Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging findings of borderline lesions at high risk for progression to hypervascular classic hepatocellular carcinoma

Title

Gd-EOB-DTPA-Enhanced MRI Findings of Borderline Lesions at High Risk for Progression to Hypervascular Classic Hepatocellular Carcinoma

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ABSTRACT

Objectives:

To assess the imaging features of hypovascular borderline lesions containing hypervascular foci on gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI), and to evaluate the ability of Gd-EOB-DTPA-enhanced MRI to diagnose high-risk borderline lesions possibly consistent with early HCC.

Methods:

Institutional review board approval was obtained for this retrospective analysis of imaging findings, and informed consent was obtained from 217 consecutive patients undergoing Gd-EOB-DTPA-enhanced MRI and angiography-assisted computed tomography (CT) for examination of hepatocellular nodular lesions in cirrhotic livers. There were 73 nodules showing hypervascular foci in borderline lesions identified by angiography-assisted CT. Signal intensity patterns of the nodules were evaluated on hepatobiliary phase Gd-EOB-DTPA-enhanced T1-weighted MRI obtained 20 minutes after intravenous (IV) injection of contrast media.

Results:

Among 73 high-risk borderline lesions, 59 were hypointense (81%) and 14 were isointense (19%), compared to background liver parenchyma. There were 27 untreated lesions followed by CT and/or MRI. Almost half of these nodules transformed into hypervascular HCC, regardless of signal intensities seen on hepatobiliary phase Gd-EOB-DTPA-enhanced MRI.

Conclusions:

Although many high-risk borderline HCC lesions are hypointense on hepatobiliary phase Gd-EOB-DTPA-enhanced MRI, some high-risk borderline lesions are isointense and transform at the same rate into hypervascular HCC.

Key words

Gd-EOB-DTPA-enhanced MR imaging

Hepatocellular carcinoma

Dysplastic nodule

Angiography assisted CT

Malignant foci

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common tumor in the world, and is the third most common cause of cancer-related death, after lung and stomach cancer[1]. Based on clinical and histopathological analyses, most HCC develops from chronic liver disease in a multistep process[2,3]. The spectrum of hepatocellular nodules ranges from benign regenerative lesions to classic HCC demonstrating vascular invasion and distant metastasis, with intermediate steps including low- and high-grade dysplastic nodules (DNs) and early HCC[4]. Among these nodules, high-grade DN and early HCC are now considered to be the precursors of classic HCC, and show a multistep progression from high-grade DN to early HCC to classic HCC. These high-grade DNs and early HCCs are called "borderline lesions" in clinical practice because they are difficult to differentiate by imaging and biopsy, and because of their biologically benign nature. The detection and characterization of early HCC is important because of its much higher potential for progression to classic invasive HCC[5].

The stepwise changes of the intranodular blood supply in parallel with the elevation of the grade of malignancy of these hepatocellular nodules have been previously verified[5]. According to computed tomography (CT) during arterial

portography (CTAP) and CT during hepatic arteriography (CTHA), borderline lesions commonly demonstrate an abundant internal portal supply on CTAP, and no definitely-increased arterial supply (hypovascular) on CTHA. When these lesions progress to hypervascular classic HCC, a hypervascular focus is almost always seen in the nodule on CTHA[5]. Therefore, the background hypovascular borderline lesion around the hypervascular focus is clinically considered to be a high-risk borderline lesion and is highly suspicious for early HCC. In addition, histological and genetic analyses revealed that these background borderline lesions were usually early HCC[6]. Diagnostic imaging of these high-risk background borderline lesions is therefore clinically important; however, the ultrasound, conventional CT, and magnetic resonance imaging (MRI) features of these lesions are similar to those of well-differentiated HCC, high-grade DN, or more benign lesions such as low-grade DN and large, regenerative nodules [7].

Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) is a new liver-specific contrast agent for use in MRI. This contrast agent accumulates in normally functioning hepatocytes in the delayed phase (hepatobiliary phase), which begins 10 to 20 min after injection [8]. It has been reported that the detectability of early-stage HCCs and some borderline lesions was extremely high using Gd-EOB-DTPA-enhanced MRI compared to other imaging methods[8].

Therefore, it is believed that this new contrast agent may enable good detection and characterization of early HCC and high-risk borderline lesions.

The purpose of this study was to assess the imaging features of hypovascular borderline lesions containing hypervascular foci on Gd-EOB-DTPA-enhanced MRI, and to evaluate the ability of Gd-EOB-DTPA-enhanced MRI to diagnose high-risk borderline lesions possibly consistent with early HCC.

