

# Histologic Characteristics of Hepatocellular Carcinomas Showing Atypical Enhancement Patterns on 4-Phase MDCT Examination

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**Objective:** To retrospectively define which histologic characteristics of small-sized hepatocellular carcinomas (HCCs) are related to atypical dynamic enhancement on multi-detector computed tomography (MDCT) imaging.

**Materials and Methods:** Seventy-three patients with 83 HCCs (3 cm or less in diameter) were included in this study. All patients underwent 4-phase MDCT imaging and subsequent surgery within eight weeks. Two independent radiologists blinded to the histologic findings retrospectively classified the HCCs as either typical (showing increased enhancement on arterial phase images followed by washout in late phase images) or atypical lesions demonstrating any other enhancement pattern. From the original pathologic reports, various histologic characteristics including gross morphology, nuclear histologic grades, presence of capsule formation, and capsule infiltration when a capsule was present, were compared among the two groups.

**Results:** An atypical enhancement pattern was seen in 30 (36.2%) of the 83 HCCs. The mean size of atypical HCCs ( $1.71 \pm 0.764$ ) was significantly smaller than that of typical HCCs ( $2.31 \pm 0.598$ ,  $p < 0.001$ ). Atypical HCCs were frequently found to be vaguely nodular in gross morphology ( $n = 13$ , 43.3%) and to have grade I nuclear grades ( $n = 17$ , 56.7%). Capsule formation was significantly more common in typical HCCs ( $p < 0.001$ ). Capsular infiltration was also more common in typical HCCs ( $p = 0.001$ ).

**Conclusion:** HCCs showing atypical dynamic enhancement on MDCT imaging are usually smaller than typical HCCs, vaguely nodular type in gross morphology in most cases, and well-differentiated in nuclear grades, and they lack of capsule formation or capsular infiltration.

**Index terms:** Hepatocellular carcinoma; MDCT; Enhancement pattern; Histology

## INTRODUCTION

The main workflow for the diagnosis of hepatocellular carcinomas (HCCs) has changed dramatically over the

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past few decades; from invasive procedures such as an angiography or biopsy to noninvasive procedures such as either dynamic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) (1). The most recent guidelines issued by the American Association for the Study of Liver Diseases (AASLD) state that a lesion seen in patients with a risk of HCC greater than 1 cm in diameter also shows the typical enhancement patterns on dynamic CT or MRI, which include arterial hypervascularity and venous or delayed phase washout, and can be treated under the diagnosis of HCC (2). If the appearance is not typical for a HCC, a second imaging study (either CT or MRI) or biopsy is necessary (2).

Of the two modalities, multi-detector CT (MDCT) is the

more widely used technique to diagnose HCCs, although gadolinium-enhanced dynamic MRI may be superior to MDCT (3, 4). CT is however more widespread and has a shorter examination time. The typical appearance of a HCC on dynamic CT or MRI is increased enhancement on the arterial phase (arterial hypervascularity) followed by decreased enhancement (washout) of the tumor in the portal venous or delayed phases (5). However, some HCCs, especially less than 2-3 cm in diameter (6, 7), and well-differentiated ones lacking typical hemodynamic changes can make diagnosing HCC a challenge (8). However, histologic differences are not well known between the HCCs showing typical and atypical dynamic imaging features. The purpose of this study was to retrospectively compare the histologic characteristics of HCCs with typical and atypical dynamic enhancement patterns on preoperative MDCT imaging in small HCCs of 3 cm or less in diameter.

## MATERIALS AND METHODS

### Patients

Our institutional review board approved this retrospective study and waived the informed consent requirement. Surgical resection pathology records from June 2007 to February 2010 were reviewed to identify the cases of patients with a pathologic HCC diagnosis. Among these patients, the study sample was selected on the basis of the following inclusion criteria: pathologic diagnoses of HCCs measuring 3 cm or less in diameter, available preoperative 4-phase MDCT scans obtained according to the standard protocol for dynamic liver CT, interval between pathologic diagnosis and CT of no longer than 8 weeks, and no history of previous adjuvant treatment, such as transcatheter arterial chemoembolization, percutaneous ethanol injection, or radiofrequency ablation. All the patients that underwent surgery were non-cirrhotic or have cirrhosis but still have well preserved liver function. In our institution, atypically enhancing but suspicious lesions for HCC were closely followed up or treated with surgical resection because of the malignant potential for development to HCC through the multistep progression of hepatocarcinogenesis (9).

