Study progression MRI findings with pathologic correlation in hepatitis B virus-associated multistage hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. It is recognized that the vast majority of HCC (90%) develops in a hepatitis/cirrhotic setting, of which the early detection is very important. Pathologically, HCC develops in a multistage fashion in the following steps: from regenerative nodules (RNs), low-grade dysplastic nodules (LGDNs), high-grade dysplastic nodules (HGDNs, the premalignant phase, borderline lesions), nodule-in-nodule HCC, early small HCCs (eHCC, the early carcinoma phase, well-differentiated), progressed small HCCs (pHCC, well to moderately-differentiated), and large HCCs (moderately to poorly-differentiated, so-called classical HCC). Characterization of cirrhotic nodules on the basis of imaging and pathologic findings is complicated by an overlap in findings associated with each type of nodule, a reflection of their multistep transitions. Recent progress in imaging modality, especially MRI, is starting to play a crucial role in the evaluation of hepatocarcinogenesis, which facilitates detection and characterization in most cases of cirrhotic nodules. In this review paper, we go over and detailedly illustrate the pathological features and MR imaging findings of these nodular lesions, and enable to understand these nodules more completely, so as to accurately diagnose cirrhotic nodules.

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Keywords: Liver cirrhosis; Precancerous; Early and progressed hepatocellular carcinoma; Magnetic resonance imaging; Pathology

1. Introduction

Liver cirrhosis is the strongest predisposing factor in hepatocellular carcinoma (HCC), approximately 90% of HCC cases develop in a cirrhotic liver [1]. HCC is becoming more prevalent not only in Asia and Africa, but also in Western countries. The incidence of HCC and its death rates have increased gradually during the past 10 years, and the estimated incidence of new cases is about 500,000–1,000,000 per year, causing 600,000 deaths globally per year [2]. Worldwide, HCC is already the fifth most common neoplasm and is the third most common cause of death from cancer, after lung and stomach cancers [3]. In China, the majority of HCCs are associated with hepatitis B virus infection. Patients diagnosed at an early stage are eligible for potentially curative therapies; 5-year survival rate is more than 50% in patients with small HCCs [4]; however, very poor prognosis is observed with advanced HCC (5-year survival rate below 10%). Therefore, early detection of HCC is important, which helps improve patient survival by allowing prompt detection and treatment.

At the macroscopic level, the carcinogenesis of HCC in cirrhosis has been described as a multistep progression. The cirrhosis-associated hepatocellular nodules are subdivided into regenerative nodules (RNs), low-grade dysplastic nodules (LGDNs), high-grade dysplastic nodules (HGDNs), nodule-in-nodule HCC, early small HCCs (eHCC, well-differentiated), progressed small; HCCs (pHCC, well to moderately-differentiated), and large HCCs (moderately to poorly-differentiated), in an ascending order of histologic grades, representing a sequence of multistep hepatocarcinogenesis. The differentiation of these lesions is important because RNs...
are benign, whereas HGDNs are premalignant. The transition from regenerative and dysplastic nodules to HCC is not characterized by discrete steps; rather, it is marked by a continuum of vascular pattern changes; the major changes that characterize the progression are progressive loss of portal vascularity and increased arterial blood flow. The presence of overlapping features (even at the histopathologic level) of some cirrhotic nodules makes their accurate characterization difficult.

Currently, MRI is an ideal imaging modality for detection and differentiation of focal cirrhotic nodules [5]. MRI provides various advantages [6], images can be obtained utilizing various scan parameters or pulse sequences, adequate information can be provided on. The T2-weighted fast spin-echo sequence with fat suppression is a very sensitive sequence for focal liver lesions. Chemical fat-saturation sequences and gradient-recalled echo (GRE) sequences with out-of-phase and in-phase image acquisitions can be used to detect hepatic or intra lesional steatosis. High-quality multiphasic dynamic MRI allows more reliable imaging of the liver in the arterial phase. Diffusion weighted images (DWI) and liver-specific hepatobiliary contrast agents, providing cellular information of the hepatocellular nodules. These characteristics make MR successfully detect the increasing size and vascularity of nodules, thereby providing support for the concept of stepwise hepatocarcinogenesis.

Familiarity with the multistep progression of cirrhotic nodules and their MRI manifestations is therefore important for optimal diagnosis and management. In this article, we review the current classification of cirrhosis-associated hepatocellular nodules, including HCC, as well as the associated histologic and MRI manifestations.

