Review

Noninvasive Diagnosis of Hepatocellular Carcinoma in Cirrhotic Liver: Current Guidelines and Future Prospects for Radiological Imaging

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Diagnostic guidelines · HCC · Imaging · Liver · Liver cancer

Abstract

Noninvasive imaging has become the standard for hepatocellular carcinoma (HCC) diagnosis in cirrhotic patients. Typical imaging features of HCC such as arterial wash-in and venous wash-out deliver very high specificity and acceptable sensitivity even in nodules from 1 to 2 cm in diameter. However, limitations apply specifically in hypovascular HCC, for which the addition of new techniques such as diffusion-weighted magnetic resonance imaging (DW-MRI) or hepatobiliary MRI is helpful. Whereas DW-MRI adds to both the sensitivity and specificity, hepatobiliary MRI additionally contributes valuable information in cirrhotic patients on the histopathology of small lesions, including early HCC and high-grade dysplastic nodules. Biopsy of small, atypical lesions is associated with a high rate of false-negative findings and should be used only after careful consideration in selected patients. Here, we review the current international guidelines on HCC diagnosis as well as the latest developments in imaging that may contribute to safe detection and accurate characterization of suspicious nodules in patients with liver cirrhosis.

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Introduction

Noninvasive imaging has become the worldwide standard for hepatocellular carcinoma (HCC) diagnosis in cirrhotic patients. Diagnostic criteria are similar in international guidelines, such as those endorsed by the American Association for the Study of Liver Diseases (AASLD) or the Asian Pacific Association for the Study of the Liver (APASL), with regard to “classic” hypervascular HCC. However, there is less consensus on the diagnostic criteria for small, atypical or hypovascular HCC, leading to different approaches being applied in different countries. Here, we will review the current international guidelines on HCC diagnosis, including the latest developments in imaging that may contribute to safe detection and accurate characterization of suspicious nodules in patients with liver cirrhosis.

Histopathology of HCC and Its Implications for Diagnostic Imaging

HCC is the most frequent cause of death in patients with liver cirrhosis [1, 2]. Carcinogenesis of HCC in cirrhotic livers mirrors a continuous development from dysplastic foci to clonal expansion [3]. Typically, transformation continues from very small heterogeneous lesions with foci of highly differentiated carcinoma cells to poorly differentiated larger tumor nodules [4–6].

The prognosis of HCC patients is dependant on lesion size even at the very early tumor stages [1, 2, 7]. With increasing tumor size, portal invasion becomes frequent and has a suspected negative effect on prognosis [8]. The Japanese literature on the histopathology of HCC has introduced the classification “early HCC” [9–11]. Information about early HCC was derived from surgical specimens, leaving uncertainty as to what the natural course of these lesions might be. Early HCC is generally hypovascular up to 2 cm in size, with no vessel infiltration and with invasiveness limited to the periportal fields. Tumor borders are ill-defined, dysplasia is frequent, and unpaired arteries are rarely found. Small foci of carcinoma cells suggest that early HCCs are precursors of HCC [12]. In contrast to early HCC with ill-defined borders and favorable prognosis, Japanese pathologists also identified “small HCC.” Small HCC has a sharp border demarcation, and microscopic portal invasion is frequent despite the small lesion size. Presumably, the prognosis of patients with small HCC is unfavorable as a result of early portal invasion and microsatellite formation, even though clinical evidence regarding prognosis is not available [8, 11, 12].

Guidelines for HCC Diagnosis

Screening of cirrhotic patients primarily is intended to detect and classify small tumor nodules. Screening for HCC is most important in high-risk groups such as patients with cirrhosis or nonalcoholic steatohepatitis and carriers of hepatitis virus B or C with or without cirrhosis [13–15]. Small HCC nodules usually produce a hypoechogenic pattern on ultrasonography. In rare cases nodules may appear hyperechogenic because of steatosis developing with hypoxia during early carcinogenesis and ongoing vascular transformation [16]. Typical HCC hypervascularity develops in lesions reaching 1–2 cm in diameter and is common in those larger than 2 cm. Dynamic contrast-enhanced imaging by computed tomography (CT) or magnetic resonance imaging (MRI) demonstrates not only arterial hyperperfusion, but an enhanced venous wash-out phenomenon compared with adjacent normal liver tissue. A pattern of combined arterial wash-in and venous wash-out has a specificity of almost 100%

Fig. 1. Diagnostic algorithm of the AASLD (from [1]). MDCT = multidetector computed tomography; US = ultrasonography.

in tumors larger than 1 cm. However, sensitivity in lesions measuring 1–2 cm is 44–62% with CT alone and 44–53% with dynamic MRI alone [17–19].

Contrast-enhanced ultrasound (CEUS) also shows the typical wash-in and wash-out phenomena characterizing HCC [20]. However, in contrast to CT or MRI, CEUS gives this pattern for cholangiocellular carcinoma also. In such cases, additional imaging by MRI or CT is necessary to show that venous wash-out is present, thus excluding cholangiocellular carcinoma [21]. Consequently, a positive result during CEUS has no clinical significance (i.e., it will be followed by MRI or CT). As a result, CEUS has been removed from the guidelines of the AASLD [1, 2].

