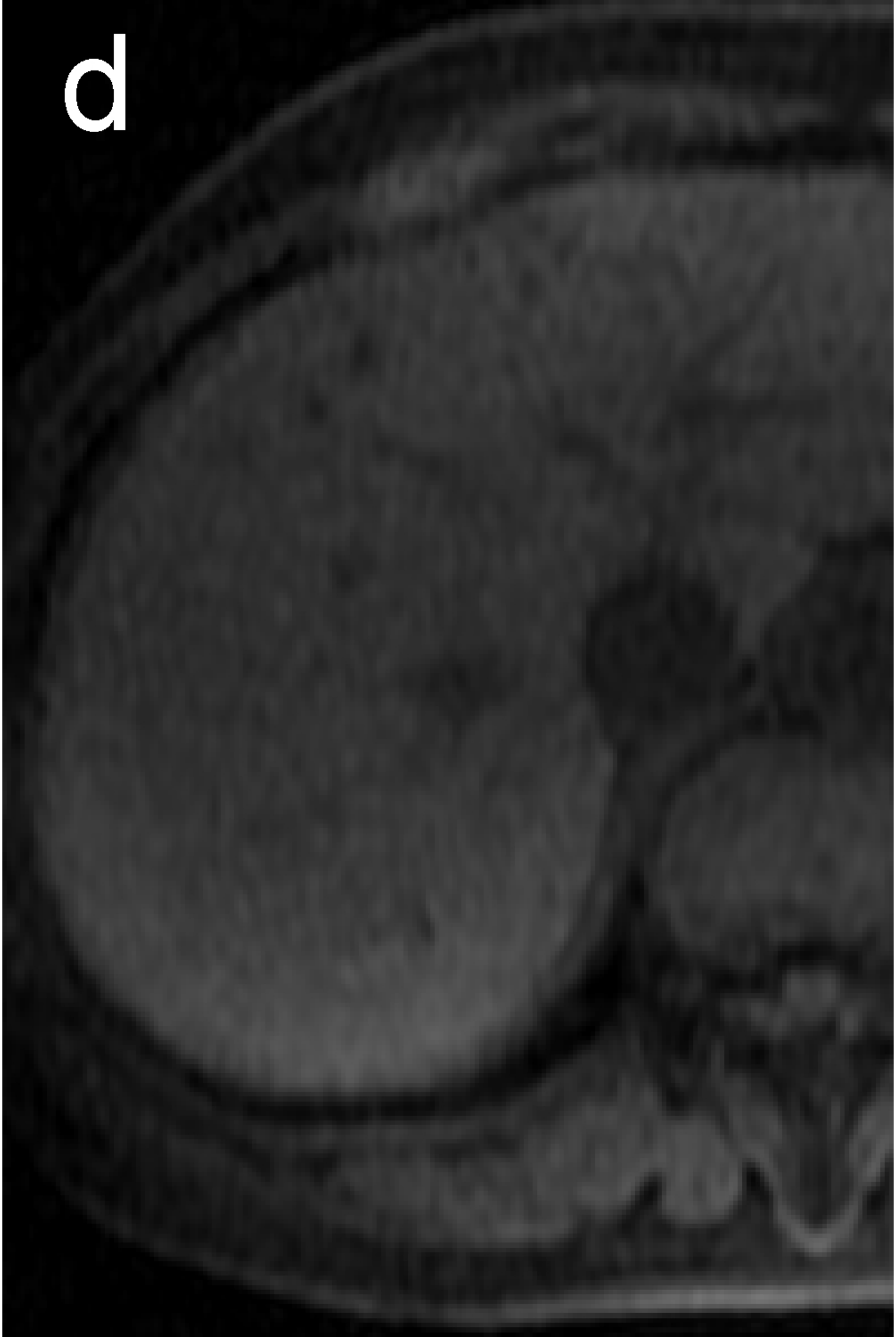
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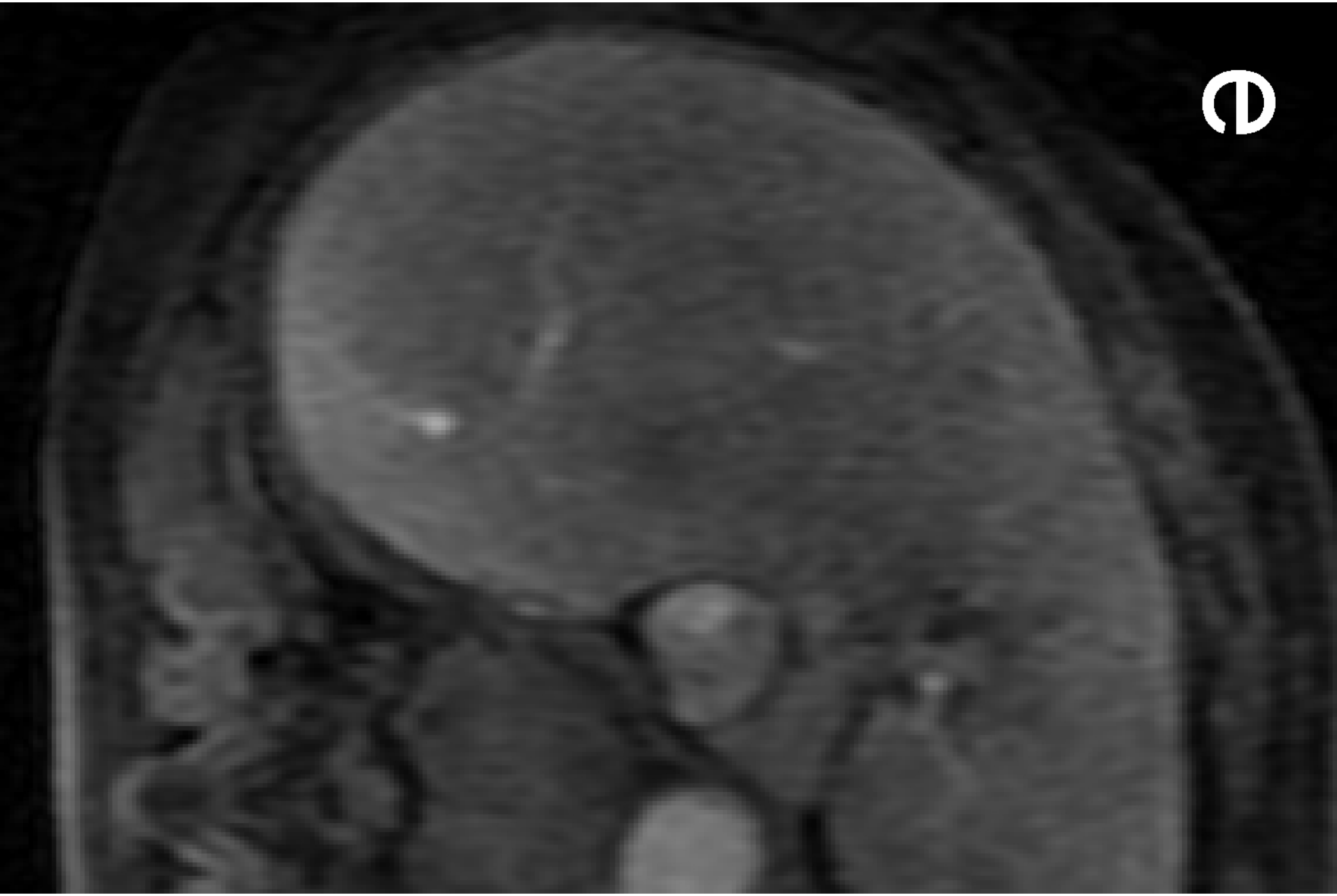


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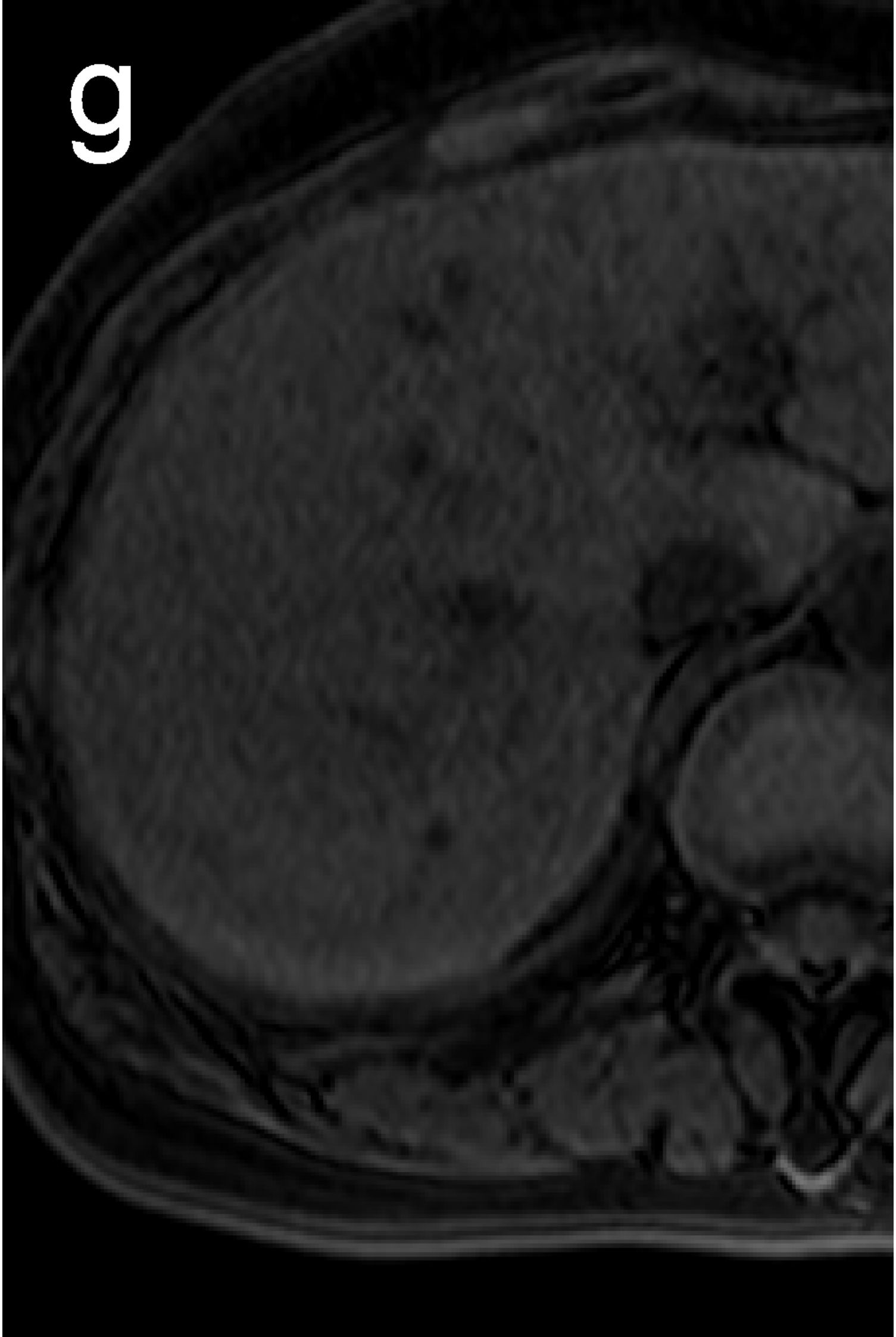
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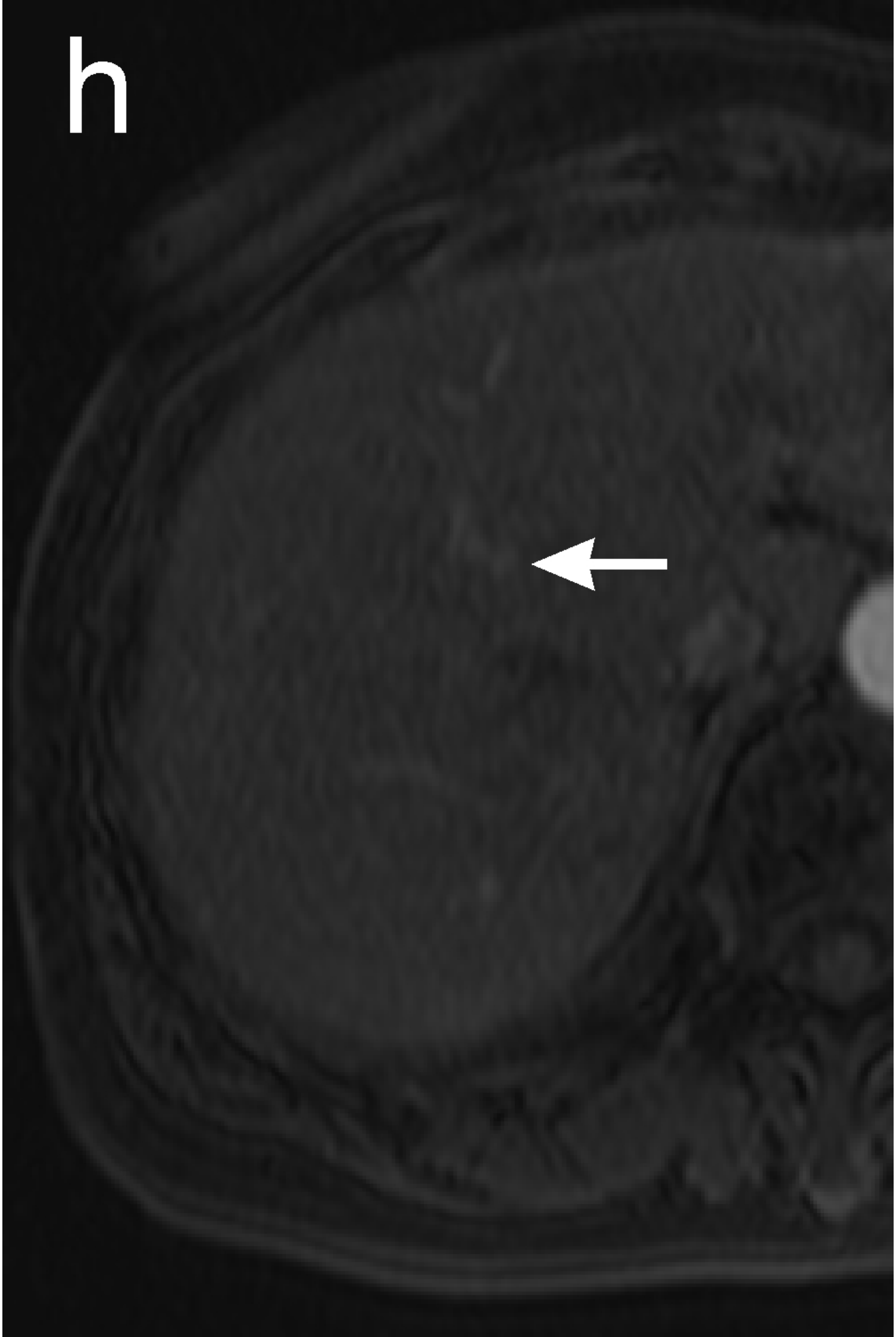
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Table 1.

