

# Characteristics of Hypovascular versus Hypervascular Well-Differentiated Hepatocellular Carcinoma Smaller Than 2 cm – Focus on Tumor Size, Markers and Imaging Detectability

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## Key Words

Hypovascular well-differentiated HCC · Early HCC · Imaging detectability · Gd-EOB-DTPA MRI · Hepatobiliary phase · International working group · Arteriportal angiography

## Abstract

**Objectives:** The characteristics of hypovascular and hypervascular well-differentiated hepatocellular carcinomas (HCCs) were compared in terms of tumor size, tumor markers and detectability by imaging modalities. **Methods:** Well-differentiated HCC nodules that are smaller than 2 cm (n = 27) were evaluated in 27 patients using histopathology and divided into 2 groups: hypovascular (n = 10) and hypervascular (n = 17). The diagnostic sensitivity of imaging modalities was then evaluated for efficiency in disclosing tumor size and tumor markers in the 2 types. **Results:** No difference was observed in tumor size and tumor markers between the 2 types; however, the sensitivity of contrast-enhanced CT, contrast-enhanced ultrasonography and arteriportal angiography was significantly different between the 2 types, whereas that by Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid enhanced magnetic resonance imaging (Gd-EOB-

DTPA MRI) demonstrated no difference. **Conclusion:** Hypovascular HCC could be diagnosed by Gd-EOB-DTPA MRI in the hepatobiliary phase.

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## Introduction

Recent studies support the division of small hepatocellular carcinoma (HCC) into 2 clinicopathological categories termed early HCC and progressed HCC; the former has a vaguely nodular appearance and is well-differentiated, whereas the latter has a distinctly nodular pattern and is mostly moderately differentiated, often with evidence of microvascular invasion [1, 2].

The characteristic imaging appearance of progressed HCC, a hypervascular lesion that shows washout in the portal venous phase, is also typical in small HCCs of the distinctly nodular type and in most moderately differentiated and some well-differentiated small HCCs [3–7]. Most early HCCs are hypovascular lesions. Hypovascular well-differentiated HCC is considered an early HCC, as proposed by the International Working Group [8].

These classic images are explained by the anatomic features of the lesions. Hypovascularity, hypervascularity and isovascularity are understood to mean signal intensity in the arterial phase of contrast-enhanced imaging relative to the non-tumorous liver. Hypervascularity is related to the development of unpaired arteries, the absence of portal vein supply and the distinctly nodular growth [9].

From the view point of vascularity, 2 well-differentiated HCCs are categorized as hypovascular HCC and hypervascular HCC; however, they cannot be differentiated by routine ultrasonography (US) patterns.

Comparison of tumor size, tumor markers and imaging detectability in hypovascular and hypervascular HCCs remains to be clarified.

Here, to characterize hypovascular well-differentiated HCC, tumor size, tumor markers and imaging detectability were evaluated and compared with those of hypervascular well-differentiated HCCs.

## Materials and Methods

### Patients

From April 2008 to December 2009, a total of 27 nodules that were smaller than 2 cm diagnosed as well-differentiated HCC by histopathological analysis in 27 patients (13 men and 14 women,  $71.5 \pm 5.99$  years) with liver cirrhosis related to the hepatitis B virus (HBV;  $n = 1$ ), hepatitis C virus (HCV;  $n = 19$ ), alcohol ( $n = 6$ ) and non-HBV/HCV ( $n = 1$ ) were retrospectively examined (table 1). The study was approved by the Ethics Committee at Kobe Asahi Hospital.

### Assay of Serum Levels of Alpha-Fetoprotein and PIVKA II

Serum alpha-fetoprotein (AFP) concentrations were determined with a commercially available electrochemiluminescence immunoassay kit (Elecsys AFP immunoassay, Roche, Mannheim, Germany). Serum prothrombin induced by vitamin K absence II (PIVKA II) level was measured by revised enzyme immunoassay (Eitest PIVKA II; Eisai, Tokyo, Japan).

### Contrast-Enhanced CT

Contrast-enhanced CT (CECT) was performed with the use of helical CT (Siemens, Germany) with pre- and post-contrast triple-phase (arterial, portal, venous and equilibrium phases) scans, after the injection of 120 ml of non-ionic contrast medium at 3 ml/s; the scans were carried out in a craniocaudal direction with 5 mm collimation in the other phases. Acquisition of the arterial and equilibrium phases was automatically started at 30 and 180 s, respectively, after the intravenous injection.

