

Relationship between the Status of Blood Supply in the Non-hypervascular Hepatocellular Nodules among Chronic Liver Diseases and the Hypervascular Change

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Abstract

Objectives: We observed the time-course changes of blood flow in non-hypervascular hepatocellular nodules that showed hypointensity in the hepatobiliary phase on Gd-EOB-DTPA-enhanced magnetic resonance imaging (EOB-MRI), and evaluated the relationship between hypervascular change and the status of blood supply in the nodules.

Methods: The study included 69 hepatocellular nodules in 33 patients demonstrating hypointensity in the hepatobiliary phase on EOB-MRI and showing non-hypervascular features on CT during hepatic arteriography (CTHA) performed during the same period.

Results: In relation to blood flow on CTHA/ CT during arterial portography (CTAP), the cumulative rate of hypervascular change at 52 weeks was 0.0% for iso/iso, 29.7% for hypo/iso, 61.5% for iso/hypo, and 55.0% for hypo/hypo. Multivariate analysis using COX proportional hazards regression showed that CTAP findings (hypo-density) and CTHA findings (hypo-density) were significant variables for hypervascular change.

Conclusions: In cases of non-hypervascular hepatocellular tumors, nodules with decreased arterial or portal blood flow that show hypointensity in the hepatobiliary phase on EOB-MRI are likely to develop into typical hepatocellular carcinoma in a shorter time.

Keywords: Hepatocellular carcinoma; Gd-EOB-DTPA; Early hepatocellular carcinoma; Borderline lesion; Angiography

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. Patients with chronic liver disease, particularly liver cirrhosis, are considered as a high-risk group for developing HCC. Since the early detection and treatment of HCC is imperative for improvement of the vital prognosis of patients, HCC surveillance is performed according to the guidelines of various associations [1-4].

In Japan, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) became clinically available as a liver-specific contrast agent for magnetic resonance imaging (MRI) in January 2008, arousing expectations for novel developments in the diagnosis and treatment of HCCs. It has been shown that this agent allows the diagnosis of hypervascular HCCs when a good arterial phase is obtained, and that contrast patterns in the arterial phase and portal phase soon after the dosing of this agent are equivalent to those of dynamic computed tomography (CT) [5-8]. On the other hand, in the hepatobiliary phase, the contrast agent is incorporated into the normal hepatic parenchyma over time, and it is reported that the tumor/liver contrast required for detection can be obtained 15-20 min after dosing as long as there is no hepatic dysfunction [5,9].

At present, the algorithm of HCC surveillance defines that the typical HCC image shows high density/intensity in the arterial phase and relatively low density/intensity in the portal and equilibrium phases on dynamic CT/MRI [1-4]. Other patterns of images are regarded as those of atypical liver tumors. CT during hepatic arteriography (CTHA) and CT during arterial portography (CTAP), which are optional examinations for atypical liver tumors, are useful for understanding the status of tumor blood supply.

Although the determination of the tumor blood supply is helpful in diagnosing the degree of differentiation, it is also true that the diagnosis of early HCC and dysplastic nodules (DNs) using only the technique of blood-flow diagnosis has overlaps [10,11]. We have become capable of detecting non-hypervascular early HCCs or DNAs as atypical liver tumors by using Gd-EOB-DTPA-enhanced MRI (EOB-MRI). However, we need to know the factors which suggest that these non-hypervascular hepatocellular tumors progress to typical HCCs.

In this regard, we retrospectively analyzed the blood flow changes in non-hypervascular hepatocellular tumors that showed hypointensity in the hepatobiliary phase on EOB-MRI and a non-hypervascular nature on CTHA which was performed during the same period. We also evaluated the relationship between hypervascular change and the status of blood supply in the nodules.

Patients and Methods

All procedures of this study were in accordance with the Helsinki Declaration of 1964 and later versions. The Ethics Committee of Tokyo Medical University approved this retrospective study and acquisition of written informed consent was waived.