2. Regenerative nodules

2.1. Pathology of RNs

RNs are the most common cirrhosis-associated hepatocellular nodules, also known as cirrhotic nodules. They consist of proliferating normal liver cells largely or completely surrounded by fibrous septa (Fig. 1F), appear round and sharply circumscribed [7], usually numerous and diffusely distributed throughout the liver parenchyma, the outer liver surface may be studded with nodules and deformed by them (Fig. 1E). They resemble normal liver tissue but also show features of regeneration such as twinning of cell plates, distortion of plate architecture [5]. RNs may be monoacinar or multiacinar, depending on whether they contain one or more terminal portal tracts. RNs also may be classified into micronodular (<3 mm), macronodular (>3 mm), and mixed types, on the basis of the nodule sizes. Most RNs have diameters of less than 2 cm. RNs with diameters of more than 2 cm are called

Fig. 1. Regenerative nodules in a 49-year-old woman with HBV-induced cirrhosis. Unenhanced T1WI with fat saturation shows heterogeneity of the liver parenchyma, with slightly high signal intensity nodules of various sizes, which appear sharply circumscribed by hypointense septa (A). The nodules show low signal intensity on T2WI with fat saturation (B), no enhancement at arterial phase (gadolinium-enhanced fat-saturated) (C), low signal intensity compared to the surrounding liver parenchyma at delayed phase (D). Photograph of explanted liver shows an outer surface studded with regenerative nodules of various sizes (E). Photomicrograph (original magnification, ×40; hematoxylin-eosin [H-E] stain) of a slice from the specimen shows the regenerative nodules surrounded by fibrotic septa (F). (Adapted and reprinted, with permission, from reference 30 offered by ZHANG Yan-yan).
Fig. 2. A large regenerative nodule (32 mm in diameter) in a 39-year-old man with HBV-induced cirrhosis. There is a subcapsular nodule at hepatic segment 3 (red circle), which demonstrates slightly high signal intensity on T₁WI with fat saturation (A), isosignal intensity to background liver parenchyma on T₂WI with fat saturation (B), similar enhancement to the surrounding parenchyma on arterial phase with fat saturation (C), and slightly low signal intensity on delayed phase (D).

Fig. 3. Dominant large regenerative nodule (50 mm in diameter). There is a subcapsular, large regenerative nodule in the left lobe of the cirrhotic liver (red circle), close to the left portal vein and mimic a mass, which demonstrates slightly low signal intensity on T₁WI (A) and T₂WI with fat saturation (B); The nodule enhances as much as surrounding parenchyma during the arterial phase with fat saturation (C), and shows slightly low signal intensity on delayed phase (D).
large regenerative nodules (LRNs) (Fig. 2A–D), but they are rare and typically lack cytological or architectural atypia. LRNs can measure 5 cm or larger and mimic a mass, they usually locate near major vessels (Fig. 3A–D). Most RNs do not progress in the dedifferentiation process. The blood supply of a RN continues to be largely from the portal vein, with minimal contribution from the hepatic artery [5]. This explains why there is no enhancement on the hepatic arterial phase on MR images.

2.2. Imaging of RNs

On MR imaging, RNs are often indistinct on T1- and T2-weighted images, better appreciated, when they are sharply circumscribed within the liver parenchyma by fibrous septa. The septa are relatively hypointense on T1-weighted images and with isointensity on T2-weighted images. RNs are usually iso-to hypointense on T2-weighted images, with variable signal intensity (low, iso, high) on T1-weighted images (Fig. 1A and B). RNs almost never show hyperintensity on T2-weighted images, except infarcted RNs [8] that are uncommonly seen in cirrhotic patients notably with before hypointensive shock and LRNs that are seen in patients with long-standing Budd-Chiari syndrome [9] and inpatients with cirrhosis due to autoimmune hepatitis [10]. Less commonly, they can be hyperintense on T1-weighted images compared to background liver tissue. The exact cause for this hyper intensity is unknown; it may be due to the presence of lipids, metal-binding proteins, proteins per se, or possibly copper [11].

RNs may occasionally contain endogenous iron (siderotic nodules, the term was coined by radiologists), which will show typically hypointense on T1- and T2-weighted images, a result of their magnetic susceptibility [7]. Chemical shift imaging aids in the diagnosis of siderotic nodules, showing drop of signal on the sequence with the longer echo-time (TE), which could be during the in-phase or opposed phase, depending on the MR machine used for imaging and its field strength, due to susceptibility effects resulting from proton de-phasing exerted by the presence of iron. Siderotic RNs may be regenerative or dysplastic, but neither unenhanced MRI findings (size, number, distribution) nor contrast-enhanced MRI features permit reliable differentiation between the two, therefore, the term siderotic nodule is now favored. There is controversy over whether the occurrence of HCC may increase in patients with siderotic nodules [12]. Siderotic RNs are not considered premalignant [7]. However, a pathologic study also indicated that iron-accumulative DNs may associate with a higher incidence of HCC [13].

