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Review Article

Liver Lesions at Risk of Transformation into Hepatocellular Carcinoma in Cirrhotic Patients: Hepatobiliary Phase Hypointense Nodules without Arterial Phase Hyperenhancement

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Abstract

Recent technical advances in liver imaging and surveillance for patients at high risk for developing hepatocellular carcinoma (HCC) have led to an increase in the detection of borderline hepatic nodules in the gray area of multistep carcinogenesis, particularly in those that are hypointense at the hepatobiliary phase (HBP) and do not show arterial phase hyperenhancement. Given their potential to transform and advance into hypervascular HCC, these nodules have progressively attracted the interest of the scientific community. To date, however, no shared guidelines have been established for the decision management of these borderline hepatic nodules. It is therefore extremely important to identify features that indicate the malignant potential of these nodules and the likelihood of vascularization. In fact, a more complete knowledge of their history and evolution would allow outlining shared guidelines for their clinical-surgical management, to implement early treatment programs and decide between a preventive curative treatment or a watchful follow-up. This review aims to summarize the current knowledge on hepatic borderline nodules, particularly focusing on those imaging features which are hypothetically correlated with their malignant evolution, and to discuss current guidelines and ongoing management in clinical practice.

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most commonly occurring cancer worldwide and, due to its constantly increasing incidence, has become the third leading cause of cancer-related death among general populations. Moreover, it represents the most common cause of death in patients with cirrhosis.[1–3] Despite its wide prevalence, only approximately 20% of HCCs are diagnosed at very early or early stages, when treatments such as liver transplantation, ablation, and surgical resection could guarantee a high 5-year survival rate. In fact, the majority of HCC patients are diagnosed in the intermediate and/or advanced tumoral stages, thus requiring other forms of treatments, such as transarterial chemoembolization, radioembolization, or systemic therapies.[4–6] Unfortunately, despite being considered effective, the latter treatments still yield a low overall survival rate. Therefore, the detection of HCC at a very early/early stage through an effective surveillance program is pivotal to improving patients' prognosis and therapeutic outcomes.[7,8]

Recent technical advances in liver imaging and surveillance of patients at high risk of developing HCC have led to an increase in the detection of borderline hepatic nodules in the gray area of multistep carcinogenesis.[9] Given their potential to transform and advance into hypervascular HCC, these nodules have progressively attracted the interest of the scientific community.[10] To date, however, no shared guidelines have been established for the decision management of these borderline hepatic nodules. It is therefore extremely important to identify features that indicate the malignant potential of these nodules and the likelihood of vascularization. In fact, more complete knowledge of their history and evolution would allow outlining shared guidelines for their clinical-surgical management, in order to implement early treatment programs and decide between a preventive curative treatment or a watchful follow-up. This review aims to summarize the current knowledge on hepatic borderline nodules, particularly focusing on those imaging features which are hypothetically correlated with their malignant evolution, and to discuss current guidelines and ongoing management in clinical practice.

HCC: beyond vascular criteria

Imaging surveillance has a key role in the management of patients with chronic liver diseases as, unlike most other cancers, HCC can be noninvasively diagnosed with imaging alone, without requiring tissue sampling confirmation. In particular, the presence of arterial phase hyperenhancement

Keywords: Nonhypervascular hypointense nodule; Hepatocellular carcinoma; Magnetic resonance imaging; Gd-EOB; Liver.

Abbreviations: APHE, arterial phase hyperenhancement; CEUS, contrast-enhanced ultrasound; DN, dysplastic nodule; DWI, diffusion-weighted imaging; HBP, hepatobiliary phase; HCC, hepatocellular carcinoma; HGDN, high-grade dysplastic nodule; HHNWA, HBP hypointense nodule without APHE; LGDN, low-grade dysplastic nodule; OATP, organic anion-transporting polypeptide; RFA, radiofrequency ablation.

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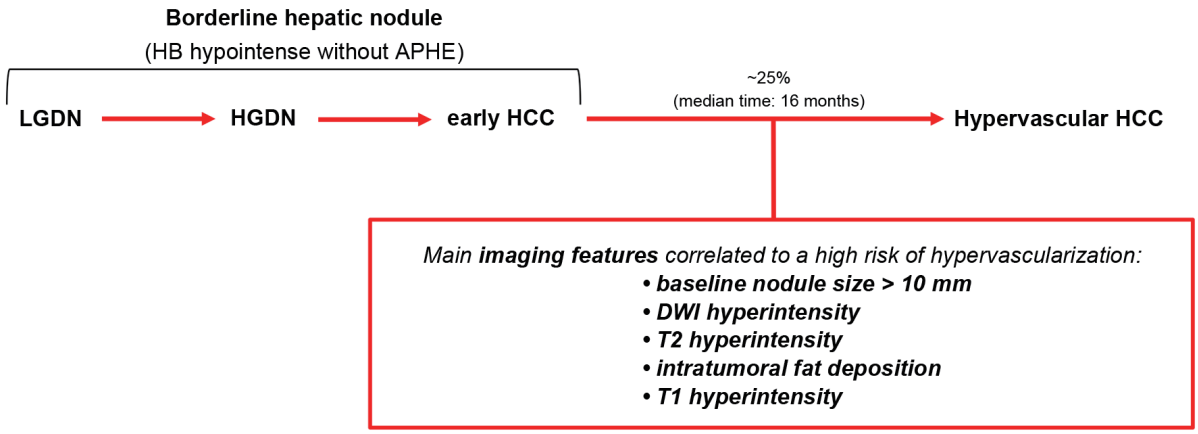

Fig. 1. Schematic of the multistep process of hepatocarcinogenesis from displastic nodules (DN) to overt hepatocellular carcinoma (HCC) and the main imaging features associated with a higher risk of malignant transformation.

(APHE) coupled with the washout of contrast media during the portal venous or the delayed phases evaluated by dynamic CT or MRI in nodules larger than 1 cm are considered diagnostic by both the European Association for the Study of the Liver (EASL) and the Liver Imaging Reporting and Data System (LI-RADS) developed by the American College of Radiology and supported by the American Association for the Study of Liver Diseases (AASLD).[11,12]

Despite specificity and positive predictive values that reach for near 100%, these imaging criteria have a low sensitivity (71%) for small nodules of 1–2 cm and for lesions showing all typical features for HCC, causing several dilemmas for clinicians.[13,14] From this perspective, the availability of an MRI contrast medium with the properties of both extracellular and liver-specific contrast agents has revolutionized clinical practice. In the hepatobiliary phase (HBP), in fact, the imaging evidence of hepatic lesions is represented by the lack of normally functioning hepatocytes, i.e. by the absence of hepatocyte-selective enhancement compared with normal parenchyma.[15] Owing to the introduction of this new MRI contrast medium, the diagnostic accuracy for HCC has rapidly improved, especially for lesions <2 cm, reducing recurrence and decreasing overall mortality.[16–21]

Along with the introduction of liver-specific contrast agents, the concurrent addition of diffusion-weighted imaging (DWI) to Gd-EOB MRI protocol has further improved both the diagnostic accuracy and the specificity in detecting overt HCC, even for nodules of <1 cm, helping to distinguish hypervascular HCC from hypervascular pseudolesions.[22–25] As a result of these technical advances in liver imaging and surveillance, there has been an increase in the detection of borderline hepatic nodules in the gray area of multistep carcinogenesis, including both dysplastic nodules (DNs) and early HCCs. These nodules, in fact, were scarcely detectable and hard to characterize by using solely dynamic imaging with extracellular space contrast agents as they do not show remarkable differences in their angio-architecture, thus appearing as isohypodense or isohypointense on contrast-enhanced CT or MRI images.[26,27] However, similar to the majority of HCCs,[28] these borderline nodules show a relative hypointensity on HBP due to the lack of gadoxetic acid uptake, being easily detected on Gd-EOB MRI.[29] Due to their potential for malignancy and potential transitioning to overt HCC, these nodules have progressively attracted the interest of the scientific community. A more complete knowledge of their history and fate, in fact, would increase the understanding of hepatocarcinogenesis, outlining the clinical implications of HCC precursors and, therefore, implementing the current diagnostic and therapeutic algorithms.[10]