MATERIALS AND METHODS

Institutional review board approval was obtained for this retrospective analysis of imaging findings. Informed consent was obtained from all patients for each examination and retrospective analysis of the imaging findings.

During the period from April 2008 to June 2009, within from 217 consecutive patients undergoing Gd-EOB-DTPA-enhanced MRI and angiography-assisted computed tomography (CT) for examination of hepatocellular nodular lesions in chronic liver disease, a total of 73 nodules demonstrating a hypervascular focus in a borderline lesion (high-risk borderline lesion) were identified by CTHA and CTAP in 42 patients. The nodules were evaluated in this retrospective study, which comprised 30 men and 12 women ranging in age from 56 to 87 years (mean age, 70.1 ± 7.9 years). There were 37

patients with associated liver cirrhosis and 5 patients with chronic hepatitis, and the specific conditions included hepatitis B virus-related cirrhosis in 5, hepatitis C virus-related cirrhosis in 25, both hepatitis B- and alcoholic-related cirrhosis in 1, alcoholic cirrhosis in 2, nonalcoholic steatohepatitis (NASH)-related cirrhosis in 3, hepatitis C virus-related chronic hepatitis in 5, and non-B and non-C viral-related cirrhosis in 1 patient.

All high-risk borderline lesion measurements were performed on CTHA images, and the largest diameter was employed for the analysis.

Hepatobiliary phase Gd-EOB-DTBA-enhanced MRI was performed within 1 month before or after CTAP and CTHA, and the ability of this technology to detect high-risk borderline nodules was analyzed.

CTAP and CTHA Examinations

CTAP and CTHA were performed after hepatic angiography combined with digital subtraction angiography (DFP-2000A; Toshiba, Japan) and a 64-slice multidetector row CT scanner (Aquilion; Toshiba) system. After femoral artery puncture, a 4-French catheter was selectively placed in the superior mesenteric artery for CTAP or in the common or proper hepatic artery for CTHA. Scanning parameters were as follows:

number of detector rows, 64; section thickness, 0.5 mm; table feed per rotation, 7.2 mm; reconstruction intervals, 3 mm; gantry rotation time, 400 msec; tube voltage, 120 kVp; and tube current, 400 mA. For CTAP, helical CT scanning began 24 sec after an infusion of 50 mL of iohexol (320 mg of iodine/mL) (Omnipaque; Daiichi, Tokyo, Japan) at 1.8 mL/sec was begun. Immediately before the injection of contrast medium, 5 µg of prostaglandin E1 (Palux; Taisyo, Tokyo, Japan) was injected into the superior mesenteric artery.

Approximately 10 min after CTAP was performed, CTHA was obtained with 3-mm reconstruction intervals. CTHA began 7 sec after injection of iohexol (320 mg iodine/mL) at 2 mL/sec was begun. The infusion continued throughout CT data acquisition. Angiographic procedures were performed by radiologists who each had more than 8 years of experience performing abdominal angiography.

MR Imaging

All individuals underwent MR imaging of the liver using a 1.5- or 3-Tesla MR system (Signa HDx; GE Healthcare, Milwaukee, Wis., USA). For signal reception in all examinations, an 8-channel anteroposterior phased-array surface coil covering the entire liver was placed around the patient.

Imaging protocols included unenhanced sequences (coronal single-shot fast spin-echo [SSFSE], transaxial T2-weighted fast spin-echo [FSE], in- and out-of-phase gradient-echo[(GRE]), dynamic GRE sequences in the arterial, portal-venous and extracellular phases, as well as delayed sequences (30–35 sec, 65–70 sec, 3 min, and 20 min respectively.). Each patient received an intravenous bolus injection of Gd-EOB-DTPA (Primovist; Bayer Schering Pharma, Osaka, Japan) as contrast agent at a dose of 25 µmol/kg body weight at a flow rate of 2 mL/sec, followed by a 20-mL saline flush. Dynamic as well as delayed imaging were performed using a fat-suppressed 3D T1-weighted GRE sequence employing parallel imaging (LAVA EFGRE ASSET breathhold: TR/TE=3.1 msec/1.4 msec; flip angle, 15°; field of view, 42×42 cm; matrix, 384×256, interpolated to 512×512; thickness, 4 mm; overlap 2 mm; ASSET acceleration, 2.0). All patients underwent delayed MR imaging 20 min after bolus administration of Gd-EOB-DTPA.

