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REVIEW ARTICLE

Imagiological Diagnosis of Gastrointestinal Diseases – Diagnostic Criteria of Hepatocellular Carcinoma

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Abstract Hepatocellular carcinoma (HCC) is one of the leading causes of neoplastic morbidity and mortality worldwide, and despite recent treatment advances, the prognosis remains dismal, with a 5-year mortality rate of 85%.

The surveillance and timely diagnosis is therefore of crucial importance in order to improve survival rates and alleviate the health burden imposed by the HCC.

Previously, HCC diagnosis warranted liver biopsy, an invasive process with limited diagnostic accuracy. In the past 15 years, HCC diagnosis based solely on imaging criteria was accepted by all the major national and international guidelines, and is now widely employed across the globe.

Current European guidelines for the HCC diagnosis support the use of both dynamic contrasted computer tomography as well as magnetic resonance imaging for the non-invasive diagnosis of HCC for nodules >1 cm in a cirrhotic liver. The non-invasive diagnosis of HCC depends on radiological hallmarks, such as homogeneous contrast uptake during the arterial phase and wash-out during the venous and late phases, but while such tumoral behaviour is frequent in nodules >2 cm, high-end equipment and superior expertise is often needed for the correct diagnosis of early HCC.

Nevertheless, the accuracy of imaging techniques for the diagnosis of HCC is permanently improving, and supports the progressively reduced need for liver biopsy during liver nodule workout in a cirrhotic liver.

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PALAVRAS CHAVE
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Diagnóstico Imagiológico de Doenças Gastrointestinais – Critérios Diagnósticos do Carcinoma Hepatocelular

Resumo O carcinoma hepatocelular (CHC) é uma das principais causas de morbi-mortalidade a nível mundial, e apesar de avanços no tratamento, o prognóstico é sombrio, com uma mortalidade aos 5 anos de 85%.

Assim, reveste-se de particular importância a vigilância e diagnóstico precoce do CHC, de forma a alterar substancialmente as taxas de sobrevida desta neoplasia.

Previamente, o diagnóstico do CHC exigia a realização de uma biópsia hepática, uma técnica invasiva com acuidade diagnóstica limitada. Nos últimos 15 anos, o diagnóstico baseado em técnicas de imagem foi sendo progressivamente aceite pelas principais recomendações nacionais e internacionais, e é agora extensamente aplicado em todo o mundo.

As recomendações europeias mais recentes para o diagnóstico do CHC aceitam a utilização de tomografia computorizada contrastada e ressonância magnética contrastada para o diagnóstico não invasivo de CHC em nódulos >1 cm no fígado cirrótico. Este diagnóstico depende da presença de alterações imagiológicas típicas, como a hipercaptação homogénea de contraste na fase arterial e o wash-out nas fases portal e tardia, características frequentes em nódulos >2 cm, mas de difícil identificação em CHC de dimensões reduzidas.

Em conclusão, as técnicas imagiológicas para o diagnóstico do CHC apresentam uma acuidade diagnóstica progressivamente mais elevada, e permitirão reduzir significativamente a necessidade de biópsia hepática durante a abordagem de nódulos hepáticos num fígado cirrótico.

1. Hepatocellular carcinoma epidemiology

Hepatocellular carcinoma (HCC) is the third most common tumour worldwide and the second leading cause of cancer-related deaths.[1] The overall 5-year survival of patients with HCC is 15%, indicating its generally poor prognosis. However, 40% of patients who are diagnosed with the disease localized to the liver have improved 5-year survival rates of 30%.[1]

Cirrhosis is the most important risk factor for HCC. More than 80% of the cases of HCC occur in the setting of cirrhosis, and in these patients, HCC is the leading cause of death.[2] Importantly, up to 20% of patients with HCC in the setting of HBV infection develop without evidence of cirrhosis. Among patients with cirrhosis, alcohol, tobacco, obesity, diabetes, older age, and male gender are associated with an increase in the risk for the development of HCC.[1]

Moreover, the risk of HCC in cirrhotic patients depends on the aetiology of cirrhosis; 2–8% per year in hepatitis C-related liver cirrhosis, 2.5% per year in chronic hepatitis B-related cirrhosis, and <2% in primary biliary and autoimmune cirrhosis.[3,4]

2. HCC surveillance

National and society guidelines recommend surveillance programmes for HCC[5–8] on the basis of reduced mortality[9,10] and cost-effectiveness.[11] Current European Association for the Study of the Liver (EASL) guidelines support HCC surveillance in cirrhotic patients Child–Pugh A and B, Child–Pugh C included in transplant lists, non-cirrhotic HBV carriers with active hepatitis or family history of HCC, and non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis.[5]