A total of 83 HCCs in 73 consecutive patients were included in the current study. Among the 73 patients, 64 had one HCC each, eight had two HCCs, and one had three HCCs. Among the 83 HCCs, 12 HCCs were 1 cm or less in diameter. Three of the 12 HCCs with diameters 1 cm or less newly appeared with typical enhancement during

the surveillance. The remaining 9 HCCs showed atypical enhancement, but were resected together during surgery for another typical HCC found in the preoperative MDCT.

### Pathological Analysis

In all cases, the pathologic reports including the gross and histological analyses, were reviewed. Tumor size, gross morphology, tumor necrosis or hemorrhage/peliosis, tumor grade, histology type, cell type, fatty change, capsule formation (capsule infiltration if a capsule was present), portal vein invasion, bile duct invasion, and microvascular invasion were reviewed. Tumor size grade was classified into three groups: group 1 was 1 cm or less in diameter, group 2 was between 1 and 2 cm in diameter, and group 3 was between 2 and 3 cm in diameter. The tumor grade of the HCCs was classified as grade I (well differentiated), grade II (moderately differentiated) and grade III (poorly differentiated), or IV, according to the nuclear grading scheme by Edmondson and Steiner (10). If the histologic grade of the tumor consisted of more than two grades, the major component of the grade was recorded for the analysis. Gross morphology was stratified into vaguely nodular, expanding, nodular and perinodular extending, multinodular confluent or infiltrative type. The histologic types were trabecular, pseudoglandular, scirrhous, compact and lymphoid. Cell types were hepatic, clear or giant. Fibrous capsule formation was recorded as either present (whether complete or partial) or absent.