The relationships between possible risk factors and hypervascularization

characteristics	group A	group B	P value
Growth rate of nodules (mean±SD; range) [mm/year]	6.3±4.5; 1.6-12.8	3.4±7.2; 0-43.2	0.003
Observation period (median±SD; range) [day]	177.5±189.5; 91-676	419.5±372.2; 47-1366	0.039
Initial size of nodules (mean±SD; range) [mm]	8.8±1.2; 6.8-10.6	9.1±3.0; 4.8–19.8	0.96
Liver cirrhosis	9/10 (90%)	48/50 (96%)	0.427
Child-Pugh classification	Child A 7/9(77.8%) Child B 2/9(22.2%) Child C 0/9(0%)	Child A 41/48(85.4%) Child B 7/48(14.6%) Child C 0/48(0%)	0.623
Multiple hypovascular lesions on the liver	8/10 (80%)	44/50(88%)	0.61
Previous treatment history for HCC (interventional or surgical)	6/10 (60%)	23/50 (46%)	0.5
Presence of hypervascular HCC	7/10 (70%)	31/50 (62%)	0.732
Age (mean±SD; range) [y]	70.7±7.8; 55-84	70.2±8.4; 53-88	0.705
Sex	male 8 female 2	Male 31 female 19	0.47

- HCC = hepatocellular carcinoma
- SD = standard deviation
- group A = "strict" high-risk nodules showing hypervascular transformation
- group B = "strict" high-risk nodules not showing hypervascularization