Image Evaluation

A "borderline lesion" diagnosis was used for a CTAP image demonstrating an intranodular portal supply, and decreased arterial supply relative to the surrounding liver seen in greater than half the nodule on a CTHA image. When a CTHA image

indicated a region of hyperdensity relative to the surrounding area of the nodule, it was defined as a "hypervascular focus", and the borderline lesion which contained it was defined as a "high-risk borderline lesion".

All images were interpreted retrospectively by 3 experienced radiologists (one with more than 10 and the others with more than 20 years of experience each in liver imaging). Each CT and MR image was evaluated with the interpreting radiologist blinded to the findings of the other imaging examination, and all images were analyzed subjectively and independently by these 3 radiologists. Disagreements were resolved by consensus. Interobserver correlation was not analyzed because of the simplicity of the image interpretation.

Hepatobiliary phase image finding of Gd-EOB-DTPA-enhanced MRI of the hypovascular part of high-risk borderline lesions were divided into the following three categories; hypointense compared to background liver, iso-intense with background liver, and hyperintense compared to background liver.

Follow up Study

Transition rate from high-risk borderline lesion to HCC was calculated with the Kaplan-Meier method among each findings of nodules seen on hepatobiliary phase

Gd-EOB-DTPA-enhanced MRI. HCC diagnosis was based on the AASLD guidelines for the management of HCC using follow up CT and MRI [9].

Statistics

Student t test was used to compare the size of high-risk borderline lesions, and log-rank (mantle-Cox) method was applied for comparison of transition rate from high-risk borderline lesion to HCC.

RESULTS

The mean largest diameter of 73 high-risk borderline HCC lesions detected on angiography-assisted CT was 13.7 ± 3.3 mm in diameter (ranged from 9 to 20 mm), and the mean largest diameter of hypervascular foci was 3.3 mm.

On hepatobiliary phase Gd-EOB-DTPA-enhanced T1-weighted MRI, 59 of the 73 high-risk borderline lesions were hypointense (80.8%, Fig. 1) and 14 were isointense (19.2%, Fig. 2), compared to background liver parenchyma. The mean largest diameter of the 59 hypointense high-risk borderline lesions was 13.7 ± 3.4 mm and of the 14 isointense high-risk borderline lesions was 13.7 ± 3.0 mm (P = 0.99, t-test).

Of the 73 hypovascular high-risk borderline lesions, 46 were treated using ultrasonography-assisted radiofrequency ablation (RFA) therapy, and 27 nodules that could not be easily seen on ultrasonography were followed using multiphasic contrast-enhanced CT and/or MRI. Among these nodules, 18 appeared hypointense and 9 appeared isointense on hepatobiliary phase Gd-EOB-DTPA-enhanced MRI. Nine of the 18 (50%) hypointense high-risk borderline lesions progressed to hypervascular HCC over a follow-up period of 1 to 16 months, and 5 of 9 (56%) isointense high-risk borderline lesions progressed to hypervascular HCC over a follow-up period of 4 to 18 months (Figs. 3, 4). There was no significant difference between the rates of transition from high-risk borderline lesions to HCC for the hypointense and isointense nodules seen on hepatobiliary phase Gd-EOB-DTPA-enhanced MRI (P = 0.59) (Fig. 5).

Comparing between nodules rapid transformation into HCC (1-9 months) and those transforming later (10 -18 months), there were no statistically significant differences in nodule size (rapid group 12.9±3.5 mm, later group 12.3±3.3 mm, p=0.74) and hypervascular foci size (rapid group 3.4±2.3 mm, later group 3.3±2.2 mm, p=0.88) in t-test.

Discussion

Cirrhosis is the strongest predisposing factor for HCC, with approximately 80% of HCC cases arising in a cirrhotic liver. The annual incidence of HCC is 2.0% – 6.6% in patients with cirrhosis compared to 0.4% in patients without cirrhosis [10]. The development of HCC in the cirrhotic liver is described either as de novo hepatocarcinogenesis or as a multistep progression, from low-grade dysplastic nodule to high-grade dysplastic nodule, to dysplastic nodule with microscopic foci of HCC, to small HCC, and finally to overt carcinoma[11, 12].

Angiography-assisted CT, including CTAP and CTHA, is a useful method for analyzing the hemodynamic characteristics of hepatic nodular lesions. According to previous analyses of cirrhotic nodule hemodynamics by angiography-assisted CT [13,14] and histological studies [15,16], the hemodynamics of the portal tract, including the normal portal vein (intranodular portal supply) and hepatic artery (intranodular arterial supply through normal hepatic arteries) are decreased in relation to the elevation of nodule malignancy grade. On the other hand, abnormal vascularization (intranodular arterial supply through newly formed abnormal arteries) gradually increases.