Liver ultrasound (US) is the diagnostic procedure of choice across all major guidelines,[12] with a pooled sensitivity for HCC of almost 95% in a recent meta-analysis.[13] In experienced hands, US allows for the detection of diminutive nodules (Fig. 1); in a Japanese study, the average size of the detected malignancy was 1.6 ± 0.6 cm, and remarkably, the tumour was larger than 3 cm in only 2% of the patients.[14] Despite being operator-dependent, with difficult identification of a focal malignant nodule in a cirrhotic liver, US is affordable, easily accepted by patients and with no associated risks, allowing for its progressively wider use. Therefore, in patients where surveillance is warranted, liver US should be performed every 6 months.[5]

The use of serological markers, such as alpha-fetoprotein (AFP), des-gamma-carboxy prothrombin (DCP) and glycosylated AFP (AFP-L3), although incorporated in Japanese[7] and Asian-Pacific,[8] are not presently supported in the EASL guidelines for HCC surveillance.[5] AFP in the surveillance setting has been shown to improve HCC detection compared to US alone in just 6–8% of the patients,[15] as only 20% of early-HCC present with elevated AFP serum levels. Additionally, AFP leads as well to an increase in the number of false positives, and consequently, in the cost for HCC diagnosis.[5,6]

Dimension is of crucial importance in liver nodules, as less than half the nodules <1 cm in a cirrhotic liver correspond to HCC,[16,17] but more than 90% of nodules >3 cm lead to the diagnosis of HCC.[18] The rate of HCC in nodules between 1 and 2 cm is 66% and almost 80% in nodules 2–3 cm.[2,19] Therefore, the current challenge in HCC diagnosis is the detection and

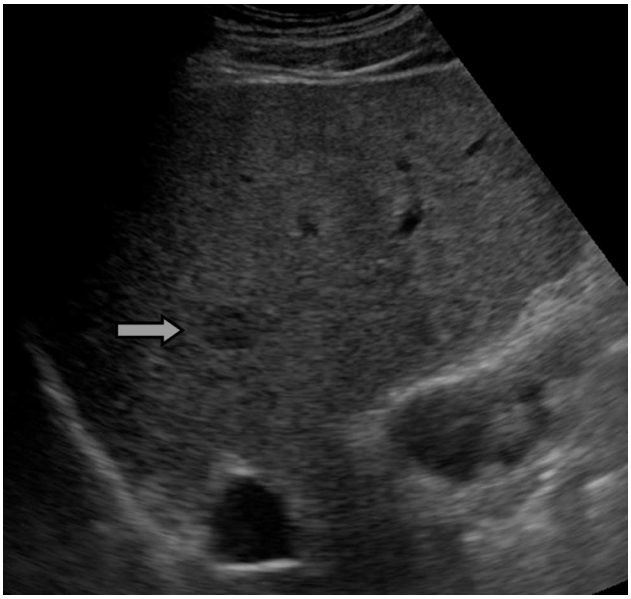

Figure 1 Small hypoechoic nodule in a cirrhotic liver corresponding to an HCC (arrow).

characterization of nodules larger than 1 but smaller than 3 cm.

In cirrhotic patients, nodules <1 cm detected by US should prompt a recall within 4 months, to assess either size or character changes,[5] in order to maximize the surveillance effectiveness, allowing for the diagnosis of early-HCC (<2 cm). Such lesions should be evaluated every 4 months for the first year, and if stable, every 6 months thereafter.[5]

Nodules >1 cm should be considered abnormal until otherwise proven, and warrant further investigation, either by guided biopsy or non-invasive diagnostic modalities.[5,16]

3. HCC diagnosis

Up until 2000, the diagnosis of HCC was confirmed only by histology findings in a liver biopsy.[20] However, percutaneous liver biopsy has a number of contraindications, such as ascitis, impaired hemostasis and antithrombotic medication.[21] Moreover, it is an invasive technique, with an associated risk of complications, the most frequent being pain and anxiety (up to 84%),[2,21] while serious side effects, such as bleeding, pneumothorax, tumour seeding, perforation and sepsis, occur in up to 1% of patients[22]; there is mortality rate for liver biopsy, although exceedingly low (<9 in 10,000).[21,22] Lastly, diagnostic accuracy of liver biopsy is limited by sampling error, as well as the uncertainty in the crucial histological differentiation between advanced dysplastic nodules and well-differentiated HCC, leading to both false negative results (up to 40% in HCC $\leq$2 cm[2,23]) as well as false positive results.[2]

