

[ ORIGINAL ARTICLE ]

## Progression of Hepatic Hypovascular Nodules with Hypointensity in the Hepatobiliary Phase of Gd-EOB-DTPA-enhanced MRI in Hepatocellular Carcinoma Cases

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### Abstract:

**Objective** We investigated the possible factors for predicting the future progression to hepatocellular carcinoma (HCC) from hypovascular nodules detected in the hepatobiliary phase of gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (Gd-EOB-DTPA-MRI).

**Methods** A total of 91 hypovascular nodules detected by Gd-EOB-DTPA-MRI in 28 patients without any past history of treatment for HCC were retrospectively examined. The nodules were categorized into those with and without HCC progression, then comparisons were made to identify any factors possibly related to a progression to HCC in each case. In addition, we performed a receiver operating characteristics (ROC) analysis to determine the cut-off value for the initial nodule size for predicting HCC progression within 12 months.

**Results** The observation period of the 28 patients was 1,172.6±95.6 (mean±standard error) days. The number of hypovascular nodules that changed to hypervascular ones was 15 (16.5%), and the cumulative incidence of hypervascular transformation was 7.1% at 12 months and 12.7% at 24 months. Of all 91 hypovascular nodules, 33 in 18 patients were diagnosed as HCC based on hypervascular transformation and/or size enlargement, while the remaining 58 did not progress to HCC. There was no significant difference regarding the background characteristics between the HCC progressed and non-progressed groups according to a multivariate analysis, or between the patients who had nodules that progressed to HCC and those with nodules that did not progress to HCC. Regarding HCC progression at 12 months, the area under the ROC (AUROC) had a level of 0.745 and showed that an initial nodule cut-off size of 9.5 mm (sensitivity, 57.9%; specificity, 87.3%) was predictive.

**Conclusion** In patients without a past HCC treatment history, it is difficult to determine whether hypovascular nodules have a high risk of progression to HCC based on background factors alone.

**Key words:** Gd-EOB-DTPA, hepatic hypovascular nodule, hepatocellular carcinoma, magnetic resonance imaging

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### Introduction

Hepatocellular carcinoma (HCC) is the sixth most common type of cancer in the world and third most frequent

cause of cancer death (1). Most cases are associated with cirrhosis related to chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (2), and surveillance is needed for patients with those high-risk conditions. The current HCC surveillance methods include imaging studies and the

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measurement of tumor markers. As for imaging, ultrasonography (US), contrast enhanced computed tomography (CT), and magnetic resonance imaging (MRI) are widely used, and recent improvements in those have enabled the early detection of HCC and thus improved the treatment of affected patients.

Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA), recently developed as a liver-specific MRI contrast agent, provides information regarding the liver hemodynamic state in the early dynamic phase as well as the hepatocyte function in the hepatobiliary phase. Gd-EOB-DTPA is taken up by hepatocytes (3), thus hepatic focal lesions without a normal hepatobiliary function can be depicted as hypointense lesions in comparison to the surrounding liver tissue with a normal hepatobiliary function in the hepatobiliary phase (4). Previous studies have shown Gd-EOB-DTPA-MRI to have a higher sensitivity for detecting HCC than other imaging modalities, especially for lesions smaller than 20 mm including hypovascular well-differentiated HCC (5, 6). However, though Gd-EOB-DTPA-MRI is useful for HCC detection, several unresolved issues related to this imaging modality remain.

We often observe hypointensity nodules in the hepatobiliary phase of Gd-EOB-DTPA-MRI that are hypovascular in the arterial phase. These tend to be diagnosed as potential dysplastic nodules or possible well-differentiated HCC, and therefore require follow-up examinations. During the follow-up period, some lesions become hypervascular and are finally diagnosed as typical HCCs, while others remain stable in regard to their size and characteristics, and may even disappear. At present, it is not known which hypovascular nodules detected by Gd-EOB-DTPA-MRI will finally become hypervascular lesions and thereafter be diagnosed as typical HCC. Additionally, in patients without a past history of HCC treatment, the natural history of these hypovascular nodules found incidentally has not yet been investigated.

