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Multiphasic Computed Tomography Enhancement Characteristics and Utility of Delayed Phase in Infiltrative Hepatocellular Carcinoma

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Abstract

Objective The aims of this study are to compare the multiphasic contrast-enhanced computed tomography (CECT) characteristics of infiltrative hepatocellular carcinoma (HCC) with nodular HCC and to assess the conspicuity of infiltrative HCC on different phases of CECT.

Materials and Methods This retrospective study comprised consecutive treatment-naive cirrhotic patients diagnosed with infiltrative and nodular HCC between January 2020 and December 2021 based on a multiphasic CECT (comprising arterial, portal venous, and delayed phases). The diagnosis of HCC was based on the Liver Imaging Reporting and Data System (LI-RADS) v2018 criteria (LR-4 and LR-5 lesions). Infiltrative HCCs are characterized by large, irregular, permeative lesions spread over multiple liver segments or lobes. Nodular HCCs comprise well-defined tumor nodules. Two radiologists independently reviewed all CT images. Additionally, lesion conspicuity on the arterial, portal venous, and delayed phases was assessed.

Results One hundred fifty-eight patients (117 nodular and 41 infiltrative HCCs; mean age: 55.6 ± 17.2 years; 90 [56.9%] males) were included. Arterial phase hyperenhancement, portal venous/delayed phase washout, and delayed phase enhancing capsule were significantly associated with nodular HCCs ($p = 0.002$, 0.0001, and <0.0001, respectively). Portal vein, hepatic vein thrombosis, biliary dilatation, and ascites were significantly associated with infiltrative HCCs ($p < 0.0001$, 0.004, <0.0001, and 0.003, respectively). The interobserver agreement for the conspicuity of infiltrative HCC was the highest for the delayed phase (weighted kappa = 0.611).

Conclusion Infiltrative HCCs show the major LI-RADS features less frequently compared with nodular HCCs, and venous thrombosis is an important clue to the diagnosis. The delayed phase of multiphasic CECT is critical to identifying these lesions.

Keywords
- CT
- hepatocellular carcinoma
- LI-RADS
- portal vein thrombosis

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Introduction

A hepatocellular carcinoma (HCC) shows different macroscopic growth patterns: nodular, massive, and infiltrative.[1,2] Infiltrative HCCs comprise 7 to 20% of the HCC cases.[3] An infiltrative HCC is characterized by diffuse involvement and multiplicity of nodules throughout the liver parenchyma. Pathologically, the tumor nodules of an infiltrative HCC have distinct, well-defined margins. However, as the tumor nodules are minute and confluent, these translate to ill-defined and permeative appearance at imaging.[1,3] Various liver associations recommend noninvasive diagnosis of HCCs and integrate the Liver Imaging Reporting and Data System (LI-RADS) for evaluation of lesions in cirrhosis.[4] The noninvasive diagnosis has a high sensitivity and specificity for nodular HCCs. However, infiltrative HCCs are difficult to diagnosis as they may lack major features described in the LI-RADS nomenclature. These lesions are often hypoenhancing in the arterial phase and do not consistently show washout in the portal venous and delayed phases.[5] Thus, the distinction between a cirrhotic liver and an infiltrative HCC can sometimes be challenging.

Portal vein thrombosis is an important feature of an infiltrative HCC reported in 68 to 100% of the cases.[1] Malignant portal vein thrombosis is characterized by expansion of the portal vein and enhancement characteristics similar to the liver lesion. Arterial phase hyperenhancement within the portal vein thrombus is uncommon in infiltrative HCCs.[6]

A confident diagnosis of infiltrative HCC is essential in guiding treatment. An infiltrative HCC is associated with decreased survival after surgical resection, and patients even respond poorly to locoregional and systemic therapy.[6–8] A few studies have described the dynamic contrast-enhanced magnetic resonance imaging (MRI) features of infiltrative HCCs. However, the multiphasic contrast-enhanced computed tomography (CECT) characteristics of an infiltrative HCC are poorly documented in the literature, and radiologists may not be well versed with the challenges associated with diagnosing this type of HCC.

We aim to compare the multiphasic CECT characteristics of infiltrative HCCs with nodular HCCs and assess the conspicuity of infiltrative HCCs on different phases of CECT.