The 2001 EASL guidelines accepted for the first time non-invasive criteria for the diagnosis of HCC in nodules >2 cm in a cirrhotic patient,[16] when coincident and suggestive findings of HCC were found in at least 2 imaging techniques – contrast-enhanced ultrasound (CEUS), dynamic CT, MRI or angiography.[24–26] Non-invasive diagnosis of HCC has been subsequently validated in prospective studies,[2] and is currently accepted by European,[5] north-American,[6] Asia-pacific[8] and Japanese[7] HCC diagnosis guidelines.

Tumour angiogenesis is a key feature for HCC growth as well as metastatic potential,[27] and a possible target for antineoplastic therapy[28] but it is also a critical malignant characteristic allowing for its non-invasive diagnosis.[29]

During the progression from dysplastic nodule to well differentiated and particularly to poorly differentiated HCC, tumour angiogenesis leads to newly formed, tortuous, excessively branched and short vessels, in a highly disorganized architecture.[27,30] This angiogenesis is driven predominantly through the formation of unpaired arteries, with the supplantation and eventual obliteration of intratumoral portal tracts.[29] As such, whereas normal liver cells and premalignant dysplastic nodules are perfused through portal branches,[31] HCC blood supply is delivered through newly formed arteries.[29,31]

Therefore, the diagnosis of HCC using imaging techniques requires the use of contrasting agents for identifying neoplastic vascularization characteristics. A typical HCC vascular pattern, similar across the different imaging modalities, has been defined as the presence of homogeneous hyperenhancement in the arterial phase followed by wash out in the venous or late phase.[32]

The use of dynamic techniques with contrast was validated almost a decade ago,[2] and current contrast-enhanced modalities include CEUS, dynamic CT and dynamic MRI.

4. CEUS

CEUS, using microbubble intravascular contrast agents such as sulfur hexafluoride with a phospholipid shell (Sonovue®), has shown to be a useful diagnostic technique for HCC in the setting of cirrhosis; the typical pattern of arterial hyperenhancement and wash out in the portal and late phases corresponds to HCC in 97% of the patients (Fig. 2).[32–34] It was included in the 2001 EASL Guidelines[16] and in the 2005 AASLD guidelines[35] in the diagnostic algorithm of HCC in the cirrhotic liver, as well as being incorporated in the 2010 Japanese guidelines for the management of hepatocellular carcinoma.[7]

In 2010, however, a study by Villana et al. in a subset of 21 cirrhotic patients with intrahepatic cholangiocarcinoma (ICC), only 11 patients (52.4%) presented with the typical peripheral rim arterial enhancement of ICC during CEUS, while in 10 (47.6%) of these patients, arterial hyperenhancement was homogeneous, suggestive of HCC.[36] This study highlighted the likely substantial incidence of incorrect diagnosis of HCC in patients with ICC, and contrasted with the contrasted MRI results, where only two patients (9.5%) presented with homogeneous hyperenhancement during the arterial phase. Recently, Li et al. found that 68.8% (11 out of 16) of the ICC in patients with cirrhosis will show imaging characteristics of HCC in CEUS, and such behaviour occurs more frequently than in patients with a non-cirrhotic liver (six out of 23; 26.1%).[37] The clinical relevance of correct differential diagnosis between HCC and ICC rests on the increasing incidence of the latter,[38] the overlapping risk factors[38] and the vastly different approaches and management of both malignancies.[5,39]

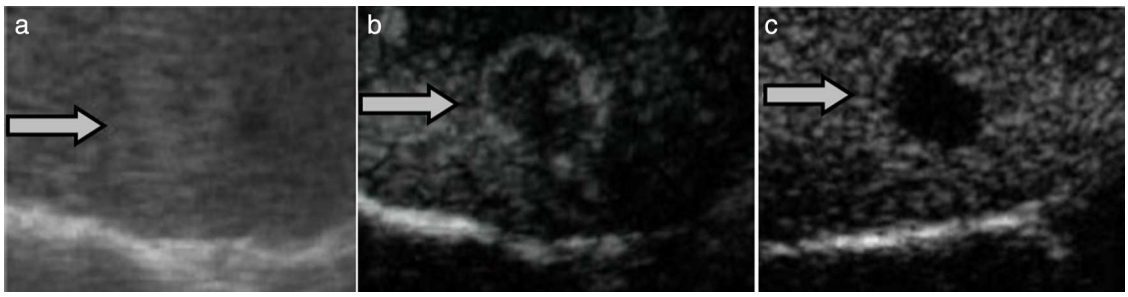

Figure 2 HCC in a cirrhotic liver during CEUS (arrow): arterial phase (a), portal phase (b) and late phase (c).

