

# Clinical utility of imaging for evaluation of hepatocellular carcinoma

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**Abstract:** The hemodynamics of a hepatocellular nodule is the most important imaging parameter used to characterize various hepatocellular nodules in liver cirrhosis, because sequential changes occur in the feeding vessels and hemodynamic status during hepatocarcinogenesis. Therefore, the imaging criteria for hepatocellular carcinoma (HCC) are also usually based on vascular findings, eg, early arterial uptake followed by washout in the portal venous and equilibrium phases. Contrast-enhanced ultrasonography, dynamic multidetector-row computed tomography (MDCT), and dynamic magnetic resonance (MR) imaging with gadopentetate dimeglumine (Gd-DTPA) are useful for detecting hypervascular HCC on the basis of vascular criteria but are not as useful for hypovascular HCC. Contrast-enhanced MR imaging with gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA), a hepatocyte-specific MR contrast agent, is superior to dynamic MDCT and dynamic MR imaging with Gd-DTPA in detecting both hypervascular and hypovascular HCC. Moreover, Gd-EOB-DTPA-enhanced MR imaging can display each histologically differentiated HCC as hypointense relative to the liver parenchyma. <sup>18</sup>F-fluorodeoxyglucose positron emission tomography imaging might not be suitable for the screening and detection of HCC, given its lower diagnostic performance. However, this technique plays an important role in determining whether HCC has spread beyond the liver.

**Keywords:** hepatocellular carcinoma, evaluation, imaging, clinical utility

## Introduction

The annual carcinogenesis rates for liver cirrhosis related to hepatitis B and C are 2.5%–3% and 5%–8%, respectively, and such cases are classified as very high risk. High-risk factors that are thought to increase the risk of carcinogenesis include male sex, older age, alcohol use, obesity, diabetes, high alpha-fetoprotein levels, and a low platelet number.<sup>1,2</sup> In patients with hepatitis C, the progression of liver fibrosis increases the carcinogenic risk. The progression of liver fibrosis is related to a decrease in the platelet count, so a platelet count <100,000 mm<sup>2</sup> is another risk factor. The rate of carcinogenesis increases dramatically in older patients with hepatitis C. On the other hand, in hepatitis B, carcinogenesis can be observed early after infection and in young patients.<sup>1,2</sup>

Recently, the incidence of carcinogenesis has increased in non-B, non-C hepatitis patients. Nearly all of these patients suffer from alcoholic hepatitis, autoimmune hepatitis, or nonalcoholic steatohepatitis; however, some have no basal liver disease. Carcinogenesis associated with alcoholic hepatitis, autoimmune hepatitis, or primary biliary cirrhosis is related to liver cirrhosis with progressive fibrosis.<sup>1,2</sup>

For the surveillance and early detection of hepatocellular carcinoma (HCC), tumor markers such as alpha-fetoprotein, AFP-L3 (lens culinaris agglutinin-reactive

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fraction of alpha-fetoprotein), PIVKA-II (protein induced by vitamin K absence or antagonist-II), and imaging modalities are usually employed. Ultrasonography (US) is the first-choice imaging modality for HCC screening because of its low cost, minimally invasive nature, and convenience. Dynamic computed tomography (CT) or dynamic magnetic resonance (MR) imaging are recommended for the screening of patients with suspected early-stage HCC or high-risk patients with liver cirrhosis. However, recently, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MR imaging is being increasingly recommended. Positron emission tomography (PET) is widely available, and its oncologic applications with the 2-[<sup>18</sup>F] fluoro-2-deoxy-D-glucose (<sup>18</sup>F-FDG) tracer have become a standard imaging modality in tumor diagnosis and staging; however, its sensitivity for HCC is not high. In this review, we discuss the clinical utility of these imaging modalities for HCC.

## Imaging modalities

Less invasive imaging modalities, such as US, CT, and MR imaging, have evolved considerably in recent times, and are essential for imaging-based screening of HCC.

