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REVIEW **Open Access**

State-of-the-art review on the correlations between pathological and magnetic resonance features of cirrhotic nodules

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Summary. Hepatocellular carcinoma (HCC) has become the second greatest cause of cancer-related mortality worldwide and the newest advancements in liver imaging have improved the diagnosis of both overt malignancies and premalignant lesions, such as cirrhotic or dysplastic nodules, which is crucial to improve overall patient survival rate and to choose the best treatment options. The role of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) has grown in the last 20 years. In particular, the introduction of hepatospecific contrast agents has strongly increased the definition of precursor nodules and detection of high-grade dysplastic nodules and early HCCs. Nevertheless, the diagnosis of liver tumours in cirrhotic patients sometimes remains challenging for radiologists, thus, in doubtful cases, biopsy and histological analysis become critical in clinical practice.

This current review briefly summarizes the history of imaging and histology for HCC, covering the newest techniques and their limits. Then, the article discusses the links between radiological and pathological characteristics of liver lesions in cirrhotic patients, by describing the multistep process of hepato carcinogenesis. Explaining the evolution of pathologic change from cirrhotic nodules to malignancy, the list of analyzed lesions provides regenerative nodules, low-grade and high-grade dysplastic nodules, small HCC and progressed HCC, including common subtypes (steatohepatitic HCC, scirrhous HCC, macrotrabecular massive HCC) and more rare forms (clear cell HCC, chromophobe HCC, neutrophil-rich HCC, lymphocyte-rich HCC, fibrolamellar HCC). The last chapter covers the importance of the new integrated morphological-molecular classification and its association with radiological features.

Key words: Liver, Liver imaging, Magnetic resonance imaging, Hepatocellular carcinoma, Cirrhosis, Immunochemistry

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common tumours in the world (Mattiuzzi and Lippi, 2019). It is the first primary malignant liver tumour and the second most common cause of cancer-related death

HCC, Hepatocellular carcinoma; FNAB, fine needle aspiration biopsy; EASL, European Association for The Study of the Liver; US, ultrasound sonography; CT, Computed Tomography; MRI, Magnetic Resonance imaging; AASLD, American Association for the study of Liver Disease; HCM, hepatocellular-contrast media; HBP, hepatobiliary phase; OATP8, organic anion transporter polypeptide 8; MRP2, multi-drug resistance protein 2; NAFLD, non-alcoholic fatty liver disease; AMRI, Abbreviated Magnetic Resonance imaging, DWI, Diffusion-weighted images; DN, dysplastic nodules; IWP, International Working Party; RN, regenerative nodule; LRN, Large Regenerative nodule; LGDN, low-grade dysplastic nodules; HGDN, high-grade dysplastic nodules; SN, Siderotic nodules; eHCC, early Hepatocellular carcinoma; spHCC, small progressed Hepatocellular carcinoma; HSP70, heat shock protein 70; GCP3, glypican-3; GS, glutamin synthetase; TERT, telomerase reverse transcriptase; CAP2, cyclase-associated protein 2; NASH, non-alcoholic steatohepatitis; TGF beta, transforming growth factor beta; ICC, intrahepatic cholangiocarcinoma; MTM-HCC, macrotrabecular massive Hepatocellular carcinoma; VEGF, vascular endothelial growth factor; TIV, tumour-in-vein; CCHCC, Clear cell Hepatocellular carcinoma; LEL-C, lymphoepithelioma-like carcinoma; PKA, protein kinase alpha; FNH, focal nodular hyperplasia.

worldwide (Mittal and El-Serag, 2013; Yang et al., 2019).

The majority of HCCs occur in the setting of liver cirrhosis, which represents the final evolution stage of all chronic progressive liver diseases, whether caused by viral hepatitis, alcohol, and/or metabolic disorders. Cirrhotic patients have an annual risk to develop HCC of between 1% to 8% and approximately one-third of them will develop HCC during their life (European Association for the Study of the Liver, 2018; Yang et al., 2019). Therefore, the surveillance of cirrhotic patients through diagnostic examinations is pivotal to detecting HCC at the earliest stage possible, in order to improve clinical outcomes and guarantee a prompt and proper treatment (Cucchetti et al., 2014; European Association for the Study of the Liver, 2018; Granito et al., 2021b; Renzulli et al., 2022b).

The aim of this review is to verify the state of the art in the diagnosis of HCC and its precursors in cirrhotic patients, considering links and differences between radiological and histological features and analyzing how pathobiological changes throughout hepato-carcinogenesis affect the resulting cross-sectional Magnetic Resonance Imaging (MRI) before and after the injection of HCM.