Therefore we can estimate nodule malignancy grade by assessing the intranodular blood supply. Determining this blood supply pattern is important for the early detection, characterization, and treatment of early-stage HCC [13, 14].

Histopathological differential diagnosis still has problems. Based on the consensus document of the International Consensus Group for Hepatocellular Neoplasia (ICGHN), differentiating an early HCC (small well-differentiated HCC of vaguely nodular type) from a high-grade dysplastic nodule (H-DN) remains difficult. The presence of stromal invasion in the histopathological specimen is the key criterion for differentiation of H-DN from early HCC [17].

Since hepatocellular invasion of intranodular portal tracts is usually a subtle microscopic histopathological finding, unless invasion obstructs the portal venous branch or hepatic arterial branch in the portal tract, it may be difficult to demonstrate stromal invasion in hepatocellular nodules by current radiological imaging technology based on intranodular hemodynamic analysis. Therefore, with the current imaging modalities, we believe it may be difficult to differentiate early HCC from H-DN according to the histopathological criteria, and we need to use different criteria for the screening of early-stage HCC by diagnostic imaging.

Our study using angiography-assisted CT revealed that there was a close correlation between the prognosis of hepatic nodules and blood supply patterns. According to that previous analysis, all completely hypovascular nodules with hypervascular foci progressed to completely hypervascular nodules (hypervascular

classical HCC) within approximately 900 days (malignant transformation). By contrast,

only approximately 30% of nodules without hypervascular foci (= hypovascular

borderline lesion) progressed to classical HCC during the same period, and

hypervascular foci appeared in all of those progressing nodules before their progression

to classical HCC [5].

Yu et al [18] have also reported that identification of a hypervascular focus in a

nonhypervascular nodule is essential for considering short-term follow-up or immediate

treatment of HCC.

Therefore, we have believed that for early detection and treatment of

hypervascular classical HCC, detecting hypovascular cirrhotic nodules with

hypervascular foci (high-risk borderline nodule) using angiography-assisted CT is

important.

However, angiography-assisted CT, including CTHA and CTAP, is not widely

performed for an in depth examination of the cirrhotic liver, because it is a more

invasive imaging modality than intravenous contrast-enhanced CT and MRI. We need

to develop a less invasive imaging method to differentiate high-risk borderline nodules

from various kinds of cirrhotic nodules.

Gd-EOB-DTPA is a novel liver-specific contrast agent for MRI. This contrast

agent accumulates in normally functioning hepatocytes in the delayed phase (hepatobiliary phase) which begins 10 to 20 min after injection. Therefore, we can assess the functioning status of cirrhotic nodules on hepatobiliary phase Gd-EOB-DTPA-enhanced MRI, which we could not do using conventional iodine contrast material for CT and Gd-DTPA contrast material for MRI.

Although it is well known that most hepatocellular carcinomas appear hypointense compared to background liver parenchyma on hepatobiliary phase Gd-EOB-DTPA-enhanced MRI[8], the imaging findings of hepatocellular carcinoma borderline lesions on hepatobiliary phase Gd-EOB-DTPA-enhanced MRI have not been well clarified.

In our preliminary analysis, 50% of hypovascular borderline lesion "without" hypervascular foci, showed isointensity, 30% showed hypointensity, and 20% showed hyperintensity on hepatobiliary phase of Gd-EOB-DTPA enhanced MRI (unpublished data).

In this study, we defined a hypovascular borderline lesion containing hypervascular foci detected on angiography-assisted CT as a "high-risk borderline lesion", and we have revealed that on hepatobiliary phase Gd-EOB-DTPA-enhanced MRI, 80.8% of high-risk borderline lesions appear hypointense compared to background

liver parenchyma.

This high-risk borderline lesion detection rate of hepatobiliary phase Gd-EOB-DTPA-enhanced MRI is better than the rates of modalities previously reported by Shinmura et al, including dynamic contrast-enhanced CT, dynamic contrast-enhanced MR, and SPIO-enhanced MR [19].