As a result, CEUS using Sonovue® contrast is no longer advocated in current European guidelines, and non-invasive diagnosis of HCC is based on contrasted CT or MRI imaging studies only.[5] Japanese guidelines advocate the use of CEUS as a first line procedure for the non-invasive diagnosis of HCC, using a novel contrasting agent, Sonazoid®.[7]

Unlike Sonovue®, Sonazoid® (perfluorobutane with a phospholipid shell: hydrogenated egg phosphatidyl serine), unavailable in Europe, is phagocytozed by Kupffer cells, and exhibits also a postvascular (or Kupffer) phase.[7,32] This phase is crucial for the characterization of HCC, as most HCC show a decrease in absence of Sonazoid® uptake, whereas dysplastic nodules and early HCC present the same rate of uptake as the surrounding liver parenchyma.[7] Recent studies with Sonazoid® are promising,[40,41] and its use is maintained and reinforced in the 2014 update of the Japanese HCC Guidelines,[42] but western studies are needed in order to validate its applicability in Europe and the United States.

5. Dynamic CT and MRI

In 2005, the concept of ''Radiological hallmark of HCC'', common to both dynamic CT and MRI, was defined by experts and included in both EASL and AASLD guidelines, and it consists of homogeneous contrast uptake during the arterial phase and washout during the venous/late phases.[5,35]

Multidetector 4-phase dynamic CT uses iodine-based contrast (1.5 mL/kg body weight, corresponding to 600 mg iodine/kg, at a rate of 4.5 mL/s) with superior time resolution and faster image acquisition.[43] Images are obtained during the precontrast, hepatic arterial (25–40 s after contrast administration), hepatic venous (70 s after contrast administration), and delayed phase (180–200 s after contrast administration). After 180–200 s, the vascular and extracellular contrast medium concentrations reach equilibrium about 200 s after infusion – this time point is called the equilibrium or parenchymal phase.[7,12,44] During this phase, a pseudocapsule may be observed, especially in cases of well-differentiated HCC.[45,46]

Dynamic MRI, using gadolinium-based contrast (0.1 mL/kg body weight, corresponding to 0.05 mmol gadobenate dimeglumine/kg, at a rate of 2 mL/s), follows the same sequence of dynamic CT in regards to phase timing and contrast enhancement. Recently, a new hepatocyte-specific contrast agent for MRI, Gd-EOB-DTPA (gadoxetate sodium), was developed, exhibiting a post-vascular phase, similar to the Sonazoid® Kupffer phase.[7,47] Where Sonazoid was phagocytozed by Kupffer cells, Gd-EOB-DTPA is absorbed by hepatocytes and excreted both through the kidney and the bile ducts. This results in a homogeneous liver enhancing (hyperintensity in T1-weighted images) 10–20 min after intravenous contrast administration. There is no contrast uptake by malignant lesions, presenting therefore as hypointense during the hepatobiliary phase.[7,12]

6. Diagnostic criteria

In the presence of a nodule 1–2 cm in a cirrhotic liver, radiological hallmarks of HCC are warranted in both 4-phase CT (Fig. 3) and dynamic contrasted MRI (Fig. 4) for the non-invasive diagnosis of HCC.[5]

Focal liver lesions in a cirrhotic liver are overwhelmingly hepatocellular adenomas or HCC, and the differential diagnosis of these lesions in the cirrhotic setting is limited – regenerative nodules, cholangiocellular carcinomas, lymphomas and hemangiomas.[32] Nevertheless, HCC under 2 cm in a cirrhotic patient still poses a particular diagnostic challenge, owning to the imaging characteristics of the cirrhotic liver background,[1] and reflects the pathological morphology progression of HCC.[7] Early HCC, defined morphologically as malignant nodules with indistinct margins,[20] reflects a key step during hepatocarcinogenesis.[48] They usually measure less than 20 mm, often less than 10 mm, rarely present with vascular invasion, not leading to intrahepatic metastasis and solely stromal invasion allows the differentiation from dysplastic nodules.[7,49] Moreover, unlike advanced HCC, vascular supply of early HCC is driven by both arterial and portal branches,[7,32] but because the tumoral blood flow is still largely dependent on underdeveloped neo-vessels, such lesions are frequently hypovascular.[48] Other characteristics include increased cell density, increased nuclear/cytoplasm ratio, pseudoglandular pattern and fatty changes.[46]