### CT Techniques

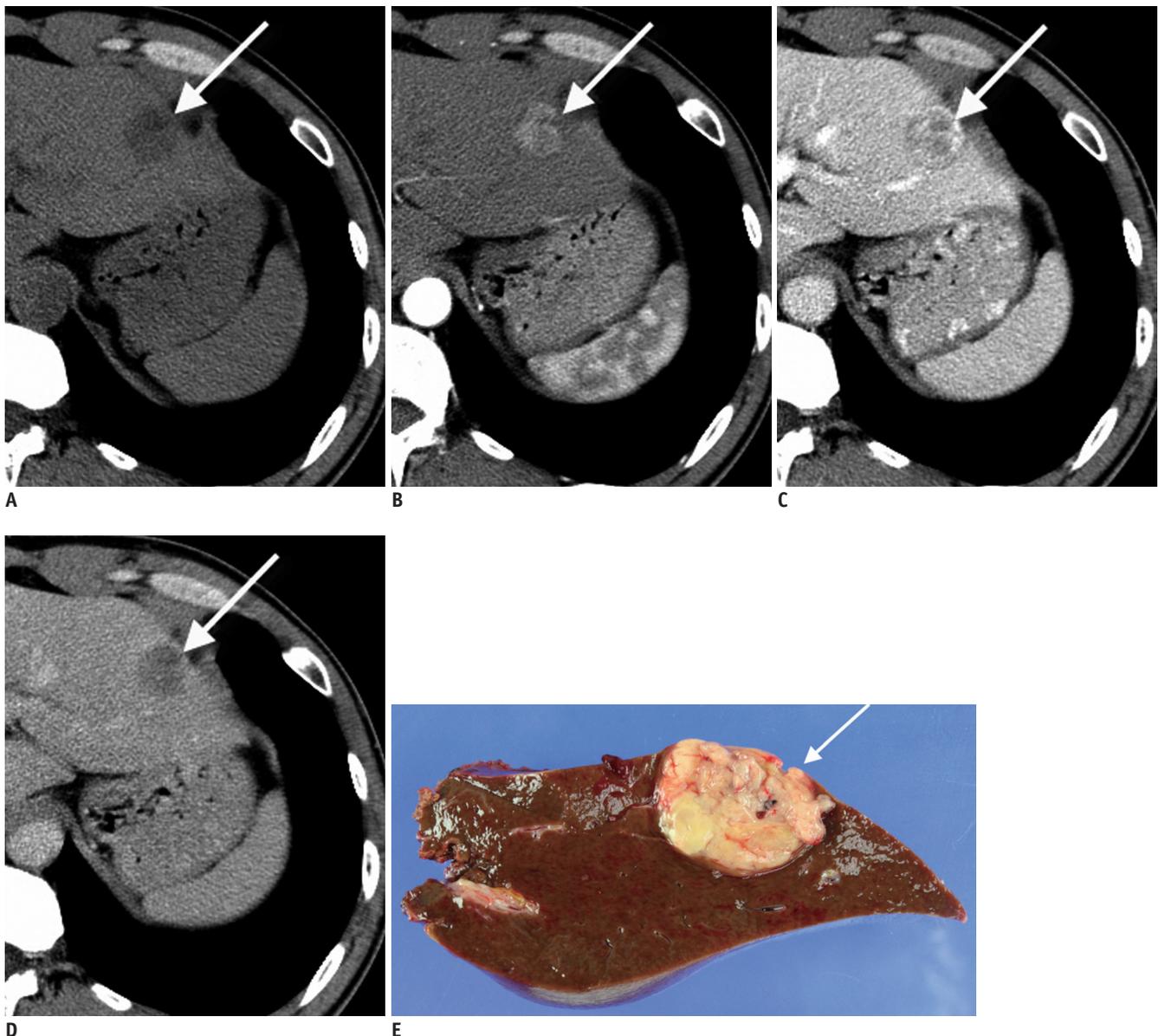
All CT scans were performed with multidetector scanners (Somatom Sensation 16 or Sensation 64; Siemens Medical Solutions, Forchheim, Germany). All patients received a 2 mL/kg dose (total volume < 150 mL) of nonionic contrast material (Iopromid [Ultravist]; Bayer Schering, Berlin, Germany, or iohexol [Omnipaque 300]; Nycomed Amersham, GE Healthcare, Milwaukee, WI, USA), intravenously with a power injector (EnVisionCT; Medrad, Pittsburgh, PA, USA), with a 30-second fixed injection duration. A precontrast scan was obtained before the administration of contrast media. Using a bolus tracking technique, arterial phase imaging was started after an 18-second delay from the time 100 Hounsfield units of aortic enhancement was attained. A 30-second scan delay after arterial phase imaging was used for portal venous phase imaging. Equilibrium phase imaging was also obtained 150 seconds after the end of portal venous phase imaging. The scanning parameters were

as follows: collimation, 16 rows x 0.75 mm or 64 rows x 0.6 mm; gantry rotation speed, 0.5 seconds; section thickness, 3 mm; image reconstruction increment, 1 mm; 120 kV; and effective tube current-time charge, 200-250 mA.

**Image Analysis**

The attenuation of HCCs were classified as hyperattenuated, isoattenuated, and hypoattenuated, compared with the surrounding liver parenchyma on

the unenhanced phase, arterial phase, portal venous phase, and equilibrium phase images. Increased arterial enhancement was considered when the tumor showed hyperattenuation compared to the surrounding liver parenchyma during the arterial phase or the attenuation of tumor seen on unenhanced images. On the portal venous phase and equilibrium phase images, each lesion was subjectively evaluated for the presence of washout. Subjective tumor washout was present if the tumor hyper-