Patient population

Among the patients who underwent EOB-MRI between January 2008 and January 2009, 33 patients who had 69 nodules that showed hypointensity in the hepatobiliary phase on EOB-MRI and non-hypervascular features on CTHA performed during the same period (within 1 month after performing EOB-MRI), and who were able to be followed for at least 9 weeks without HCC treatment, were included in this study. There were 20 men and 13 women with a mean age of 69.9 ± 7.3 (median 71) years. The background liver diseases were associated with hepatitis C virus in 23 cases, hepatitis B virus in 7, and alcohol in 3.

MR imaging

Magnetic resonance imaging was performed using a 1.5-T MR imaging system (Avanto; Siemens, Erlangen, Germany). T1-weighted images (T1WI) included in-phase and opposed-phase images. The T1WI parameters (in-phase and opposed-phase) were as follows: TR/TE 120/4.76, 2.38 ms; flip angle 75°; one average; matrix 256×140 ; parallel acquisition technique (PAT) factor 2 with the generalized auto calibrating partially parallel acquisition (GRAPPA) algorithm; slice thickness 6 mm; slice gap 1.2 mm; and acquisition time 13 s. The T2WI parameters were as follows: TR/TE 3600/99 ms; flip angle 150°; echo train length 29; matrix 256×75 (%); slice thickness 6 mm; one average; PAT factor 2 with the GRAPPA algorithm; and acquisition time 14 s. The T2WI image was obtained while the subjects held their breath.

Gadoxetic acid (0.025 $\mu\text{mol/kg}$) was injected at a total rate of 2 mL/s via the antecubital vein, followed by 40 mL of physiological saline. The dynamic study incorporated the arterial phase, the portal phase, and a period of 4 min after the contrast material injection (transitional phase). A three-dimensional (3D) volumetric interpolated breath-hold examination (3D-VIBE) was used with the dynamic study. The 3D-VIBE parameters were as follows: TR/TE 4.28/1.78 ms; flip angle 15°; matrix 256×85 (%); PAT factor 2; slice thickness 3 mm; and acquisition time 20 s. The monitoring imaging technique (the CARE bolus method) was used to obtain the optimal arterial phase. The hepatobiliary phase was obtained by 3D-VIBE 20 min after injecting the contrast material.

CTHA and CTAP imaging

Angiography-assisted CT (CTHA and CTAP) was performed using an angiography-combined 16-detector row CT system (Advantx ACT, GE Medical Systems, Milwaukee, WI, USA). Immediately after injecting prostaglandin E2 (Liple®; Mitsubishi Tanabe Pharma, Osaka, Japan) through a catheter, 76 mL of contrast material (Iomeprol 350 mgI/mL; Eisai, Tokyo, Japan), which was diluted twice with physiological saline, was injected at a rate of 2 mL/s. CTAP was performed 30 s after starting the injection of the contrast material through a catheter into the superior mesenteric artery. The parameters for CT acquisition were as follows: table speed 13.7 mm/0.5 s; collimation 10 mm; and reconstruction 5 mm. CTHA was performed 6

s after the contrast material injection through a catheter into the common hepatic or proper hepatic artery. A total of 10–30 mL of contrast material (Iomeprol, 350 mgI/mL) was injected at a rate of 0.8–1.5 mL/s.

Image analysis

Two blinded readers with at least 10 years of experience reviewed randomly the images of MRI, angiography-assisted CT (CTHA and CTAP), and dynamic CT. Disagreements were extensively discussed and an agreement was obtained by consensus. Tumor size was defined as the maximal diameter in the hepatobiliary phase on EOB-MRI. Hypervascularity was defined as higher intensity/density than the surrounding liver parenchyma in the arterial phase of dynamic CT/MRI or CTHA. For the other case of hypervascularity, we called this as a “non-hypervascular” feature. Nodules that showed hypointensity in the hepatobiliary phase on EOB-MRI were classified according to blood flows on CTHA/CTAP. Nodular blood flow was rated as “iso” when it was iso-density in comparison with the surrounding liver tissue, and as “hypo” when it was hypo-density in comparison with the surrounding liver tissue; the nodules were classified into 4 groups in terms of iso/iso (group A), hypo/iso (group B), iso/hypo (group C), and hypo/hypo (group D). We evaluated fat deposition in the nodule according to the intensity of in-phase and opposed-phase T1-images on MRI. When the intensity of the nodules decrease on opposed-phase T1-image compared to in-phase one, we determined the nodule had fat deposition. The exclusion criteria for hypointense hepatocellular nodules in the hepatobiliary phase on EOB-MRI were as follows: (a) lesions less than 3 mm in diameter because the slice thickness for the hepatobiliary phase on EOB-MRI was 3 mm, (b) delayed enhancement on dynamic MRI because of the exclusion of hepatic hemangiomas, (c) very high intensity on T2-weighted images because of the exclusion of hepatic hemangiomas or cysts.