In this retrospective longitudinal study, we examined the natural course of Gd-EOB-DTPA-MRI-detected hypovascular nodules in patients without a past HCC treatment history. We also analyzed the possible factors related to a future HCC progression from these nodules.

## Materials and Methods

The present study was approved by the ethics committee of Shimane University Hospital, which waived the requirement for written informed consent because it was a retrospective analysis of medical records.

### Patients

We recruited patients who were initially examined using Gd-EOB-DTPA-MRI at Shimane University Hospital from June 2008 to June 2013 for any reason. All nodules found by that modality were then investigated in detail, after excluding liver hemangiomas and liver cysts. Nodules found in patients previously treated for HCC prior to the initial Gd-

EOB-DTPA-MRI examination were also excluded, as were those that were hypervascular in the arterial phase and washed out in a later phase, as such nodules can easily be diagnosed as HCC (7-9). Nodules  $\geq 5$  mm in diameter, hypovascular in the arterial phase, and those showing hypointensity in the hepatobiliary phase of Gd-EOB-DTPA-MRI were included, as such nodules potentially progress to HCC and were defined as hypovascular nodules for this study. As a result, 91 hypovascular nodules observed in 28 patients were included and evaluated.

### Study groups

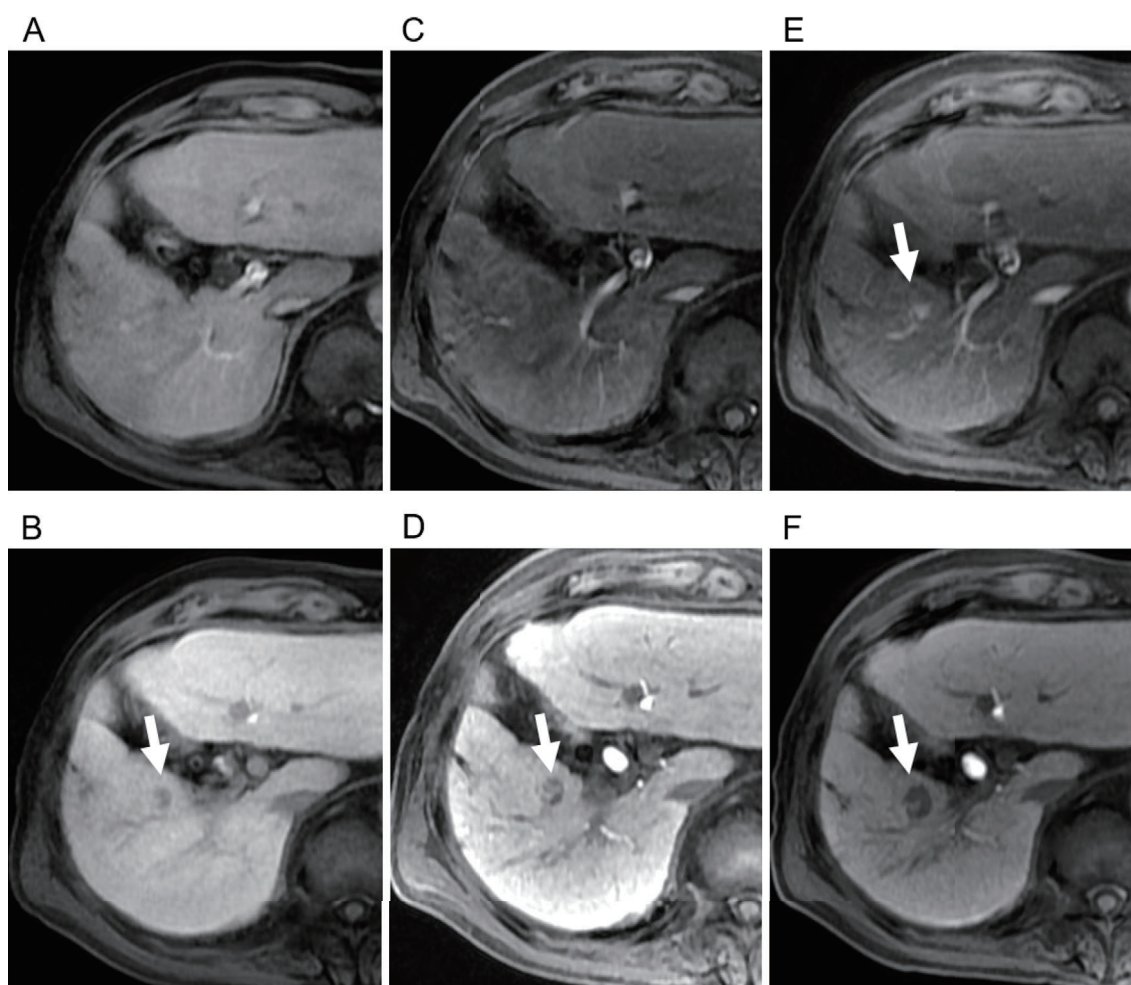
Nodules that were histopathologically diagnosed as HCC during the follow-up period were determined to be nodules that progressed to HCC during the study period. In addition, the HCC diagnosis was also made based on the hypervascularization of the nodules in the arterial phase of Gd-EOB-DTPA-MRI and/or those that showed an enlargement of 2 mm or more in diameter. The nodules were categorized into those that did and did not progress to HCC, and we made comparisons to reveal any factors possibly related to HCC progression. In addition to an analysis of each type of nodule, we also analyzed the characteristics of the patients who did and did not have nodules that progressed to HCC.