Another type of RN is steatotic. Steatotic RNs result from fatty accumulation and tend to occur in multiples. Chemical shift imaging aids also in the characterization of steatotic RNs. They appear as hyperintense lesions on in-phase gradient images and exhibit signal loss on out-of-phase images (Fig. 4A and B) [5], due to destruction of the magnitude vector within the same voxel, exerted by fat and water molecules having opposite directions and resulting in decreased signal intensity; indicative of intracellular (microscopic fat).

Several studies have shown that nodules with high signal intensity on T1-weighted images are in most cases benign [14,15], a notable exception is fat-containing, a single large size (>1.5 cm) nodule strongly suggests malignancy (Fig. 4). Otherwise, the presence of numerous nodules <1 cm suggests benignity [16].

Regardless of their intrinsic signal features, a reliable finding of RNs is the absence of any detectable enhancement on the arterial phase, compared with the background hepatic parenchyma (Figs. 1–3) [5,8]. They have normal hepatocellular and phagocytic functions and virtually all RNs enhance to the same degree as adjacent liver on delayed T1-weighted images after administration of hepatobiliary-specific [5,17], which gives the liver a homogeneous appearance. Occasionally, RNs may have sufficient hepatocellular function to take up the hepatocellular agent but not to excrete it; such nodules show hyperintense signal on hepatobiliary phase images. Though most RNs usually show no interval growth or disappear during serial imaging [15], RNs with a diameter of more than 15 mm at imaging have an increased likelihood of being dysplastic or malignant. However, an absence of early enhancement after gadolinium administration, preserved uptake of gadobenate dimeglumine suggestive of benignity. The differential diagnosis between LRNs and low-grade DNs are often found to be difficult, especially for the biopsied material, as neangiogenesis and cytological atypia are subtle in low-grade DNs. Fortunately, this distinction does not appear to have significant practical consequences at present.

3. Dysplastic nodules

Dysplastic nodules (from a few mm up to 2 cm, usually 1–1.5 cm, single or multiple) are evident on gross examination of hepatic specimens as distinct nodular lesions that differ from the surrounding parenchyma with regard to size, color, texture and bulging cut surface. DNs are usually, but not always, detected in cirrhotic livers with the incidence of 15%–28% [5]. They are characterized histologically by progressive architectural derangement, nuclear crowding, atypia, and a variable number of unpaired arterioles or capillaries, classified as LGDNs or HGDNs depending on the degree of cellular and architectural atypias. LGDNs can evolve into HGDNs [18]. In practice, histologic differentiation of LGDNs and HGDNs is often very difficult, especially in biopsy [19], because the portal and arterial supplies of these nodules are variable and inconsistent.

3.1. Pathology of LGDNs

LGDNs are distinct from the surrounding cirrhotic liver because of the presence of a peripheral fibrous scar which is not a true capsule, but rather condensation of scarring around the nodules. At histologic analysis, LGDNs are characterized by preserved hepatic architecture, low-grade cytologic atypias, slightly increased cell density, minimal nuclear atypia (Fig. 5I), normal or slightly increased nuclear/cytoplasmic ratio, varying numbers of portal tracts, absent mitotic figures, and very rare
Fig. 4. A large, fat-containing regenerative nodule in a 61-year-old man with HBV-induced cirrhosis, malignant transformation. There is a prominent right hepatic nodule (21 mm in diameter) (red circle), which demonstrates minimally increased T1 signal on the in-phase images (A), low signal intensity on the out-of-phase (B), indicating the presence of fat. It shows low signal intensity on T2WI with fat saturation (C), part of the nodule enhances as much as surrounding parenchyma during
the arterial phase, part shows no enhancement (Gadoxetic acid-enhanced with fat saturation) (D), and shows slightly low signal intensity on delayed phase (E). 7 months later, the diameter of the lesion increases to 31 mm, but the prevalence of fat decreases. It demonstrates slightly high signal intensity on the in-phase (G), iso to heterogeneous signal intensity on the out-of-phase (H), iso signal intensity on T2WI with fat saturation in addition to a high point signal (white arrow) (I), which shows obvious enhancement at arterial phase (white arrow) (J), the other part of the lesion enhances as much as surrounding parenchyma, at delayed phase, it shows low signal intensity (K). Histologic analysis showed it to be a steatotic high grade dysplastic nodule.