Materials and Methods

Patients

The institutional ethics committee approved this retrospective study, and the need to obtain informed written consent was waived. Consecutive treatment-naive cirrhotic patients with the diagnosis of infiltrative and nodular HCCs between January 2020 and December 2021 were retrieved from the departmental CT database. The diagnosis of liver cirrhosis requires a multidisciplinary and multipronged approach and is based on the histology or clinical evidence of portal hypertension like ascites, splenomegaly, history of hepatic encephalopathy, and varices on endoscopy. In addition, transient elastography with liver stiffness measurement (LSM) more than 12.5 kPa or the imaging features of a shrunken liver, surface nodularity, dilated portal vein (>13 mm), or identification of portal collaterals or ascites also help establish the diagnosis of cirrhosis. Besides a detailed evaluation of risk factors of cirrhosis, namely, ethanol and metabolic syndrome, the etiological workup for cirrhosis also included viral serology and autoimmune workup. The cases were identified by two radiologists (one trainee, a second-year resident, and the other a radiologist with 2 years of posttraining experience in CT imaging) based on the description of the multiphasic CT reports. A valid case for screening must have been scanned using a triphasic protocol comprising arterial, portal venous, and delayed phases with or without a noncontrast scan. The Digital Imaging and Communications in Medicine (DICOM) images of the eligible cases were retrieved and screened for inclusion by a radiologist with 2 years of posttraining experience in CT imaging. The shortlisted cases were then evaluated by a radiologist with 9 years of posttraining experience in abdominal CT, and the final inclusion was based on consensus. Cases that lacked all three phases of acquisition and those with nondiagnostic image quality, vascular causes of HCC, HCC in noncirrhotic liver, and those younger than 18 years were excluded from the study.

All the LI-RADS 4 and 5 observations (after applying the LI-RADS v2018 criteria) were further analyzed and categorized into nodular and infiltrative HCCs.[9] An infiltrative HCC comprises large, irregular, permeative lesions that are continuous and spread over multiple liver segments/lobes.[10,11] A nodular HCC, on the other hand, comprises well-defined tumor nodules.

Computed Tomography Acquisition

Multiphasic CT scans were acquired on multirow detector CT scanners (SOMATOM Definition Flash, Siemens, and Phillips CT scanner). The multiphasic CECT protocol comprised a late arterial phase acquired using a bolus tracking technique (whereby acquisition was triggered when the attenuation reached above 120 HU in the abdominal aorta at the level of the celiac axis), portal venous phase at 70 to 90 seconds, and a delayed phase at 180 seconds after intravenous injection of 80 to 100 mL of nonionic iodinated contrast (Omnipaque 300 mg, GE Healthcare) using a pressure injector at a rate of 3.5 to 4 mL/s. The patients were imaged supine with suspended deep inspiration with the arms extended overhead to reduce beam hardening artifacts. The volumetric data were transferred to a server-based workstation.

Image Analysis

All CT images were independently reviewed by two radiologists (M.G. with 1 year and T.S. with 2 years of posttraining experience in CT imaging). CT scans were assessed for the size of the observed lesion (in the phase of the scan where the margins of the lesion were best seen); liver segment/s involved; enhancement characteristics in the late arterial, portal venous, and delayed phases; vascular thrombosis (defined per the LI-RAD v2018[9] definite criteria for tumor in vein, i.e., unequivocal soft tissue within a vein with or without expansion of the vein) of the portal vein/hepatic

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vein; biliary dilatation; multiplicity of observations; ascites; lymph nodes; and extrahepatic metastases (abdominal lymphadenopathy, pulmonary nodules, where chest CT scans were available). The discordant cases were read by a radiologist with 9 years of posttraining experience in abdominal imaging.

Additionally, lesion conspicuity on the arterial, portal venous, and delayed phases was independently assessed by the two radiologists in cases with infiltrative HCCs. A three-point system was used: (1) definitely absent, (2) equivocal, and (3) definitely present for evaluating lesions in each phase.[12]

Baseline Parameters

Age, sex, and cause of cirrhosis were recorded in all cases.

