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Outcome of Small (10–20 mm) Arterial Phase-Enhancing Nodules Seen on Triphasic Liver CT in Patients with Cirrhosis or Chronic Liver Disease

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OBJECTIVE: To determine the outcome of small arterial phase-enhancing nodules, 10–20 mm, seen on serial triphasic liver CT scans in a hepatocellular cancer-screening population.

METHODS: Of 58 patients referred for triphasic liver CT, 20 (18 men, 2 women) with 32 nodules formed the study group. Each patient in the study group had at least two CT scans, a minimum of 3 months follow-up, at least one nodule measuring 10–20 mm, no prior diagnosis of hepatocellular carcinoma, and no nodule greater than 20 mm typical of hepatocellular carcinoma at the time of the first CT. Serial CT scans were reviewed by an abdominal imaging radiologist who classified the nodules as stable, decreasing, or increasing in size.

RESULTS: A mean of six CT studies (range 2–10) were performed for each patient with a mean follow-up of 25 months (range 4–47 months). Of 32 nodules, 14 (44%) were stable, 9 (28%) decreased, and 9 (28%) increased in size. Nodules that increased in size were treated as hepatocellular carcinoma: six were hepatocellular carcinoma, two were biopsy negative but showed recurrent tumor after radiofrequency ablation, and one was a high-grade dysplastic nodule. Mean doubling time for these nine nodules was 5.7 months (range 2.3–10.8 months).

CONCLUSIONS: Most small (10–20 mm) arterial phase-enhancing nodules seen on triphasic liver CT are not hepatocellular carcinoma. Serial CT is useful to guide management in these patients. Growth of small arterial phase-enhancing nodules can be used as an indicator that the nodule should be treated as hepatocellular carcinoma.

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INTRODUCTION

Patients with cirrhosis and chronic liver disease are at increased risk for the development of hepatocellular carcinoma. In general, the prognosis for hepatocellular carcinoma is poor. However, patients with small, localized hepatocellular cancers are eligible for a variety of treatment options including liver transplantation, liver resection, and tumor ablation that may improve survival (1). Therefore, screening for hepatocellular carcinoma is advocated in patients with cirrhosis and chronic liver disease (2). Screening typically includes the measurement of serum α-fetoprotein (AFP) and imaging of the liver with cross-sectional techniques including ultrasound, CT, and MRI (3, 4).

On contrast-enhanced CT, the majority of hepatocellular carcinomas are hypervascular compared to the surrounding liver parenchyma during the arterial phase. On portal venous phase images, hepatocellular carcinomas are usually hypoattenuating relative to the liver parenchyma (also referred to as "washout" of intralesional contrast) (4–7). In patients with cirrhosis, small lesions ($\leq$20 mm) seen on CT or MRI with arterial phase enhancement that become isoattenuating relative to the liver parenchyma on portal venous phase images present a diagnostic dilemma. The differential diagnosis for small arterial phase-enhancing lesions in this setting includes an area of perfusion abnormality related to fibrosis, an arterioportal shunt, a regenerating or dysplastic nodule, and hepatocellular carcinoma (8–12). Arterial phase-enhancing lesions 10 mm or smaller are common and are especially difficult to characterize due to their small size (13). Based on MRI studies, most of these small areas of arterial enhancement ($\leq$20 mm) turn out to be benign entities rather than foci of hepatocellular carcinoma (11, 12). Because of their nonspecific imaging features, lesions seen only on the

arterial phase measuring less than 20 mm can either be followed with serial imaging to assess for interval growth (8, 11, 12) or may undergo biopsy. The European Association for the Study of the Liver (EASL) has recommended that in patients with cirrhosis, nodules less than 10 mm in size can be followed with imaging to assess for interval growth. For nodules 10–20 mm in size, biopsy is recommended (2). At our institution, in patients at risk for hepatocellular carcinoma, solid nodules discovered on ultrasound that are larger than 10 mm are usually further characterized with CT. In this setting, we have noted that many small lesions ($\leq$20 mm) seen only on arterial phase CT scans are transient findings and therefore, the recommendation of performing a biopsy for nodules 10–20 mm may result in a significant number of unnecessary biopsies being performed.

The purpose of our study was to determine the outcome of arterial phase-enhancing lesions, 10–20 mm in size, found on serial triphasic CT scans in a hepatocellular cancer screening population.