History of imaging diagnosis and its limits

Up until 2000, the diagnosis of HCC was essentially based on the histological examination of tissue samples obtained through invasive fine needle aspiration biopsy (FNAB). In 2001, however, the European Association for The Study of the Liver (EASL) conference considerably changed the management algorithm for this neoplasm, by introducing the evaluation of the unique imaging feature of "arterial hypervascularization" as an important cornerstone in the non-invasive diagnosis of HCC (Bruix et al., 2001). In particular, according to the EASL (Bruix et al., 2001), all cirrhotic patients with liver nodules smaller than 1 cm should undergo active surveillance with ultrasound sonography (US) whereas those with liver nodules larger than 2 cm should be investigated through Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) or Angiography. Moreover, FNAB was limited to small nodules between 1 cm and 2 cm in size and the challenging or doubtful cases at imaging, always after considering both the risks and the benefits of the procedure (Bruix et al., 2001).

Shortly after, in 2005, the American Association for the study of Liver Disease (AASLD) further strengthened the central role of imaging in the surveillance of cirrhotic patients at risk of developing HCC, adding the "washout" appearance in the venous or delayed phases in contrast-enhanced CT or MRI studies as another strong non-invasive criterion for HCC diagnosis (Bruix and Sherman, 2005). In addition, the AASLD guidelines further reduced the use of FNAB and recommended histological confirmation only for nodules larger than 1 cm with atypical vascular patterns in one or both imaging techniques (Bruix and Sherman, 2005).

Non-invasive diagnosis of HCC has been subsequently validated in prospective and retrospective studies, and radiology currently plays a central role in the diagnostic algorithm and surveillance of cirrhotic patients (Forner et al., 2008; Sangiovanni et al., 2010; Khalili et al., 2011). In fact, radiological features of HCC are often enough to make a correct diagnosis and biopsies are performed only when cross-sectional imaging shows atypical features (Agni, 2017).

During the last 10 years, the introduction of new hepatocellular-contrast media (HCM), such as gadoxetic acid (Gd-EOB-DTPA, Primovist, Bayer-Schering Pharma, Berlin, Germany) or gadobenate dimeglumine (Gd-BOPTA, Multihance, Bracco Imaging, Milan, Italy), in MRI has led to the acquisition of new diagnostic functional parameters compared to those obtained with the sole dynamic vascular phases, which allow evaluating the presence and activity of hepatocytes during the hepatobiliary phase (HBP) (Russo et al., 2005; Park et al., 2012). These new liver-specific hepatocellular agents enter the hepatocyte by the organic anion transporter polypeptide 8 (OATP8) and then are excreted in the bile canaliculi by multi-drug resistance protein 2 (MRP2). This peculiar feature can be extremely useful in HCC detection since OATP expression and the consequent caption of Gd-EOB-DTPA and Gd-BOPTA progressively decrease during hepatocarcinogenesis, and malignant nodules appear hypointense compared to the background liver during the hepatobiliary (HB) phase (Narita et al., 2009; Vasuri et al., 2011, 2018). The inverse relationship between OATP levels and malignancy explains the greater sensibility of MRI for the detection of HCC compared to CT, especially for small lesions (62% vs 48%, when lesions are smaller than 20 mm) when it guarantees high specificity (85% - 100%) (Chou et al., 2015; Lee et al., 2015), but also the greater sensitivity of MRI hepato-specific contrast agents compared to simple MRI extracellular-only contrast agents (Kumada et al., 2011; Golfieri et al., 2012; Kobayashi et al., 2012; Lee et al., 2015; Kim et al., 2017a,b).

In fact, extracellular contrast agents can define only the assessment of the lesion vascularity, which is typical of progressed HCC, whereas almost all pre-malignant lesions, but also 40% of HCCs, may show iso- or hypo-enhancement during vascular phases (Golfieri et al., 2011; Choi et al., 2014a,b). Hence, the hypointensity on HBP represents the best sensitive method for detection of very early, early and progressed HCC (Kumada et al., 2011; Golfieri et al., 2012; Kobayashi et al., 2012; Kim et al., 2017a,b).