### Ultrasound

Gray-scale US is very important and useful for the screening or surveillance of HCC<sup>3</sup> and is sometimes useful for the differential diagnosis of liver tumors, particularly those with characteristic findings. US is inexpensive and noninvasive. However, it is sometimes difficult to precisely evaluate the whole liver by US in patients with obesity or liver atrophy and in those who cannot hold their breath.

The specific US findings of HCC are mosaic pattern, peripheral halo sign, and posterior enhancement. An evaluation of the arterial flow by Doppler US is also useful for diagnosing hypervascular (typical) HCC. However, this is difficult in small HCC because early-stage tumors are usually hypovascular. In addition, well differentiated HCC might have high echogenicity, reflecting intratumoral fat deposition (fatty metamorphosis) and thus might be difficult to differentiate from hemangioma, which also has high echogenicity. Conventional color Doppler US and power Doppler US have a limited ability to depict intralesional vascularity because both techniques are insensitive to slow-flowing and deeply located blood vessels, and are usually associated with multiple artifacts. Therefore, the diagnostic capabilities of these techniques for HCC are limited. For such lesions, contrast-enhanced US, dynamic CT,

or MR imaging should be performed for the differential diagnosis.

Contrast-enhanced US is helpful for correctly diagnosing HCC. A variety of microbubble-based contrast agents for liver US are currently available for clinical use in many European, Asian, and South American countries,<sup>4</sup> eg, SonoVue® (Bracco Imaging, Milan, Italy), Definity® (Lantheus Medical Imaging, Boston, MA, USA), and Sonazoid® (Daiichi Sankyo, Tokyo, Japan). These contrast media facilitate the evaluation of liver tumor hemodynamics, including the hypervascularity (hyperenhancement in the arterial phase) associated with typical HCC. Contrast-enhanced US is most sensitive for evaluating the arterial enhancement of HCC.

Negative enhancement or “washout of contrast medium” during the portal venous and equilibrium phases is another important characteristic of HCC, as typical lesions lack a portal venous supply. In HCC, washout is generally slower and milder than in liver metastasis.<sup>5</sup>

Benign nodules, such as regenerative or dysplastic nodules, are usually isoechoic or slightly hypoechoic in the arterial and portal venous phases. Contrast-enhanced US is helpful for characterizing potential mimickers of HCC on imaging, such as nontumoral arterioportal shunts or hemangiomas.

Sonazoid can evaluate not only the tissue vascularity but also the presence of Kupffer cells because it accumulates in these cells in the Kupffer (post-vascular) phase.<sup>6</sup> Typical hypervascular HCCs usually lack Kupffer cells, whereas benign hepatocellular lesions contain these cells. Therefore, Sonazoid is useful for differential diagnosis. However, its diagnostic utility for early-stage HCC and well differentiated HCC has not been confirmed because these tumors often contain Kupffer cells.

Sonazoid-enhanced US detection of focal liver lesions has been reported to be superior to that of multidetector row computed tomography (MDCT).<sup>7</sup> Contrast-enhanced US is now recognized as a useful imaging modality for the noninvasive diagnosis of newly detected small liver nodules during HCC surveillance.<sup>8</sup> The sensitivity, specificity, and positive predictive value of contrast-enhanced US for diagnosis of HCC is 88.8%, 89.2%, and 91.3%, respectively.<sup>9</sup> This diagnostic ability is strongly associated with nodular size; the sensitivity in nodules 1.0–2.0, 2.1–3.0, and 3.1–5.0 cm in size is 69%–80%, 97%, and 100%, respectively, and the accuracy is 82%–87%, 97%, and 100%.<sup>10</sup>

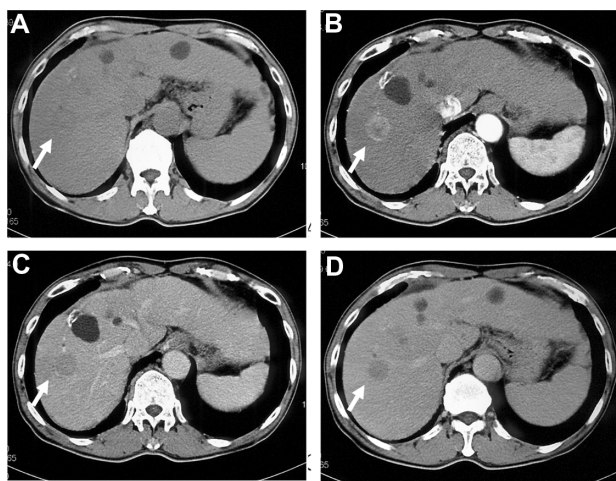
### Computed tomography

Dynamic CT with a bolus injection of contrast medium is essential for diagnosing liver tumors.<sup>11,12</sup> Moreover, dynamic