### Contrast-Enhanced US

US was carried out with an SSA-660A system (Toshiba Medical Systems, Tochigi, Japan). The vascular findings on phase-inversion harmonic US were shown as tumor vessel flow in the early vascular phase about 15–40 s after the injection of Sonazoid (GE

**Table 1.** Patient baseline characteristics in hypovascular and hypervascular HCCs

	Hypovascular HCC (n = 10)	Hypervascular HCC (n = 17)
Age, years, mean $\pm$ SD	71.0 $\pm$ 6.88	71.8 $\pm$ 5.61
Range	60–81	59–81
Sex, male/female	5/5	8/9
Cause, n		
HBV	1	0
HCV	8	11
Non-HBV/HCV	0	1
Alcohol	1	5

HealthCare, Piscataway, N.J., USA). Real-time replenishing images were acquired during the vascular phase (<2 min after the injection) by release-burst imaging. Images of liver parenchyma were acquired in the post-vascular Kupffer phase, at least 10 min after the intravenous injection of Sonazoid. Hepatic malignancies were visualized as defects in the post-vascular phase. An additional contrast agent was injected to confirm tumor vessel flow in the defect, a technique known as defect reperfusion imaging [10].

### Gadolinium-Ethoxybenzyl-Diethylenetriamine Pentaacetic Acid Enhanced MRI

Images by MRI scans (Philips, The Netherlands) were obtained using the 1.0-Tesla superconducting system (Gyrosan 10T-NT, Philips, The Netherlands). Enhanced MRI was used to acquire coronal images by the gradient-echo technique (fixed-field gradient) at 150/3.5 ms TR/TE, 80° flip angle and a 168  $\times$  256 matrix. In each sequence, the respiration suspension time was 20–30 s. Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid enhanced (Gd-EOB-DTPA) MRI (Primovist; Bayer HealthCare, Osaka, Japan) at a dose of 0.025 mmol/kg body weight was injected intravenously as a rapid bolus at 2 ml/s. Dynamic contrast-enhanced MRI was initiated at 30 and 70 s, 2–3 and 20 min after the start of the bolus injection to acquire multiphasic (arterial, portal, late and hepatobiliary) images.

### CT Arteriportal Angiography (CTA and CTAP)

**CT during Arteriography (CTA).** At angiography, 45 ml of diluted contrast medium was injected through a catheter at 2 ml/s into the common hepatic artery. The whole liver was then scanned at intervals of 5–10 mm.

**CT during Arterial Portography (CTAP).** At angiography, 115 ml of diluted contrast medium was injected through a catheter at 2 ml/s into the superior mesenteric artery, according to the scanning time of the entire liver, using a power injector during sequential scanning, with incremental changes in the position of the table. Infusion of contrast material was initiated 20 s before CTAP. The whole liver was then scanned at intervals of 5–10 mm.

### US-Guided Biopsy

US-guided biopsy was carried out with the use of a 21-gauge Majima needle (Top, Japan). The diagnosis of HCC was made by K.S. and Y.H. using the same specimen.

### Histological Diagnosis

Specimens were routinely processed and stained with hematoxylin and eosin and by the Masson trichromatic method. The diagnosis of HCC was made according to the criteria of the International Working Party [8].

### Imaging Patterns for Conclusive Diagnosis of HCC by the 4 Modalities

The following patterns disclosed by the 4 imaging modalities were conclusive diagnosis of HCC: (1) CECT, hypervascularity in the arterial phase and washout in the equilibrium phase; (2) Sonazoid contrast-enhanced ultrasonography (CEUS), hypervascularity in the early vascular phase and defect in the Kupffer phase; (3) Gd-EOB-DTPA MRI, hypervascularity in the arterial phase and/or defect in the hepatobiliary phase and (4) CT arteriportal angiography, hypervascularity by CTA and/or perfusion defect by CTAP (table 2).

### Imaging Studies

To minimize differences in the results between the operators, imaging studies were carried out and reviewed by M.K. and T.M. using the same examination protocol.

### Statistical Analysis

The comparisons of sensitivity of tumor size, tumor markers and imaging detectability between hypovascular and hypervascular HCCs were assessed by univariate analysis using the Mann-Whitney U test and  $\chi^2$  test. Variables with a p value of <0.05 were considered statistically significant. All statistical analyses were carried out with EXCEL multivariate statistical analysis software, version 6.0 (ESUMI Inc., Toyo, Japan).