Subsequent blood flow changes were followed using dynamic CT/MRI or CTHA/CTAP every 3 to 6 months.

	CTHA	
CTAP	Iso-density	Hypo-density
Iso-density	Group A 28 (40.6%)	Group B 19 (27.5%)
Hypo-density	Group C 14 (20.3%)	Group D 8 (11.6%)

EOB-MRI: Gadolinium Ethoxybenzyl Diethylenetriamine Pentaacetic Acid; (Gd-EOB-DTPA)-Enhanced Magnetic Resonance Imaging; CTHA: Computed Tomography during Hepatic Arteriography; CTAP: Computed Tomography during Arterial Portography

Table 1: Incidence of blood flow on CTHA/CTAP in non-hypervascular nodules showing hypointensity in the hepatobiliary phase on EOB-MRI.

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation, and differences in the mean values were assessed using the unpaired Student t-test. The cumulative risk for hypervascular change of non-hypervascular nodules was calculated according to the Kaplan-Meier method, and differences were assessed by the log-rank test. We calculated relative risk using the COX proportional hazards regression

analysis. P-values<0.05 were considered to indicate a statistically significant difference.

Results

Nodule characteristics

The mean tumor diameter was 11.0 ± 5.7 (median 10) mm, and the mean follow-up period was 44.5 ± 17.2 (median 48) weeks. There were 28 nodules (40.6%) in group A, 19 nodules (27.5%) in group B, 14 nodules (20.3%) in group C, and 8 nodules (11.6%) in group D (Table 1).

Comparison of nodules between with and without hypervascular change

During the follow-up period, 20 nodules (29.0%) became hypervascular and developed into typical HCC which were followed for 44.9 ± 15.0 weeks on the average, whereas the 49 nodules without hypervascular change were followed for 44.3 ± 18.2 weeks, showing no significant difference between the 2 groups (p=0.89).

The characteristics of non-hypervascular hypointense nodules in the hepatobiliary phase on EOB-MRI with and without hypervascular

change are shown in Table 2. The mean tumor diameter was 13.7 ± 7.6 mm in the 20 nodules with hypervascular change and 9.9 ± 4.4 mm in the 49 nodules without hypervascular change; the tumor diameter was significantly larger in the nodules with hypervascular change (p=0.04).

Cumulative rate of hypervascular change

The cumulative rate of hypervascular change among all the nodules was 31.6% at 52 weeks and 67.1% at 72 weeks. A hypervascular change occurred in 7 of 19 nodules (36.8%) in group B, 8 of 14 nodules (57.1%) in group C, and 5 of 8 nodules (62.5%) in group D, whereas no hypervascular change was found in 28 nodules in group A. In relation to the group classification, the cumulative rates of hypervascular change at 52 weeks were 0.0% for group A, 29.7% for group B, 61.5% for group C, and 55.0% for group D; however, there were no statistically significant differences among the groups (Figure 1).

When nodules were classified into those measuring 10 mm or more in diameter (37 nodules) or those measuring less than 10 mm in diameter (32 nodules), the cumulative rates of hypervascular change at 52 weeks were 36.8% for the former group and 25.0% for the latter group, showing a significant difference (p<0.05) (Figure 2).