MDCT has been recently employed for liver imaging because MDCT with increased gantry rotation speeds and numbers of detector rows has become widely available.<sup>11,13</sup>

Typical HCC usually exhibits hypervascularity in the arterial phase and contrast washout in the portal venous and equilibrium phases of dynamic MDCT. These findings are useful for the diagnosis (Figure 1). The arterial phase comprises the most important set of images because, during the arterial phase, HCC displays strong contrast uptake relative to the low enhancement of the liver parenchyma. However, early HCC or borderline lesions exhibit isoattenuation to low attenuation to the liver parenchyma in the arterial phase and isoattenuation in the equilibrium phase; therefore, dynamic CT is less useful for such lesions.

Currently, low-dose CT is expected to afford a novel and less invasive examination. Iodine contrast agents are more conspicuous at low tube voltage (eg, 80 kVp) than at high tube voltage (120–140 kVp) settings,<sup>14,15</sup> and hypervascular HCC can thus be demonstrated more clearly with low-dose CT. CT images taken at 80 kVp might display a higher contrast-to-noise ratio for hypervascular HCCs.<sup>16</sup> Moreover, the radiation dose is significantly reduced when CT images are obtained at 80 kVp versus 140 kVp.<sup>17</sup> Low-dose imaging might result in high levels of image noise, particularly in large patients,<sup>18</sup> but new imaging algorithms such as iterative reconstruction can dramatically reduce the image noise and improve the image quality.



**Figure 1** A 68-year-old man with a hepatocellular carcinoma in segment 8. **Notes:** (A) A noncontrast CT image cannot clearly depict a liver nodule (arrow). (B) Arterial-phase CT image (performed with an iodine concentration of 370 mg I/mL) shows a hyperattenuating nodular lesion in segment 8 (arrow). (C) On portal-phase CT imaging, the lesion is depicted as a fairly discrete hypoattenuating nodule (arrow). (D) An equilibrium-phase CT image shows a discrete hypoattenuating nodule (arrow). On combination of four-phase image sets, the lesion is definitely diagnosed as typical hypervascular hepatocellular carcinoma. **Abbreviation:** CT, computed tomography.

## Magnetic resonance imaging

Typical HCC lesions are hypointense on T1-weighted and hyperintense on T2-weighted images; in contrast, well differentiated or early HCC often exhibits hyperintensity to isointensity on T1-weighted images and isointensity to hypointensity on T2-weighted images.

Nonspecific (extracellular) contrast medium, such as gadopentetate dimeglumine (Gd-DTPA), has been used widely in dynamic MR imaging. Typical HCC exhibits hyperenhancement in the arterial phase and contrast washout in the portal venous and equilibrium phases on dynamic MR imaging, similar to the features observed with dynamic CT. In fact, the sensitivity of hypervascular HCC detection is not significantly different between dynamic MDCT and dynamic MR imaging.<sup>12</sup> Therefore, when selecting imaging modalities, we should consider not only the sensitivity for detection of HCC but also the image quality, cost, and radiation exposure.