Fig. 5. Low-grade dysplastic nodule in a 60-year-old man with HBV-induced cirrhosis. There is a 20-mm nodule in liver segment 5 (red circle), it shows high signal intensity on the out-of-phase (A), low signal intensity on T2WI with fat saturation (B), no enhancement at arterial phase (gadolinium-enhanced fat-saturated) (C), low signal intensity at delayed phase (D). The diameter of the lesion increases to 27 mm on the 5-month follow-up, but the MRI findings are similar to the previous performance (E–H). Photomicrograph (original magnification, ×100; H-E stain) shows low-grade cytologic atypias, slightly increased cellular, minimal nuclear atypia in the nodule are indicative of low-grade dysplasia (I).
aberrant arteries (small arteries unaccompanied by bile ducts, so-called unpaired arterioles). LGDNs may have diffuse siderosis or increased copper retention, or uniform steatosis in livers without fatty change. They closely resemble LRN histologically, distinction between them may be difficult or impossible. LGDNs are considered to have low malignant potential with slow, infrequent progression to HCC [20], should be followed up and urgent treatment is not required. Intervals of screening are only dictated by the growth rate of the tumor, which on average takes six months to double its volume.

3.2. Imaging of LGDNs

Similar to RNs, LGDNs show variable (low, iso or high) signal intensity on T1-weighted images depending on their content and low or iso signal intensity relative to adjacent liver on T2-weighted images and demonstrate enhancement similar to that of the background liver parenchyma on all dynamic phases, without any detectable enhancement during arterial phase (hypovascular nodules) (Fig. 5) [21], because the blood supply is mainly derived from portal vein. The MR imaging characteristics of LGDNs overlap with those of RNs, it is not possible to differentiate LGDNs from RNs due to their similar imaging features, but there are no significant practical consequences [5,8].

3.3. Pathology of HGDNs

At histologic analysis, HGDNs display at least moderate cytologic and architectural atypia but insufficient for diagnosis of malignancy. One or more of the following may be seen (Fig. 6F): mild nuclear atypia, high nuclear-to-cytoplasmic ratio, cytoplasmic basophilia or clear change, increased cell density (1.3—2 times greater than that of adjacent cirrhotic parenchyma), mildly thickened cell plates (two to three cells wide), pseudoglandular formation, reduced numbers of portal tracts, progressive sinusoidal capillarization, increased numbers of unpaired arteries [22], forming subnodules within dysplastic nodules. Such subnodules may demonstrate fatty change, steatosis, Mallory body clustering, or iron resistance (siderotic nodules [23]). Occasional subnodules may display features that are diagnostic of well differentiated HCC and are difficult to distinguish histologically, particularly those that are small. HGDNs may even express a-fetoprotein (AFP) but are
not frankly malignant, they are the most advanced HCC pre-
cursors [21,24], with a risk of malignant transformation of
about 30%–40% at 24 months. The size at baseline (larger the
nodule, higher the risk) and changes in size and/or in the
vascular pattern (shifting from hypo- to hyper-enhancing
pattern on arterial phase) during follow-up, were reliable
predictors of malignant transformation [25]. But most of
HGDNs remained stable over a long time period, often
exceeding two years and a few even disappeared at follow-up,
therefore, the treatment of HGDNs is under investigation.

3.4. Imaging of HGDNs

At MR imaging, HGDNs demonstrate variable (low, inter-
mediate, or high) non-specific signal intensity on T1-weighted
images, depending on their content, and are usually iso-
or hypointense on T2-weighted images, a few percentage of
HGDNs tend to have slightly higher signal intensity on T2-
weighted images; Most of HGDNs are hypovascular
(Fig. 6A–E), minority can enhance in the arterial phase due to
the unpaired arteries (not in great numbers) and fade to iso
intensity [26], without washout (Fig. 7A–D), because supply
from the portal venous system remains comparable with the
background liver [27,21]. DNs and early HCCs cannot be
distinguished by unenhanced MR imaging alone, they may
show similar imaging findings on both extracellular contrast-
enhanced MR imaging and SPIO-enhanced MR imaging
[28]. Recently, Gadoxetic acid (Gd-EOB-DTPA), a tissue-
specific contrast material, seems promising tools to differenti-
tiate early HCC from DNs [17]. Dynamic imaging can be
performed using this agent for hepatobiliary phase imaging
(10–20 min after injection) for the evaluation of functional
status. On hepatobiliary phases, HGDNs usually show an
efficient hepatocellular activity and often tend to appear iso-
or slightly hypointense relative to surrounding parenchyma. In
some nodules impaired uptake and slow clearance of hepato-
cellular agents may justify hypointense signal similar to a
focal nodular hyperplasia pattern characterized even by a
central scar. A few nodules may be hypointense due to
impaired uptake/excretion of hepatocellular agents, this
behavior may suggest malignant transition. When HGDNs are
seen as an increase in size and development of washout on
delayed phase or hepatobiliary phase, allowing definite diag-
nosis of HCCs (Fig. 7).