	Nodules with hypervascular change	Nodules without hypervascular change	Univariate Analysis	Multivariate Analysis		
	n=20	n=49		p-value	p-value	RR
Sex (male:female)	14:6	24:25	0.104			
Age (years)	73.0 (48.0-80.0)	65.0 (59.0-78.0)	0.426			
Background liver disease (HCV:HBV:Alcohol)	14:5:1	40:6:3	0.617			
Size of the tumor (≥10 mm: <10 mm)	14:6	23:26	0.024			
In AFP	3.8 (1.5-10.4)	3.9 (1.5-9.8)	0.19			
AFP-L3 (%)	4.8 (0.0-75.8)	3.7 (0.0-65.2)	0.125			
InPIVKA-2	3.0 (2.6-9.9)	3.0 (1.9-6.3)	0.153			
Fat deposition in the tumor (+:-)	18:2	45:4	0.749			
CTHA (iso-density:hypo-density)	8:12	34:15	0.013	0.011	3.43	
CTAP (iso-density:hypo-density)	7:13	40:9	0.005	0.005	3.752	

Continuous variables were expressed as median (range). RR: Relative Risk. 95% CI: 95% Confidence Interval. HCV: Hepatitis C Virus, HBV: Hepatitis B Virus, Ln AFP: Natural Logarithm of Alpha-Fetoprotein (ng/mL), AFP-L3: L3-Lectin Binding Alpha-Fetoprotein, Ln PIVKA-2: Natural Logarithm of Protein Induced by Vitamin K Absence or Antagonist-2 (mAU/mL), CTHA: Computed Tomography during Hepatic Arteriography, CTAP: Computed Tomography during Arterial Portography

Table 2: Characteristics and Cox proportional hazards regression analysis based on non-hypervascular nodules with and without hypervascular change.

Cox proportional hazards regression analysis based on nodules with and without hypervascular change

A univariate analysis of factors contributing to the hypervascular change of non-hypervascular hypointense nodules in the hepatobiliary

phase on EOB-MRI revealed that CTHA finding (hypo-density), CTAP finding (hypo-density), and tumor diameter (≥10 mm) were significant variables for hypervascular change (Table 2). In addition, a multivariate analysis showed that CTHA finding (hypo-density) and

CTAP finding (hypo-density) were significant variables for hypervascular change (Table 2). In regard to predicting hypervascular change of non-hypervascular hypointense nodules in the hepatobiliary phase on EOB-MRI by size of the tumor (≥ 10 mm), CTHA (hypo-density), and CTAP (hypo-density), the positive predictive values are 0.70, 0.44, and 0.59, respectively. The sensitivity are 0.7, 0.60, and 0.65, respectively. The specificity are 0.53, 0.69, and 0.82, respectively. An example case is shown in Figure 3.

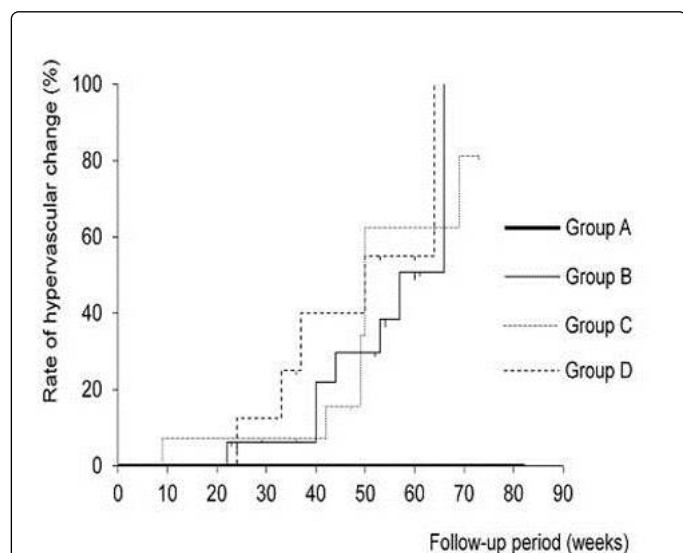


Figure 1: Cumulative rates of hypervascular change by classification of blood flow. Group A (CTHA iso-density / CTAP iso-density). Group B (CTHA hypo-density / CTAP iso-density). Group C (CTHA iso-density / CTAP hypo-density). Group D (CTHA hypo-density / CTAP hypo-density)

