Current Opinion about Hepatocellular Carcinoma <10 mm

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Keywords

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Abstract

Background: Early detection of hepatocellular carcinoma (HCC) is important. Advances in liver imaging techniques have facilitated the detection of HCC at an early stage. However, there is a controversial discussion on how to diagnose very small HCC by imaging. The aim of the current review is to present current published data on HCC ≤10 mm and discuss on how to best diagnose and treat such lesions. **Summary:** It is still challenging, however, to accurately characterize HCC <10 mm. The accuracy of contrast-enhanced ultrasound may be critical for early treatment decisions for cancer patients, particularly when CECT and/or CEMRI are inconclusive. **Key Messages:** The characterization of focal liver lesions <10 mm is frequently delayed until a follow-up imaging procedure demonstrates growth or stability. A repetition of ultrasound examination after 3 months for new nodules <1 cm should be recommended.

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Introduction

Early detection of hepatocellular carcinoma (HCC) is important since multiple treatment options are available for small HCC, BCLC (Barcelona Clinic Liver Cancer) stage A, including curative resection, liver transplantation, or radiofrequency ablation [1, 2]. The best candidates for resection are patients with a solitary tumor and preserved liver function. The best candidates for liver transplantation are those within Milan criteria (solitary tumor ≤5 cm or up to 3 nodules ≤3 cm) [1]. According to current guidelines, generally noncurative treatments such as transarterial chemoembolization, radioembolization, or systemic therapy options may be more effective in small tumors [3–7]. Advances in liver imaging techniques have facilitated the detection of HCC at an early stage, including borderline hepatic nodules in hepatocarcinogenesis [5, 6, 8].

Hepatocarcinogenesis is a multistep process characterized by progressive cellular and molecular dedifferentiation of hepatocytes and culminating in the emergence of HCC [9]. However, as small lesions may often also be regenerative nodule (RN) or dysplasia nodule (DN), discussed to be precursors of HCC, only few HCC with a diameter of ≤10 mm have been published [10–17]. There is a controversial discussion on how to diagnose very small HCC by imaging. The liver imaging reporting and

data system (LI-RADS) published by the American College of Radiology (ACR) allows only the category LI-RADS 4 for focal liver lesions (FLLs) ≤ 10 mm and not LI-RADS 5, which represents the confirmation of HCC [9, 18, 19]. The aim of the current review is to present current published data on HCC ≤ 10 mm and discuss on how to best diagnose and treat such lesions.

Do They Exist?

In previous studies, HCC < 10 mm were reported in patients with liver cirrhosis under surveillance [14, 15, 17, 20–27]. In the 2018 practice guideline by the American Association for the Study of Liver Diseases (AASLD), HCC < 10 mm was defined as “subthreshold” HCC [6]. A 10-mm threshold is used because lesions < 10 mm are rarely malignant. Even if malignant, such nodules are difficult to diagnose reliably due to their small size, and as long as the patient is in regular surveillance, they may be followed safely [28–30].

Analysis of Histopathological Studies

Multistep hepatocarcinogenesis in the cirrhotic liver may start from RN, developing into DN subsequently transforming into HCC [31]. In addition to DN, premalignant lesions also include dysplastic foci, both being characterized by cytologic or structural atypia [32]. Clinically, conspicuous small nodules can pathologically be either preneoplastic lesions with uncertain malignant potential, such as macroregenerative nodules, low-grade dysplastic nodules (LGDN), or high-grade dysplastic nodules (HGDN). Dysplastic foci are small microscopic lesions being composed of hepatocytes with precancerous features, such as small cell change, but do not form masses or nodules and are therefore not detectable with *in vivo* imaging. DN are precancerous hepatocellular lesions that have dysplastic features without histologic evidence of malignancy. They are subclassified into LGDN and HGDN on the basis of the degree of cellular abnormalities. Dysplastic nodules usually measure between 0.5 and 1.5 cm in diameter. Clinically HGDN are considered precursors of HCC [33, 34].