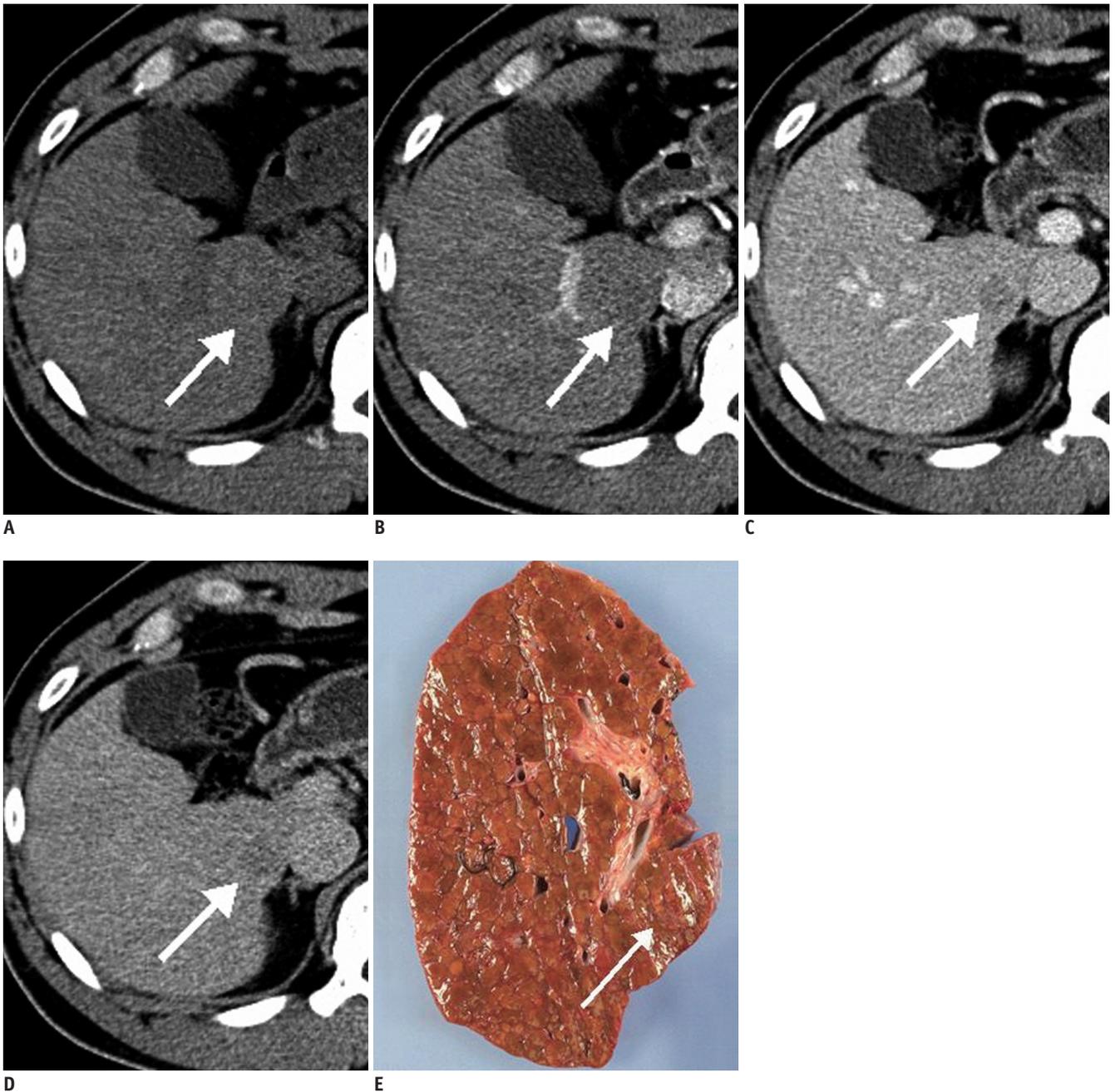
**Fig. 1. 43-year-old man with underlying B-viral hepatitis.**

(A) Precontrast, (B) hepatic arterial, (C) portal venous, (D) equilibrium phase images from 4-phase multi-detector CT scan. Hypoattenuating lesion (arrow) is seen on precontrast phase image (A). Lesion (arrow) shows increased arterial enhancement on arterial phase image (B) and washout of contrast enhancement on portal venous (C) and equilibrium phase images (D). (E) Gross specimen of lesion (arrow). Histologic examination demonstrated poorly differentiated (nuclear grade III) hepatocellular carcinoma of expanding type gross morphology with partial capsule formation and infiltration.