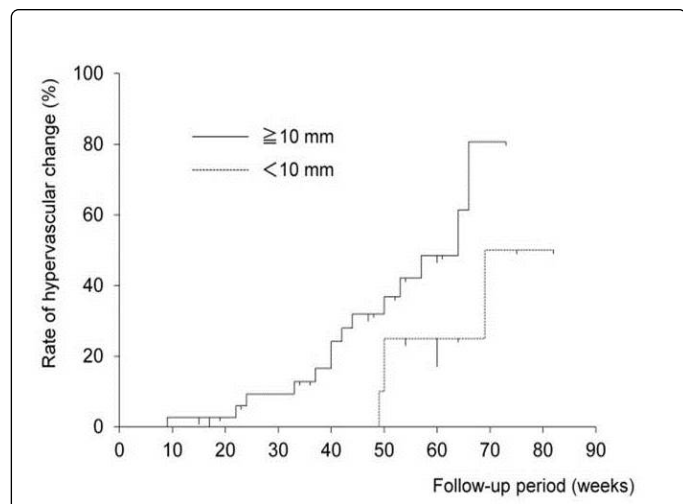


Figure 2: Cumulative rates of hypervascular change by tumor diameter.

Discussion

The present results indicate that among non-hypervascular nodules showing hypointensity in the hepatobiliary phase on EOB-MRI, not only nodules in which the portal blood flow decreased but also nodules in which the arterial blood flow decreased without a decrease in the portal blood flow had a potential to progress to hypervascular HCC in a short time, although nodules in which the arterial and portal blood flows were held did not change to hypervascular HCC. Thus, when we find non-hypervascular hepatocellular nodules showing hypointensity in the hepatobiliary phase on EOB-MRI, detailed examination of blood flow in these nodules is useful for predicting their prognosis.

CTHA/CTAP is an invasive examination and is expected to be used less frequently for diagnosing HCC in the future. However, it is the only method available for evaluating portal blood flow and appears to be highly useful in diagnosing the differential grade of HCC. Hayashi et al. carried out a retrospective study of findings in HCCs on repeated CTHA/CTAP, and analyzed the speed of multistep carcinogenesis [12]. According to their study, nodules in which portal blood flow is maintained while hepatic arterial blood flow is decreased develop into typical HCCs in 30%-40% of cases in about 3 years, and the appearance of hypervascular foci in the nodule is a useful predictor of such development. The incidence of hypervascular change reported by Hayashi et al. is lower than that of our present result. This discrepancy may be explained by the fact that the nodules examined by Hayashi et al. were detected using CTHA/CTAP alone, whereas ours were detected by EOB-MRI. We believe that hepatocellular nodules can be detected more accurately by EOB-MRI than by examination of changes in blood flow alone.

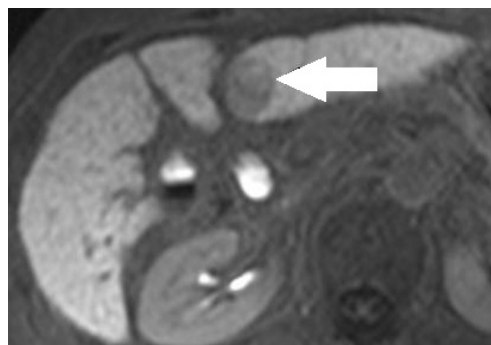


Figure 3A: A case of a tumor measuring 22 mm in diameter in the liver (S3) with a hypervascular change and a tumor measuring 19 mm in diameter in the liver (S6) without any hypervascular change, the arrow shows a tumor. Low signal intensity in the liver (S3) in the hepatobiliary phase on Gd-EOB-DTPA-enhanced magnetic resonance imaging (EOB-MRI) (at the time of enrollment).

Contrast-enhanced ultrasound (CEUS) can depict a decrease in the arterial blood flow in hepatocellular nodules, and Hayashi et al. reported that nodules displaying obvious and complete hypovascularity in the early vascular phase were likely to be HCC [13]. The radiation exposure level from CT is almost 8 mSv [14]. Thus, that of CTHA/CTAP is over 8 mSv. Therefore, we recommend CEUS to be performed instead of CTHA when non-hypervascular hepatocellular nodules are detected.

In the present study, the cumulative rate of hypervascular change was significantly higher in nodules measuring 10 mm or more than in nodules measuring less than 10 mm, suggesting that the former group of nodules more rapidly developed into typical HCCs. Kojiro et al. reported that hypovascular nodules measuring 15 mm or less in diameter are more likely to have a lower grade of malignancy [15].