### MRI technique

Gd-EOB-DTPA-MRI was performed using a commercially available 1.5- or 3.0-T system (Signa HDx; GE Healthcare, Milwaukee, USA). For signal reception, an 8-channel phased-array surface coil that covered the entire liver was used. The arterial and hepatobiliary phases of dynamic fat-suppressed gradient-echo (GRE) T1-weighted images (T1WIs) were performed at 20-30 seconds and 20 minutes, respectively, after the administration of Gd-EOB-DTPA (Primovist<sup>®</sup>; Bayer Schering Pharma, Berlin, Germany) at 0.025 mmol/kg body weight at a speed of 1 mL/s through an intravenous cubital line, followed by flushing with 20 mL of saline. The images were acquired in the transverse plane and viewed in 5-mm slices.

### Statistical analysis

A statistical analysis was performed using the IBM SPSS Statistics software program, v. 19.0 (IBM, Chicago, USA). Clinical variables were compared between the groups using either Mann-Whitney's U test or Pearson's chi-square test. Mann-Whitney's U test was used to compare continuous values, including the observation period, patient age, peripheral blood platelet count, prothrombin time (PT), albumin, total-bilirubin (T-bil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), NH<sub>3</sub>, alfa fetoprotein (AFP), protein induced by vitamin K absence or antagonist-II (PIVKA-II), and the nodule size. Pearson's chi-square test was used to compare any categorical values, including gender, background liver etiology [hepatitis B viral infection, hepatitis C viral infection, or no such viral infection (non-B, non-C)], the presence of



**Figure 1.** Representative course of hypervascular transformation of hypovascular nodules observed in a 77-year-old man with chronic hepatitis C. Shown are images from the arterial/hepatobiliary phase of Gd-EOB-DTPA-MRI at the initial follow-up examination (A, B), then 2 (C, D), and 4 (E, F) years after the initial examination. In the hepatobiliary phase, a hypointense nodule was observed at the initial examination (B) and it showed a gradual growth thereafter (D, F: arrows). The nodule was not hypervascular in the images shown in (A) and (C), after which a hypervascular portion was observed (E: arrow). Gd-EOB-DTPA: gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid

ascites and hepatic encephalopathy, and the background liver condition (chronic hepatitis, Child-Pugh grade A or B liver cirrhosis).