For MR imaging of the liver, tissue-specific MR contrast media that accumulate in Kupffer cells via phagocytosis or in hepatic cells via hepatocyte functioning are clinically available, and these media increase the tumor detection sensitivity.<sup>19–21</sup> In particular, Gd-EOB-DTPA, a T1-shortening agent, has become an essential contrast medium for liver imaging because of its high diagnostic capacity.<sup>20–24</sup>

Gd-EOB-DTPA acts as both an extracellular and hepatocyte-specific contrast agent, enabling evaluation of the hemodynamics of a liver tumor.<sup>25</sup> Typical HCC exhibits hyperenhancement in the arterial phase of dynamic MR imaging with Gd-EOB-DTPA and a T1-weighted sequence. Moreover, Gd-EOB-DTPA is taken up by hepatocytes in the hepatocyte phase, which occurs approximately 15–20 minutes after injection of contrast medium. However, in the absence of hepatocyte function, HCC does not take up Gd-EOB-DTPA; therefore, such HCC lesions will be hypointense relative to the liver parenchyma, which does take up Gd-EOB-DTPA.<sup>26,27</sup> Some hypervascular and well or moderately differentiated HCC (5%–10%) exhibit hyperintensity in the hepatocyte phase.<sup>22,28</sup> These nodules express OATP1B3 (OATP8) on their cell membranes, which acts as a transporter of Gd-EOB-DTPA. As such, these nodules can take up Gd-EOB-DTPA.<sup>29–31</sup> Focal nodular hyperplasia is another type of hepatocellular nodule that exhibits hyperintensity in the hepatocyte phase. Focal nodular hyperplasia is usually isointense in the hepatocyte phase and presents with wheel-like vessels on contrast-enhanced US. These imaging findings facilitate the differential diagnosis.

Gd-EOB-DTPA-enhanced MR imaging is superior to dynamic MDCT and dynamic MR imaging with Gd-DTPA for detection of both hypervascular and hypovascular HCC;<sup>32-34</sup> it can detect very tiny lesions in the hepatocyte phase that cannot be detected on dynamic CT and dynamic MR imaging with Gd-DTPA. Moreover, Gd-EOB-DTPA-enhanced MR imaging can show each histologically differentiated HCC as hypointense relative to the liver parenchyma.<sup>22,23</sup> This means that hypovascular and well differentiated HCC, including early HCC, could appear as hypointense areas in the hepatocyte phase.<sup>22</sup>

## Positron emission tomography

PET is widely available, and its oncologic application with <sup>18</sup>F-FDG has become a standard imaging modality for diagnosis and staging of tumors. However, the sensitivity of FDG-PET for detecting HCC is only 50%,<sup>35</sup> because in the normal liver, the concentration of glucose-6-phosphatase is high, leading to rapid clearance of glucose-6-phosphate or FDG-6-phosphate from hepatocytes and a consequently mild appearance of the liver on PET. On the other hand, the detection of extrahepatic FDG-avid metastases that originated from HCC has also been reported; these metastases appear to be more FDG-avid, especially in cases of less differentiated HCC. Sugiyama et al reported that the sensitivity of FDG-PET was 83% for extrahepatic metastases >1 cm at the largest diameter and 13% for lesions ≤1 cm. There were no false-positive lesions among the investigated.<sup>36</sup> Therefore, the most important roles of FDG-PET for HCC patients are assessment of the malignant potential of hepatic lesions of unknown origin via simultaneous visualization of the liver and extrahepatic tissue and assessment of known HCC with clinically suspected extrahepatic metastasis.

## Screening

As a diagnostic algorithm, US is the first-choice imaging modality for HCC screening. The American Association for the Study of Liver Diseases and European Association for the Study of the Liver guidelines<sup>3,37</sup> accept only four-phase CT or dynamic contrast MR imaging as the second-choice examination modality for HCC diagnosis and contrast-enhanced US as the third choice. The Asian Pacific Association for the Study of the Liver and Japanese Society of Hepatology guidelines<sup>38,39</sup> also accept contrast-enhanced US as a diagnostic tool. The Japanese Society of Hepatology guidelines even accept contrast-enhanced US as the second-choice modality; however, the Asian Pacific Association for the Study of the Liver guidelines recommend use of either CT or MR imaging

as the second-choice modality, with contrast-enhanced US as the third-choice modality in the absence of typical diagnostic CT and/or MR imaging findings.

