Hypovascular Hepatic Nodules Showing Hypointense on the Hepatobiliary-Phase Image of Gd-EOB-DTPA-Enhanced MRI to Develop a Hypervascular Hepatocellular Carcinoma: A Nationwide Retrospective Study on Their Natural Course and Risk Factors

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Key Words

Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid · Enhanced MRI · Hepatocellular carcinoma · Hypervascular transformation

Abstract

Objective: We aimed to investigate the natural outcome of nonhypervascular lesions detected in the hepatobiliary phase of gadolinium ethoxybenzyl diethylenetriamine pen-

taacetic acid (Gd-EOB-DTPA)-enhanced MRI by performing a longitudinal study retrospectively enrolled in a nationwide manner. **Methods:** Between February 2008 and March 2011, 224 patients with 504 nodules that were diagnosed as nonhypervascular by imaging were recruited from institutions that participated in the present study. We examined the natural outcome of nonhypervascular lesions and evaluated the risk factors. **Results:** Of the 504 nodules, 173 (34.3%) showed hypervascular transformation. The overall cumulative incidence of hypervascular transformation was 14.9% at 12

months and 45.8% at 24 months. Multivariate analysis using the Cox regression model revealed previous treatment history for hepatocellular carcinoma (HCC; relative risk = 1.498; $p = 0.036$, 95% CI 1.03–2.19) and hyperintensity on T2-weighted images (relative risk = 1.724; $p = 0.015$, 95% CI 1.11–2.67) were identified as independent factors for hypervascular transformation. **Conclusions:** Patients who have a previous treatment history for HCC and with hypointense nodules showing hyperintensity on T2-weighted images need careful follow-up because of the high incidence of hypervascular transformation.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and is a major cause of death in patients with cirrhosis; therefore, it is important to detect and treat HCC at an early stage. The development of screening programs for high-risk HCC patients, involving periodic ultrasonography (US) and computed tomography (CT), has enabled small HCCs less than 2 cm in diameter to be easily detected and safely resected. As a result, we have encountered more early-stage HCCs [1], low-grade dysplastic nodules and high-grade dysplastic nodules. Histological features of these nodules are sequential and they often display heterogeneous internal histological features, the precise differential diagnosis between borderline lesions and early-stage, highly well-differentiated HCC (early HCC) is often difficult even by histological examination [2, 3]. Consequently, the imaging findings of these two are similar and overlapping, typically showing nonhypervascularity on dynamic CT, dynamic MRI and contrast-enhanced US; and internal portal blood supply on CT during arterial portography (CTAP) [4]. A previous study reported the existence of a significant correlation between the intranodular blood supply, as evaluated by CTAP and CT during hepatic arteriography (CTHA), and the prognosis of hepatocellular nodules associated with liver cirrhosis [5]. CTAP and CTHA are recognized as the most sensitive modalities for detecting HCC and borderline lesions [6–12]; however, a less invasive and more accurate diagnostic procedure is preferable. A hepatocyte-specific contrast agent, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA; Primovist®), was approved in Japan in January 2008. This contrast agent is hepatocyte specific and enhances the blood pool – it is taken up by hepatocytes and excreted into the biliary tract. The liver paren-

Table 1. Baseline characteristics of the patients

Sex (male/female)	134/90
Median age, years (range)	70 (49–88)
Child-Pugh classification (A/B/C)	187/37/0
Etiology and histology of underlying liver disease	
HCV-related chronic hepatitis	26
HCV-related cirrhosis	118
HBV-related chronic hepatitis	14
HBV-related cirrhosis	40
Others	26
Past history of HCC (yes/no)	180/44
Coexistence of hypervascular HCCs (yes/no)	85/139

chyma is strongly stained white in the hepatocyte phase on T1-weighted images, 20 min after the intravenous injection of Gd-EOB-DTPA. This liver-specific MRI phase has been reported to increase the detection of focal liver lesions, including HCC [13–17], and is expected to detect early pathological change in hepatocarcinogenesis [18–20]. Hypointense lesions in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI that show nonhypervascularity on dynamic imaging are commonly encountered, and it is recommended that these lesions be monitored closely due to their potential for malignancy and transitioning to HCC through a multistep progression of hepatocarcinogenesis [21–23]. Several studies have reported the outcome of patients with these hypointense lesions [22–29]; however, only a small number of such cases have been reported and all were from a single center. The present investigation was a longitudinal retrospective nationwide study that examined the natural outcome of nonhypervascular lesions in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI.