Small HCCs are defined as HCCs measuring 2 cm or less in diameter and are divided into of 2 subtypes: early HCC (eHCC) and small progressed HCC (small pHCC). eHCC usually form vaguely nodular tumors without having a tumor capsule and loss of portal tracts as subtle signs

of invasion, while small pHCC are distinctly nodular tumors in most cases, often developing a tumor capsule and microscopically showing expansile or infiltrative growth sometimes accompanied by vascular invasion or even intrahepatic metastasis [33, 34]. Small foci of HCC may be present within at least one-third of DN, and these can easily be missed in a small biopsy (sampling error). Different grades of dysplastic changes could also affect different parts of the nodule. Little is known about the possibility of correctly making a definite differential diagnosis of LGDN, HGDN, and HCC from a small biopsy specimen sampled from a part of a nodule [35]. However, the risk of HCC is generally higher when the nodule size increases. In nodules > 1 cm, the rate of HCC was reported to be 66% [14, 20, 36].

The key pathologic alterations occurring in multistep hepatocarcinogenesis include a corresponding gradual decrease in hepatocyte function, decreased Kupffer cell density, decreased portal tracts, progressive sinusoidal capillarization and recruitment of unpaired arterioles, transition of venous drainage from hepatic veins to portal veins, increased fat content in early hepatocarcinogenesis, and decreased expression of organic anionic transporting polypeptides [37, 38].

HCCs that have not (yet) developed exclusive arterial supply and thus do not take up contrast in the arterial phase of imaging techniques correspond mostly to indistinctly or vaguely nodular, well-differentiated lesions without satellites/microvascular invasion. They correspond to “carcinoma in situ” entities and, theoretically, local recurrence after treatment should be negligible [39]. Thus, early detection and effective prevention of HCC development is, in principle, the most impactful strategy to improve the prognosis of patients [40].

Analysis of Imaging Studies

It is still challenging, however, to accurately characterize borderline hepatocellular nodules, including LGDN, HGDN, and early HCC, at imaging because they usually have similar imaging features [33, 37].

Contrast-Enhanced Ultrasound

Contrast-enhanced ultrasound (CEUS) is indeed valid as a primary diagnostic imaging modality in the characterization of HCC [41–44]. Previous studies concluded that the accuracy of CEUS does not depend on lesion diameter and that CEUS allowed small FLLs to be characterized effectively [12]. The size of the detectable noncys-

tic FLLs was comparable between conventional ultrasound (2–9 mm, mean 6 mm), CEUS (2–9 mm, mean 5 mm), and CT (1–9 mm, mean 5 mm) [12]. However, the use of contrast-enhanced technique did not increase the sensitivity of ultrasound for the detection of borderline hepatic nodules. The main reason may be that the highest contrast between the lesion and liver parenchyma was seen in the arterial phase, making it literally impossible to image the entire liver during this short period [8].

Since increased arterial vascularization is the hallmark of malignancy, its detection by CEUS could become essential to diagnosis confirmation [21]. In a DEGUM trial, CEUS was proven to have a high diagnostic accuracy for the differential diagnosis of small (≤ 20 mm) and subcentimetric (≤ 10 mm) FLLs in clinical practice [15]. The overall diagnostic accuracy of CEUS in FLLs ≤ 10 mm ($n = 62$) was 80.6%. The positive predictive value of CEUS in the classification of malignant FLLs ≤ 10 mm was 92.7%, and the negative predictive value was 85.7% [15], among which 7 (11.3%) FLLs that were ≤ 10 mm remained unclear [15]. In another prospective study, 13 (14.6%) FLLs were < 10 mm, among which 2 were finally diagnosed as moderately differentiated HCC nodules [20].