Despite its high sensibility and specificity in diagnosis, MRI with HCM is currently not recommended as a first-line imaging technique for screening in patients with cirrhosis, due to its high cost, low availability and long acquisition times, which limit its widespread use in clinical practice. In fact, EASL and AASLD clinical practice guidelines currently

recommend performing surveillance in cirrhotic patients without any nodules through a US every 6 months (Heimbach et al., 2018; European Association for the Study of the Liver, 2018) which is more easily accessible and much cheaper than MRI. However, US shows critical limits in its sensibility (Simmons et al., 2017) and comorbidity such as obesity and non-alcoholic fatty liver disease (NAFLD) may reduce its performance, especially for small lesions, possibly delaying the diagnosis of early HCC and the relative treatment (Simmons et al., 2017; Harris et al., 2019) In fact, Kim et al. (2017b), have found that performances of a US strategy have a sensitivity of only 63% for early HCC, and as low as 20% for very early HCC.

To overcome the limits of US, recent studies have introduced the concept of Abbreviated MRI (AMRI), i.e. the use of a shorter number of MRI sequences to simplify the interpretation of images and thus abbreviate acquisition time (An et al., 2020). The AMRI protocols include localizer, Diffusion-weighted images (DWI), T2-weight and HBP T1-weight contrast-enhanced sequences which can be performed in 15 minutes instead of 40 minutes for complete MRI and 30 minutes for US (An et al., 2020). The results of AMRI are promising and a recent systematic review and meta-analysis have demonstrated that US sensitivity is significantly lower than AMRI and, moreover, there is even no significant difference in both sensitivity and specificity between Contrast-Enhanced and Non-Contrast-Enhanced AMRI (87% vs 86% and 94% vs 94%, respectively) (Gupta et al., 2021). Therefore, although the performance of AMRI in lesions <2 cm is still low, more and more new studies seem to suggest that AMRI could replace US and become the first-line screening technique in the near future (An et al., 2020; Gupta et al., 2021).

Besides hepato-specific agents, MRI has also allowed the possibility to obtain functional data by Diffusion-weighted images (DWI), which helped increase confidence for HCC diagnosis and decrease false positives. In fact, the reduction of diffusivity in hypovascular nodules on DWI performed with a moderate to high range of b values (400-800 s/mm^2), which appear as hyperintensity, may be considered a strong criterion for malignancy (Hwang et al., 2015). It has been proposed that this MRI tool can replace US with Sonazoid contrast agent (which is not in widespread use in Occident) as a second-line diagnostic tool in hypovascular and hypointense nodules in HBP in a new non-invasive diagnostic algorithm based on MRI (Renzulli et al., 2016).

Although clinical practice for other solid tumours, such as colon cancer, has established that detecting precursor lesions increases the survival of high-risk patients, for HCC there are no different surveillance protocols based on the number or different evolution of dysplastic nodules (DN) in cirrhotic patients (Montminy et al., 2020). In fact, the presence of 1 or 10 precursor lesions does not change the diagnostic surveillance approach and this does not allow to increase the early diagnosis of HCC or the survival rate of cirrhotic patients (Cucchetti et al., 2014; European Association for the Study of the Liver, 2018; Harris et al., 2019; Yang et al., 2019; An et al., 2020). Meanwhile, it is crucial to understand hepatocarcinogenesis since knowledge of the related imaging findings may aid in the early detection of HCC (Gheonea et al., 2015; Narsinh et al., 2018).

Hepatocarcinogenesis

In the background of chronic liver disease, HCC follows a dysplasia-carcinoma sequence that starts from regenerative lesions (Hanna et al., 2008; Kudo, 2009). The International Working Party (IWP) of the World Congress of Gastroenterology proposed a globally standardized nomenclature of liver nodules in 1995 (International Working Party, 2015) based on their morphological features. The IWP classified cirrhotic liver nodules as regenerative lesions and dysplastic or neoplastic lesions. The first group consists of hyperplasia and regenerative nodules (RN), which includes also Large Regenerative nodules (LRN). The second group includes dysplastic nodules, divided into low-grade dysplastic nodules (LGDN), and high-grade dysplastic nodules (HGDN), as well as frankly neoplastic lesions (International Working Party, 2015). In 2009 this classification was updated and HCC was subclassified into early HCC and progressed HCC (International Consensus Group for Hepatocellular Neoplasia, 2009; International Working Party, 2015). With the most recent WHO 2019 classification, further categorization in early, small-progressed and progressed HCC was made in order to remark the different biological behavior of these entities (Nagtegaal et al., 2020).

During the progression from a benign nodule to overt HCC some main events occur in regenerative nodules, such as neoangiogenesis and loss of portal veins, fat or iron metamorphosis, a progressive decrease of hepatocyte activity and development of tumour capsule and fibrous septa (Choi et al., 2014b; Park et al., 2017).