MATERIALS AND METHODS

This was a retrospective study, approved by our Research Ethics Board. The study involved patients with a history of cirrhosis or chronic liver disease who were undergoing screening with ultrasonography for the development of hepatocellular carcinoma. Patients with lesions >10 mm in diameter, detected at ultrasound, who were referred for further evaluation with CT scanning, were eligible for the study. For inclusion in our study, a patient had to have a dedicated triphasic (unehanced, arterial, and portal venous phases) CT of the liver at our institution; at least 3 months of follow-up imaging with triphasic liver CT; and at least one arterial phase-enhancing lesion measuring between 10 and 20 mm in maximum diameter that did not show washout during the portal venous phase. Patients were excluded from the study if there was a known diagnosis of hepatocellular carcinoma at the time of the first CT; there was a second lesion >20 mm with imaging features typical of hepatocellular carcinoma; or any lesion showing arterial phase enhancement had washout on portal venous phase images typical of a hepatocellular carcinoma. Patients with nodules that were stable or decreasing in size on serial CT scans that had less than 18 months of follow-up with triphasic liver CT were also excluded.

A total of 58 patients were referred for a triphasic liver CT as part of the recall procedure after finding a nodule >10 mm on screening ultrasound. Twenty-four patients, who had a total of 82 CT scans, did not have an arterial phase-enhancing lesion of 10 mm or more and were excluded from the study. Eight patients with hepatocellular carcinoma present on the initial CT and one patient without a follow-up CT were also excluded. Five patients with nodules that were stable or decreasing in size were excluded because they had less than 18 months of follow up with serial triphasic liver CT. The remaining 20 patients had 123 CT scans that showed 32 arterial phase-enhancing lesions between 10 and 20 mm in size. These patients formed the study group. The group included 18 men and 2 women, with a mean age of 61 yr (range 46–74 yr). Liver disease was caused by hepatitis B infection (n = 10), hepatitis C (n = 8), combined hepatitis B and C (n = 1), and alcohol abuse (n = 1). Altogether, 16 patients had cirrhosis and 4 patients had chronic hepatitis without known cirrhosis.

Since this was a retrospective study, CT scans were obtained on a variety of helical CT scanners including a 4-slice multidetector CT scanner (Lightspeed QX/i; General Electric Medical Systems, Milwaukee, WI), 89 studies; an 8-slice multidetector CT scanner (Lightspeed Ultra, General Electric Medical Systems), 31 studies; and a single detector CT scanner (HiSpeed, General Electric Medical Systems), 3 studies. The amount of intravenous contrast given was 2 ml/kg of iohexol (Omnipaque 300; Amersham Health, Inc., Princeton, NJ) to a maximum of 200 ml. Injection rate was 5 ml/sec into an antecubital vein. Scan parameters were as follows: collimation 5 mm, reconstruction interval 2.5 mm, 120 kV, 170–380 mA. Imaging included unenhanced, arterial (30 s after injection), and portal venous (60 s after injection) phase scans.

An abdominal imaging radiologist reviewed each CT study along with the original radiology report. For each patient, CT scans were reviewed chronologically. Only round or oval-shaped lesions were included in the image analysis. Peripheral wedge-shaped or geographic areas of arterial enhancement were not counted as lesions but were interpreted as perfusion abnormalities. Each lesion was measured and the location was recorded. At the time of image review, the radiologist was unaware of the final diagnosis for each lesion.

If a lesion increased by more than 30% from baseline maximum diameter, it was classified as increasing in size (Fig. 1). If a lesion measured less than 30% of its baseline maximum diameter on serial CT scans, it was classified as decreasing in size. Lesions that did not change by more than 30% from baseline maximum diameter on serial CT scans were considered stable (Fig. 2).

Tumor volume doubling time was calculated as follows: Tumor volume doubling time = $[\ln(2) \times T]/\ln[V(t)/V(0)]$, where T is the interval between the first and the last measurement and V(t) is the final volume and V(0) is the initial volume.

RESULTS

There were 20 patients who had 123 CT scans with 32 arterial phase-enhancing nodules between 10 and 20 mm in size. Each patient had a mean of six serial CT examinations (range 2–10) with a mean follow-up period of 25 months (range 4–47 months). Thirteen patients had one nodule each, five patients had two nodules each, one patient had three nodules, and one patient had six nodules. The mean size of each lesion on the baseline CT was 12 mm (range 10–20 mm).