Statistical Analysis

Discrete categorical data were represented as percentages or proportions. Continuous data were expressed as mean with standard deviation. For normally distributed continuous variables, an independent *t*-test was used to compare the means between two subgroups; otherwise, the Mann–Whitney *U* test was applied. The chi-squared test or Fisher's exact test (whichever is applicable) was used for categorical variables. The interobserver agreement for detecting lesions in various acquisition phases between two reporting radiologists was calculated using the kappa statistics. The degree of agreement was classified as slight ($\kappa < 0.20$), fair (κ: 0.21–0.40), moderate (κ: 0.41–0.60), substantial (κ: 0.61–0.80), and near perfect (κ: 0.81–1.00). Statistical analyses were performed using SPSS (IBM SPSS Statistics; version 22, IBM Corp, Armonk, New York, United States). A *p*-Value less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

CT reports of 1,218 patients with HCC from January 2020 to December 2021 were analyzed from our institutional database. After excluding the noncirrhotic patients, those with vascular causes of cirrhosis, patients treated for HCC, and overlapping scans, CT reports of 212 unique patients with HCC were retrieved. One hundred and sixty-two were nodular variety, and 50 were infiltrative HCCs. In the nodular group, 15 scans could not be retrieved, 21 scans did not have all the phases, and 9 were nondiagnostic. In the infiltrative HCC group, five scans could not be retrieved, three did not have all the phases, and one was nondiagnostic. Thus, 158 patients, 117 with nodular and 41 with infiltrative HCC. were included in the analysis (►**Fig. 1**).

The mean age was 55.6 ± 17.2 years, and the mean age in the cohort of nodular HCC and infiltrative HCC was 54.4 ± 16.2 and 60 ± 18.5 years, respectively. There were 90 (56.9%) males and 68 (43.1%) females (►**Table 1**).

The etiologies of cirrhosis were hepatitis B ($n = 69$), hepatitis C ($n = 32$), alcohol (31), and metabolic associated liver disease (MASLD) ($n = 26$).

Enhancement Patterns in Various Phases

Infiltrative HCCs showed arterial phase enhancement in 56.1% compared with 98.3% of the nodular HCCs ($p = 0.002$; ►**Figs. 2–4**). Infiltrative HCCs showed portal

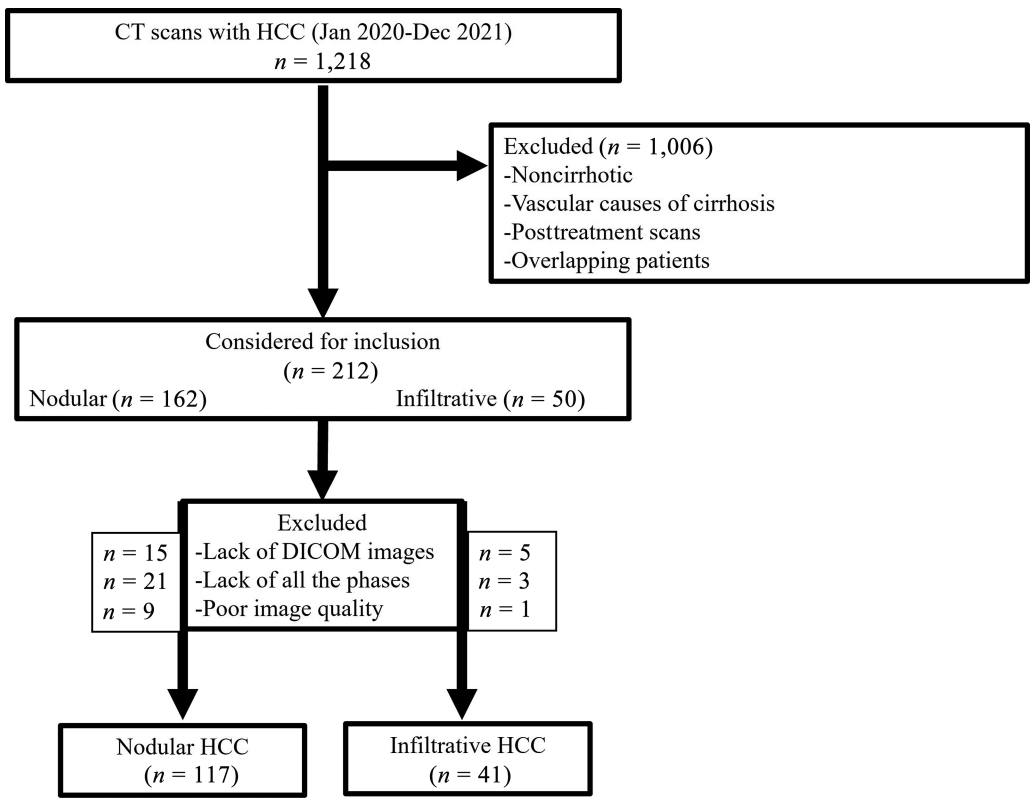

Fig. 1 Flow diagram showing patient recruitment. CT, computed tomography; HCC, hepatocellular carcinoma.