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or iso-attenuating to the liver on an arterial phase image subsequently appeared to be hypoattenuated compared to the surrounding liver parenchyma on the portal venous or equilibrium phase images. Two independent radiologists blinded to the histologic findings retrospectively stratified the HCCs into either typical or atypical HCCs. Disagreements in interpretation were resolved by consensus. Typical HCCs

were defined as lesions that showed increased arterial enhancement on arterial phase images followed by washout in late phase images (Fig. 1). Atypical HCCs were defined as lesions that did not show a typical enhancement pattern (Fig. 2). After classifying HCCs as typical and atypical, the gross and histologic characteristics of the HCCs were compared between the two groups.



**Fig. 2.** 49-year-old man with B-viral liver cirrhosis. (A) Precontrast, (B) hepatic arterial, (C) portal venous, (D) equilibrium phase images from 4-phase multi-detector CT scan. On precontrast (A) and arterial phase (B), lesion (arrow) showed isoattenuation compared to surrounding parenchyma. On portal venous (C) and equilibrium phase (D), lesion (arrow) shows hypoattenuation compared to surrounding parenchyma. (E) Gross specimen of lesion (arrow). Histologic examination showed well-differentiated (nuclear grade I) hepatocellular carcinoma of vaguely nodular type in gross morphology without capsule formation.

### Statistical Analysis

An independent *t* test was used to compare age and mean difference in tumor size between the two groups. A chi-square test was used to compare sex differences between two groups. The chi-square test or Fisher's exact test was used to compare categorical data according to the expected frequency in each cell of the tables. *p* values of less than 0.05 were considered statistically significant. All statistical analyses were performed using a statistical software (SPSS, version 17.0.1, SPSS, Chicago, IL, USA).

## RESULTS

A total of 83 HCCs ( $2.09 \pm 0.71$  cm in diameter, 0.4 cm to 3.0 cm in range) in 73 patients ( $54.7 \pm 10.5$  years old, 60 men and 13 women) were included in this study. A total of 69 (94%) out of the 73 patients had liver cirrhosis. Most of the patients had cirrhosis caused by a hepatitis B virus infection ( $n = 60$ ; 82.2%), and the rest had cirrhosis caused by a hepatitis C virus infection ( $n = 6$ ; 8.2%) or alcohol ( $n = 3$ ; 4.1%).

Fifty-three (63.8%) HCCs were classified as typical, whereas 30 (36.2%) were classified as atypical HCCs (Table 1). Sixteen of the 30 atypical HCCs show delayed phase washout without arterial enhancement. Moreover, nine of the 30 atypical HCCs show arterial enhancement only without delayed phase washout. Five of the 30 atypical HCCs showed neither arterial enhancement nor delayed phase washout.

The mean size of the atypical HCCs ( $1.7 \pm 0.7$ ) was significantly smaller than that of the typical HCCs ( $2.3 \pm 0.6$ ,  $p < 0.001$ ). According to the criteria of 2 cm in diameter, 40 (48.2%) HCCs were 2 cm or less in diameter and 43 (51.8%) HCCs were between 2 cm and 3 cm in diameter. Among 40 HCCs 2 cm or less than 2 cm in diameter, 19 (47.5%) were typical HCCs and 21 (52.5%) were atypical HCCs. However, among the 43 HCCs between 2 cm and 3 cm in diameter, 34 (79.1%) HCCs were typical HCC and 9 (20.9%) HCCs were atypical HCCs. Sex and age were not significantly different between the typical and atypical HCCs.

Gross morphology of the vaguely nodular type was significantly more common in atypical HCCs ( $p < 0.001$ ). However, the expanding type was significantly more common in typical HCCs ( $p = 0.001$ ). As for Edmondson-Steiner nuclear histologic grades, well-differentiated (Grade I) HCCs were more common in atypical HCCs ( $p < 0.001$ ), but moderate (grade II) or poorly differentiated (grade III)

HCCs were significantly more common in typical HCCs ( $p < 0.001$ ). Capsule formation was significantly more common than for typical HCCs ( $p < 0.001$ ). Capsular infiltration was more common in typical HCCs ( $p = 0.001$ ).

Other pathologic characteristics including tumor necrosis, hemorrhage/peliosis, histologic types, cell types, fatty change, portal vein invasion, bile duct invasion and microvascular invasion, showed no significant differences between the atypical and typical HCCs.