## Vascularity of HCC

The hemodynamics represent the most important imaging finding for characterization of various hepatocellular nodules in the context of liver cirrhosis because sequential changes occur in the supplying vessels and the hemodynamic state during hepatocarcinogenesis.<sup>40</sup> Typical HCC usually exhibits hypervascularity, whereas early and well differentiated HCC exhibits hypovascularity. Regenerative nodules and benign hyperplastic nodules usually contain normal hepatic arteries and portal veins within the lesion.<sup>41</sup> It is very important to identify these imaging findings in each modality when diagnosing HCC. The major organizations for liver studies, including the American Association for the Study of Liver Diseases,<sup>3</sup> Asian Pacific Association for the Study of the Liver,<sup>10</sup> European Association for the Study of the Liver,<sup>37</sup> and Japanese Society of Hepatology,<sup>38</sup> have each published diagnostic guidelines for HCC. The Asian Pacific Association for the Study of the Liver<sup>39</sup> and Japanese Society of Hepatology<sup>38</sup> guidelines recommend an algorithm that begins with tumor arterial enhancement. Tumor vascularity is a very important diagnostic factor for liver tumors.

## Hypervascular HCC

Advanced HCC lesions usually exhibit hypervascularity. Therefore, the detection of typical HCC is almost equal to detection of hypervascular HCC. Contrast-enhanced US exhibits the same hypervascular HCC detection sensitivity as dynamic CT.<sup>19</sup> Gd-EOB-DTPA MR imaging exhibits better detection sensitivity than dynamic CT or dynamic MRI with Gd-DTPA and sensitivity similar to that of superparamagnetic iron oxide-enhanced MR imaging and CT during arterial portography and hepatic angiography.<sup>12,22,23</sup> However, contrast-enhanced US, dynamic CT, or dynamic MR imaging with Gd-DTPA is employed for HCC screening because the imaging quality and diagnostic ability of each modality might change depending on each institutional situation (eg, the specialties of radiologists and technologists and quality of the imaging unit). Table 1 shows the different studies in which the performance of dynamic-enhanced CT or MR imaging for HCC diagnosis was verified against histologic findings as a reference standard. The low sensitivity of dynamic-enhanced CT and MR imaging for diagnosing small HCC nodules could be explained by difficulties in detection and characterization of nodules with atypical enhancement.<sup>42-51</sup>



**Table I** Reported sensitivities and specificities of dynamic-enhanced CT and MRI with extracellular contrast material in diagnosing hepatocellular carcinoma against histological findings as a standard of reference

Reference	Imaging technique	Mean diameter (mm)	Sensitivity (%)	Specificity (%)
Lim et al <sup>42</sup>	Dynamic CT	19	71	
Krinsky et al <sup>43</sup>	Dynamic MRI	18	55	
Rode et al <sup>44</sup>	Dynamic CT	>8	53.8	
	Dynamic MRI	>8	76.9	
Krinsky et al <sup>45</sup>	Dynamic MRI	>20	100	
		10–20	52	
		<10	4	
Brancatelli et al <sup>46</sup>	Dynamic CT		60.8	52
Valls et al <sup>47</sup>	Dynamic CT	>20	93.6	
		<20	61	
Kim et al <sup>48</sup>	Dynamic CT	>10	91.3	95.3
		<10	29	
	Dynamic MRI	>10	90.2	97
		<10	29	
Ronzoni et al <sup>49</sup>	Dynamic CT	17	77	75
Forner et al <sup>50</sup>	Dynamic MRI	<20	61.7	96.6
Sofue et al <sup>51</sup>	Dynamic CT	21	92.9	93.7