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Table 1 Baseline characteristics

Characteristic	Nodular HCC ($n = 117$)	Infiltrative HCC ($n = 41$)	*p*-Value
Mean age (y)	54.4 ± 16.2	60 ± 18.5	0.002
Gender (M/F)	65 (55.5%)/52 (44.4%)	28 (62.2%)/13 (31.7%)	0.02
Mean size (cm)	5.64 (±2.78)	11.82 (±3.48)	0.005
Site of lesion			
Right lobe	48 (41.0%)	6 (14.63)	0.01
Left lobe	53 (45.2%)	0	
Both lobes	16 (13.6%)	35 (85.36%)	
Multiplicity of lesions	47 (40.1%)	41 (100%)	<0.001

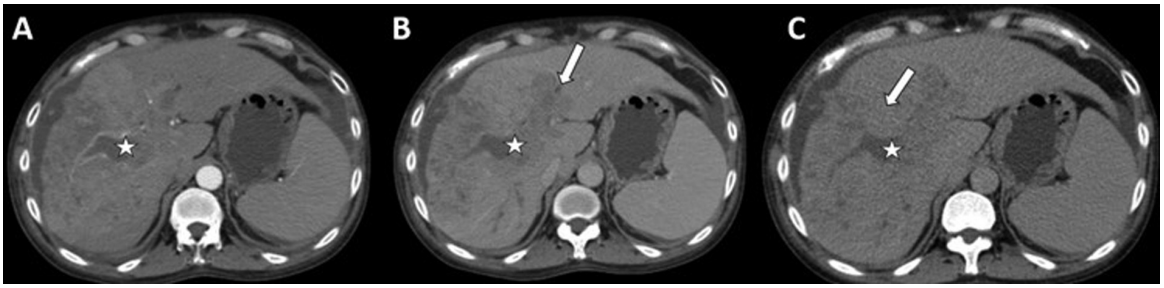

Fig. 2 A 56-year-old male patient with chronic hepatitis B infection related cirrhosis. (**A**) An ill-defined heterogeneous mass lesion in the right lobe of the liver with patchy arterial phase enhancement. The lesion is better appreciated in the (**B**) portal venous and (**C**) delayed phases as shown by the *arrows*. Portal vein thrombus is depicted via asterisk symbols.

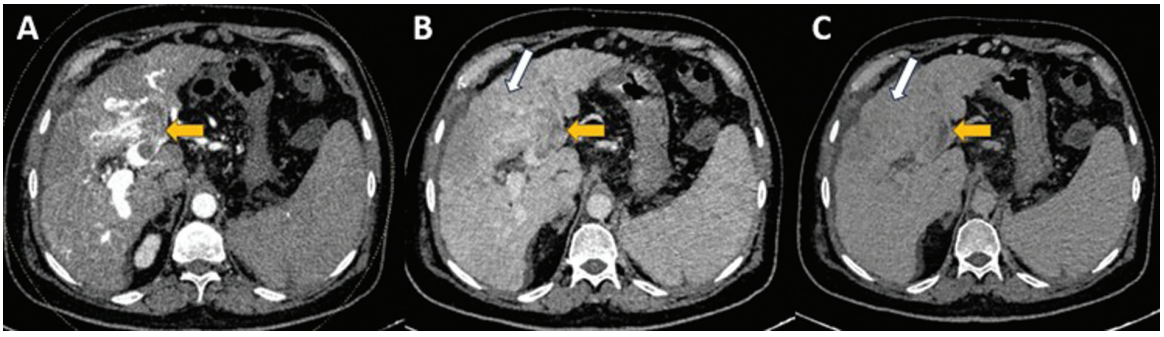

Fig. 3 A 61-year-old female patient with chronic hepatitis C infection related cirrhosis. (**A**) An ill-defined heterogeneous mass lesion in the right lobe of the liver with patchy arterial phase enhancement. Note that there is better conspicuity of the lesion in the (**B**) portal venous and (**C**) delayed phases. The *yellow arrows* depict a tumoral portal vein thrombus.