Multistep progress of hepatocarcinogenesis from DN to overt HCC

HCC develops in patients with underlying chronic liver disease or cirrhosis via a multistep process of carcinogenesis, ranging from a DN to early HCC and, finally, to overt HCC (Fig. 1).[30–32] All these precursors of overt HCC are collectively called borderline hepatic nodules in clinical practice and, even nowadays, their detection and precise differentiation remain difficult and often uncertain, mainly because of the similarity of their pathological features.[33–35] Pathologically, most HCCs develop from clonal cells that have expanded into dysplastic foci, defined as clusters of hepatocytes with precancerous features such as small cell change. However, as these small lesions measure <1 mm, they are not detectable by *in vivo* imaging, remaining a challenge for future investigation.[36]

DNs are usually from 1–1.5 cm in diameter and contain dysplastic features without histological evidence for malignancy; however, they are considered full-fledged precancerous hepatocellular lesions. DNs can be differentiated from the surrounding parenchyma by size, color, and texture and may contain more copper and/or iron than the liver background.[34,37] According to the grade of cytological and architectural atypia, they are subcategorized into low-grade (LGDN) and high-grade (HGDN),[38–40] with the latter showing a higher risk of malignant transformation within a few years.[41] HGDNs may contain unpaired arteries and have an intermediate degree of sinusoidal capillarization, but LGDNs and most HGDNs have relatively preserved arterial blood supply, and therefore are not well visualized by both dynamic CT or MRI, usually appearing as isohypodense or isohypointense.[42,43]

Early HCCs are an incipient stage of HCC development, analogous to carcinoma *in situ* of other organs, that gradually replaces the liver parenchyma, without displacing or completely destroying the surrounding portal tracts and central veins that conversely, may happen in overt HCC).[34,42] Early HCCs typically measure 1–1.5 cm in diameter and, macroscopically, are mostly vaguely nodular with indistinct margins and without a tumor capsule and are often referred to as HCC of vaguely nodular type.[38] Beside the presence of stromal in-

vasion, an early HCC is essentially indistinguishable from an HGDN at gross pathologic examination.[44] Moreover, as vascular invasion is not observed, early HCCs are considered hypovascular, and frequently show hypo- or iso-enhancement on arterial phase imaging, and are thus not reliably detected using extracellular agents.[38,45] As an early HCC progresses to overt HCC, the intratumoral vascularity increases with the subsequent development of hypervascularization. However, the rate at which they transform has not been defined and some progressed HCCs probably develop from smaller inner subnodules within an HGDN rather than transitioning through a vaguely nodular morphology known as a nodule-in-nodule appearance.[46,47]

Imaging-pathological correlation of borderline hepatic nodules: role of hepatic-specific contrast media

Hepatic-specific contrast media permit diagnosis of HCC based not only on vascularity but also on hepatocellular function. Following intravenous administration, these agents rapidly distribute in the vascular-interstitial compartment, enhance the extracellular space, and permit the acquisition of dynamic images that allow for HCC diagnosis based on perfusion characteristics. After distribution in the extracellular space, these agents enter hepatocytes via organanion-transporting polypeptides (OATP8, also known as OATP1B1/3) located in the cell membrane and subsequently excreted into the biliary canaliculi and into the sinusoidal space by multidrug resistance-associated proteins (MRP2 and MRP3).[48] These transporter molecules are expressed only in functioning hepatocytes and are not present in cells of nonhepatocyte origin such as vascular endothelium, cholangiocytes, fibrous tissue, or liver metastases from extrahepatic origins.[49] In most HCCs, especially those scarcely differentiated, OATP8 expression is absent and accumulation of gadoxetic acid is not observed during the HBP, which explains why they appear as hypointense nodules compared to the surrounding liver parenchyma in this phase.[50]

As OATP8 expression gradually decreases during hepatocarcinogenesis, borderline hepatic nodules appear hypointense during HBP, even if they do not yet show hypervascularity on dynamic images.[41,51] In particular, the decrease of the OATP8 expression is believed to occur before the characteristic vascular changes of overt HCC (i.e. the reduction in portal venous flow and the complete neo-arterialization with the elevation of arterial flow), thus possibly representing the *primum movens* in hepatocarcinogenesis.[52] The molecular mechanism of OATP8 expression reduction is still a matter of debate, even if it is now partially attributed to hepatocyte nuclear factor 3b overexpression, which has been documented in about 70% of overt HCCs.[53]

Despite the addition of hepatic-specific contrast media has improved the per-lesion sensitivity for the diagnosis of HCC and allowed for the detection of premalignant nodules, differentiation of LGDNs, HGDNs, and early HCCs based only on HBP images remains almost impossible due to their similar hypointensity.[54] However, it has been recently outlined that coupling Gd-EOB MRI with DWI may result in increased accuracy for the differential diagnosis of early HCCs and HGDNs, along with an increased diagnostic sensibility for overt HCC.[55] In fact, the hyperintense appearance of a lesion in DWI is thought to be sustained by reduced mobility of water molecules owing to decreased extracellular space associated with hypercellularity.[44] Therefore, as hypercellularity progressively increases from HGDNs to early HCCs and reaches maximum expression in overt HCCs, the inclusion of DWI analysis during Gd-EOB MRI may be used to discriminate early HCCs from nonmalignant iso- or hypovascular HBP hypointense nodules, increasing both sensitivity and specificity of the technique.[56,57]

Nonetheless, the determination of a definitive diagnosis of such borderline hepatic nodules based only on imaging findings remains challenging, even with multi-imaging modalities. Therefore, unless aggressive diagnostic procedures such as percutaneous biopsy or curative techniques are considered, such nonhypervascular hypointense nodules must be followed up with imaging and clinical evaluation to detect as soon as possible any changes that might be an early indicator of arterial hypervascularization and, thus, malignant transformation.[10,58] As these nodules have rapidly become a clinically relevant topic of active investigation, the Hepatobiliary Agent Working Group of LI-RADS proposed HBP hypointense nodule without APHE) (HHNWAs) as a standard term to refer to this peculiar entity to avoid inconsistent and unwieldy terminology. In fact, as this term is intended to describe a hepatocellular nodule at risk for transformation to progressed HCC, it should not be applied to benign (LR-1) or probably benign (LR-2) observations such as a cyst and slow-filling hemangioma that also appear hypointense in the HBP and may lack APHE, even if they usually present a distinctive marked T2 hyperintensity.[59]

HBP hypointense nodules without APHE: an increasing burden

The overall prevalence of HHNWAs varied markedly across previous studies (3.4–79.1%),[56,60] and it is reported to be higher in patients already diagnosed with HCC (15.7–79.1%) compared with patients without a history of HCC (7.0–28.8%),[61] and in patients with advanced liver fibrosis or hepatitis B virus infection.[62,63] Nonetheless, a recent Korean study including more than 16.000 patients with chronic liver disease or cirrhosis observed the presence of HHNWAs in only 1.85% of subjects, thus significantly resizing their prevalence among patients at high risk for developing HCC.[64] Overall, about 25% of HHNWAs ultimately develop arterial hypervascularity during surveillance or postoperative or postprocedural follow-up, in a median time of 16 months, although a wide range has been reported across the studies (11.9–81.6% and 6–30 months, respectively).[65–69] similarly, even the reported 1-year cumulative incidence of hypervascular transformation is widely variable, ranging from 3.2 to 73.5%.[67,69] These conflicting results are probably due to the retrospective nature of the studies and to differences in the follow-up period (ranging from 90 to 1,521 days),[61,68] as well as to the inclusion of a relatively small number of patients with different characteristics (with or without a history of HCC, in surveillance and/or diagnostic setting, with different nodule sizes, etc.).