There is no typical imaging for HGDNs, needing all of
them to be biopsied for characterization. In addition to the
histological features which are necessary limited to the frag-
ment biopsied, false negative results are reported to range
between 5% up to 30% at the first biopsy [29], hence, diagnosis of non-malignancy need to be confirmed by enhanced follow-up. According to the latest guidelines from the American Association for the Study of Liver Diseases (AASLD), DNs should not be treated or managed as cancers, patients with known or suspected DNs should not be monitored more aggressively than patients without such nodules [30]. As HGDNs represent an intermediate step in the development of HCC in cirrhotic liver [24], intensified screening is important to identify liver cancer at the smallest possible size to optimize treatment, though the screening intervals of DNs is 6 months or 3 months is still questioned [31], we advise more frequent surveillance imaging (usually 3 mo) despite the controversy.

4. Nodule in-nodule HCC

4.1. Pathology of nodule in-nodule HCC

There is a morphologic continuity, a focus of well differentiated HCC originates within a larger dysplastic nodule referred to as a so-called “nodule-in-nodule” (this term is also used for intra tumoral heterogeneity in HCC: the outer tumor consists of well differentiated HCC tissue and the subnodule showing expansive growth is moderately differentiated). The nodule-in-nodule pattern is uncommon, occurring in approximately 6% of patients with HGDNs [32].

4.2. Imaging of nodule in-nodule HCC

On T1-weighted images, such lesions usually show high, iso or low signal intensity of a large nodule, with internal foci that are iso or low intense to the liver. On T2-weighted images, the classic MR description is a low signal intensity of a large nodule containing a focus of higher signal intensity, which may demonstrate high signal intensity on DWI and enhancement on arterial phase, low intense on hepatobiliary phase (Fig. 8) [8,21], the remaining part of lesion (dysplastic nodule) does not enhance on arterial phase and has lower signal intensity, appear iso or slightly high signal intensity to surrounding parenchyma on hepatobiliary phase.

5. Small HCC

As stated in 2009 by the International Consensus Group for Hepatocellular Neoplasia, small HCC is arbitrarily defined as carcinoma measuring less than or equal to 2 cm in diameter and classified in two types: one with indistinct margins known as “HCC of vaguely nodular type” or “small and early HCC”

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Fig. 8. HCC within a high-grade dysplastic nodule in a 54-year-old man with HBV-induced cirrhosis (nodule-in-nodule appearance). There is a hyperintense nodule (17 mm in diameter) containing a smaller low-signal-intensity nodule in liver segment 6 on T₁WI (A), the outer nodule shows isointense, the inner nodule shows hyperintense on T₂WI (B), arterial phase image shows apparent enhancement of the whole nodule (C), but only the inner nodule shows clear washout at delayed phase (D). Photograph of explanted liver shows a nodule-within-a-nodule abnormality (white arrow) (E). Photomicrograph of a specimen (original magnification, ×100; H-E stain) shows a HCC within the high-grade dysplasia nodule (black arrows) (F). (Adapted and reprinted, with permission, from reference 30 offered by ZHANG Yan-yan).
(eHCC) [21] and the other with distinct margins known as “HCC of distinctly nodular type” or “small and progressed HCC” (pHCC). At macroscopical level, the former is a low-grade, early stage and slowly growing tumor of vaguely nodular appearance and is hard to be recognized. Histologically eHCC is considered as well-differentiated cancer with a little cellular and structural atypia, correspond to carcinoma in situ of other organs. The distinctly nodular type is well demarcated and often encapsulated, can be interpreted as advanced cancer despite small tumor size, about 80% are moderately differentiated form and the remnant 20% consist of varying mixture and moderately differentiated cancerous tissues. Smaller lesions are less likely to be associated with microscopic vascular invasion and are more responsive to curative treatments. Thus, HCCs should be diagnosed when they are smaller than 2 cm.