In addition to the guidelines of the AASLD, other international recommendations for the diagnosis of HCC exist. Typically, a hypoechogenic lesion is detected during ultrasound examination of a cirrhotic patient. International guidelines such as those from the AASLD or the APASL do not have major differences regarding the diagnosis of classical hyperperfused HCC (fig. 1, 2). Both guidelines support noninvasive diagnosis based on a typical pattern of arterial wash-in and venous wash-out. In the AASLD guidelines, the threshold for lesion work up is 1 cm [1, 2]. Lesions smaller than 1 cm should undergo surveillance by ultrasound at 3-month intervals. Either MRI or CT findings demonstrating the typical vascular pattern of HCC are

Fig. 2. Diagnostic algorithm of APASL for hypovascular lesions (from [23]). SPIO, superparamagnetic iron oxide; CEUS, contrast-enhanced ultrasonography.

sufficient for a definitive diagnosis. Lesion biopsy is recommended only for suspicious nodules without wash-in and wash-out and after confirmation by a second alternative imaging technique (i.e., MRI after an initial CT). This approach algorithm enables noninvasive HCC diagnosis in patients with liver cirrhosis for a lesion size larger than 1cm with very high specificity. In a study of lesions from 1- to 2-cm in diameter by Forner et al. [17], MRI demonstrated a specificity of 96.6% and a sensitivity of 62% using the AASLD criteria. Leoni et al. studied a cohort of 43 HCC lesions of the same size. Using the same criteria (wash-in and wash-out with at least one imaging method), specificity was 87% and sensitivity was 70%. In tumors of 2–3 cm, sensitivity improved to 96% [22].

In contrast to the AASLD criteria, APASL criteria do not stratify with respect to nodule

size [23]. APASL differentiates between hypo- and hypervascular lesions. Hypovascular nodules larger than 1 cm are especially demanding. In a study by Bolondi et al. of 72 lesions in cirrhotic livers, 41 had a maximum diameter of 1–2 cm and 31 lesions had a maximum diameter of 2.1–3 cm [24]. Of the tumor nodules 1–2 cm in diameter, 44% demonstrated arterial wash-in in two independent examinations; of the other 56% of lesions 1–2 cm in diameter, 50% demonstrated a hypovascular pattern in at least one of two imaging methods, and 50% demonstrated a hypovascular pattern in two imaging techniques. In essence, 20% of lesions displayed a hypovascular pattern in 2 imaging techniques, but only 64% of these were benign. This study was undertaken using the old EASL criteria, which do not consider the wash-out pattern. However, even if the AASLD criteria had been applied, hypovascular tumor characteristics would have led to a 35% false-negative rate in this selected cohort of tumors between 1 and 2 cm in diameter.

The Role of Biopsy in HCC

Tumor seeding is a major concern of clinicians when considering biopsy of suspected HCC. In a meta-analysis by Silva et al., tumor seeding in the puncture tract was found after 2.7% of biopsies [25]. In another meta-analysis in which Perkins et al. analyzed 99 articles, the risk for tumor seeding was calculated at 2.3%. Interestingly, tumor seeding in the puncture tract seems to be reduced by around 50% with thermal tumor ablation such as radiofrequency ablation. During such interventions, the puncture tract usually is ablated during retraction of the radiofrequency probe, thus minimizing the risk of cell seeding [26, 27].

A practical issue of lesion biopsy in small tumors is the risk of false-negative findings. Forner et al. described 30% false negatives at first biopsy of lesions smaller than 2 cm [17]. A second biopsy confirmed the false-negative finding in 61% of cases. Another limitation is that on histopathology, 35% of high grade-dysplastic nodules (HGDNs) demonstrate islets of HCC cells, which are not necessarily included in the sample acquired by a small percutaneous biopsy needle [19, 24].

The Emerging Role of Hepatobiliary MRI

In recent years, hepatobiliary MRI employing gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) (Primovist or Eovist) or gadobenate dimeglumine (Gd-BOPTA) (Multihance) has gained increasing attention. Gd-EOB-DTPA is of specific interest because of its favorable preference for biliary excretion compared with Gd-BOPTA. Whereas 50% of Gd-EOB-DTPA on average is eliminated via the biliary path (the other 50% undergoes renal elimination), Gd-BOPTA undergoes only around 8% biliary excretion. The higher excretion rate with Gd-EOB-DTPA leads to a significantly higher signal intensity in hepatocytes, allowing distinct forecasts of the histopathological properties of a given lesion [28, 29]. Gd-EOB-DTPA is taken up by functional hepatocytes employing the organic anion transporting polypeptide (OATP) mechanism [30]. The latency period until uptake is sufficient for hepatobiliary imaging is 20 min, with dynamic imaging similar to standard contrast MR being performed during that interval [31, 32]. HCC, precursor lesions of HCC, or benign lesions originating from hepatic tissue such as focal nodular hyperplasia or adenoma demonstrate a gradual uptake of Gd-EOB-DTPA, depending on their degree of differentiation (in the case of HCC) or, more specifically, the functionality of their OATP transporter mechanism. The uptake leads to a signal increase in T1-weighted sequences.