## Results

Among the 27 well-differentiated HCC nodules, 10 were categorized as hypovascular and 17 as hypervascular, with no difference in size between the 2 types (hypovascular HCC:  $11.9 \pm 2.6$  mm, hypervascular HCC:  $12.0 \pm 3.7$  mm). The average AFP value was  $7.7 \pm 5.4$  ng/ml for hypovascular HCC and  $53.7 \pm 118.9$  ng/ml for hypervascular HCC. The average PIVKA II was  $35.6 \pm 43.8$  mAU/ml for hypovascular HCC and  $52.3 \pm 98.6$  mAU/ml for hypervascular HCC. Tumor markers showed no difference between the 2 types (AFP:  $p = 0.236$ , PIVKA II:  $p = 0.613$ ; table 3).

Imaging sensitivity for hypovascular HCC was 0% (0 of 10) by CECT, 0% (0 of 10) by CEUS, 90% (9 of 10) by Gd-EOB-DTPA MRI and 60% (6 of 10) by CT arteriportal angiography. For hypervascular HCC, the respective sensitivity was 41% (7 of 17) by CECT, 47% (8 of 17) by CEUS, 82% (14 of 17) by Gd-EOB-DTPA MRI and 100% (17 of 17) by CT arteriportal angiography. A difference was observed in the sensitivity by CECT ( $p = 0.022$ ), CEUS ( $p = 0.011$ ) and CT arteriportal angiography ( $p =$

**Table 2.** Imaging patterns for conclusive diagnosis of HCC by the 4 modalities

Modality	Imaging pattern
CECT	Hypervascularity in the arterial phase and washout in the equilibrium phase
CEUS	Hypervascularity in the early vascular phase and defect in the Kupffer phase
Gd-EOB-DTPA MRI	Hypervascularity in the arterial phase and/or defect in the hepatobiliary phase
CTA and CTAP	Hypervascularity by CTA and/or perfusion defect by CTAP

**Table 3.** Tumor size and tumor marker in hypovascular and hypervascular HCCs

	Hypovascular HCC (n = 10)	Hypervascular HCC (n = 17)	p value
Tumor size, mm	$11.9 \pm 2.6$	$12.0 \pm 3.7$	0.940
AFP, ng/ml	$7.7 \pm 5.4$	$53.7 \pm 118.9$	0.236
PIVKA II, mAU/ml	$35.6 \pm 43.8$	$52.3 \pm 96.8$	0.613

Values are shown as means  $\pm$  SD.

**Table 4.** The sensitivity of imaging in hypovascular and hypervascular HCCs

	Hypovascular HCC (n = 10)	Hypervascular HCC (n = 17)	p value
CEUS	0	8	0.011
CECT	0	7	0.022
Gd-EOB DTPA MRI	9	14	0.523
CTA and CTAP	6	17	0.012

Values are shown as number of persons.

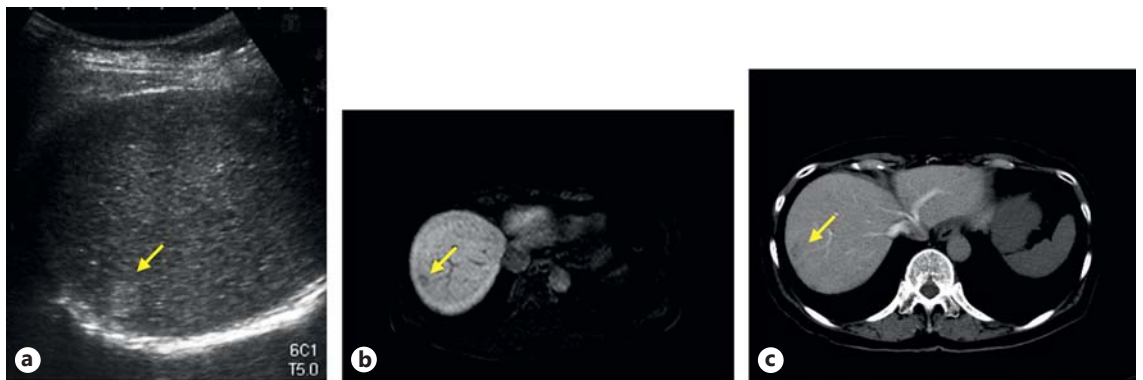
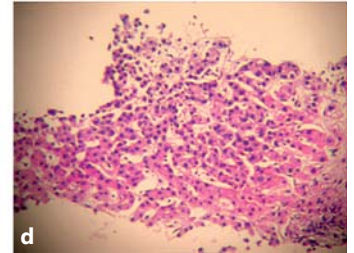
0.012) between the 2 types of HCCs; no difference was observed in the sensitivity by Gd-EOB-DTPA MRI ( $p = 0.523$ ; table 4).