A multivariate analysis was also conducted using the findings of a logistic regression analysis with the factors shown to be significantly different between the groups by Mann-Whitney's U test or Pearson's chi-square test. A p value <0.05 was considered to indicate a statistically significant difference.

A Kaplan-Meier time-to-event curve was produced to estimate the cumulative hypervascular transformation of nodules from a hypovascular state. This analysis was also done to estimate the cumulative progression ratio of nodules to HCC, which was defined as described above.

A receiver operating characteristics (ROC) analysis was performed for nodules followed for more than 12 months to determine the cut-off value of the initial nodule size for predicting HCC progression at 12 months.

## Results

The mean age of the 28 patients at the time of the initial Gd-EOB-DTPA-MRI examination was  $68.8 \pm 1.8$  (standard error: SE) years old. The mean observation period was  $1,172.6 \pm 95.6$  days and 16 of the 28 patients were treated during the observation period for hypovascular nodules that showed a progression to HCC. Fig. 1 presents a representative course that showed the hypervascular transformation of hypovascular nodules. All enrolled patients had chronic liver diseases, ranging from chronic hepatitis to Child-Pugh grade B liver cirrhosis (Table 1).

In the 28 patients, we identified 91 hepatic hypovascular nodules with a risk of potential progression to HCC. Of those, 15 (16.5%) hypovascular nodules changed to hypervascular ones in the arterial phase and the mean observation period until that transformation was  $808.0 \pm 137.9$  days.

**Table 1. Baseline Characteristics of All Patients (n=28).**

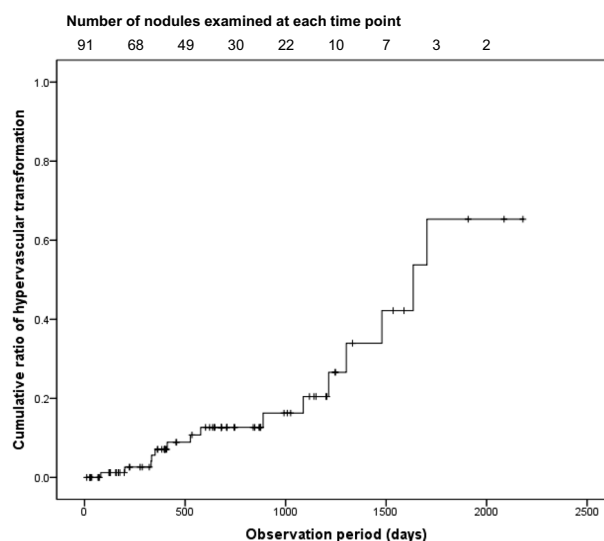
All patients (n=28)	
Observation period (days)	1,172.6±95.6
Sex	
male	12
female	16
Age (years)	68.8±1.8
Etiology	
hepatitis B virus	3
hepatitis C virus	16
non-B, non-C	9
Therapy for HCC during observation period	
yes	16
no	12
Number of Gd-EOB-DTPA-MRI examinations	5.6±0.6
Number of hypovascular nodules	3.3±0.5
Platelets (×10 <sup>4</sup> /μL)	10.5±0.9
PT (%)	87.3±5.2
Albumin (g/dL)	3.9±0.1
T-Bil (mg/dL)	0.94±0.06
AST (U/L)	60.4±4.9
ALT (U/L)	50.0±4.8
LDH (U/L)	224.8±9.2
NH <sub>3</sub> (μg/dL)	93.8±21.8
Ascites	
+	1
-	27
Encephalopathy	
+	3
-	25
AFP (ng/mL)	18.7±3.3
PIVKA-II (mAU/mL)	47.4±17.0
Clinical diagnosis	
chronic hepatitis	8
liver cirrhosis Child-Pugh grade A	15
liver cirrhosis Child-Pugh grade B	5

Data were expressed as means±standard error.