5.1. Pathology of early HCC (small well-differentiated HCC or vaguely nodular type HCC)

Early HCC may be invisible at gross specimen analysis and detectable only with microscopy. On microscopic examination, early HCCs are well differentiated neoplasms, the histologic features include [23]: relatively uniform population of small cells with nuclear atypia and high nuclear/cytoplasmic ratio; increased cell density (greater than that accepted in HGDNs, more than twice that of the surrounding parenchyma); plates three or more cells thick; varying number of portal tracts; irregular, thin trabeculae and/or pseudoglandular pattern; diffuse fatty change; reduced number of trapped portal tracts; increased number of unpaired arteries; stromal invasion (tumor cell invasion into the intralesional portal tracts); without vascular invasion and metastatic spread. Stromal invasion remains most helpful in differentiating early HCC from HGDNs because the features listed above may also be recognized in HGDNs [33].

An important feature detected in approximately 40% of cases is fatty change, a major clue calling attention to this tumor type [34]. Fatty change is caused by relative hypoxia due to cellular crowding and low blood supply. The prevalence of fatty change decreases along with the increasing tumor size; therefore, fatty change is uncommon in tumors larger than 3 cm and/or moderately differentiated HCCs. Early HCCs are the earliest recognizable form of HCC, account for about 10%—20% of HCC, establishing a definitive diagnosis usually requires a biopsy, most hypovascular HCCs and those with equivocal imaging findings are early HCCs. They have a 5-year survival rate of 89% [35,36], and have been found to recur within 3 years of resection in only 8% of cases [36].

5.2. Imaging of early HCC (small well-differentiated HCC or vaguely nodular type HCC)

A specific imaging diagnosis of early HCC arising in cirrhosis is very difficult. On T1-weighted images, they mainly demonstrate isointense or hyperintense, a small part appear hypointense; on T2-weighted images, they usually appear slightly hyperintense, some may appear isointense or even hypointense [20]. Cell crowding, fat accumulation and copper deposition may be responsible for hyperintensity on T1-weighted images; while hemosiderin, decreased blood supply and/or reduced sinusoidal space was thought to be the cause of hypo- or iso intensity on T2-weighted images [37]. A nodular showing hyper intensity on T1-weighted images practically narrows the differential diagnosis. In this setting, T2-weighted images may aid in further differential diagnosis, since DNs are usually of low signal intensity on T2-weighted images, while early HCCs are typically either isointense or slightly hyperintense. Therefore, increased signal intensity of a nodule on both T1- and T2-weighted images makes early HCC the most likely diagnosis.

Early HCCs demonstrate relative arterial hypovascularity (Fig. 9) (most are hypo- or isointense in the arterial phase) due to the poorly developed neo-arterialization and decreased portal supply, which is indicated by hypo intensity in the portal phase, resulting therefore indistinguishable from HGDNs. Such lesions are expected to demonstrate progressively increased arterialization and a continued decrease in portal blood until they become typical HCCs [27].

Some early HCCs show intense enhancement on dynamic gadolinium-enhanced arterial phase MR images (Fig. 10). Arterial hyper-enhancement is the most common and important imaging finding in the diagnosis of HCC, but it can be seen in HGDNs. The key distinguishing feature of HCC is the development of delayed “washout”; defined as arterially enhancing nodules becoming hypointense compared to the background liver on the delayed phase imaging (not to be confused with “fade out”, which is defined as arterially enhancing nodules becoming isointense to background liver on delayed phase imaging). A few early hypervascular HCCs do not show washout on delayed images [29,38].

A recent report suggested that gadoxetic acid-enhanced MR imaging may be useful for the improvement of the diagnosis of early HCC [39]. On hepatobiliary-phase MR images, liver parenchyma that contains functioning hepatocytes demonstrates enhancement, and early HCCs that contain malfunctioning hepatocytes demonstrate no enhancement and appear as hypointense lesions [39]. However, well-differentiated small HCCs may demonstrate enhancement on hepatobiliary-phase images, a result of residual hepatocyte activity and the reason for false-negative findings in some cases. Morphological signs of malignance consider signal hypo intensity and hyper intensity on T1- and T2-weighted images, respectively; signal hyper intensity is also observed on DWI related to higher cellular density. Finally, hypo intensity on hepatobiliary phase is another valid sign.

Dynamic imaging is fundamental not only for nodule characterization at baseline but also for the follow-up. Since it is extremely difficult to perform biopsy of small nodules that are smaller than 1 cm and visible only on arterial phase or hepatobiliary-phase, close follow-up by imaging is recommended according to American international practice guidelines [27,39]. These lesions should be re-examined at a 3-mo interval to assess for lesions interval growth or development of
washout. As HCC may demonstrate slow growth, the lack of interval growth on short-term follow-ups does not exclude the possibility of malignancy, only nodules that are stable for 2 years are considered benign [8]. Patient with liver nodule that has a negative biopsy results should undergo repeated follow-up at 3-6-month intervals until the nodule disappears, enlarges, or has findings characteristic of HCC. If the lesion enlarges but remains atypical for HCC, another biopsy is recommended.