In addition, follow-up study of high-risk borderline lesions found that 50% of hypointense nodules and 56% of isointense nodules seen by hepatobiliary phase Gd-EOB-DTPA-enhanced MRI transformed into hypervascular HCC within a follow-up period of 1 to 18 months. There was no significant difference between the transition rates to hypervascular HCC between the hypointense and isointense nodules. These results indicate that both the hypo- and isointense nodules have similar degrees of malignant potential. Therefore it is important to note that not only hypointense, but also isointense nodules seen on hepatobiliary phase Gd-EOB-DTPA-enhanced MRI may transform to hypervascular HCC.

There are several limitations to this study. Since all the objective cases have definite hypervascular HCC in other part of the liver, we did not perform core needle biopsy for diagnose of these borderline lesions. So there were no histopathological confirmations of the borderline lesions and HCCs in this study. Another limitation is

that, in this study, although we focused on the borderline lesions with hypervascular foci, some regions of borderline lesions without hypervascular foci may transform to hypervascular HCC. We have no data about the sensitivity/specificity of the detection rate of hypervascular foci on angiography-assisted CT and other intravenous contrast enhanced images. In addition, regarding the follow-up analysis determining the transformation rate from high-risk borderline lesion to hypervascular HCC, because the number of nodules studied was low, there may be some bias in our results.

Although there are several study limitations, the results of our study indicate that for early detection and treatment of many hypervascular HCCs, it is important to follow hypovascular nodules which appear hypointense on hepatobiliary phase Gd-EOB-DTPA-enhanced MRI until they reveal staining on dynamic contrast-enhanced CT or MRI. However, it is important to point out that some high-risk borderline lesions appearing isointense on hepatobiliary phase Gd-EOB-DTPA-enhanced MRI also transformed into hypervascular HCC. So it would be better to use angiography-assisted CT together with Gd-EOB-DTPA enhanced MRI for screening and early detection of hypervascular HCC.

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Figure Legends

Fig.1 Hypovascular borderline HCC lesion with hypervascular foci (high-risk borderline lesion) in an 81-year-old man with cirrhotic liver from chronic B-viral hepatitis.

(a): Transverse CTAP shows isodense lesion (arrow) with a small hypodense spot (arrowhead) in segment III of the liver.

(b): Transverse CTHA shows an area of spotty hyperdensity (arrowhead) within a hypodense nodule (arrow).

(c): Transverse T1-weighted image of hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI shows hypointense nodule (arrow) containing an area of spotty isointensity (arrowhead) which corresponds to a hyperdense area on CTHA.

Fig.2 Hypovascular borderline HCC lesion with hypervascular foci (high-risk borderline lesion) in a 58-year-old female with cirrhotic liver from chronic C-viral hepatitis.

(a): Transverse CTAP shows isodense lesion (arrow) with a small hypodense spot (arrowhead) in segment II of the liver.

(b): Transverse CTHA shows an area of spotty hyperdensity (arrowhead) within a hypodense nodule (arrow).

(c): Transverse T1-weighted image of hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI shows an area of isointensity which is difficult to identify as a nodular lesion without other imaging findings (arrow).

Fig.3 Hypovascular borderline HCC lesion with hypervascular foci (high-risk borderline lesion) in a 66-year-old female with cirrhotic liver from chronic C-viral hepatitis.

(a): Transverse CTHA shows an area of spotty hyperdensity (arrowhead) within a hypodense nodule (arrow).

(b): Transverse T1-weighted image of hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI shows isointense nodule(arrow) containing an area of spotty hypointensity (arrowhead) which corresponds to hyperdense area on CTHA.

(c) Transverse arterial phase-enhanced CT 5 months after the initial EOB study shows well-attenuated mass lesion corresponding to the previous hypodense nodule (arrow).

(d): Transverse T1-weighted image of hepatobiliary phase Gd-EOB-DTPA-enhanced MRI 5 months after the initial EOB-enhanced study shows hypointense nodule (arrow).

Fig.4 Hypovascular borderline HCC lesion with hypervascular foci (high-risk borderline lesion) in a 59-year-old man with cirrhotic liver from chronic C-viral hepatitis.

(a): Transverse CTHA shows a spotty area of hyperdensity (arrowhead) within a hypodense nodule (arrow).

(b): Transverse T1-weighted image of hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI shows hypointense nodule (arrow).

(c); Arterial phase contrast-enhanced transverse CT, 4 months after the initial EOB-enhanced study, shows early contrast enhancement in the right lobe of the liver (arrow).

Fig.5 Graph shows nonmalignant transformation curves (calculated by Kaplan-Meier method) for both hypointense and isointense nodules on hepatobiliary phase of contrast-enhanced MRI.