## DISCUSSION

Our results showed that the various histologic characteristics of HCCs are related to atypical dynamic enhancement patterns on contrast-enhanced dynamic CT.

In our study, 63.8% (50/83) of HCCs showed the typical enhancement pattern of HCCs, including increased enhancement on the arterial phase and washout on portal venous or delayed phase images (11). This typical enhancement pattern is consistent with hepatocarcinogenesis, which causes vascular changes toward a predominantly hepatic arterial supply with a lack of portal venous supply (12-14). However, the predominant enhancement patterns of HCC during the arterial and portal venous phases were significantly different based on tumor size and cellular differentiation of the tumor. In our study, the mean size of HCCs showing typical enhancement patterns was larger than that of HCCs with atypical enhancement patterns ( $p < 0.001$ ). In addition, there was a significantly higher proportion of typical HCCs among HCCs between 2 cm and 3 cm in diameter ( $p = 0.0057$ ). These results are similar to those of previous studies (15-17). Also, in our study, well-differentiated HCCs were more common among atypical HCCs ( $p < 0.001$ ), while moderate and poorly differentiated HCCs were significantly more common among typical HCCs ( $p < 0.001$ ). A previous study that evaluated the relationship of the vascularization of small HCC and the cellular differentiation has shown that abnormal arterial supply within a nodule increases as the grade of the malignancy increases, while, the normal hepatic arterial and portal venous supply to the nodule gradually decreases (18). Another study reported that well-differentiated and small HCCs more often showed various atypical CT enhancement features (19, 20).

Early HCCs showed the typical dynamic enhancement pattern less often than more advanced lesions in our study. Thirteen (43.3%) atypical lesions were vaguely nodular in

**Table 1. Histologic and Clinical Characteristics of Atypical and Typical Hepatocellular Carcinoma**

	Atypical (n = 30)	Typical (n = 53)	P
Mean age = 55 ± 10.6 / M : F = 69 : 14 (n = 83)			
Sex (M/F)	25 / 5	44 / 9	0.971
Age	53 ± 10.2	56 ± 10.8	0.295
Size grade			
Mean	1.71 ± 0.764	2.31 ± 0.598	< 0.001
1 cm or less	9 (30.0%)	3 (5.7%)	0.001
< 1 - 2 cm	12 (40.0%)	16 (30.2%)	
< 2 - 3 cm	9 (30.0%)	34 (64.2%)	
Gross type			
Expanding	5 (16.7%)	28 (52.8%)	0.001
Multinodular confluent	9 (30.0%)	19 (35.8%)	0.636
Nodular/Perinodal extension	1 (3.3%)	5 (9.4%)	0.411
Vaguely nodular	13 (43.3%)	1 (1.9%)	< 0.001
Infiltrative	2 (6.7%)	0 (0.0%)	0.128
Tumor necrosis (available n = 82 )			
No	25 (86.2%)	40 (75.5%)	0.252
Yes	4 (13.8%)	13 (24.5%)	
Hemorrhage/Peliosis (available n = 82 )			
No	27 (93.1%)	38 (71.7%)	0.022
Yes	2 (6.9%)	15 (28.3%)	
Grade (major)			
1.0	17 (56.7%)	6 (11.3%)	< 0.001
2.0	10 (33.3%)	40 (75.4%)	
3.0	3 (10.0%)	7 (13.3%)	
Grade (worst)			
1.0	16 (53.3%)	1 (1.8 %)	< 0.001
2.0	8 (26.7%)	26 (49.1%)	
3.0	6 (20.0%)	26 (49.1%)	
Histology type			
Trabecular	30 (100.0%)	53 (100.0%)	
Pseudoglandular	8 (26.7%)	18 (34.0%)	0.624
Scirrhus	1 (3.3%)	3 (5.7%)	1.000
Compact	3 (10.0%)	7 (13.2%)	0.741
Lymphoid	0	4 (7.5%)	0.291
Cell type			
Hepatic	29 (96.7%)	53 (100.0%)	0.361
Clear	11 (36.7%)	20 (37.7%)	1.000
Giant	1 (3.3%)	4 (7.5%)	0.649
Fatty change (available n = 82)			
No	14 (48.3%)	32 (60.4%)	0.291
Yes	15 (51.7%)	21 (39.6%)	
Capsule formation (available n = 82)			
No	19 (65.5%)	8 (15.1%)	< 0.001
Yes	10 (34.5%)	45 (84.9%)	