Fig. 9. Biopsy-proved hypovascular small early HCC in a 43-year-old man with HBV-induced cirrhosis. There is a 16-mm nodule in liver segment 8 (black arrow), it shows slight hypointense on T1WI (A) and hyperintense on T2WI with fat saturation (B), poor arterial enhancement (gadolinium-enhanced fat-saturated) (C), delayed washout with capsule enhancement (D). The diameter of the lesion increases to 25 mm on the 9-month follow-up, and the MRI findings are similar to the previous performance (E–H).

Fig. 10. Small early HCC in a 70-year-old woman with HBV-induced cirrhosis. There is a 7-mm nodule in liver segment 7, it shows ambiguity due to ascites, may shows isointense on T1WI (A) and T2WI with fat saturation (B), increased arterial enhancement (gadolinium-enhanced fat-saturated) (C), and delayed washout (D) (black arrows).
5.3. Pathology of progressed HCC (small moderately-differentiated HCC or distinctly nodular type HCC)

Small and progressed HCCs (pHCCs) are usually moderately differentiated, or consist of a mixture of well-differentiated and moderately differentiated components. They have morphologic and histologic characteristics similar to those of large HCCs and are easily differentiated from the background cirrhotic liver. It is not a great diagnostic issue for radiologists and pathologists. Histologic features include (Fig. 11F): advanced architectural distortion (widening and irregularity of hepatocyte plates, presence of pseudoglandular structures, absence of portal tracts, numerous nontriadal arteries and well-developed sinusoidal capillarization), nuclear atypia, necrosis, and microscopic invasion of stroma and portal tracts. pHCC often forms subnodules with less cellular differentiation in the so-called nodule-in-nodule form. Invasion of portal vein branches by tumor cells and intrahepatic metastases have been described in 27% and 10% respectively [36] and are associated with a 5-year survival rate of 48% [21,35].

6. Large HCC (moderately to poorly differentiated HCC)

6.1. Pathology of large HCC (moderately to poorly differentiated HCC)

Large HCC is defined as a tumor larger than 2 cm in diameter [40] and tend to be characterized by moderate to poor differentiation. Because of intralesional steatosis, cholestasis, hemorrhage, and lipofuscin, the color of large HCC typically differs from that of the surrounding liver parenchyma, making them readily identifiable at gross pathologic analysis. At histologic analysis, large HCC is characterized by an abnormally high number of muscularized, unpaired arterioles and capillarized vessels [20]. Large HCCs may exhibit a broad spectrum of morphologic features, including evidence of necrosis and a mosaic pattern characterized by a seemingly random...
distribution of confluent small nodules with intervening fibrous septa and areas of necrosis, a tumor capsule, an intratumoral nodule (“nodule-in-nodule” appearance), extra capsular extension with the formation of one or more satellite nodules, vascular invasion, extra hepatic dissemination (including lymph node and distant metastases) [26,41]. The presence of extra capsular extension or macrovascular invasion, and poor histologic differentiation are associated with a higher risk of tumor recurrence after treatment.

6.2. Imaging of large HCC (moderately to poorly differentiated HCC)

Some large HCCs have a characteristic MR imaging appearance and are usually diagnosed with no difficulty. They typically are hypointense on T1-weighted images and moderately hyperintense on T2-weighted images, with arterial intense enhancement and washout in the delayed phase.

Most large HCCs appear as mosaic pattern, which is a configuration of confluent small nodules separated by thin septa and necrotic areas within the tumor. This appearance most likely reflects the histopathologic features of HCC, with several centers of variable dedifferentiation, as well as the characteristic growth pattern of HCC. They show heterogeneous lesions at MR imaging, have variable (iso-, hyper-, or hypo-) signal intensity on T1-and T2 weighted images, and demonstrate inhomogeneous enhancement after administration of gadolinium-based contrast material (Fig. 12) [5,8]. Better histologic differentiation, the presence of copper protein, and fatty infiltration may all be responsible for the hypersignal intensity on T1 weighted image. Intralesional fat is characterized by signal intensity decrease on out-of-phase images in comparison with in-phase images and low signal intensity on fat-saturated images. The hemorrhage component of HCCs is marked hyperintense on T1-weighted images and hypointense on T2-weighted images. Intralesional necrosis typically manifests as one or more areas of low signal intensity on T1-weighted images and high signal intensity on T2-weighted images with no enhancement [5].