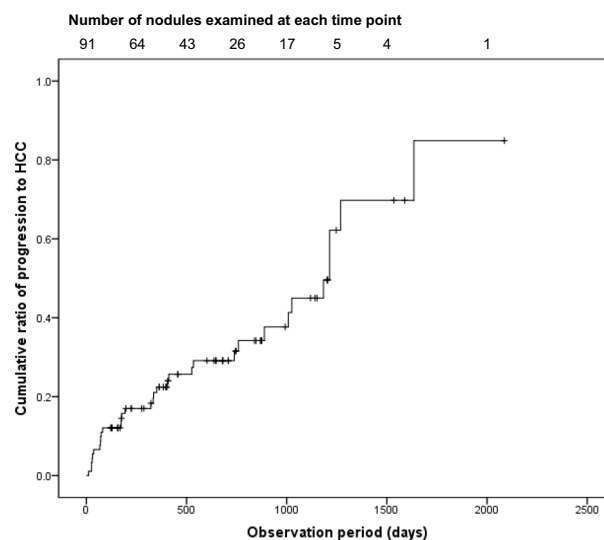
AFP: alpha fetoprotein, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, PIVKA-II: protein induced by vitamin K absence or antagonist-II, PT: prothrombin time, T-Bil: total-bilirubin

Fig. 2 shows the cumulative ratio of hypervascular transformation, which was 7.1% at 12 and 12.7% at 24 months. Fig. 3 presents the cumulative ratio of hypovascular nodule progression to HCC including hypervascular transformation and nodule enlargement, which was 22.4% at 12 and 29.1% at 24 months.

Among all 91 hypovascular nodules, 33 in 18 patients were finally classified as showing HCC progression, while the remaining 58 were classified as non-progression. A univariate analysis revealed significant differences in regard to the etiology of liver damage ( $p=0.001$ ), plasma PIVKA-II concentration ( $p=0.023$ ), and background liver condition ( $p=0.039$ ) between the nodule groups (Table 2). However, according to the multivariate analysis findings, those did not remain as significant predictive factors.



**Figure 2. Cumulative ratio of hypervascular transformation. The cumulative incidence of hypervascular transformation was 7.1% at 12 and 12.7% at 24 months.**



**Figure 3. Cumulative ratio of the progression of hypovascular nodules to HCC. The cumulative incidence of the progression to HCC including hypervascular transformation and enlargement of the nodules was 22.4% at 12 and 29.1% at 24 months. HCC: hepatocellular carcinoma**

While 18 patients had nodules that progressed to HCC, there were 10 patients with nodules that showed no such progression. As for the differences between these patient groups, age ( $p=0.002$ ) and etiology of liver damage ( $p=0.013$ ) were found to be significant in a univariate analysis (Table 3). However, in a multivariate analysis, those did not remain as significant predicting factors.

Among the 91 original hypovascular nodules, 17 were followed for less than 12 months without any progression to HCC. We conducted a ROC analysis of the remaining 74 nodules to predict their progression to HCC at 12 months. The initial nodule size yielded an area under the ROC

**Table 2. Baseline Nodule Characteristics and Results of Univariate Analysis (n=91).**

	All (n=91)	Progression to HCC (n=33)	No progression to HCC (n=58)	Univariate analysis p value
Observation period (days)	668.8±52.8	466.2±79.8	635.1±54.8	0.027
Sex				0.228
Male	35	10	25	
Female	56	23	33	
Age (years)	71.9±1.0	73.6±1.3	70.8±1.3	0.083
Etiology				0.001
hepatitis B virus	7	1	6	
hepatitis C virus	51	27	24	
non-B, non-C	33	5	28	
Platelets (×10 <sup>4</sup> /μL)	10.7±0.6	10.6±0.8	10.8±0.8	0.992
PT (%)	84.1±2.5	88.5±2.8	80.3±3.8	0.091
Albumin (g/dL)	3.8±0.1	3.9±0.1	3.8±0.1	0.365
T-Bil (mg/dL)	0.85±0.03	0.79±0.05	0.89±0.04	0.146
AST (U/L)	64.3±2.8	64.3±4.5	64.3±3.7	0.757
ALT (U/L)	51.8±2.6	54.8±5.1	50.1±2.8	0.493
LDH (U/L)	225.0±5.3	229.7±9.7	222.2±6.2	0.775
NH <sub>3</sub> (μg/dL)	79.5±8.6	81.8±16.0	77.5±8.6	0.705
Ascites				0.265
+	2	2	0	
-	55	31	24	
Encephalopathy				0.706
+	4	3	1	
-	53	30	23	
AFP (ng/mL)	19.7±1.7	22±3.2	18.5±1.9	0.395
PIVKA-II (mAU/mL)	51.3±8.4	34.1±8.2	64.8±13.2	0.023
Background liver				0.039
chronic hepatitis	16	10	6	
liver cirrhosis Child-Pugh grade A	57	19	38	
liver cirrhosis Child-Pugh grade B	18	4	14	
Nodule size (mm)	7.8±0.3	9.0±0.7	7.2±0.2	0.204