Despite these differences, HHNWAs still seem to show a consistent nonnegligible incidence of hypervascular transformation. Furthermore, this risk seems to increase with time, as highlighted by a recent systematic review and meta-analysis in which the pooled cumulative incidence rates at 1-, 2-, and 3-years were reported to be 16.2%, 27.8%, and 35.0%, respectively;[70] moreover, the risk of hypervascular transformation continues to be present even at the extended 5-year follow-up, especially in case of nodules ≥10 mm and in patients with a history of HCC,[61,71] thus strongly recommending a long-term follow-up for these nodules. Interestingly, Toyoda *et al*.[72] demonstrated that HHNWAs detected in cirrhotic patients before the start of direct-acting antiviral (DAA) therapy retained the potential to progress to typical hypervascular HCC even after the eradication of HCV. How-

ever, Shimizu *et al*.[73] reported that eradication of HCV by DAAs could reduce the hypervascularization rate of HHNWAs and some of these nodules might even disappear. Therefore, the role of antiviral therapy in the natural history of these nodules is still unclear.

Risk factors for hypervascularization in HBP hypointense nodules without APHE

One of the main reasons for the controversy surrounding the management of HHNWAs is the lack of information on the natural course and the malignancy risk associated with these nodules. The main aim of the studies currently available in the literature was to investigate which imaging features could be associated with the risk of hypervascular transformation to achieve a reliable risk stratification of the patients and, thus, provide tailor-made management. However, until now, the results were rather inconsistent, possibly due to the heterogeneity of study populations and variation in the follow-up periods.

Among the various predictive factors for hypervascular transformation, the initial nodule size was the most commonly described. In particular, the mean nodule size of HHNWAs on first examination ranged from 7.8 to 14 mm,[74,75] and an initial nodule size >10 mm proved to be a strong predictor for progression to hypervascular HCC, sometimes even independently of others.[61,66,76–79] Conversely, in one study, hypointense nodules ≥9 mm resulted in those at higher risk of malignant evolution.[60] In another study a diameter ≥15 mm was identified as the significant cutoff.[67] Whatever the most accurate value is, when a tumor grows to a sufficient diameter is thought to proliferate more actively due to dedifferentiation and to develop enough unpaired arteries to show hypervascularization.[68,80] In support of this evidence, other studies have demonstrated that a higher growth rate and a shorter tumor volume-doubling time of HHNWAs were associated with nodular progression to hypervascular HCC (Figs. 2 and 3).[81–83] After all, tumor size is an important prognostic factor also for progressed HCC, since its increase is associated with a higher frequency of vascular invasion, extrahepatic metastasis and a decrease in patient survival.

Diffusion restriction on DWI was one of the most reported imaging features associated with subsequent malignant transformation, despite the use of different techniques (Figs. 2 and 3).[26,79,80,84,85] High-grade tumors have densely packed cells that inhibit the effective motion of water molecules, thus affecting the signal intensity of the lesions on DWI with restricted diffusion. Given that one of the major histologic differences between DNs and early HCCs is the degree of cellular density.[86] Kim *et al*.[26] hypothesized that DWI might be more sensitive in depicting histologic changes of borderline hepatocellular nodules than liver imaging using an extracellular space contrast agent. In particular, since in their study almost all hypervascular HCCs showed hyperintensity at DWI on the last follow-up, they questioned whether the HHNWAs showing diffusion restriction were already HCC. However, among the HHNWAs showing DWI hyperintensity, two lesions proved to be HGDNs at histologic examination and not early HCCs. Therefore, they concluded that diffusion restriction might not necessarily reflect HCC in the multistep hepatocarcinogenetic pathway. Nevertheless, it needs to be emphasized that three HHNWAs first showed hyperintensity on DWI between the initial and last MR examination and then subsequently transformed into hypervascular HCC on the last MR examination. Therefore, it may be a reasonable assumption that DWI hyperintensity might reasonably represent the imaging feature that immediately anticipates the stage of hypervascular HCC. However, not all borderline hepatocellular nodules may show these typical sequential signal intensity changes during hepatocarcinogenesis. Therefore, despite its role in imaging categorization of borderline nodules and detecting their transition into hypervascular HCCs is still not well established, the addition of DWI to dynamic contrast-enhanced MRI can certainly improve the diagnostic accuracy for HHNWAs and help predict their outcome.

High signal intensity on T2-weighted images is thought to reflect peliotic changes in the intratumoral sinusoids of the lesions as well as varying degrees of fibrosis and scarring.[87,88] In fact, mild-moderate T2 hyperintensity is a typical feature of HCC and has been described in 77% of HCCs of >3 cm. Conversely, DNs are generally isointense or hypointense on T2-weighted images and the presence of hyperintensity is believed as highly suggestive of malignancy.[89] Therefore, it is not surprising that some authors reported that hyperintensity on T2-weighted images is an independent risk factor at baseline for subsequent HHNWA hypervascularization (Fig. 2).[83,84,90]

Few studies have reported the presence of intralesional fat as a significant predictor of hypervascularization in HHNWAs.[66,74,82,91] The feature can be recognized for the characteristic signal drop on out-of-phase T1-weighted images compared with the in-phase images, owing to the chemical shift artifact (Figs. 3 and 4).[92] Fatty change occasionally occurs during hepatocarcinogenesis and, except for the steatohepatic variant of HCC, its prevalence decreases incrementally with tumor size and histologic grade, thus generally being associated with a more favorable prognosis.[93] Conversely, in the early stage of hepatocarcinogenesis, fat deposition progressively increases from LGDNs to HGDNs, reaching a peak in early HCCs,[86] where it is observed in approximately 40% of cases.[94] In early HCC, in fact, the lack of blood supply that results from a gradual shift from the portal vessels to newly formed nontriad arteries, together with the increased cellular density, may cause transient hypoxia and, thus, lead to intratumoral fatty metamorphosis.[94]

As T2 hyperintensity is a well-known feature of HCC, two different studies excluded T2-hyperintense HHNWAs from their analysis of hypervascular transformation to minimize the risk of inclusion of early HCC and focus only on DNs.[78,81] In both studies, hyperintensity on T1-weighted images was associated with progression to hypervascular HCC. The result was confirmed also by Higaki *et al*.[82] who included T2-hyperintense HHNWAs in their study. T1 hyperintensity was presumed to be correlated with iron accumulation. However, iron accumulates within hepatocytes during the early dysplastic phase of hepatocarcinogenesis, preferentially in LGDNs, and the amount progressively decreases during malignant progression. Most HGDNs, early HCCs, and progressed HCCs becoming iron free.[95,96] Therefore, T1-hyperintensity might rather reflect intratumoral copper or fat deposition which are both seen in greater quantity in HGNDs and, especially, early HCC, the immediate precursor of hypervascular HCC (Fig. 5).[97]