Materials and Methods

Our retrospective analysis of data was approved by the institutional review board of Kinki University Faculty of Medicine. The requirement to obtain informed consent was waived.

Patients

Between February 2008 and March 2011, 224 patients with 504 nodules that were diagnosed as nonhypervascular by imaging modalities including Gd-EOB-DTPA-enhanced MRI were recruited from institutions that participated in the present study. Baseline characteristics of the patients are shown in table 1.

Image Analysis: Evaluation of Tumor Vascularity

Evaluation of tumor vascularity was performed using at least 2 imaging modalities including Gd-EOB-DTPA-enhanced MRI at each institution according to the local standard of care. All im-

Table 2. Characteristics of vascularized and nonvascularized nodules

Variables	Hypervascularization		p value
	yes (n = 173)	no (n = 331)	
Tumor size, mm	9.74±4.04	9.11±4.04	0.059
Past history of HCC treatment (yes/no)	139/34	232/99	0.014
Precontrast MRI T1WI (hyper-iso/low)	24/149	27/304	0.061
Fat containing nodule on in- and opposed-phase images (yes/no)	36/137	64/267	0.72
Precontrast MRI T2WI (hyper/iso-low)	25/148	28/303	0.037
Dynamic image ¹ arterial phase (iso/low)	108/65	235/96	0.0501
Dynamic image ¹ portal phase (iso/low)	124/49	245/86	0.59
Observation period, days	379	566	0.00

Continuous variables are expressed as median with range. T1WI = T1-weighted imaging; T2WI = T2-weighted imaging; hyper = hyperintensity; iso = iso intensity; low = low intensity on MRI.

¹ Dynamic image means any of the available modalities were used (Gd-EOB-DTPA-enhanced MRI, dynamic CT, contrast-enhanced US, CTHA and CTAP). When CTHA and CTAP were performed, we adopted those image findings.

ages were interpreted independently by an experienced board-certified radiologist or gastroenterologist who knew that the patients were at risk for HCC but had no other clinical information. A nonhypervascular nodule was defined as a nodule in which all parts showed nonhypervascularity relative to the surrounding liver parenchyma during the arterial phase of dynamic imaging when any of the available modalities were used (Gd-EOB-DTPA-enhanced MRI, dynamic CT, CTHA and contrast-enhanced US). The exclusion criteria for hypointense lesions in the hepatobiliary-phase image of Gd-EOB-DTPA-enhanced MRI were as follows: (a) hypervascularity on initial dynamic MRI (i.e. exclusion of classical HCC and other hypervascular tumors); (b) delayed enhancement on initial dynamic MRI (i.e. exclusion of slow-fill hemangiomas); (c) strong high intensity on T2-weighted images (i.e. excluding cysts), and (d) lesion size of <2 mm (since the slice thickness for the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI was 3 mm).

Statistical Analysis

Continuous variables were presented as the median and range. Continuous variables such as tumor size and observation period were compared by Mann-Whitney U test, and other categorical variables were compared by Fisher's exact test or χ^2 test. Based on the analysis of lesions, the cumulative risk of a nonhypervascular tumor turning into classical HCC was calculated according to the Kaplan-Meier method. We calculated relative risk using Cox proportional hazard regression analysis. Based on the analysis of tumors, hypervascularization curves were constructed according to the Kaplan-Meier method, and the log-rank test was used for statistical comparisons. A p value <0.05 was considered to denote a statistically significant difference. All analyses were performed with SPSS statistics software (version 11, SPSS, Chicago, Ill., USA) for Microsoft Windows.