Fourteen nodules (44%) were stable, and 9 (28%) nodules became smaller. The mean initial size of the nodules that

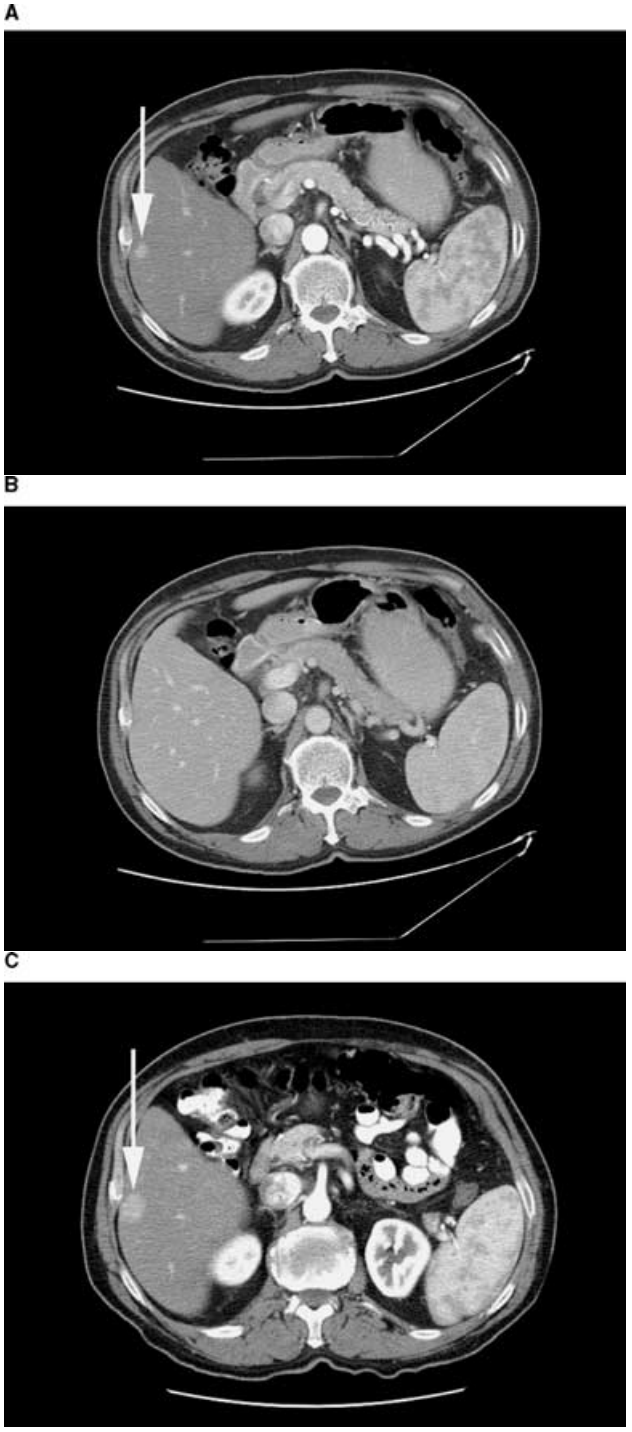

Figure 1. (*A*) Arterial phase CT scan shows 12 mm nodule (arrow) in right lobe of liver in 64-yr-old man with hepatitis C virus cirrhosis. (*B*) Portal venous phase CT scan shows no corresponding abnormality. (*C*) Follow up arterial phase CT scan 7 months later shows nodule (arrow) has increased in size to 23 mm. Liver resection was performed and the pathology was hepatocellular carcinoma.