Data were expressed as means±standard error.

AFP: alpha fetoprotein, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, PIVKA-II: protein induced by vitamin K absence or antagonist-II, PT: prothrombin time, T-Bil: total-bilirubin

(AUROC) with a level of 0.745 (Fig. 4), with an optimal cut-off value of 9.5 mm (sensitivity, 57.9%; specificity, 87.3%).

## Discussion

Hepatic nodules that appear as hypovascular in the arterial phase and hypointense in the hepatobiliary phase of Gd-EOB-DTPA-MRI are challenging since it is difficult to predict their development into HCC, as some are known to progress to typical HCC with hypervascular transformation, whereas others do not show such progression. Although some studies have focused on the natural history of these nodules, most of those included patients with a previous history of HCC treatment (10-16). Hyodo et al. and Inoue et al. reported that a previous treatment history for HCC was a risk factor for hypervascular transformation of hypovascular nodules (15, 16), thus, it is important to closely follow patients with a HCC treatment history (17, 18). On the other

hand, the possible predictive risk factors for future HCC transformation have not yet been adequately investigated in cases without a previous HCC treatment history. None of the present patients in this study had received any HCC treatment prior to the study, in contrast to those other reports.

In the present cases, 15 of 91 hypovascular nodules (16.5%) showed hypervascular transformation during the follow-up period and the cumulative incidence of hypervascular transformation at 12 months was 7.1%. Previous reports have shown that 11.9% to 34.3% of hypovascular nodules became hypervascular, with a hypervascular transformation rate at 12 months ranging from 14.9% to 43.5% (10-16). The patients in those previous studies included those with a past HCC treatment history, thus recurrent and intrahepatic metastatic lesions may have been among the hypervascular transformed lesions investigated, which may explain why the cumulative incidence of hypervascular transformation in our study was lower in compari-

**Table 3. Baseline Patient Characteristics and Results of Univariate Analysis (n=28).**

	Progression to HCC (n=18)	No progression to HCC (n=10)	Univariate analysis p value
Observation period (days)	554.1±118.7	738.3±99.6	0.250
Sex			0.172
Male	6	6	
Female	12	4	
Age (years)	73.0±2.0	61.4±1.9	0.002
Etiology			0.013
hepatitis B virus	1	2	
hepatitis C virus	14	2	
non-B, non-C	3	6	
Platelets (×10 <sup>4</sup> /μL)	10.4±1.0	10.4±1.9	0.924
PT (%)	88.8±3.6	82.7±7.7	0.741
Albumin (g/dL)	3.8±0.1	4.0±0.2	0.470
T-Bil (mg/dL)	0.85±0.07	1.06±0.11	0.142
AST (U/L)	61.3±5.4	59.6±9.8	0.549
ALT (U/L)	50.0±6.0	50.8±8.0	1.000
LDH (U/L)	221.4±11.4	225.0±14.3	0.848
NH <sub>3</sub> (μg/dL)	102.0±27.5	66.3±15.2	0.735
Ascites			0.448
+	1	0	
-	17	10	
Encephalopathy			0.927
+	2	1	
-	16	9	
AFP (ng/mL)	22.6±5.2	13.8±3.6	0.342
PIVKA-II (mAU/mL)	41.4±14.4	136.0±72.2	0.282
Background liver			0.756
chronic hepatitis	6	2	
liver cirrhosis Child-Pugh grade A	9	6	
liver cirrhosis Child-Pugh grade B	3	2	

Data were expressed as means±standard error.