Table 3. Univariate analysis

Variables	p value
Tumor diameter >11 mm	0.018
Previous treatment history for HCC	0.023
Coexistence of hypervascular HCC	0.32
MRI finding	
T1-weighted imaging	0.00
T2-weighted imaging	0.004
Fat-containing nodule on in- and opposed-phase images	0.84
Image findings of dynamic study ¹	
Arterial phase	0.06
Portal phase	0.30

Bold p values are statistically significant.

¹ Dynamic study means any of the available modalities were used (Gd-EOB-DTPA-enhanced MRI, dynamic CT, contrast-enhanced US, CTHA and CTAP). When CTHA and CTAP were performed, we adopted those image findings.

Results

Nodule Characteristics

Table 2 shows the characteristics of the nodules that were vascularized and those that were not. Of the 504 nodules, 173 (34.3%) showed hypervascular transformation in the arterial phase of dynamic imaging during the follow-up period. The results of data analysis using Fish-

Fig. 1. Cumulative rates for hypointense lesions to hypervascularization. The cumulative rates for hypointense lesions that became classical HCC were 14.9% at 1 year and 45.8% at 2 years.

Fig. 2. Differences in the incidence of hypervascular transformation in relation to previous treatment history for HCC. The log-rank test p value was 0.023, indicating that the incidence of hypervascular transformation was significantly higher among patients who had a previous history of treatment for HCC.

er's exact test showed that, at the start of follow-up, nodules with and without vascularization showed significant differences in the proportion of patients who had a past history of HCC ($p = 0.014$) and the incidence of tumors displaying hyperintensity on T2-weighted images ($p = 0.037$). There were no differences between nodules with and without vascularization with respect to average tu-

Table 4. Multivariate analysis

Variables	Relative risk	95% CI	p value
Previous treatment history for HCC (yes)	1.498	1.026–2.187	0.036
Tumor diameter >11 mm	1.344	0.971–1.860	0.075
T1-weighted imaging (low)	0.979	0.675–1.420	0.910
T2-weighted imaging (hyper)	1.724	1.111–2.673	0.015

Bold p values are statistically significant.

mor diameter, T1-weighted images, being fat containing on in- and opposed-phase images, and arterial and portal-phase images of dynamic study.

Cumulative Incidence of Hypervascular Transformation

The overall cumulative incidence of hypervascular transformation was 14.9% at 12 months and 45.8% at 24 months (fig. 1). Univariate analysis using the log-rank test revealed that a past history of HCC, tumor diameter >11 mm, and T1- and T2-weighted images were correlated with hypervascular transformation (table 3). Next, the four significant factors identified by univariate analysis were analyzed by multivariate analysis using the Cox regression model (table 4). Previous treatment history for HCC (relative risk = 1.498; $p = 0.036$, 95% CI 1.03–2.19) and hyperintensity on T2-weighted images (relative risk = 1.724; $p = 0.015$, 95% CI 1.11–2.67) were identified as independent factors for hypervascular transformation. Subsequently, we compared the incidence of hypervascular transformation of tumors with these risk factors based on the Kaplan-Meier curve. The incidence of hypervascularization was significantly higher in the groups with these prognostic factors (fig. 2–4).

Discussion

Since the introduction of Gd-EOB-DTPA-enhanced MRI in clinical practice, there have been several reports describing the effectiveness of the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI for the detection of HCC, including early HCC, because these lesions tend to show hypointensity on hepatobiliary-phase images [17, 30]. Although these hypointense lesions have been reported to exhibit a high rate of hypervascular transformation [22–29], the natural histories of such nodules had not

Fig. 3. Differences in the incidence of hypervascular transformation in relation to the T2-weighted images. The log-rank test *p* value was 0.004, indicating that the incidence of hypervascular transformation was significantly higher for hyperintense tumors.