Neoangiogenic processes include the development of new abnormal arteries and sinusoidal capillarization (Narsinh et al., 2018). Mutated cells induce the production of vascular growth factors which cause the formation of new unpaired arteries (defined as arteries not accompanied by bile ducts and/or portal veins) and the transformation of sinusoids in "systemic" capillaries due to the loss of fenestrae and the deposition of a basal membrane (Choi et al., 2014b). Simultaneously, the portal tracts (including the portal veins and the normal hepatic arteries) gradually decrease in number leading to a specular decrease in the portal and arterial flow (Kudo, 2009; Choi et al., 2014b). In RN and LGDN, portal vascularization is intact and imaging appearance, after contrast enhancement, is indistinguishable from the background liver (Hanna et al., 2008). With the

transition from low-grade to high-grade dysplasia, vascular pattern progresses from portal to arterial perfusion (Hanna et al., 2008; Kudo, 2009).

While HGDN and some early HCC show hypovascularity in contrast-enhanced images due to triad deficiency and parallel vessel immaturity (Narsinh et al., 2008; Choi et al., 2014b), in progressed HCC, an increase in new arteries results in marked hypervascularity in the arterial phase and overt washout appearance in MRI portal venous phases (Fung et al., 2021).

As discussed before, hepatocellular activity can be mostly expressed by the presence of OATPs, which progressively diminishes on the road to malignancy (Kitao et al., 2011). The absence of OATPs accounts for HBP hypointensity which can be seen eventually before arterial hypervascular changes (Narsinh et al., 2018).

Moreover, hemodynamic changes may influence intranodular lipid and iron content (Kudo, 2009; Balci et al., 2009). The shift from portal to arterial predominance and sinusoidal capillarization determine hypoxia which supports intracellular fat deposition (Kudo, 2009; Narsinh et al., 2018). Thus, since lipid content is inversely proportional to the extent of lesions and cell differentiation, it is maximum in the early stages of HCC. As HCC enlarges and progresses, fat content regresses (Balci et al., 2009; Fung et al., 2021). Iron accumulation is usually observed in LGDN or in some HGDN which are called siderotic nodules. Increasing iron intracellular content is assumed to be a result of the clonal proliferation of iron-avid hepatocytes, whereas its absence in progressed HCC has been ascribed to increased iron use by tumours or increased cellular proliferation, resulting in iron dilution among offspring cells (Choi et al., 2014b). Therefore, intralesional fat and iron depositions are typical features of precursor lesions and early and well-differentiated HCC (Narsinh et al., 2018).

Regenerative nodules

Regenerative nodules (RN) are the most frequently detected hepatic lesions in patients with cirrhosis (Hanna et al., 2008). In response to liver necrosis and toxic damage, RN form as a consequence of a localized proliferation of hepatocytes and their supportive stroma (Coleman, 2003). The 1995 IWP distinguished RN in monoacinar or multiacinar cirrhotic nodules by the number of portal tracts. However, radiologically RN are classified only by size as micronodules (less than 3 mm) or macronodules (more than 3 mm) (International Working Party, 1995). They are often less than 2 cm, typically between 0.5 and 1.5 cm.

The so-called large regenerative nodules (LRN) are a common subtype of RN and are located in a liver that is otherwise abnormal, either with cirrhosis or with severe disease of portal veins, hepatic veins, or sinusoids, such as Budd-Chiari syndrome. In these conditions, the liver gradually increases hepatocyte number and corollary arterial perfusion in response to a chronic vascular obstruction (Stromeyer and Ishak, 1981; Mamone et al., 2019).

They usually have a larger size compared to other RN (0.5-1 cm) (Sempoux et al., 2018) and tend to be more likely dysplastic or cancerous (Hanna et al., 2008; Roncalli et al., 2011).

Histological-Radiological correlations

CT scans of the cirrhotic liver are often negative for RN because of isodensity in both unenhanced and contrast-enhanced sequences, so MRI is crucial for a correct diagnosis (Park et al., 2017). On MRI, RN signal intensity in T1-weight sequences may vary from classical isointensity to more rare hyperintensity, especially when the lesions include a great quantity of proteins or copper (Vilgrain et al., 1999; Gheonea et al., 2015; Mamone et al., 2019). Radiologists may have difficulties in differentiating them from dysplastic lesions due to their strong T1 signal, which is typical of DN (Park and Kim, 2011; Choi et al., 2014b; Renzulli et al., 2022a). Besides, in out-of-phase images, fatty nodules may be seen as hypointense (Balci et al., 2009; Farooqui et al., 2013). On the contrary, even if RN usually display isointensity on unenhanced T2- and T2*-weighted imaging, occasionally they can show poor signal, which clearly allows to differentiate them from HCC without contrast-enhanced images (Hanna et al., 2008; Merkle et al., 2016). In rare cases RN show hyperintensity on T2-weighted sequences, similar to LRN and infarcted lesions in cirrhosis, particularly before the ischemia event (Vilgrain et al., 1999; Park and Kim, 2011; Mamone et al., 2019).