**Abbreviations:** CT, computed tomography; MRI, magnetic resonance imaging.

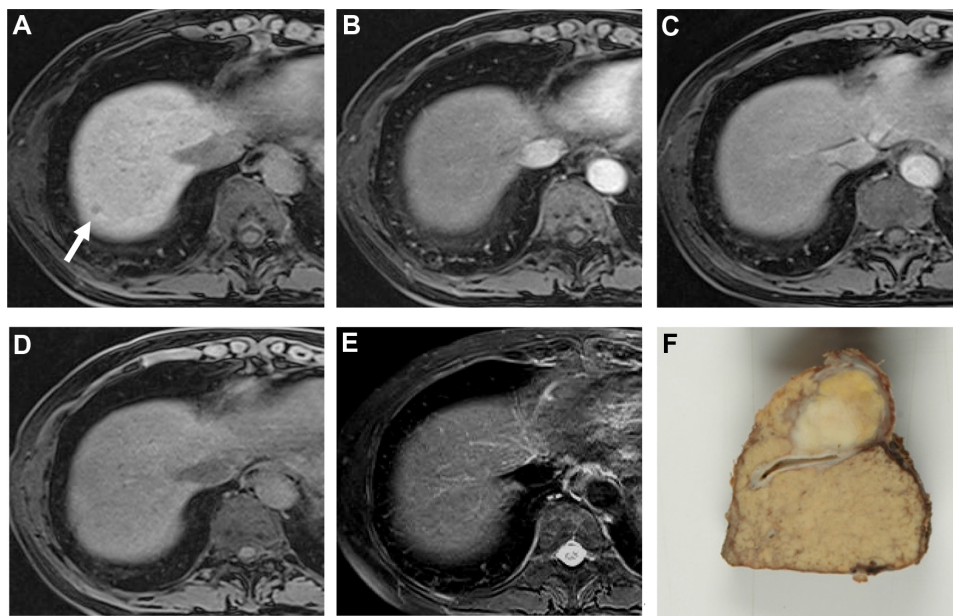
Enhancement of the arterial parenchyma due to an arterial-portal venous shunt might appear as a false-positive lesion during dynamic MDCT investigations of HCC. Some HCC, which do not exhibit washout of contrast medium during the portal or equilibrium phase, may be difficult to diagnose. Sonazoid-enhanced US or Gd-EOB-DTPA-enhanced MR imaging is performed for the differential diagnosis of an arterial-portal shunt. Hypo-echo in the Kupffer phase of Sonazoid-enhanced US or hypointensity in the hepatocyte phase of Gd-EOB-DTPA-enhanced MR imaging is diagnostic for HCC.

Shimizu et al<sup>52</sup> demonstrated that a significant percentage of small early arterial-enhancing lesions in patients with cirrhosis or chronic hepatitis were not HCC. Of 104 small (<20 mm) arterial-enhancing lesions that were round or oval, only 28% were classified as HCC based on interval growth or a pathologic confirmation. More than half (52%) of these lesions were considered to be definitely not HCC and 20% of the lesions, which featured a stable size and appearance, were considered likely pseudolesions. Moreover, in the study by Shimizu et al, 48% of the small HCCs were detected only in the arterial phase, and these nodules did not exhibit the typical washout pattern in the portal and delayed phases.

## Hypovascular HCC

As stated above, it is crucial to detect lesion hypervascularity in order to make a diagnosis of HCC, because this feature is among the most reliable characteristics of HCC. However, early or well differentiated HCC often exhibits hypovascularity.<sup>8,53</sup> Several studies<sup>54–56</sup> have demonstrated that 27%–34% of small HCCs are hypovascular. Therefore, the actual criteria, which are based only on a “typical” vascular enhancement pattern, should be reconsidered, especially for cases of HCCs that are <20 mm in diameter. Dynamic MDCT and dynamic MR imaging with Gd-DTPA are not particularly useful for detecting hypovascular lesions, nor is superparamagnetic iron oxide-enhanced MR imaging because hypovascular HCC often contains Kupffer cells<sup>57</sup> and thus takes up superparamagnetic iron oxide. Currently, there are no reports indicating the usefulness of enhanced US for detecting hypovascular HCC. Instead, Gd-EOB-DTPA-enhanced MR imaging was reported to be superior to other imaging modalities for detection of these lesions.<sup>22,23</sup>