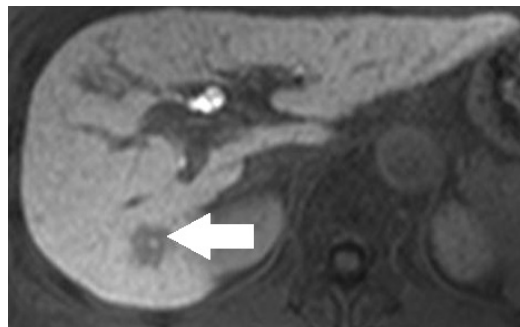


Figure 3B: Low signal intensity in the liver (S6) in the hepatobiliary phase on EOB-MRI (at the time of enrollment).

Moreover, Kim et al. described that none of the 12 small HCCs with diameters of 1 cm or less had microvascular invasion (MVI), whereas 15 (33%) of the 46 small HCCs with diameters of 1.1-2.0 cm had MVI ($p=0.025$) [16]. These previous studies corroborate our results, and several other reports also describe the same findings for hypovascular hypointense nodules in the hepatobiliary phase on EOB-MRI [17-22].

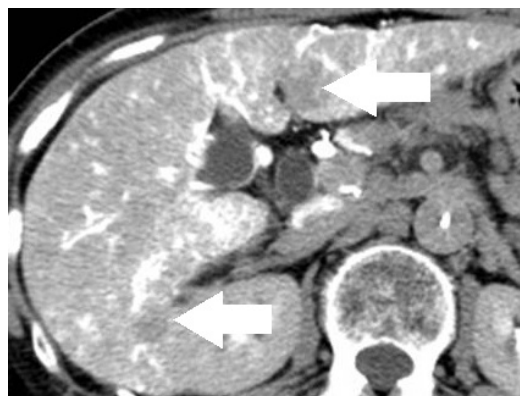


Figure 3C: Both S3 and S6 tumors show a low density on computed tomography during hepatic arteriography (CTHA) (at the time of enrollment).

Table 3 shows the studies evaluating the factors that affect hypervascular change in hypovascular nodules showing hypointensity in the hepatobiliary phase on EOB-MRI [17-28]. In 4 studies including the present study, non-hypervascular nodules were defined using CTHA [17,21,24]. Only our study was analyzed using COX proportional hazards regression based on non-hypervascular nodules with and without hypervascular change, which revealed that nodules

showing hypoattenuation on CTHA or CTAP had a malignant potential. The larger the size of the enrolled nodules in each study, the more the cumulative rate of hypervascular change at 1 year tends to be.

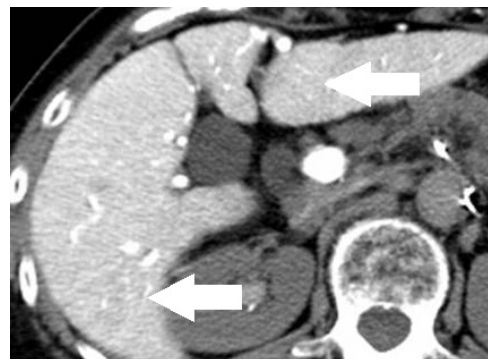


Figure 3D: Both S3 and S6 tumors show iso-density on computed tomography during arterial portography (CTAP) (at the time of enrollment).

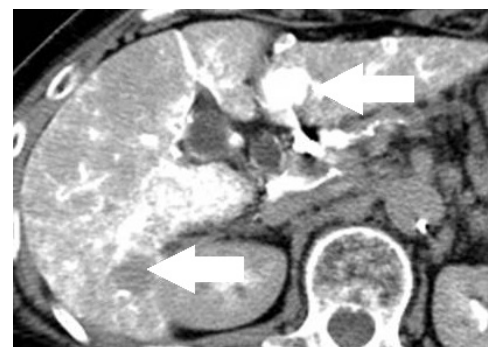


Figure 3E: On CTHA, the S3 tumor shows a high density whereas the S6 tumor shows a low density (after 6 months).