A close correlation between functional OATP and histopathological grading from low-grade dysplastic nodules (LGDN) via HGDNs to differentiated HCC has been shown in a number of studies. Well differentiated HCCs commonly demonstrate functional OATP with significant Gd-EOB-DTPA uptake in tumor cells [33, 34]. Since biliary ducts are missing in such lesions, Gd-EOB-DTPA will be retained and the signal enhancement is very intense [30, 33–38]. In a study by Golfieri et al. of 127 cirrhotic patients, 62 lesions were examined using dynamic and hepatobiliary MRI. Of these lesions, 20 were HGDNs or early HCC, 21 were LGDNs, 17 were regenerative nodules, and 4 were nodular regenerative hyperplasia. All findings were confirmed by histopathology. The inclusion of Gd-EOB-DTPA hepatobiliary late-phase imaging to dynamic contrast-enhanced sequences improved the sensitivity, specificity, accuracy, and positive and negative predictive values to greater than 95% (i.e., 88.4–99.4%, 88–95%, 88–98.5%, 97–99%, 65–97.5%, respectively). Of these 62 lesions, 20 displayed signs of malignancy on histopathology (32% were early HCC or HGDN), with 19 diagnosed by hepatobiliary MRI alone. Golfieri et al. concluded that hepatobiliary MRI increased the sensitivity of the diagnosis of HGDN or early HCC by 11%. The negative predictive value was increased by 32.5% [39]. Based on these results, the current guidelines of the Japan Society of Hepatology (JSH) have already incorporated the use of Gd-EOB-DTPA and Sonazoid ultrasound for atypical hypovascular lesions [4].

In a study that used hepatobiliary MRI in patients with Child-Pugh A cirrhosis who had undergone liver transplantation or resection, Kim et al. found a significant correlation of the signal intensity with poorly, moderately, and highly differentiated HCC [35]. In a longitudinal study, Akai et al. followed hypovascular lesions rated nonmalignant despite no uptake of Gd-EOB-DTPA in the hepatobiliary phase: 97 lesions measured 5–10 mm, 24 lesions measured 11–15 mm and 9 lesions were larger than 15 mm. Over time, confirmed transformation to HCC occurred in 3.2%, 11.1%, and 15.9% at 1, 2, and 3 years [40]. In a similar patient cohort, Kumada et al. described a change of perfusion patterns of hypovascular lesions to arterial hyperperfusion – a surrogate for malignant transformation – in 27.6% and 43.5% of lesions at 6 and 12 months [41].

Diffusion-Weighted MRI

Diffusion-weighted magnetic resonance imaging (DW-MRI) of the liver has also gained increasing attention in recent years. In DW-MRI, intracellular proton movement is visualized and displayed as a parametric image. A number of studies have evaluated both the sensitivity and specificity of DW-MRI with respect to suspected HCC in cirrhosis [42]. In addition, the method has the potential to assess tumor response after the treatment of solid tumors with systemic or local therapies that induce structural changes in tumor cells [43]. However, DW-MRI is highly sensitive to field inhomogeneities and tissue movements, making liver imaging especially challenging. Recently, Vandecaveye et al. compared dynamic MRI employing wash-in and wash-out criteria with DW-MRI (with b values of b0, b100, b600, and b1000). Hepatobiliary MRI was not performed. For detection of malignant lesions, DW-MRI with b600-SI(ratio) yielded a sensitivity of 95.2% (compared to 80.6% for conventional MRI) and a specificity of 82.7% (compared to 65.4%). In lesions smaller than 2 cm, DW-MRI demonstrated improved sensitivity compared with conventional MRI (91.2% versus 67.6%), improved specificity (82.9% versus 61%), improved positive predictive value (81.6% versus 59%), and improved negative predictive value (91.9% versus 69.4%) [44].

Conclusions

Noninvasive imaging with either CT or MRI yields very high specificity with an acceptable sensitivity even for HCCs smaller than 2 cm if arterial wash-in and arterial wash-out criteria are applied. However, atypical hypovascular HCCs may be frequently missed; for such atypical lesions, the addition of new techniques such as DW-MRI or hepatobiliary imaging is advantageous. Whereas DW-MRI enhances both the sensitivity and specificity, hepatobiliary MRI frequently yields valuable additional information on the histopathology of small lesions, including early HCC and HGDN, in cirrhotic patients. However, the inclusion of hepatobiliary MRI in international guidelines (other than the Japanese guidelines) is still pending. Biopsy of small, atypical lesions is associated with a high rate of false-negative findings and should be used after careful consideration in selected patients only.

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