### Representative Cases

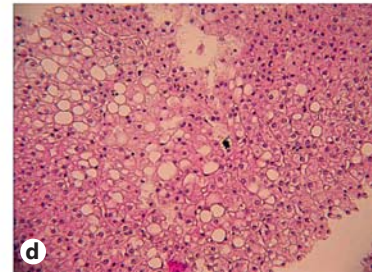
**Case No. 1.** Hypervascular well-differentiated HCC was detected by CT arteriportal angiography (CTA and CTAP) in a 63-year-old woman with alcohol-related liver cirrhosis (AFP 5.2 ng/ml, PIVKA II 34 mAU/ml). US revealed a 15 mm hypochoic nodule in segment 8 (fig. 1a).



**Fig. 1.** Case No. 1: Hypervascular well-differentiated HCC detected by CT arteriportal angiography. Imaging and histological findings of the nodule in segment 8. **a** US reveals a 15-mm hypoechoic nodule (arrow); **b, c** CTA reveals a hypervascular nodule (**b**) and CTAP (**c**) reveals a perfusion defect (arrow); **d** Histological finding of US-guided biopsy HE stained well-differentiated HCC characterized by moderate hypercellularity with slight cell atypia and eosinophilia are observed.



**Fig. 2.** Case No. 2: Hypovascular well-differentiated HCC detected by Gd-EOB-DTPA MRI and CTAP. Imaging and histological findings of the nodule in segment 8. **a** US reveals a 14-mm hyperechoic nodule in segment 8 (arrow); **b** Gd-EOB-DTPA MRI reveals a defect in the hepatobiliary phase (arrow); **c** CTAP reveals a perfusion defect (arrow); **d** HE staining. Slight hypercellularity with cell atypia and diffuse fatty change.



CEUS revealed no hypervascularity in the early phase and no defect in the Kupffer phase. CECT revealed no hypervascularity in the early phase and no washout in the equilibrium phase. Gd-EOB-DTPA MRI revealed no hypervascularity in the arterial phase and no defect in the hepatobiliary phase. CTA revealed a hypervascular nodule (fig. 1b) and CTAP revealed a perfusion defect (fig. 1c). US-guided biopsy revealed well-differentiated HCC characterized by moderate hypercellularity with slight cell atypia and eosinophilia (fig. 1d).

*Case No. 2.* Hypovascular well-differentiated HCC was detected by Gd-EOB-DTPA MRI and CT arteriportal angiography (CTAP) in a 68-year-old woman with chronic HCV infection (AFP 11.0 ng/ml, PIVKA II 14 mAU/ml). US revealed a 14 mm hyperechoic nodule in segment 8 (fig. 2a). CEUS revealed no hypovascularity in the early phase and no defect in the Kupffer phase. CECT revealed no hypervascularity in the early phase and no washout in the equilibrium phase. Gd-EOB-DTPA MRI revealed no hypervascularity in the arterial phase but disclosed a de-

fect in the hepatobiliary phase (fig. 2b). CTA revealed no enhanced lesion, but CTAP revealed a perfusion defect (fig. 2c). Histological analysis of a US-guided biopsy revealed well-differentiated HCC characterized by slight hypercellularity with cell atypia and diffuse fatty change (fig. 2d).

## Discussion

Recently clinicians have been able to conduct CTA, thereby acquiring data on lesions and intra-nodular blood flow simultaneously [11, 12].

Moreover, development of newly introduced diagnostic imaging techniques, Sonazoid CEUS and Gd-EOB-DTPA MRI has provided higher degrees of detectability for small HCC.

The status of imaging studies in the diagnosis of HCCs that are smaller than 2 cm has changed with the introduction of new contrast agents used in US and MRI. First, Sonazoid was exclusively approved in Japan in 2007 as a second-generation US contrast agent; Kudo et al. [10, 13, 14] have recently developed defect reperfusion imaging (featuring the properties of very stable Kupffer phase images and real-time fine blood flow images obtained with Sonazoid) for typical HCC, which is depicted by CT but not by B-mode scanning. The method is a breakthrough for accurate localization and treatment guidance [10]: dramatic resolution of many limitations in the diagnosis and treatment of HCC, such as detection of small HCCs [15], evaluation of treatment response [16] and needle insertion guidance; additionally, detection is even more sensitive than with multidetector CT [15].