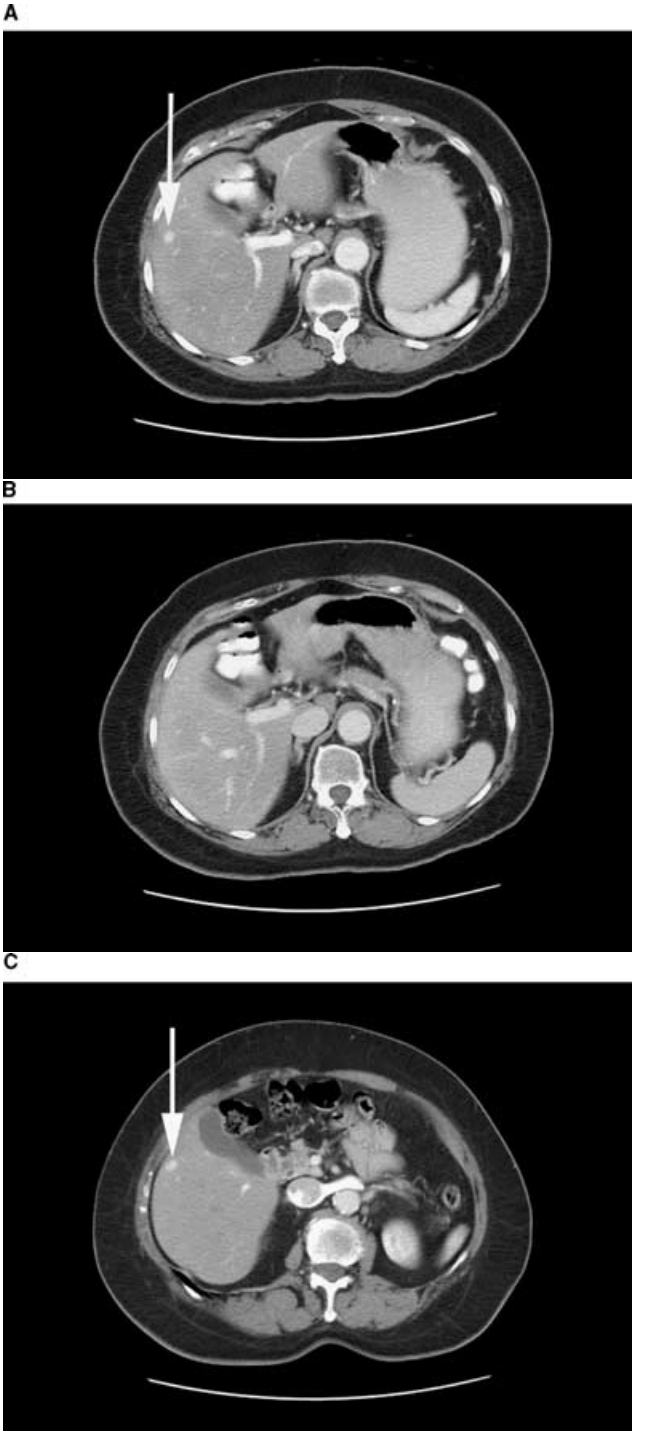

Figure 2. (*A*) Arterial phase CT scan shows 10 mm nodule (arrow) in right lobe of liver in 69-yr-old woman with chronic hepatitis B infection. (*B*) Portal venous phase CT shows no corresponding abnormality. (*C*) Arterial phase CT scan performed 24 months later shows that the nodule (arrow) is stable.

were stable was 12 mm (range 10–16 mm) and that became smaller was 13 mm (range 10–17 mm). The mean follow up for nodules that were stable or became smaller was 30 months (range 20–47 months).

Nine nodules (28%) increased in size over time and were treated as hepatocellular carcinomas: six were pathology-proven hepatocellular carcinomas (3 = biopsy, 2 = liver resection, and 1 = liver transplantation), two were biopsy

Table 1. Nodules Treated as Hepatocellular Carcinoma

Size at Baseline CT (mm)	Size at Diagnosis (mm)	Time Interval (months)	Pathology Diagnosis
11	14	4	HCC
11	15	6	No HCC
13	17	21	HCC
10	22	15	HCC
14	30	22	HCC
12	18	5	No HCC
20	27	9	HGDN
12	23	7	HCC
11	21	19	HCC
Mean: 13	21	12	

HCC = hepatocellular carcinoma, HGDN = high-grade dysplastic nodule.

negative but showed recurrent tumor after radiofrequency ablation on serial CT, and one was a biopsy proven high-grade dysplastic nodule. The mean initial size of nodules that increased in size was 13 mm (range 10–20 mm). The size of the nodules treated as hepatocellular carcinoma at baseline and at the time of diagnosis is summarized in Table 1.

The mean tumor volume-doubling time for the nine nodules treated as hepatocellular carcinoma was 5.7 months with a range of 2.3–10.8 months (Fig. 3).