**Table 1. Histologic and Clinical Characteristics of Atypical and Typical Hepatocellular Carcinoma**

	Atypical (n = 30)	Typical (n = 53)	P
Capsule infiltration (available n = 82)			
No	22 (75.9%)	19 (35.8%)	0.001
Yes	7 (24.1%)	34 (64.2%)	
Portal vein invasion (available n = 78)			
No	24 (96.0%)	52 (98.1%)	0.541
Yes	1 (4.0%)	1 (1.9%)	
Bile duct invasion (available n = 78)			
No	24 (96.0%)	51 (96.2%)	1.000
Yes	1 (4.0%)	2 (3.8%)	
Microvascular invasion (available n = 78)			
No	17 (68.0%)	29 (54.7%)	0.266
Yes	8 (32.0%)	24 (45.3%)	

gross morphology, and 17 (56.7%) atypical lesions were well-differentiated by tumor grade. These characteristics are compatible with early HCCs, defined as well-differentiated lesions that are usually less than 2 cm in diameter, vaguely nodular in gross morphology, not showing the capsule formation, and usual hypovascularity (21).

A fibrous capsule that is known to be frequently observed around a tumor during the growth of HCCs was more frequently seen in typical HCCs in our study. And our study also showed that moderate and poorly differentiated HCCs were significantly more common among typical HCCs ( $p < 0.001$ ). The capsule is formed by a host of mesenchymal cells and not by HCC cells. In addition, the capsule formation may result from interactions between the tumor and host liver and interfere the growth and invasion of HCCs (22). This is supported by clinical evidence that the prognosis of patients with a HCC having capsule is better than for those without capsule (23-26) Therefore progressed HCC with typical enhancement pattern in spite of its small size more often forms capsule than indolent early HCC with atypical enhancement pattern in our study.

There are limitations to our study. First, our study is retrospective and we included surgically confirmed HCCs to compare the dynamic imaging patterns with histologic characteristics. Therefore, small HCCs that were diagnosed based on the presence of a typical dynamic pattern, which was subsequently treated by locoregional. This might have increased the proportion of atypical lesions in our study. Second, the definitions we used for increased arterial enhancement and presence of washout may differ from those used by other investigators. We determined the presence of increased arterial enhancement by comparing it with precontrast images; some investigators may

determine the presence of increased arterial enhancement on the arterial phase images alone. However, we believe that increased arterial enhancement can be correctly assessed by referring to precontrast images because some lesions showing hypoattenuation on precontrast images may show isoattenuation on arterial phase images even though they have increased the arterial vascularity within the lesions. We considered washout to be present when a lesion showed hypointensity relative to the surrounding liver on late phase images. Some radiologists could argue that washout may not be present when a lesion does not show increased arterial enhancement. However, we thought that such comparison would cause greater interobserver variability. Third, atypical HCCs are consisted of diverse subgroups according to the presence of the arterial enhancement or delayed phase washout. We considered atypical HCCs as lesions that did not show a typical enhancement pattern and was not divided into subgroups in the analysis process. Further studies are needed to define the characteristics of diverse subgroups of atypical HCCs. Lastly, we did not analyze how many hypovascular lesions transform to hypervascular lesions. A recent study revealed that hypoattenuating hepatic nodular lesions in chronic liver disease depicted on dynamic CT has high malignant potential (27). There are chances that atypically enhancing HCCs progressed to typically enhancing HCCs according to the hepatocarcinogenesis, but we analyzed only the preoperative CT scan of just before the surgery, not serial CT scans.

We conclude that various histologic characteristics of HCC are associated with atypical dynamic enhancement on contrast-enhanced dynamic CT images. HCCs with atypical enhancement patterns tend to be smaller than HCCs with a

typical enhancement pattern and are vaguely a nodular type in gross morphology and well-differentiated in histologic grades. Capsule formation and capsular infiltration are significantly more common in typical HCCs. Awareness of atypical enhancement patterns in small HCCs and their histologic implications may guide patient management.

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