Second, Gd-EOB-DTPA, a new liver-specific contrast agent used in MRI [17–19], was approved in Japan in 2008; this newly introduced agent is a hepatocyte-specific MRI contrast medium with a different mechanism that utilizes neither dynamic nor Kupffer cell imaging. It is useful in cases that would be difficult to diagnose by techniques such as dynamic MRI or superparamagnetic iron oxide MRI. Typical HCC displays high intensity with Gd-EOB-DTPA in the arterial-dominant phase and low intensity in the portal-dominant phase and thereafter. Thus, the diagnosis of HCC can be made approximately 10–20 min after the injection of Gd-EOB-DTPA.

The improvement in these 2 imaging modalities with the use of the newly introduced contrast agents has provided higher sensitivity for the diagnosis of nodules that are smaller than 2 cm than with SonoVue CEUS and CECT [20] or with SonoVue CEUS and Gd-EOB-DTPA MRI [21].

The sensitivity of CECT, Sonazoid US, Gd-EOB-DTPA MRI and CT arteriportal angiography has been compared in the diagnosis of HCC in nodules that are smaller than 2 cm [22]. In a study of 34 moderately differentiated ( $n = 24$ ) and well-differentiated HCC ( $n = 10$ ) nodules, the overall sensitivity has been 53.9% by CECT, 67.6% by Sonazoid-enhanced US, 76.5% by Gd-EOB-DTPA MRI and 88.2% by CT arteriportal angiography. A significant difference has been observed in the sensitivity between CECT and CT arteriportal angiography, but not among Sonazoid-enhanced US, Gd-EOB-DTPA MRI and CT arteriportal angiography. The authors have concluded that changing the main diagnostic modality for HCCs that are smaller than 2 cm from CT arteriportal angiography to Sonazoid-enhanced US and Gd-EOB-DTPA MRI is recommended [23].

From the view point of vascularity, well-differentiated HCC can be categorized as hypervascular and hypovascular HCCs. The present study was carried out because, to date, the difference between these categories in terms of tumor size, tumor markers and imaging detectability has not been characterized.

The results demonstrated no difference between hypervascular and hypovascular HCCs in tumor size and tumor markers including AFP and PIVKA II [24] (table 4); in other words, they could not be differentiated through tumor size or tumor markers.

In the diagnosis of hypovascular HCC, CECT and CEUS were totally ineffective, Gd-EOB-DTPA MRI was markedly effective and arteriportal angiography was moderately effective (table 3).

Histopathological findings have demonstrated that early HCC tumors are vaguely nodular and are characterized by various combinations of the following major features [25–27]: (1) increased cell density of more than 2 times that of the surrounding tissue, with an increased nuclear/cytoplasm ratio and an irregularly thin-trabecular pattern, (2) a varying number of portal tracts within the nodule (intra-tumoral portal tracts), (3) a pseudoglandular pattern, (4) diffuse fatty change and (5) a varying number of unpaired arteries.

Although most hypervascular and hypovascular well-differentiated HCCs (like representative cases 1 and 2) were characterized by the above major histological features, stromal invasion, described by the International Consensus Group for Hepatocellular Neoplasia as helpful in differentiating early HCC from high-grade dysplastic nodules [9], is invasion into portal tracks of septal stroma within a hepatocellular nodule and is confirmed by Victoria blue staining.

Stromal invasion, which may be difficult to identify in early HCC because tumor cells show little or no cytologic atypia, is often focal; its identification is still more difficult when dealing with biopsied liver tissue in which only limited portions of nodules are sampled. CK7 immunostaining is useful in identifying stromal invasion. Ductular reaction, confirmed by CK7 immunostaining, is frequently found in non-cancerous hepatocellular nodular lesions, whereas it is less frequently found in HCCs with true stromal invasion [23].

Early HCC takes longer to recur and has a higher 5-year survival rate than progressed HCC [28]. The prognosis of early HCC is considered good because of the absence of portal invasion and daughter nodules [29].

Thus, the diagnosis of hypovascular well-differentiated HCC will gain increasing importance in the management of HCC.

In conclusion, in view of the invasiveness of CT arterioportal angiography, the imaging algorithm focused on Gd-EOB-DTPA MRI in the hepatobiliary phase for the diagnosis of hypovascular HCC is routinely used in clinical settings in Japan [4, 19]. Here, we strongly recommend the use of this imaging modality in other countries where HCC is endemic.

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### Disclosure Statement

The authors declare that they have no financial conflict of interest.

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