DISCUSSION

Patients with untreated symptomatic hepatocellular carcinoma have a dismal prognosis with survival rates ranging from 0% at 4 months to 1% at 2 yr (14–16). The goal of screening patients with chronic liver disease is to detect hepatocellular carcinomas while they are small, asymptomatic, and potentially curable. Treatment options for these patients are aimed at a complete response and include liver transplantation, surgical resection, and image-guided tumor ablation. Patients with early-stage hepatocellular carcinoma (asymptomatic single hepatocellular carcinoma $\leq$5 cm or up to 3 nodules $\leq$3 cm) may achieve a 50%–75% 5-yr survival rate with an appropriate treatment (1).

Imaging tests for the diagnosis of hepatocellular carcinoma rely primarily on the findings of contrast-enhanced multiphase imaging whether contrast-enhanced ultrasound, CT, or MRI is used. Because of its widespread availability, cost and relative lack of operator-dependent variability, CT has become the dominant imaging modality for the diagnosis of hepatocellular carcinoma in patients undergoing surveillance for cirrhosis or chronic liver disease.

On multiphase contrast-enhanced CT, the typical pattern of hepatocellular carcinoma is enhancement on the arterial phase with intralesional washout of contrast material on the portal venous phase (4, 6, 7). Small hepatocellular carcinomas usually enhance homogeneously while larger lesions tend to be heterogeneous. Unfortunately, small areas of enhancement seen only on arterial phase imaging are common and nonspecific in patients with cirrhosis. Areas of arterial phase enhancement can be secondary to perfusion abnormalities, such as arterioportal shunts, transient hepatic attenuation differences (THAD), or benign lesions including small "flash-filling" hemangiomas, focal nodular hyperplasia, and regenerating nodules (8–12). In a study that evaluated small ($\leq$20 mm) early-enhancing lesions on contrast-enhanced MRI, Shimizu *et al*. (12) found that the majority of these lesions (72%) were pseudolesions rather than hypervascular hepatocellular carcinoma. Because of the difficulties in

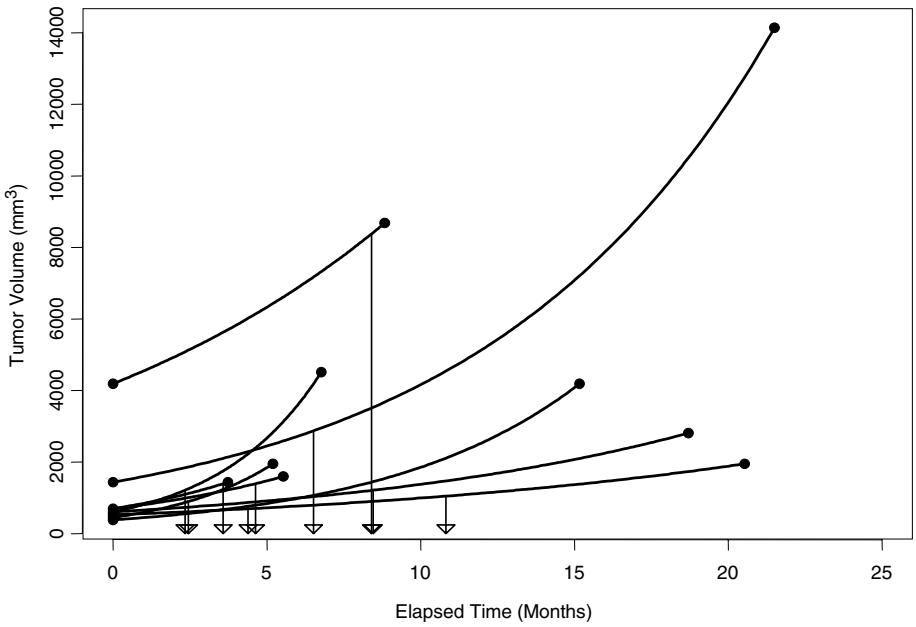

Figure 3. Graph shows initial and final volumes with assumed growth trajectories for each nodule treated as hepatocellular carcinoma. Arrows projecting down to x-axis show individual doubling times. Mean tumor volume doubling time was 5.7 months with a range of 2.3 to 10.8 months.

confidently diagnosing small hepatocellular carcinomas on imaging studies, follow-up of small arterial phase-enhancing nodules has been recommended to assess growth (8, 11, 12). Interval growth of an arterial phase-enhancing nodule is felt to indicate that the nodule is a hepatocellular carcinoma. In a study by Jeong *et al*. (11), using contrast-enhanced MRI, growth of small (<20 mm), early-enhancing nodules in patients with cirrhosis had a positive predictive value of 100% and a negative predictive value of 98% for hepatocellular carcinoma.