A tumor capsule is a characteristic sign of large HCC, is present in 60%—82% of cases [42], and it becomes thicker within increasing tumor size. At histologic analysis, capsule is composed of two layers, an inner fibrous layer and an outer layer containing compressed vessels and bile ducts that appears as a thin circumferential rim around the periphery of the tumor. The tumor capsule is usually hypointense on both T1- and T2-weighted images in most cases with typical late enhancement after administration of gadolinium-based contrast material. A large nodule in the left lobe of liver, it shows hyperintense on T2WI with fat saturation (A), heterogeneous enhancement with randomly distributed areas of hyper- and hypointensity (mosaic pattern) (gadolinium-enhanced fat-saturated) (C), and delayed heterogeneous washout (D). DWI (b = 800 s/mm²) shows restricted diffusion within the nodule (hyperintense) (B).

Fig. 12. Poorly differentiated large HCC with a mosaic pattern of enhancement in a 47-year-old woman with HBV-induced cirrhosis. There is a large nodule in the left lobe of liver, it shows hyperintense on T2WI with fat saturation (A), heterogeneous enhancement with randomly distributed areas of hyper- and hypointensity (mosaic pattern) (gadolinium-enhanced fat-saturated) (C), and delayed heterogeneous washout (D). DWI (b = 800 s/mm²) shows restricted diffusion within the nodule (hyperintense) (B).
contrast material, although capsules with a thickness of more than 4 mm can have an outer hyperintense layer on T2-weighted images [42]. Delayed pseudo-capsule enhancement of hepatic nodules aids in the diagnosis of HCC, and can be helpful in lesions that do not show classical features of HCC on dynamic imaging.

Extra capsular extension of the tumor, with partial projections or formation of satellite lesions is frequently seen in large HCC (43%–77%) [41]. The satellite lesions often appear as multiple subcentimeter nodules outside the tumor margins.

Vascular invasion occurs frequently in large HCC and can affect both the portal vein as well as the hepatic veins [43]. Differentiation of tumor thrombus and nonneoplastic bland thrombus is critical. A tumor thrombus, indicative of HCC, may be an important clue for the diagnosis of diffuse infiltrating cancer and conveys a high risk of hematogenous dissemination of cancer and precludes liver transplantation as a treatment option. A bland thrombus is a frequent finding in the setting of cirrhosis, may occur in the absence of HCC, and maybe of minimal importance for decision making with regard to the management, depending on its location and extent. At MR imaging, vascular invasion can be seen as lack of a signal void on T1-weighted and flow-compensated T2-weighted images. On gadolinium-enhanced images, the tumor thrombus typically expands the vascular lumen, enhances during the arterial phase, and manifests as a filling defect during delayed phase [26,41]. A nonneoplastic bland thrombus does not enhance at the arterial phase and, instead of expanding the lumen, causes it to contract.

About 10%–20% of HCCs are hypovascular (atypical manifestations), typically, hypovascular HCCs are small, well-differentiated tumors. Though rarely, an HCC that is larger than 2 cm and poorly differentiated may be hypovascular [19]. Such lesions may be difficult to detect on gadolinium-enhanced MR images despite their large size and aggressive behavior, but they are usually visible on SPIO enhanced images. They characteristically accumulate less SPIO than the surrounding liver parenchyma and have relatively high signal intensity on T2-and T2*-weighted SPIO-enhanced images [44]. A very few cases still require biopsy in order to make a diagnosis [27].

7. Summary

In cirrhotic liver, HCC typically develops in a stepwise fashion, including RNs, DNs, small HCCs, large HCCs. Though most of RNs and DNs are benign, an understanding of the histologic and imaging features is important because these lesions may cause diagnostic confusion at MR imaging, with resultant errors in interpretation and management. The importance of pathologic-imaging correlation cannot be overemphasized, not only on a daily diagnostic basis, but also for the overall understanding and advancement of this field.

In this review paper, we went over the multistep process of hepatocarcinogenesis, along with the histopathologic features and the imaging findings associated with each stage, and hope that these review articles will enhance the knowledge of radiologists about current imaging modalities and various contrast agents for the detection and characterization of cirrhotic nodules, enable us to understand these nodules more comprehensively and help us distinguish benign lesions from premalignant and malignant ones.

Because of the similar morphologic criteria, differentiating RNs from LGDNs, HGDNs from early HCCs on the basis of dynamic imaging is still difficult, even for biopsy results, are associated with a high rate of false-negative results. Imaging diagnosis of hypovascular HCCs (absence of typical findings) is also a challenge. We believe that the application of new techniques, including molecular makers of hepatocellular malignancy, newly developed tissue-specific contrast media may overcome these limitations and increase the diagnostic power among these hepatic nodules in the future.

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