However, absence of contrast hyperenhancement in CEUS during the arterial phase in nodules < 2 cm in a cirrhotic liver does not predict a less malignant profile [21]. In a prospective study including 168 asymptomatic patients with cirrhosis and newly discovered solid liver nodules < 20 mm, 19 nodules were < 10 mm, but only 3 (16%) were finally diagnosed as HCC. All 3 HCCs showed hyperenhancement during the arterial phase of CEUS [21]. Also, Leoni et al. [13] demonstrated that 21 of 55 HCCs between 10 and 20 mm had an isoenhancement pattern at CEUS, which is atypical for malignancy. Meanwhile, a hyper/hypopattern was demonstrated in 16/55 HCCs between 10 and 20 mm [13]. These findings confirmed the progression of neovascularization with increasing size of the neoplasm.

It was reported that Sonazoid-enhanced CEUS could precisely evaluate not only tumor enhancement, but also the tumor vessels [45]. The tumor vessel patterns observed during the arterial phase of CEUS may be useful for differentiating RN from HGDN and early HCC in patients with chronic liver disease. Most of the early HCC and HGDN exhibited a peripheral vessel pattern during the arterial phase of CEUS [45].

Computed Tomography

The introduction of multidetector computed tomography (MDCT) scanners with thin collimation, near-iso-

tropic voxel, and consequent high spatial resolution resulted in an increased ability to detect subcentimetric lesions within the liver parenchyma [12]. Until now, no study has investigated the sensitivity or specificity of perfusion CT, dual-energy CT, or PET/CT in the detection or characterization specifically of small HCC in a cirrhotic liver.

This may be of particular interest and importance as for small HCC < 10 mm, the contrast and spatial resolution of CT may not be sufficient for detection, especially of the smallest lesions in the heterogeneous background of cirrhotic liver parenchyma. Liver lesions with a size of 10 mm or less may appear indeterminate on MDCT because the attenuation and contrast-enhancement pattern of small lesions may remain nonspecific due to limited spatial resolution [44].

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) was reported to be of high specificity for 5–20 mm liver nodules [20]. Golfieri et al. [23] showed that 24 of 32 HCCs < 10 mm (75%) were detected due to an arterial hypervascularity on SPIO MRI. Dynamic MRI demonstrated high sensitivity (83.9%) and low specificity (36.1%) for HCC lesions < 10 mm [22]. Also, Gd-EOB-DTPA MRI showed an additional increase in sensitivity (100%), specificity (95%), and accuracy (100%) for diagnosis of HCC lesions < 10 mm [23]. Two studies reported higher sensitivities in the detection of HCC < 10 mm with gadoxetic acid-enhanced MRI compared to multiphasic 16- to 64-MDCT [24, 25].

Characterization of RN, DN, and early HCC in cirrhosis based on diffusion-weighted MR imaging and ADC values is limited. DN are typically hyperintense on T1-weighted images and iso- or hypointense on T2-weighted images. Diffusion-weighted MR imaging does provide added diagnostic value in the detection and characterization of HGDN and HCC, and it may not be helpful for LGDN and RN in a cirrhotic liver [46]. Currently, MRI or abbreviated MRI would be considered for small suspected HCC when ultrasound is compromised by severe patient obesity, hepatic steatosis, or parenchymal heterogeneity [29].

How Can HCC < 10 mm Be Diagnosed?

Detection

DN and early HCC are often detected during HCC surveillance with ultrasound. Identification of a DN or early HCC from the background nodularity of a cirrhotic

Fig. 1. HCC smaller than 10 mm. A 40-year-old patient with a history of liver cirrhosis. **a** B mode ultrasound detected a very small hypoechoic lesion (8 mm) in the right lobe of the liver. **b** No color flow signals could be detected inside the lesion. After injection of contrast agents, the lesion showed quick and complete hyperen-

hancement in the arterial phase (**c**) of CEUS. The lesion was iso-enhanced during the portal venous phase (**d**) and showed wash out in the late phase of CEUS (**e**). Surgical resection and histopathological results proved it was an HCC lesion (**f**). HCC, hepatocellular carcinoma; CEUS, contrast-enhanced ultrasound.

liver is challenging. Moreover, RN in a cirrhotic liver may be as large as 2 cm, whereas in turn some early HCCs may be <1 cm. Bolondi et al. [35] found that CEUS (61%) had a higher detection rate for early arterial enhancement than CT (49%) for lesions ≤ 2 cm.