Our study focused on small (≤20 mm) arterial phase-enhancing lesions seen on triple-phase contrast-enhanced CT of the liver. Triple-phase CT can be performed on single or multidetector CT scanners and has become a widely available and common method of imaging patients at risk for the development of hepatocellular carcinoma. Although a variety of CT scanners were used during our study, almost all CT scans (98%; 120/123) were performed on current technology, multidetector CT scanners. In our study, 20/58 (34%) patients with cirrhosis or chronic liver disease referred for triphasic liver CT were found to have arterial phase-enhancing nodules measuring 10–20 mm in diameter that were followed with serial liver CT. In these 20 patients, 9/32 (28%) nodules grew in size and were managed as hepatocellular carcinomas. Based on pathology (7 lesions) and follow-up after treatment (2 lesions), eight lesions were diagnosed as hepatocellular carcinomas and one as a high-grade dysplastic nodule (a premalignant lesion). Of the remaining 23 lesions, 14/32 (44%) were stable on serial imaging and 9/32 (28%) decreased in size. The mean follow up for nodules that were stable or became smaller was 30 months (range 20–47 months). Because we used 18 months as our minimum time interval to follow nodules that were stable or decreasing in size, it is very unlikely that any of these nodules represented a slow-growing hepatocellular carcinoma (17, 18). In other words, 23/32 (72%) of arterial phase-enhancing nodules 10–20 mm in size were not hepatocellular carcinoma. This is in keeping with contrast-enhanced MRI studies by Jeong *et al*. (11) and Shimizu *et al*. (12) where 87% and 72% of arterial phase-enhancing lesions ≤20 mm were benign, respectively.

In our study, we chose to focus on lesions that were 10–20 mm in size. In practice, these are the most problematic lesions with regard to the diagnosis and management. In patients with cirrhosis or chronic liver disease, we have observed that areas of arterial enhancement less than 10 mm in size are commonly present on triphasic liver CT and nonspecific. In the event that one of these tiny lesions was to be a hepatocellular carcinoma or to develop into a hepatocellular carcinoma, it would still be detectable at a small size provided the patient was being followed at regular intervals since the doubling time of hepatocellular carcinomas less than 10 mm in diameter has been estimated to be 7–8 months (17). In addition, we feel that lesions larger than 20 mm can be confidently diagnosed as hepatocellular carcinomas based on imaging features alone (2).

Despite technological improvements, imaging techniques remain insensitive to the detection of small (≤20 mm) hepatocellular carcinomas. In a study by Peterson *et al*. (19), triphasic single-slice CT was only 37% sensitive in detecting hepatocellular carcinoma prospectively in patients undergoing pretransplantation surveillance with CT. Tumor nodules not detected with triphasic CT ranged in size from 2 to 40 mm (mean 13 mm). In a prospective study by Lim *et al*. (20), triple-phase helical CT detected 15/21 (sensitivity, 71%) of hepatocellular carcinomas before liver transplant. Of the tumors greater than 2 cm in size, 9/11 (82%) hepatocellular carcinomas were detected with CT but only 6/10 (60%) hepatocellular carcinomas less than 2 cm in size were detected with CT. Krinsky *et al*. (21) prospectively assessed MR imaging for the detection of hepatocellular carcinoma in the cirrhotic liver by using explantation correlation. In their study, MRI detected only 1/3 (33%) hepatocellular carcinomas less than 10 mm and 6/12 (50%) hepatocellular carcinomas 10–20 mm in size.

The suggested interval for surveillance in patients with cirrhosis is 6 months (2). This interval is based on data of tumor volume doubling time. The estimated tumor-doubling time for hepatocellular carcinoma ranges from 4 to 12 months for a lesion to grow from undetectable to 20 mm (17, 18, 22, 23). In our study, the mean doubling time for lesions 10–20 mm in size was 5.7 months, consistent with the literature.

In summary, small arterial phase-enhancing nodules are a common finding on triphasic liver CT in patients with cirrhosis or chronic liver disease. Since most arterial-phase enhancing nodules 10–20 mm in size are not hepatocellular carcinomas, serial imaging can be used to guide management in these patients. Our study supports previously published articles that indicate that interval growth of a small arterial phase-enhancing nodule in a patient with cirrhosis or chronic liver disease can be used as an indicator that the lesion should be treated as a hepatocellular carcinoma (8, 11, 12).

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