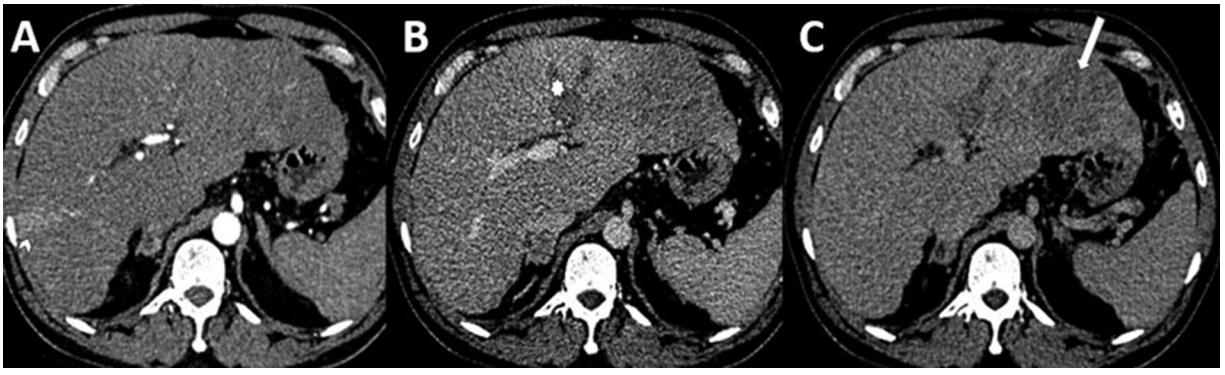

Fig. 4 A 41-year-old male patient with ethanol-related cirrhosis. (**A**) There is an ill-defined infiltrative lesion in the left lobe of the liver with no arterial phase enhancement. (**B**) Portal vein thrombosis is seen in the left branch of portal vein (*). (**C**) The lesion is well appreciated in the delayed phase. Transient hepatic attenuation difference is shown by the *arrowhead* in (**A**).

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venous washout in 73.2% compared with 94% of nodular HCCs ($p = 0.001$). In the delayed phase images, none of the infiltrative HCCs showed an enhancing capsule compared with its presence in 23.1% of nodular HCCs ($p < 0.001$).

Tumor Thrombus

Portal vein thrombosis (PVT) was seen in almost all infiltrative HCCs (97.6%) compared with 3.4% of the nodular HCCs ($p < 0.001$). Hepatic vein thrombosis was also significantly more common in infiltrative HCCs (24.3%) than nodular HCC (5.9%; $p = 0.004$).

Intrahepatic biliary radicle dilatations (IHBRDs; $p < 0.001$) and ascites ($p = 0.003$) were more common in infiltrative than in nodular HCCs (►**Table 2**).

Interobserver Agreement

The interobserver agreement for conspicuity of infiltrative HCCs between the two radiologists was as follows: arterial phase, $\kappa = 0.048$ (slight), portal venous phase, $\kappa = 0.120$ (slight), and delayed phase, $\kappa = 0.611$ (substantial).

Discussion

In this study, comparing the multiphasic CT characteristics of nodular and infiltrative HCCs, we found that arterial phase hyperenhancement and contrast washout in the portal venous or delayed phases were seen in significantly lesser number of infiltrative HCCs. The conspicuity of infiltrative HCCs was the greatest in the delayed phase of multiphasic CT acquisition. Vascular tumor thrombosis and the ill-marginated nature of the lesion were most consistent in infiltrative HCCs.

In a retrospective study analyzing the lesion (infiltrative HCC) conspicuity on various MRI sequences in 19 patients with infiltrative HCC, Rosenkrantz et al observed that the venous phase was significantly better at depicting the lesion.[10] The authors did not evaluate the equilibrium phase of contrast enhancement. However, our study assessed the delayed phase on CT, where the lesions were most conspicuous.

In a comprehensive review article by Reynolds et al, the arterial phase enhancement in infiltrative HCC has been variously described as minimal, patchy, or miliary.[1] The miliary pattern may be seen more commonly in cases of PVT.[2] Similarly, the concept of "washout" in infiltrative HCC is somewhat different from classic nodular HCCs. Washout, that is, relative hypoenhancement of the lesion in the venous and delayed phases relative to surrounding liver parenchyma, is more heterogeneous and irregular in infiltrative HCCs than in classical nodular HCCs.[1,2,11] The aberrant enhancement patterns in infiltrative HCCs may be linked to these lesions' underlying cirrhotomimetic histopathology with frequent intravascular thrombi presence.[13] To the best of our knowledge, there is a lack of consensus on strictly defining the enhancement patterns of infiltrative HCCs, and no characteristic pattern has been found. However, most studies describe the enhancement patterns of infiltrative HCC as heterogeneous at best.