Characterization

Arterial hypervascularization, detected at contrast-enhanced imaging techniques, is now regarded a distinctive feature of HCC in cirrhosis as nonneoplastic nodules still have a prevalent portal vascularization [35]. Therefore, in lesions showing hyperenhancement (hypervascularization) in the arterial phase, the late phase should be examined after at least 4 min, so that the contrast hypoenhancement is not missed [47] (Fig. 1). The accuracy of CEUS for the detection of malignant subcentimeter lesions may be critical for early treatment decisions for cancer patients, particularly when CECT and/or CEMRI are inconclusive [44].

Ultrasound-Guided Fine Needle Biopsy

In a screening population, more than half of very small nodules arising in cirrhotic livers were estimated to be hepatocellular carcinoma, and approximately 90% of these malignancies can be reliably identified with ultrasound-guided fine needle biopsy (FNB) [48]. As early as 1994, a multicenter Italian study proved that ultrasound-guided FNB showed correct diagnoses for 87.5% of small (10 mm in diameter) liver lesions [49]. Also, the use of ultrasound-guided FNB allowed to diagnose and initiate treatment almost immediately for 82.8% HCC nodules (≤ 10 mm) in the study of Caturelli et al. [48].

Differential Diagnosis

Dysplastic Nodules

DN are typically hypovascular or isovascular to the liver during the arterial phase and are isoechoic to liver in the subsequent phases. The frequent hypovascularity of DN in the arterial phase is explained by a transient phase in which both arterial and portal supplies decrease before neoangiogenic unpaired arteries develop. According to the principal guidelines on the management of HCC, such as those of the AASLD, diagnosis of early (hypovascular) HCC and HGDN is impossible by imaging. However, a recently published, novel imaging diagnostic algorithm demonstrated a significantly higher sensitivity than that of the AASLD imaging criteria for HCC in patients with cirrhosis evaluated by Gd-EOB-DTPA MRI, even for lesions ≤ 2 cm [50].

Small HCC

A nodule in nodule pattern (partial nodular hyperenhancement within a hypovascular nodule in the arterial phase) is an uncommon but useful finding for diagnosing early HCC with CEUS. This pattern represents a DN with a subfocus of HCC. Early HCC with well-differentiated histologic features may be hypovascular in the arterial phase on CEUS [51, 52].

Late Kupffer cell phase imaging with perflubutane-enhanced ultrasound has been tried for differentiating DN and early HCC. However, 21 of 33 (64%) well-differentiated HCCs were nearly isoechoic in the Kupffer cell phase [53]. Ohama et al. [54] reported that none of 9 DN and only 3 of 33 (9%) hypovascular well-differentiated HCCs were hypoechoic in the Kupffer cell phase. Therefore, perflubutane-enhanced CEUS has a limited role in differentiating DN from early HCC [54].

Conclusion

The characterization of focal liver lesions <10 mm is frequently delayed until a follow-up imaging procedure demonstrates growth or stability. Nevertheless, in cancer patients and particularly those with an initial workup for a newly diagnosed malignancy, early characterization of small or very small lesions is critical to their prognosis, management (options), and treatment [12]. Currently, the American Association for the Study of Liver Diseases (AASLD) practice guidelines recommend a repetition of ultrasound examination after 3 months for new nodules <1 cm. Diagnostic studies are recommended only for new nodules >1 cm [3, 6]. Overall, there is still no definite answer to whether a much earlier diagnosis would imply a better outcome.

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The authors have no conflicts of interest to declare.

Author Contributions

C.F. Dietrich is accepting full responsibility for the conduct of the manuscript; he and all others had control of the decision to

publish; C.F. Dietrich and Y. Dong drafted the manuscript; all authors critically revised the manuscript for important intellectual content. Each author made a statement that they approved the final draft submitted.

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