A prospective study including 89 cirrhotic patients with liver nodules <20 mm demonstrated a specificity of 100% when using radiological hallmarks in two imaging techniques, but with a sensitivity of just 33%.[2] Of note, the specificity when using isolated MRI was just below 97%, with a sensitivity of 61.7%. Another prospective study found similar results; using a step-wise combination of the different non-invasive modalities, the authors concluded that a single imaging technique with typical HCC pattern allows for a certain diagnosis of HCC (no false positive results) and with a sensitivity of 65%, significantly superior to a dual positive examination ($p = 0.028$).[50] These results underlined the fact that while the typical vascular pattern permits a safe diagnosis of HCC, the low sensitivity of these procedures mean

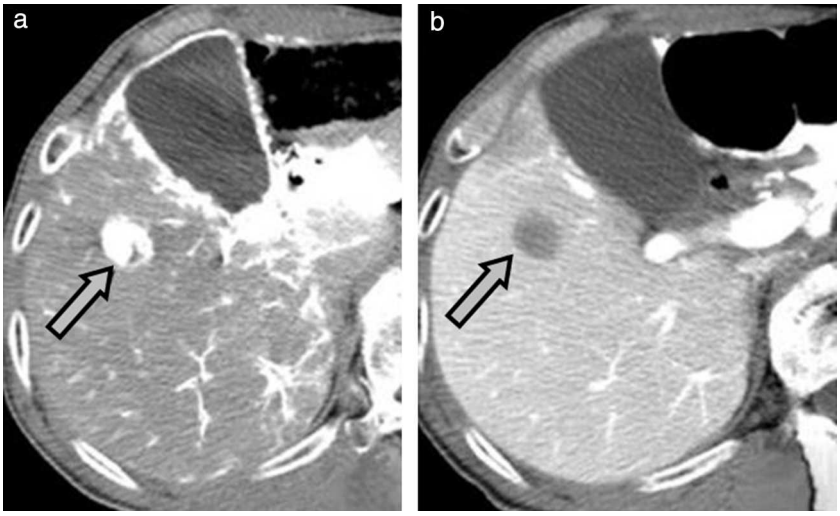

Figure 3 HCC during dynamic CT (arrow): arterial phase (a) and portal phase (b).

that the absence of radiological hallmarks in these patients should not lead to the exclusion of malignancy.

A recent study showed a 10% false positive result for HCC when using MRI alone.[51] Moreover, local disparities in expertise and suboptimal equipment may worsen the diagnostic accuracy of a single technique, and the risk of frequent false positive results led to the recommendation of two concurrent positive radiological hallmarks, with one technique being sufficient in excellence centres with high-end radiological equipment.[5] Finally, it has been estimated that 15% of patients with HCC, in particular early-HCC, will not present with the radiological hallmarks of arterial enhancement and washout.[2] When imaging characteristics are insufficient to establish the diagnosis of HCC, biopsy may also be required to distinguish early-HCC from high-grade dysplastic nodules. In a landmark study by Forner et al.,[2] non-invasive HCC diagnosis (using a combination of dynamic MRI plus CEUS) achieved a sensitivity of 33% and a specificity of 100%, and subsequent follow-up biopsies led to the diagnosis in the remaining patients.

A consensus conference on pathology for hepatobiliary malignancies recommended core biopsies over fine-needle aspiration as it allows for the assessment of both architectural and cytological features.[31] The diagnostic capability of liver biopsy may be further amplified by the use of an immunohistochemistry panel (glypican 3, heat shock protein 70, glutamine synthetase, cytokeratin and enhancer of zeste homologue 2),[46,52,53] as the combination of these markers has