We also found vascular thrombosis, that is, PVT, and hepatic vein thrombosis to be significantly associated with infiltrative HCCs. PVT has been described as a core diagnostic feature of infiltrative HCCs and is sometimes the only clue to diagnosis.[1,2,8] In a retrospective MRI-based study by Park et al, PVT was highly suggestive of infiltrative HCCs.[11]

In our study, IHBRD was also significantly more common with infiltrative HCCs. Literature suggests IHBRD to be seen in approximately 13 to 26% of cases.[1] In a retrospective study by Kim et al, there was a difference in the pattern of IHBRD in diffuse HCC and intrahepatic cholangiocarcinoma; dilatation was predominantly intratumoral in HCC and along the periphery of the lesion in intrahepatic cholangiocarcinoma.[14]

Ascites was more common in patients with infiltrative HCC in our study. This can be secondary to the core pathology, that is, liver cirrhosis with portal hypertension or as part of the malignant process. Either way, the presence of ascites

Table 2 Multiphasic contrast-enhanced CT characteristics

Features	Nodular HCC ($n = 117$)	Infiltrative HCC ($n = 41$)	*p*-Value
APHE	115 (98.3%)	23 (56.1%)	0.002
Portal venous washout	110 (94%)	30 (73.2%)	<0.001
Capsule	27 (23.1%)	0	<0.001
Vascular tumor thrombus	9 (7.7%)	40 (97.6%)	<0.001
PVT	4 (3.4%)	40 (97.6%)	
HVT	7 (5.9%)	10 (24.3%)	
IHBRD	4 (3.4%)	20 (48.8%)	<0.001
Ascites	55 (47%)	30 (73.1%)	0.003
Abdominal lymphadenopathy	13 (11.1%)	6 (14.6%)	0.364
Pulmonary metastases[a]	4/59 (6.7%)	2/29 (6.9%)	0.912

Abbreviations: APHE, arterial phase hyperenhancement; CT, computed tomography; HCC, hepatocellular carcinoma; HVT, hepatic vein thrombosis; IHBRD, intrahepatic biliary radicle dilatation; PVT, portal vein thrombosis.
[a]The denominator represents the number of patients who underwent chest CT.

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indicates a poor prognosis. A retrospective study by Kneuertz et al reported ascites in approximately 30% of infiltrative and multifocal HCCs.[6]

The presence of extrahepatic disease in HCCs is of paramount importance in planning the management of patients, including decisions on liver transplant/systemic chemotherapy or interventional radiology procedures like transarterial chemoembolization (TACE) or transarterial radioembolization (TARE).[1,6–8,13] There was no significant difference in the percentage of metastases between infiltrative and nodular HCCs.

We acknowledge a few limitations to our study. First, it was a retrospective study with its associated selection bias. Second, the sample size was limited, specifically the lesser number of cases of infiltrative HCC. Third, we did not compare the CT features with the MRI characteristics. MRI may provide excellent information on the signal/enhancement characteristics of the lesion, and diffusion-weighted imaging with apparent diffusion coefficient values could add to the information. Fourth, all the lesions were not subjected to histopathological examination, and the diagnosis was based on the LI-RADS criteria (LI-RADS 4 and LI-RADS 5 lesions). Although this approach is consistent with the current recommendations to diagnose HCC noninvasively (in cirrhosis), there may be concerns regarding accurate diagnosis of HCC in LI-RADS 4 category of lesions. LI-RADS 4 lesion are HCCs in 75% of the cases.[15] At our center, LI-RADS 4 lesions are managed based on a multidisciplinary discussion, in line with the recommendations.[16] We included only those LI-RADS 4 lesions in this study that the multidisciplinary team recommended further management on the lines of HCC. Fifth, we did not include LR-M lesions as only 29 to 44% are HCCs.[17] Finally, there may be concerns about the accurate diagnosis of infiltrative HCC in the absence of histopathological confirmation. However, the diagnosis was based on the evaluation by a multidisciplinary team and CT scans were read by an expert radiologist.

Conclusion

In conclusion, infiltrative HCCs commonly show atypical enhancement patterns. PVT is an important clue to the diagnosis. The delayed phase adds to the conspicuity of the infiltrative HCCs. However, studies with a larger sample size and robust database are needed to develop the diagnostic criteria for infiltrative HCCs.

Funding
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Conflict of Interest
None declared.

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