Together with imaging findings, clinical and laboratory data that might predict an increased risk of malignant transformation of HHNWAs have been investigated. Despite a previous HCC history was confirmed by a recent metanalysis as a possible risk factor for hypervascularization,[70] all the other analyzed clinical variables showed poor results and high heterogeneity. In particular, Child-Pugh class B cirrhosis, alpha fetoprotein levels >100 ng/mL and high M2BPGi levels were anecdotally and inconsistently reported as risk factor for HCC transformation.[63,64,81,83,90] Interestingly, Sangiovanni *et al*.[98] reported that DAA treatment was associated with an early

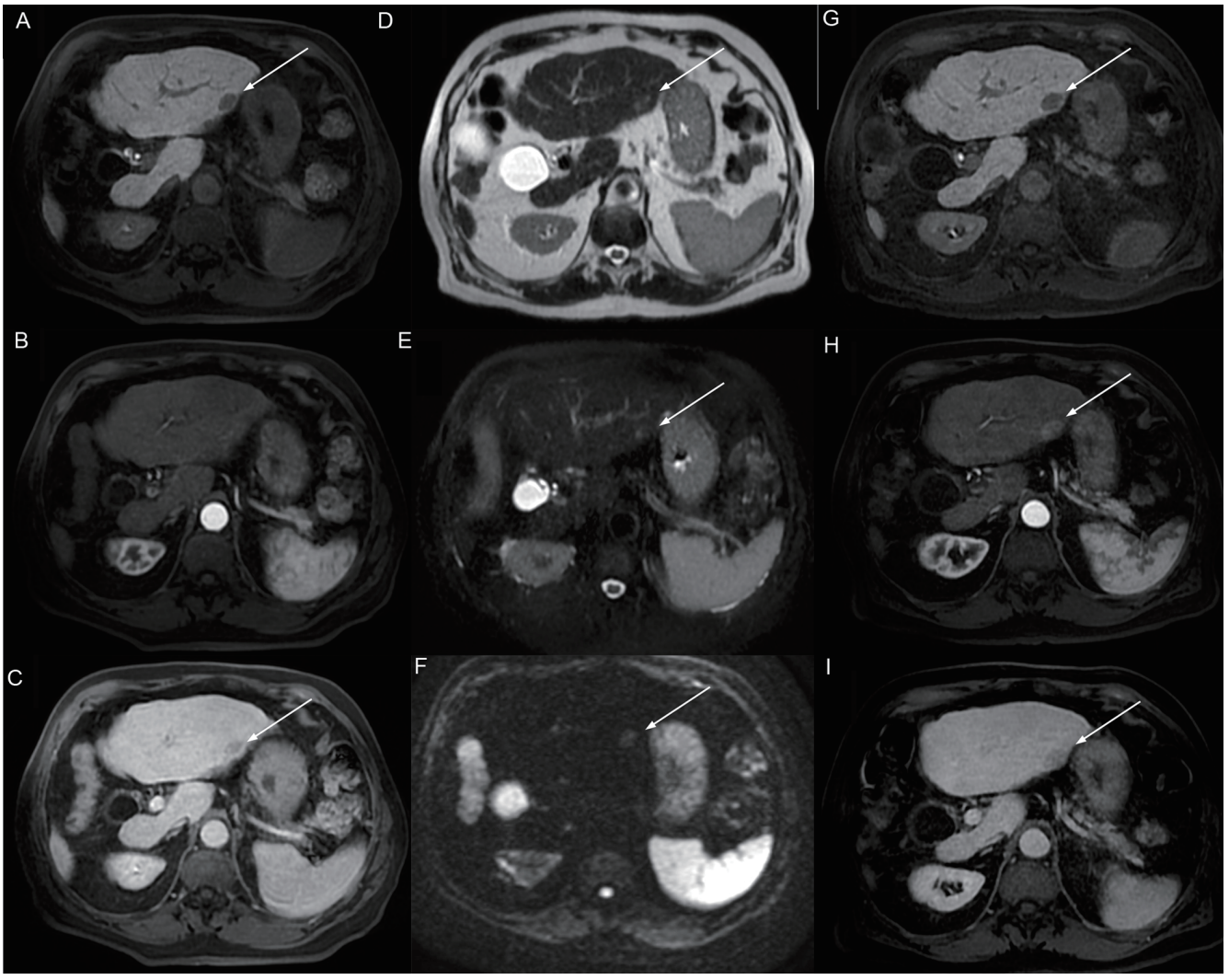

Fig. 2. Axial MR images demonstrate a 17 mm nodule in the liver segment 2. (A–C) It appears hypointense in the hepatobiliary phase (HBP) compared to the surrounding parenchyma (arrow in A), is not visible in the arterial phase (B) and shows washout in the portal venous phase (arrow in C). (D–F) The same nodule also appears slightly hyperintense in both T2-weighted and fat-saturated T2- weighted images (arrow in D and E, respectively) and corresponds to a moderate diffusion restriction in diffusion-weighted imaging (DWI) (arrow in F). (G–I) Follow-up axial MR images of the same nodule performed after 6 months demonstrated a slight dimensional increase in HBP (21 mm vs. 17 mm) (arrow in G) and the appearance of arterial phase hyperenhancement (arrow in H); this latter imaging feature, paired with the persistence of washout in the portal venous phase (arrow in I), allowed the noninvasive diagnosis of overt hepatocellular carcinoma (HCC).

high incidence of *de novo* HCC in patients with undefined or nonmalignant hepatic nodules, including both LGDNs and HGDNs. Therefore, they suggested that DAA therapy promoted the progression of premalignant nodules to clinically overt HCC, thus these patients might need careful and stricter follow-up.

Current management of HBP hypointense nodules without APHE: to treat or not to treat?

In recent years, HHNWAs have progressively attracted the interest of the scientific community as their identification would allow the detection of malignant lesions at an early stage, as already happens in other fields of oncology, thus improving the prognosis of patients. For example, it has been clearly demonstrated that colonoscopic removal of preneoplastic lesions such as adenomatous polyps, not only prevents colorectal cancer-related death but also reduces its cumulative risk over the years.[99,100] To date, however, no consensus guidelines have been established for decision management of HHNWAs, and it is still not clear whether aggressive treatment of these precursors could result in an overall survival gain compared with watchful waiting until progression to hypervascular HCC.[101] Currently, management strategies used for HHNWAs include the execution of alternative diagnostic imaging and/or an invasive biopsy to exclude a malignant evolution, a watchful waiting and/or active treatment of the lesion [through surgery or radiofrequency ablation (RFA)]. In general, the adopted strategy is decided based on the characteristics of both the nodule (in particular, its size) and the patient.

According to European guidelines, a biopsy is recommended to confirm the diagnosis whenever a liver nodule ≥1 cm with atypical or indeterminate imaging features is seen on conventional dynamic imaging. Furthermore, if the results of bioptic sampling are unclear, a second biopsy is still