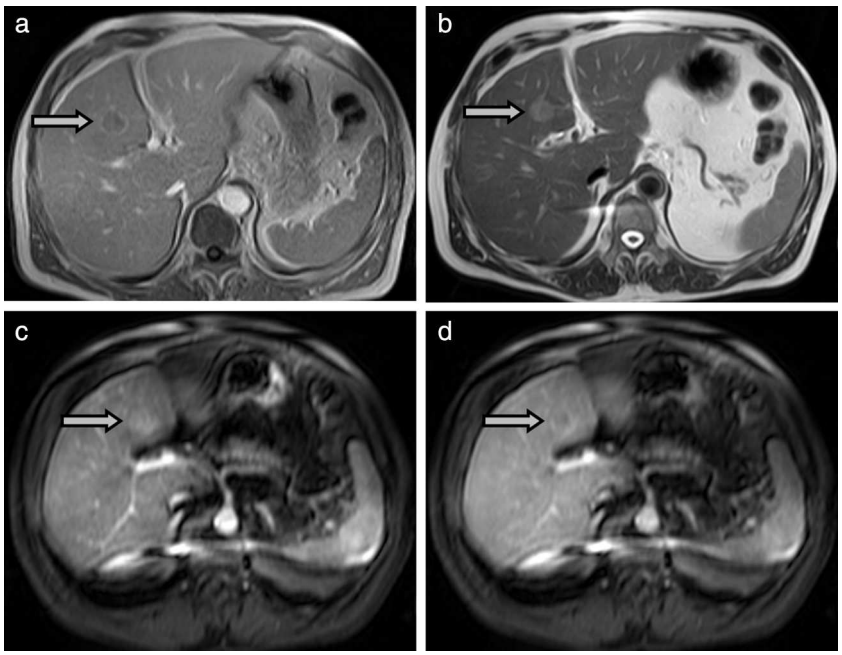

Figure 4 HCC during dynamic MRI (arrow): T1 weighted scan (a), T2 weighted scan (b), dynamic arterial phase (c), dynamic late phase (d).

shown promising results in the diagnosis of early-HCC versus dysplastic nodules in prospective studies.[52,53] The use of the coaxial biopsy technique, in which the actual needle is introduced percutaneously into the tumour inside a sheath, can mitigate the risk of tumour seeding by insulating the needle inside the sheath.[1]

Contrarily to smaller nodules, the non-invasive diagnosis of liver nodules >2 cm is very effective, as the accuracy for HCC diagnosis using either dynamic CT or MRI is over 90%.[43] Therefore, radiological hallmarks in a single technique are sufficient for the diagnosis of lesions >2 cm.[5]

7. Dynamic CT versus dynamic MRI

When comparing dynamic MRI and dynamic CT, several studies compared either one with histology as gold standard.[54,55]

Diagnostic accuracy for hypervascular HCC using dynamic CT is reported to be 61–83%,[56,57] compared to 71–87% in dynamic MRI.[58–60] In direct comparison studies, the latter was shown to be superior for HCC diagnosis (sensitivity 76.9% vs 53.8%),[61] while the results were conflicting for the recurrence of HCC following arterial chemoembolization.[58,62,63] Most studies however are limited by selection bias, non-blindness and potential for generalization for all centres.[54,55] Therefore, the decision to use either MRI or CT should be based on local expertise and equipment.

With the recent advent of Gd-EOB-DTPA MRI, this reality may change soon. In fact, in a large study including 163 patients and comparing Gd-EOB-DTPA MRI with dynamic MRI, dynamic CT and US, diagnostic accuracy with the former was 90%[43] for lesions 1–2 cm, significantly superior ($p < 0.001$) to dynamic MRI (84%), dynamic CT (79%) and US (64%).[43]

The superiority of Gd-EOB-DTPA MRI was demonstrated by other authors, displaying diagnostic accuracy approaching 90%, when compared to standard dynamic MRI (accuracy 71–87%) and CT (accuracy 61–83%).[58–60]

However, the differential diagnosis between early-HCC and dysplastic nodule remains to be difficult, and some early-HCC present with isointense contrast uptake during the postvascular phase, while some dysplastic nodules present with low-intense contrast enhancing.[7]

8. HCC in the non-cirrhotic liver

Current diagnostic criteria for HCC are approved only for a cirrhotic liver background,[5] but up to 10% of the HCC may be diagnosed in a healthy liver[64] or in the setting of non-alcoholic fatty liver disease[65] or hepatitis B virus infection.[1] Few studies have reported on the imaging characteristics of HCC in a non-cirrhotic liver,[64,66,67] but most report on a higher frequency of an isolated large mass when compared to HCC in the cirrhotic liver. The applicability of non-invasive diagnostic criteria to such patients has been met with disappointing results.[68] A recent study with 32 patients,[67] however, has shown HCC to have the same contrasting enhancement in both the cirrhotic and non-cirrhotic liver, and diagnostic criteria were encountered in more than 90% of the patients, and the authors suggest extending such criteria to the non-cirrhotic liver.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors declare no conflict of interests.

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