Figure 3F: On CTAP, the S3 tumor shows a low density whereas the S6 tumor shows iso-density (after 6 months).

	No. of nodules	Size of nodules (mm)	Definition of hypovascularity	Follow-up interval	Cumulative rate of hypervascular change at 1 year	Factors that affect hypervascular change
Kumada et al. [17]	49	median 14	CTHA	3 months	43.5%	Size: 15 mm or greater.
Motosugi et al. [18]	135	8.4 ± 3.6	Dynamic CT	ND	15.5%	Size: more than 10 mm. Fat-containing nodules
Akai et al. [19]	130	mean 8.1	EOB-MRI	ND	3.2%	Size: 10 mm or greater (p = 0.064)
Kobayashi et al. [24]	99	11.0 ± 2.8	CTHA	ND	17.0%	Hypo-density in the hepatobiliary phase on EOB-MRI
Takayama et al. [20]	103	mean 9.3 (n=31) and 7.9 (n=72)	EOB-MRI	more than 3 months	18.4%	Size: 9 mm or greater Hypoattenuation on the delayed phase imaging of the initial dynamic CT
Takechi et al. [21]	112	7.9 ± 3.1	CTHA	median 3 months	ND	Size: more than 10 mm Hypoattenuation on CTAP
Kim et al. [23]	214	ND	EOB-MRI	ND	ND	Hyperintensity on DW images
Higaki et al. [25]	76	9.8 ± 2.7 (n=24) and 9.9 ± 3.2 (n=52)	EOB-MRI	mean 123.0 days	ND	Growth rate of nodules Presence of fat within nodules Hyperintensity on T1-weighted images
Hyodo et al. [26]	160	9.5 ± 5.1 (n=50) and 9.8 ± 3.7 (n=110)	at least 2 modalities including EOB-MRI	mean 186 days	25.0%	Hyperintensity on T2-weighted images Previous local therapy for hypervascular HCC Child-Pugh B cirrhosis Coexistence of hypervascular HCC
Iannicelli et al. [22]	28	mean 11	EOB-MRI	at least 3 months	ND	Size: more than 10 mm
Inoue et al. [27]	504	9.74 ± 4.04 (n=173) and 9.11 ± 4.04 (n=331)	at least 2 modalities including EOB-MRI	ND	14.9%	Previous treatment history for HCC Hyperintensity on T2-weighted images
Kanefuji et al. [28]	73	median 9	EOB-MRI	ND	ND	The estimated regression coefficients were 0.36 for age, 6.51 for lower signal intensity in the arterial phase, 8.70 or 6.03 for positivity of hepatitis B virus or hepatitis C virus, 9.37 for des-gamma-carboxy prothrombin, and -4.05 for fat deposition.
present study	69	11.0 ± 5.7	CTHA	3 to 6 months	31.6%	Size: 10 mm or more Hypoattenuation on CTHA Hypoattenuation on CTAP

ND: Not Described; Dynamic CT: Dynamic Computed Tomography; EOB-MRI: Gadolinium Ethoxybenzyl Diethylenetriamine Pentaacetic Acid (Gd-EOB-DTPA)-Enhanced Magnetic Resonance Imaging; CTHA: Computed Tomography during Hepatic Arteriography. CTAP: Computed Tomography during Arterial Portography; DW images: Diffusion-Weighted Images; HCC: Hepatocellular Carcinoma

Table 3: Studies evaluating the factors that affect hypervascular change of hypovascular nodules showing hypointensity in the hepatobiliary phase on EOB-MRI.

Regarding limitations, this work was a retrospective study involving a small number of nodules, and it did not have sufficient pathological evaluation. However, this study has been able to evaluate in detail the status of blood supply in non-hypervascular hepatocellular nodules using CTHA/CTAP and observe the nodules using the same imaging

equipment every 3 to 6 months. In the future, long-term prospective studies involving a large number of non-hypervascular hepatocellular nodules are needed.

Conclusion

For non-hypervascular hepatocellular nodules showing hypointensity in the hepatobiliary phase on EOB-MRI, those with decreased arterial or portal blood flow are likely to develop into a typical HCC in a shorter time.

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