Gd-EOB-DTPA-enhanced MR imaging can detect hypovascular and well differentiated HCC lesions. Using Gd-EOB-DTPA-enhanced MR imaging for chronic liver disease, we often encounter tiny hypovascular nodules (<15 mm in diameter) that can only be detected as hypointense nodules on hepatocyte-phase images (Figure 2).<sup>58,59</sup> The clinical management of these tiny hypovascular nodules is currently discussed because precancerous lesions may be present at a particular rate in hypovascular HCC. For example, hypovascular nodules exhibiting hypointensity on hepatocyte-phase Gd-EOB-DTPA-enhanced MR images can transition to HCC within 2 or 3 years at a rate of 11.1% or 15.9%, respectively.<sup>60</sup> High intensity on T2-weighted images, fat deposition, a diameter of 10–15 mm at the time of detection, and hypointensity on the hepatocyte-phase Gd-EOB-DTPA-enhanced MR images are reported risk factors for carcinogenesis.<sup>58,61–63</sup> Tiny hypovascular nodules with a doubling time of <500 days exhibit a high level of tumor hypervascularization during follow-up.<sup>63</sup> Therefore, the recommended management for these tiny hypovascular nodules that are detected only on Gd-EOB-DTPA-enhanced MR images is as follows: biopsy can be performed for lesions ranging from 10 mm to 15 mm in diameter;<sup>3,37</sup> lesions <10 mm in diameter should be followed up with dynamic MDCT, enhanced (Sonazoid) US, or Gd-EOB-DTPA-enhanced MR imaging, and biopsy can be performed when the lesion increases in size; imaging examinations are recommended every 3–6 months for



**Figure 2** A small hepatocellular carcinoma in a 55-year-old man.

**Notes:** (A) A hepatobiliary phase image of Gd-EOB-DTPA-enhanced magnetic resonance imaging shows a small hypointense lesion in segment 8 (arrow). The lesion is not seen on other sequences, ie, (B) arterial phase, (C) portal phase, (D) precontrast T1-weighted image, and (E) a fat-suppressed T2-weighted image. (F) The lesion shows considerable enlargement on the follow-up image obtained one year after the first examination. Surgical specimens revealed a well differentiated hepatocellular carcinoma.

**Abbreviation:** Gd-EOB-DTPA, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid.

lesions approximately 15 mm in diameter because lesions should be treated before reaching 20 mm in diameter,<sup>63</sup> and a lesion can be treated when it exhibits hypervascularization on follow-up images.

## Infiltrating HCC

Although infiltrating HCC accounts for 7%–13% of all HCC cases<sup>64,65</sup> and is thus not an uncommon HCC subtype, it remains poorly characterized in the literature. Infiltrating HCC exhibits a diffuse, permeating appearance on cross-sectional imaging and is difficult to detect in settings such as the heterogeneous background of a cirrhotic liver; therefore, infiltrating HCC is often not diagnosed until it has progressed to an advanced stage.<sup>66</sup> Specifically, infiltrating HCC often presents as predominantly hypointense on T1-weighted images and usually as homogeneous and mild to moderately hyperintense on T2-weighted images.<sup>65</sup> On gadolinium-enhanced dynamic imaging, the majority of infiltrating HCC lesions appear as inhomogeneous areas of enhancement on arterial-phase images and as corresponding washout on more delayed phases of contrast enhancement. In addition, infiltrating HCC-associated portal vein thrombus commonly displays significant neovascularity or “arterialization” of the tumor thrombus. In fact, it is not uncommon for neovascularity of portal vein thrombus to be the only initial detectable imaging characteristic of an infiltrating HCC.<sup>65,67</sup>

## Staging

A chest CT, bone scintigraphy, or PET/CT examination should be performed for a patient with risk factors for extrahepatic metastasis, such as the presence of portal vein tumor thrombus, an alpha-fetoprotein level >200 ng/mL, a PIVKA-II level >300 mAU/mL, a platelet count >130×10<sup>3</sup>/μL, or age <65 years. Extrahepatic metastasis of HCC occurs rarely in new-onset cases (1.0%–2.3%)<sup>68</sup> but is found more frequently (21%–24%) during the follow-up period after treatment.<sup>69</sup> A brain CT or MR imaging can be performed if neurologic symptoms or lung metastasis are present.

## Disclosure

The authors have no conflicts of interest to disclose with respect to this review paper.

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