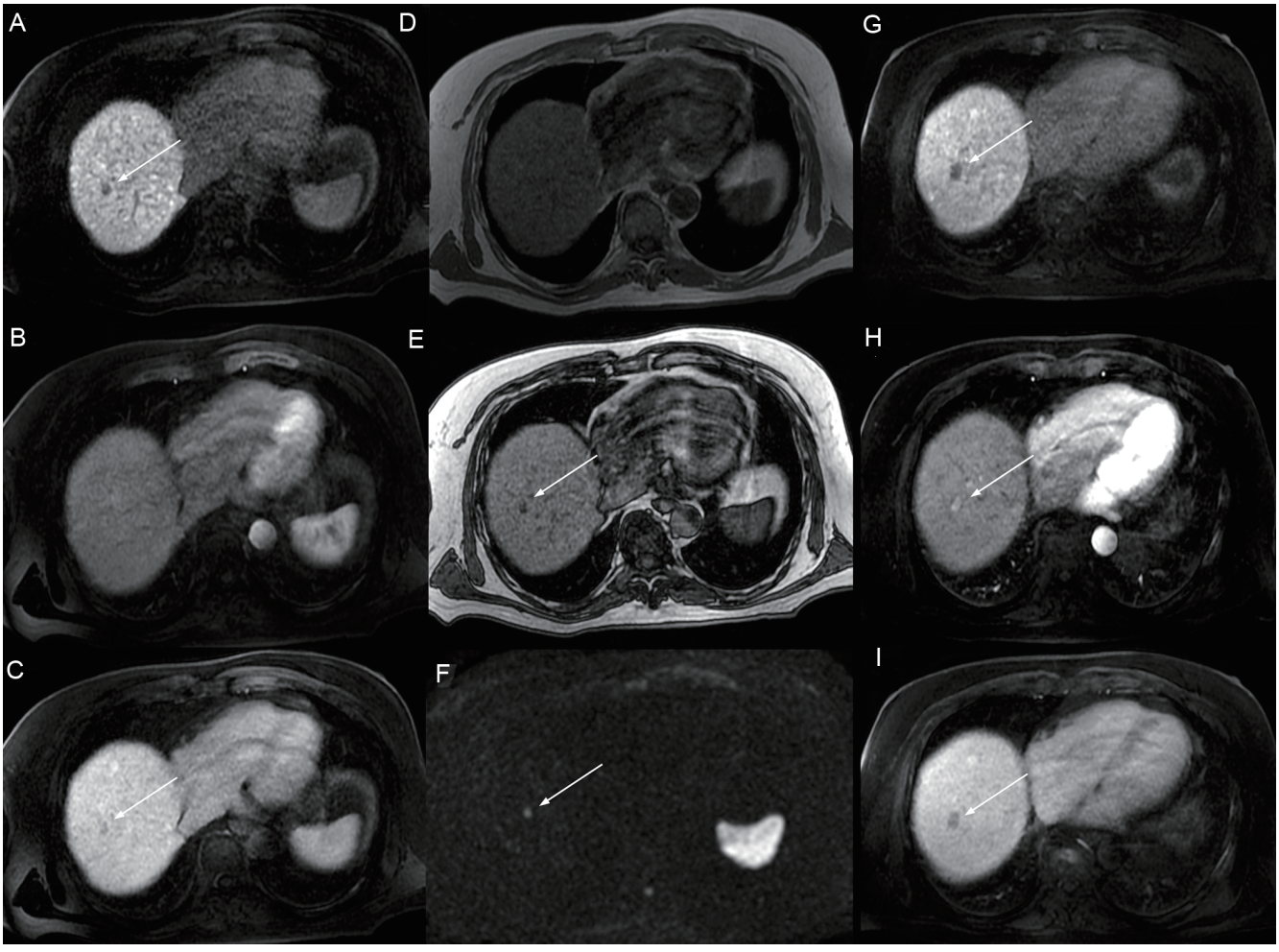

Fig. 3. Axial MR images demonstrating a hypointense nodule of 11 mm in the hepatobiliary phase (HBP) located in the liver segment 8. (A–C) It (arrow in A) does not show hypervascularization in the arterial phase (B) but exhibits a washout appearance in the portal venous phase (arrow in C). (E–D) The presence of intralesional fat was documented by the characteristic signal drop on out-of-phase T1-weighted images (arrow in E) since the lesion was not clearly visible in the in-phase T1-weighted images (D). (F) In addition, diffusion-weighted imaging (DWI) showed evident diffusion restriction of the lesion (arrow). (G–I) Follow-up axial MR images of the same nodule performed after 1 year demonstrated a slight increase of lesion size (15 mm vs. 11 mm) (arrow in G) and revealed the appearance of arterial phase hyperenhancement (arrow in H); together with the persistence of washout in the portal venous phase (I), arterial hypervascularization confirmed the malignant evolution to overt hepatocellular carcinoma (HCC).

advisable.[102] American guidelines, which support and integrate LI-RADS, are more cautious and conservative regarding the necessity of hepatic biopsy, recommending against routine use and limiting it to selected cases in the context of multidisciplinary care. In particular, a diagnostic workup may include a biopsy for nodules ≥1 cm and categorized as LI-RADS 4.[103] In Eastern countries, where its use is more widespread and endorsed, a contrast-enhanced ultrasound (CEUS) study with sonazoid is highly recommended and generally precedes the performance of invasive procedures. In particular, the Asian Pacific Association for the Study of the Liver recommends performing CEUS in all HHNWAs, regardless of their size, whereas the Japan Society of Hepatology (JSH) restricts its use to nodules ≥1.5 cm. If CEUS confirms the absence of a defect in the Kupffer phase, thus excluding the diagnosis of HCC, then a biopsy can be considered, as long as the nodule is at least 1 cm.[104,105] Japanese authors also provide for the possibility of utilizing superparamagnetic iron oxide agents (SPIO) for MRI and/or CT during hepatic arteriography or arterioportography as a further alternative to CEUS.[104]

In the remaining cases, and in particular, in patients with very small HHNWAs <1 cm or <1.5 cm based on specific guidelines), watchful waiting and strict follow-up are advocated. Theoretically, it should be dictated by the intrinsic risk of neoplastic evolution. Despite indications that such surveillance is not uniform among different guidelines, an interval of 3–6 months is the most commonly suggested, as it would ensure that, in case of malignant transformation, the nodule would not grow beyond curability (Fig. 6).[102–105] Both American and European guidelines recommend diagnostic evaluation for HCC with either dynamic CT or MRI because of their similar diagnostic performance.[102,103] However, as HHNWAs are detectable only by Gd-EOB MRI, they could be easily missed with CT and dynamic MRI, thus additional improvement should be considered. Conversely, Asian Pacific guidelines state that the combined interpretation of dynamic and HBP of Gd-EOB MRI with DWI improves the diagnostic accuracy for the detection of HCC and recommend Gd-EOB MRI as a first-line diagnostic tool for HCC surveillance.[105]