been investigated in a nationwide study involving a large number of cases. Therefore, we aimed to identify tumor imaging findings associated with subsequent hypervascular transformation in nonhypervascular tumors that show hypointensity in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI in patients with chronic liver diseases. Among the initial imaging findings analyzed in the present study, previous treatment history for HCC and hyperintensity on T2-weighted images were significantly correlated with hypervascular transformation, indicating that these parameters may be useful predictive marker factors for hypervascular transformation of nonhypervascular tumors. Even though we performed curative therapy by resection or radiofrequency ablation to prevent HCC recurrence, the recurrence rate was nonetheless extremely high [31–33]. A longer duration of infection with hepatitis B or C virus is usually associated with progression of liver fibrosis. In that condition, oxidative stress in the liver is considered to be higher, and genetic and epigenetic mechanisms activate oncogenes and inactivate tumor suppressor genes. Activation of these pathological processes results in hepatocarcinogenesis [34–36]. Patients who have a previous history of treatment for HCC are likely to have suffered from the condition for a long time, resulting in a high prevalence of hepatocarcinogenesis. Considering this status, it is speculated that nonhypervascular tumors of patients who have past history of HCC have been suffering such an oxidative stress for a long time, leading to hypervascular transformation

as the next step at an earlier period. Another variable associated with an increased risk of hypervascular transformation was hyperintensity on T2-weighted images. Hyodo et al. [27] reported that the most important variable associated with an increased risk of hypervascular transformation was hyperintensity on T2-weighted images. They discussed that T2-weighted images might reflect peliotic changes in the intratumoral sinusoids of HCC, and that nodular regeneration, fibrosis and scarring that occur in the course of cirrhosis occasionally appear as hyperintense round lesions on T2-weighted images. For that reason, it is speculated that nonhypervascular tumors, for example dysplastic nodules with fibrosis and scarring, can be hyperintense on T2-weighted images [37, 38]. The findings from our present study suggest that the combination of T2-weighted images and hepatobiliary-phase images of Gd-EOB-DTPA-enhanced MRI could be useful in the prediction of hypervascular transformation of previously nonhypervascular nodules.

Based on patient background in the present study, the enrolled patients are considered to represent the daily practice of patients who are suffering from chronic liver diseases. Therefore, when we detected nonhypervascular tumors on hepatobiliary-phase image, it was important to recheck the findings of the T2 image of the precontrast MRI and to confirm the presence or absence of treatment history for HCC. Although we conducted a cooperative study and collected many nonhypervascular tumors and investigated the natural outcome of hypointense lesions in a nationwide manner, this study did have some limitations. The principal limitation was the variety of imaging equipment used. This limitation may have been inevitable because this was a multicenter study. Second, this was a retrospective study and, therefore, on imaging analysis our study was potentially limited by consensus review, although well-trained radiologists and physicians reviewed the images. Third, the interval between follow-up examinations was not consistent; a fixed follow-up interval would have enabled us to calculate more accurately. Fourth was the lack of a pathological diagnosis of the nodules examined. However, we consider that our image-based findings have clinical implications even though the pathological findings were unknown. Also, the purpose of the present study was to evaluate the incidence and predictive factors for hypervascular transformation in nonhypervascular tumors detected on the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI, not to distinguish between dysplastic nodules, early HCCs and well-differentiated HCCs that show to be nonhypervascular on dynamic study.

Fig. 4. A 79-year-old man with hepatitis C-related cirrhosis. **a–c** Initial dynamic CT. The hepatic nodule in segment 8 of the liver showed no contrast enhancement (arrow). **d–e** Initial Gd-EOB-DTPA-enhanced MRI. The nodule showed fat deposition on chemical-shift imaging (arrow, in-phase, **d**; out-of phase, **e**). On T2-weighted imaging, the nodule showed slight hyperintensity (arrow, **f**). Images for the arterial phase (arrow, **g**) and hepatobiliary phase (arrow, **h**) of Gd-EOB-DTPA-enhanced MRI at the start

of follow-up showed a hypointense nodule. **i** The arterial-phase image from Gd-EOB-DTPA-enhanced MRI 16 months after the start of follow-up showed a hypervascular spot in the nodule: tumor (arrow), hypervascular spot (arrowheads). **j** A hepatobiliary-phase image of Gd-EOB-DTPA-enhanced MRI 16 months after the start of follow-up showed a markedly hypointense nodule (arrow).

In conclusion, patients who have a previous treatment history for HCC and with hypointense nodules showing hyperintensity on T2-weighted images need careful follow-up because of the high incidence of hypervascular transformation.

Disclosure Statement

The authors have no conflicts of interest to declare.

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