AFP: alpha fetoprotein, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, PIVKA-II: protein induced by vitamin K absence or antagonist-II, PT: prothrombin time, T-Bil: total-bilirubin

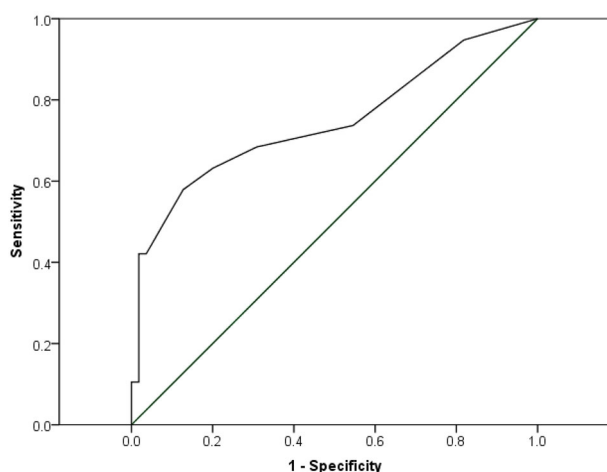
son to other reports.

In the present study, we compared 2 types of hypovascular nodules, those that did and did not show progression to HCC, and 2 types of patients, those who did and did not have hypovascular nodules that progressed to HCC. However, there was no statistical difference in regard to the background factors including all clinical data between those 2 groups of nodules and patients. It is difficult to classify hypovascular nodules into those with a high risk of progression to HCC based on background factors alone at the initial time of identification, and thus it is important to closely monitor all hypovascular nodules.

Some previous reports have noted that the initial nodule size is a risk factor for the future development of HCC (10-13). Although the present analysis was limited to lesions followed for at least 12 months, our results suggested that the initial nodule size of the nodule is useful for predicting HCC progression within 12 months. Motosugi et

al., Kumada et al. and Takechi et al. reported 11, 15, and 9 mm, respectively, as the optimal nodule size cut-off values (10, 11, 13), which are slightly larger than that determined in the present study (cut-off 9.5 mm), because these results covered only nodules showing hypervascular change. On the other hand, Takayama et al. reported 9 mm as an optimal nodule size cut-off value for progression to hypervascular and/or an enlarged lesion (12), very similar to that found in the present study.

This study is associated with some limitations, including its retrospective nature. In addition, the interval between Gd-EOB-DTPA-MRI examinations was dependent on the attending physician and varied among the patients. A future prospective study with a consistent follow-up interval would make more precise risk assessment possible. Furthermore, a histopathological diagnosis of nodules was lacking in this study. The parameters used for the HCC diagnosis were hypervascular transformation and/or remarkable enlargement.



**Figure 4.** A receiver operating characteristics (ROC) analysis for predicting HCC progression at 12 months. The area under the ROC (AUROC) was 0.745 and the optimal cut-off value was determined to be 9.5 mm (sensitivity, 57.9%; specificity, 87.3%). HCC: hepatocellular carcinoma

Finally, the number of patients and nodules included in this study was rather limited. It will be necessary to conduct a prospective study to investigate nodule size and the etiology of liver damage that was shown to be a significant factor according to a univariate analysis among all nodules and patients.

In conclusion, in patients without any past HCC treatment history, it is difficult to divide hypovascular nodules into those with a high risk of progression to HCC based on background factors alone at the time of initial identification. Since hypovascular nodules have the potential for HCC development, it is important to closely follow up such affected patients.

The authors state that they have no Conflict of Interest (COI).

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