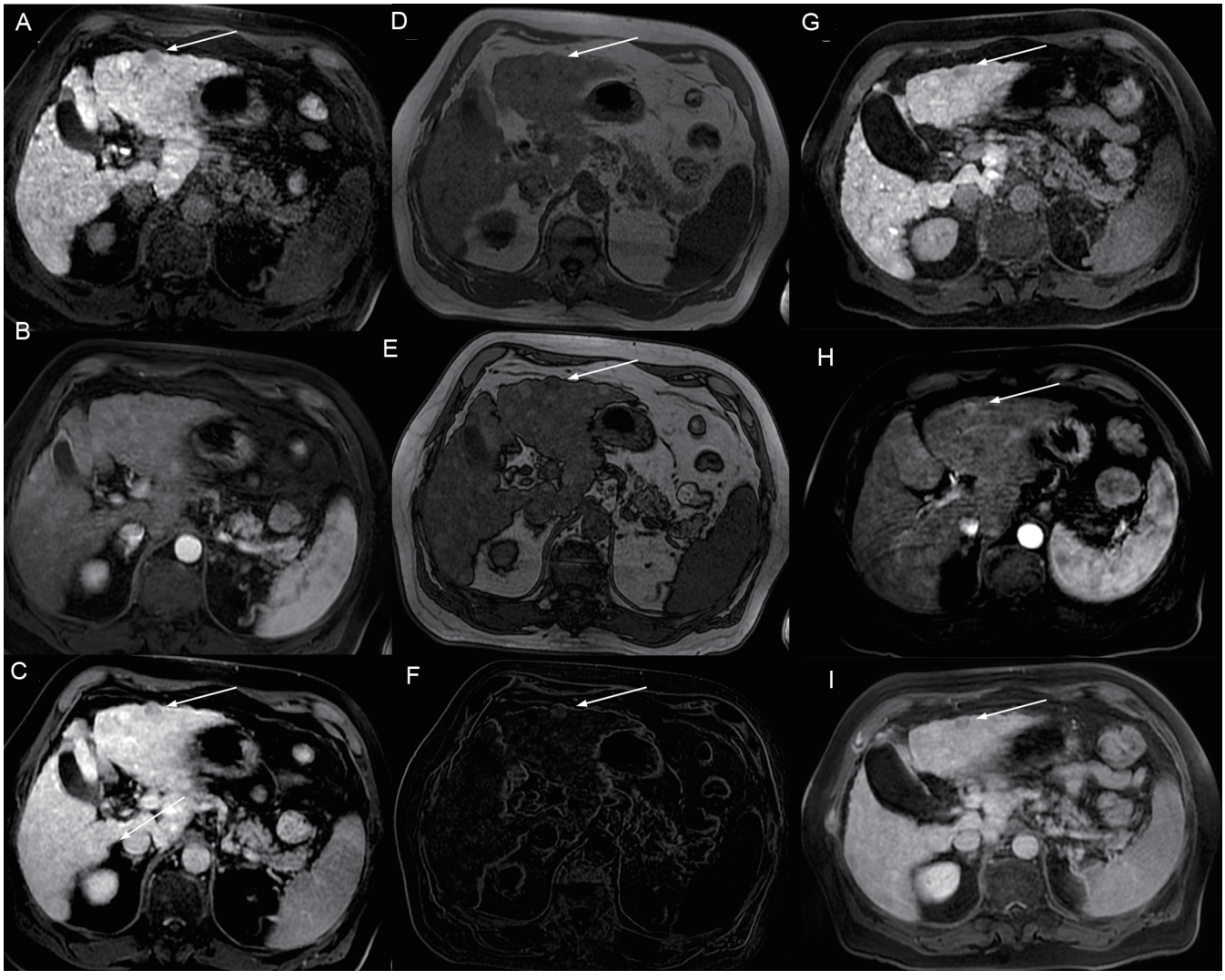

Fig. 4. Axial MR images demonstrating a 14 mm hypointense nodule in the hepatobiliary phase (HBP) located in the liver segment 3. (A–C) It (arrow in A) does not show hypervascularization in the arterial phase (B) but exhibits a washout appearance in the portal venous phase (arrow in C). (D–F) In-phase T1-weighted images documented the presence of slightly hyperintense components (arrow in D) but the more evident loss of signal intensity in the out-of-phase T1-weighted images (arrow in E), confirming the intratumoral fatty metamorphosis; the digital subtraction of the out-of-phase from in-phase T1-weighted images made the chemical shift artifacts even more evident and the nodule appeared strongly hyperintense on a dark background (arrow in F). (G–I) Follow-up axial MR images of the same nodule performed after 1 year confirmed the dimensional stability of the lesion in HBP (arrow in G) but revealed the appearance of arterial phase hyperenhancement (arrow in H); together with the persistence of washout in the portal venous phase (I), arterial hypervascularization confirmed the malignant evolution to overt hepatocellular carcinoma (HCC).

Similarly, Japanese guidelines agree that Gd-EOB MRI is the most sensitive tool for the detection of any initial change of hepatocarcinogenesis and therefore recommends performing Gd-EOB MRI as much as possible.[104] This distinct awareness of the detection of HHNWAs that seems to exist between the Western and the Eastern worlds can probably be explained by the differences in the healthcare organization and accessibility of resources, including the limited worldwide availability of hepato-specific contrast media such as sonazoid for CEUS or SPIO agents for MRI.[104]

Despite these recommendations, it is essential to acknowledge that a strategy of obtaining a biopsy of all those indeterminate nodules that require it would inevitably result in a considerable number of unnecessary procedures. Moreover, biopsy has many technical limitations, as in the case of difficult nodule locations or nonoptimal patient characteristics, and is hampered by the risk of false negative results due to sampling error, especially in the setting of small nodules as HHNWAs generally are.[106] Furthermore, histologic differentiation of DNs and early HCC is challenging, particularly when pathologists have to deal with small samples obtained by fine needle biopsy.[64,104,107] Finally, the risk of seeding should never be underestimated.[106] Therefore, since invasive diagnostic procedures are not always feasible and cannot be routinely suggested in real clinical scenarios, a strict follow-up is usually the most common strategy for all HHNWAs.

Recently, a new diagnostic algorithm for HHNWAs in patients under surveillance for chronic liver disease was developed.[101] It is based on the JSH algorithm but goes beyond it by adapting it to Western countries, taking into account both differences between the two and the latest results concerning the diagnosis of HCC (Fig. 7).[101] In particular, As sona-

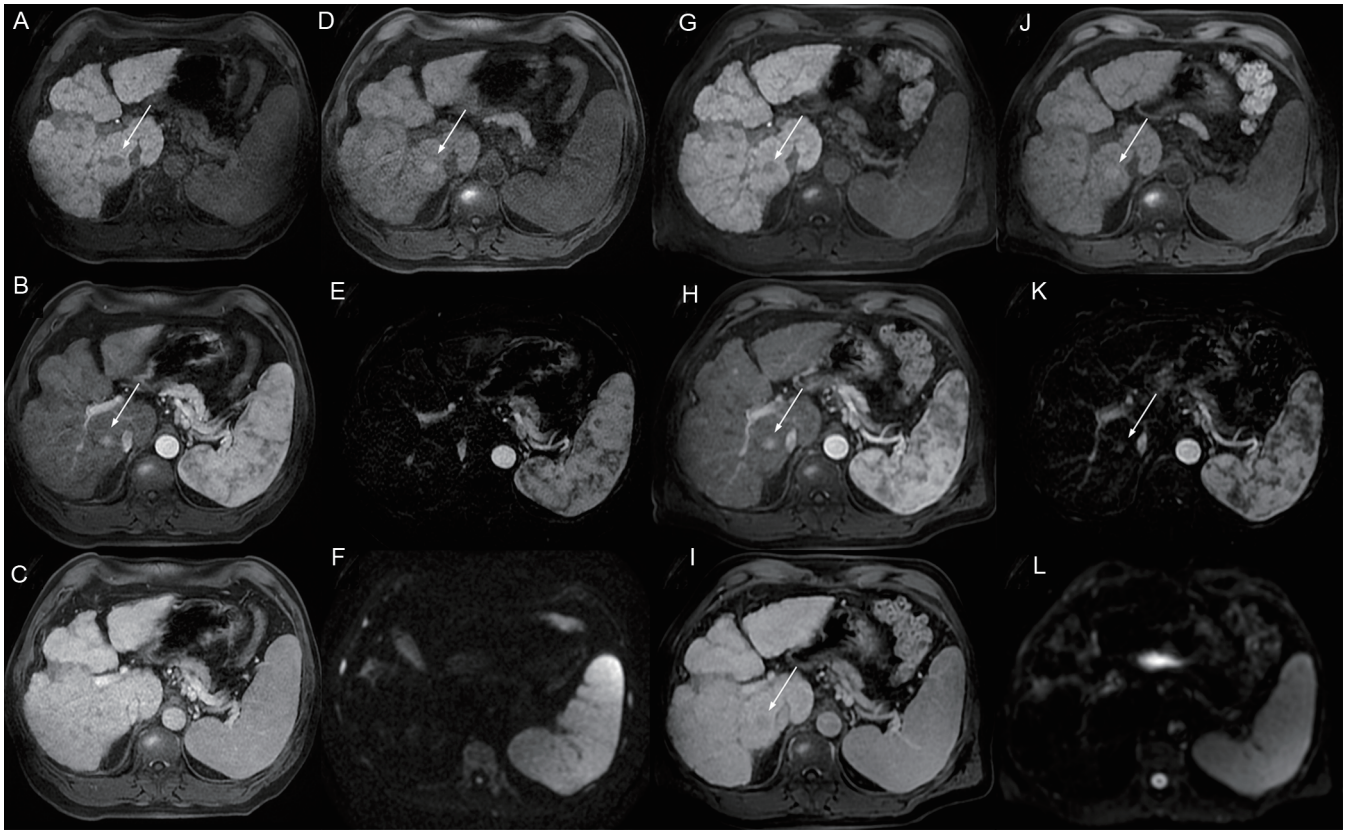

Fig. 5. Axial MR images showing a 17 mm nodule in liver segment 6. (A–C) It appears hypointense in the hepatobiliary phase (HBP) compared to the surrounding parenchyma (arrow in A) but was not visible in the portal phase (arrow in C). (D–E) The nodule appears moderately hyperintense in the arterial phase (arrow in B) but this appearance was found to be related to its hyperintensity in the precontrast T1-weighted images (arrow in D) rather than a true hypervascularization, as demonstrated by the arterial subtraction images (E). (F) No significant restriction was noted with diffusion-weighted imaging (DWI). (G–J) Follow-up axial MR images of the same HBP hypointense nodule performed after 6 months (arrow in G) demonstrated the appearance of the typical hepatocellular carcinoma (HCC) imaging features, i.e. the arterial phase hyperenhancement and the portal venous washout (arrows in H and I, respectively); in particular, the arterial hypervascularization was now evident in the subtraction images (arrow in K) and no longer attributable exclusively to baseline hyperintensity in T1-weighted images (arrow in J). (L) Interestingly, DWI did not have a significant diffusion restriction corresponding with the lesion.

zoid is not commercially available in Western countries, the evaluation of the DWI behavior has been suggested as the second diagnostic step to study HHNWs as hyperintensity on DWI has been demonstrated to be useful in differentiating hypovascular HCCs (early HCCs) from DNs.[55] If the nodule does not appear hyperintense on DWI, CEUS can be performed to depict an early arterial phase enhancement, which might be missed on dynamic CT and MRI due to their lower frame rates.[108] If CEUS is unable to detect hypervascularization, biopsy must be performed for each HHNWA ≥1 cm whenever feasible. In the remaining cases (unfeasible biopsy due to clinical-technical difficulties, nodules of <1 cm or nodules not visible by CEUS) or whenever biopsy confirms a premalignant lesion (LGDNs or HGDNs), a follow-up every 3–6 months with Gd-EOB-MRI (or dynamic CT or CEUS) is recommended.

Early treatment of HHNWAs is controversial and recommendations on this issue by international guidelines are discordant. Unless they are not histologically proven overt HCCs, American and European guidelines do not recommend the systematic treatment of these lesions due to their still controversial long-term outcomes and potential risk of overtreatment; conversely, Asian and Japanese guidelines are more designed toward treating HHNWAs whether when their malignant transformation is confirmed by biopsy or other imaging techniques (such as CEUS) or when a size growth or a nodule-in-nodule appearance is detected, even in the absence of a proven HCC.[102–105] These management discrepancies can be explained by confusion in the pathological interpretation of early HCC and DNs by pathologists. In particular, many of the early HCCs diagnosed by Japanese pathologists are interpreted as HGDNs rather than HCCs by Western pathologists; conversely, many of the HGDNs diagnosed by Western pathologists are diagnosed as early HCCs by Japanese pathologists.[109] In addition, Western clinicians have raised concerns of the accurate selection of lesions with true neoplastic potential, especially when multiple lesions are encountered.[102,103] On the contrary, Japanese clinicians believe that deciding when to start treatment of each borderline/atypical lesion is more important than differentiating early/well-differentiated HCCs from DNs.[104]

To date, few studies have investigated the prognostic significance of the presence of HHNWAs and the outcomes of early treatment. First of all, two different studies[110,111] have demonstrated that patients with preoperative HHNWAs are at increased risk of HCC recurrence after hepatectomy, even after more than 1 year. Similarly, other studies identified the presence of HHNWAs as a predictive factor for HCC recurrence after RFA.[71,112,113] More interesting, recurrence was not related to the resected or ablated HCC but to the develop-

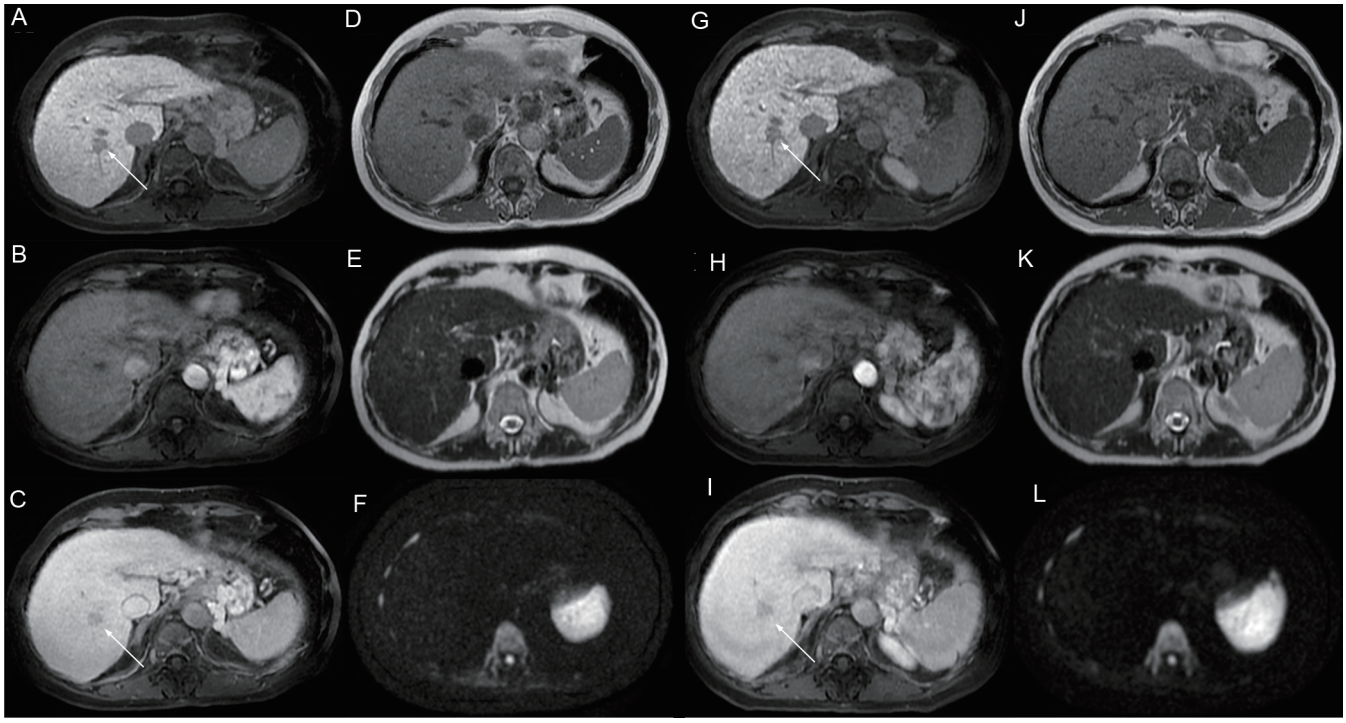

Fig. 6. Axial MR images showing a hypointense 16 mm nodule in the hepatobiliary phase (HBP) located in liver segment 8. (A–C) It (arrow in A) does not show hypervascularization in the arterial phase (B) but exhibits a washout appearance in the portal venous phase (arrow in C). (D–F) The same nodule was not visible also in T1 and T2-weighted images and in diffusion-weighted imaging (DWI) (D, E, and F, respectively). (G–L) Follow-up axial MR images of the same nodule performed after 2 years confirmed the dimensional stability of the lesion in HBP (arrow in G), the absence of arterial hypervascularization (H) and persistence of washout (arrow in I); the nodule was still not detectable in T1 and T2-weighted images of by DWI (J, K, and L).

ment of new HCC secondary to the hypervascularization of the preoperatively observed HHNWAs. For this reason, the authors considered that the presence of HHNWAs, especially when multiple, indicated enhanced hepatocarcinogenesis in the whole liver. This theory was also supported by the results of Cho *et al*.,[84] where two-thirds of the observed HHNWAs transformed into hypervascular HCCs within 1 year, suggesting that such nodules should be regarded as malignant rather than premalignant. An investigation Kim *et al*.[114] of whether prompt treatment of HHNWAs was beneficial, reported the outcomes of nine HCC patients in which HHNWAs were resected because of their location within the intended surgical field of the tumor. Interestingly, patients who did not have residual HHNWAs after surgical resection of HCC had a longer disease-free survival than those who did not have such nodules. Three-year disease survival rates were 48.6 months vs. 25.8 months. However, the same results were not achieved by Takeshi *et al*.,[115] who reported no difference in overall survival or recurrence-free survival in HCC patients with untreated HHNWAs and those with HHNWAs treated by additional hepatectomy and/or local ablation therapy. Similarly, in a study by Kim *et al*.,[116] complete necrosis was successfully obtained in 100% of HGDNs, but did not translate into either a long-term overall or a disease-free survival benefit, because of the occurrence of *de novo* HCCs aside from the initial DNs (48%) as the natural course of multicentric hepatocarcinogenesis. Additionally, they noted that RFA of all nodules is not clinically feasible in patients with multiple HHNWAs, as they might be in a distant or difficult locations, and that liver dysfunction might limit the amount of tissue removed. Finally, early reports seem to suggest that the presence of HHNWAs also have a significant role in choosing the best treatment for every patient. For example, a recent meta-analysis[117] reported a higher trend for intrahepatic distance recurrence in patients with HHNWAs treated with RFA compared with treated by hepatectomy, probably because of immunomodulation and the proangiogenic pathway of RFA. Further studies are warranted before drawing firm conclusions.

Conclusion

The recent introduction of Gd-EOB MRI in liver imaging screening and surveillance in patients at high risk for developing HCC has led to an increase in the detection of borderline hepatic nodules, in particular those with HHNWAs. HHNWAs include borderline nodules in the gray area of multistep hepatocarcinogenesis, including LGDNs, HGDNs, and early HCCs. They are considered to be precursors for the development of hypervascular HCCs. About 25% of HHNWAs ultimately develop arterial hypervascularity during follow-up. To date, initial nodules of >10 mm, hyperintensity in both DWI and T2-images, and intratumoral fat deposition have been reported as imaging characteristics correlated with increased risk of hypervascularization. However, proper management of patients with HHNWAs is still controversial, and treatments recommended by international guidelines are discordant. Therefore, stratification by the results of imaging evaluation would help to identify those at increased risk of hypervascularization, establish shared follow-up strategies, indicated for biopsy, aid in treatment selection.

Funding

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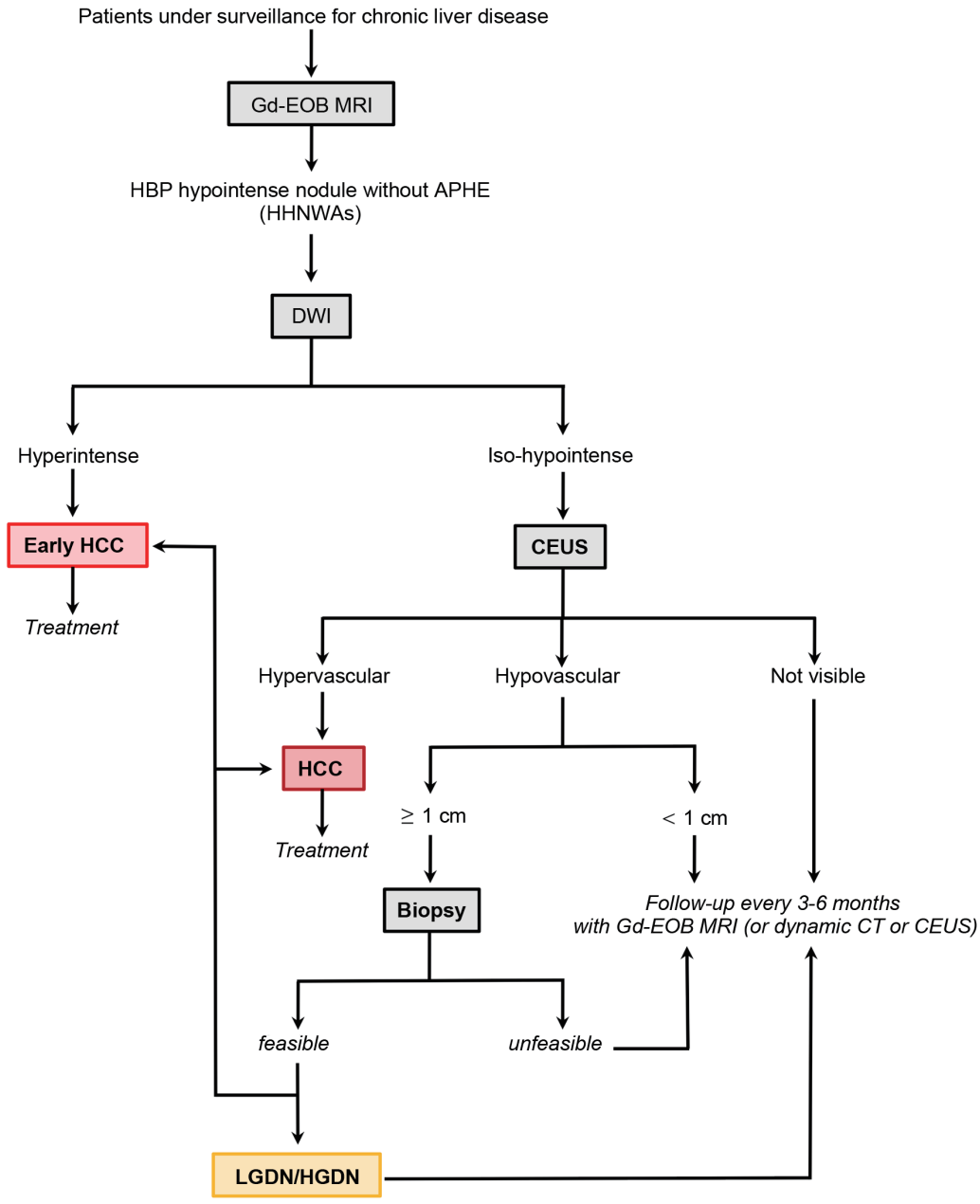

Fig. 7. Diagnostic algorithm for evaluation of hepatobiliary phase (HBP) hypointense nodules without arterial phase hyperenhancement (APHE) (HHNWAs) in patients under surveillance for chronic liver disease, modified from Renzulli *et al*.[101]

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

All authors made significant contributions to this study and have approved the final manuscript.

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