Siderotic nodules (SN) exhibit a different pattern on MRI compared to classical RN. Both regenerative and dysplastic nodules include SN as subtype lesions (Zhang and Krinsky, 2004). Due to their high iron concentration, SN display low signal on T1- and T2* weighted unenhanced imaging (Gheonea et al., 2015). When SN include hyperintense foci that appear as a nodule-in-nodule, it indicates malignancy (Zhang and Krinsky, 2004; Park and Kim, 2011).

Another type of regenerative lesion is the steatotic nodules, which are generally multiple with hyperintensity with in-phase gradient pictures and hypointensity in out-of-phase sequences, because of their fat accumulation (Balci et al., 2009; Gheonea et al., 2015).

After contrast injection, most RN display either isointensity to the nearby liver or less enhancement appearing as a nodule with constant moderate hypointensity. Usually, neither hypervascularity in the arterial phase nor decreasing enhancement in delayed phases are associated with RN (Hanna et al., 2008).

Due to increased arterial perfusion, LRN may be able to emulate HCC appearance showing hyperintensity in the arterial phase. Nevertheless, the absence of wash-out and the persistence of enhancement until delayed

phases may help radiologists in a correct differential diagnosis (Renzulli et al., 2011).

In benign nodules, hepatocyte function is preserved or, in some cases (e.g. LRN), is increased, so RN appear isointense (or moderately hyperintense) in HBP (Hanna et al., 2008; Sempoux et al., 2018).

Dysplastic nodules: Low-grade dysplastic and high-grade dysplastic nodules

The definitive distinction between LGDN and HGDN is based on histology. LGDN show mild cellular atypia, normal nuclear-to-cytoplasmic ratio, absence of mitotic figures, the persistence of portal tracts and portal plates of 1 or 2 hepatocytes in thickness. Cholestasis is a common finding (Kondo et al., 1987). HGDN are characterized by a moderate-to-severe cellular atypia, increased nuclear-to-cytoplasmic ratio, nuclear hyperchromasia and eventual cytoplasmic basophilia; the portal plates can be >2 hepatocytes in thickness.

The main features differentiating between HGDN and early HCC are the persistence of portal tracts and the absence of stromal invasion in the former (Kondo et al., 1987). The radiological distinction between LGDN and HGDN is fundamental since the former is ascribable to the "common" cirrhotic RN while HGDN must be regarded as premalignant and, therefore, has to be stringently monitored or may be even considered for treatment, exactly like a HCC (Gatto et al., 2013; Choi et al., 2014b).

Histological-Radiological correlations

Since the radiological and the histological definitions of DN are not completely overlapping, the finding of discordant cases between radiologists and pathologists should not be a surprise, as found in our previous experience, in which we found a small subgroup of histologically-proven eHCC diagnosed as HGDN by the radiologists (Vasuri et al., 2019).

The signal intensity of both types of DN varies on T1-weighted MR images, and they are frequently iso- or hypointense on T2-weighted MR images. After Gadolinium injection, LGDN displays enhancement comparable to that of surrounding parenchyma, while HGDN may have an arterial enhancement similar to HCC, even if they are generally hypovascular (Hanna et al., 2008; Gheonea et al., 2015).

Such radiological features appear differently in particular nodules. Hyperintensity on T1-weighted images often identifies a larger quantity of intracellular fat within HGDN, evidence that can be confirmed by hypointensity on out-of-phase images (Balci et al., 2009; Choi et al., 2014b). On the contrary, siderotic lesions develop hypointensity on T1-weighted images and the presence of diffuse iron concentration is supported by the high hypointensity on T2-weighted and T2*-weighted sequences (Zhang and Krinsky, 2004; Choi et al., 2014b). Considering that HCC may develop in a SN on rare occasions, these radiological features may help the radiologist in the differential diagnosis of HCC (Choi et al., 2014b).

As discussed above, vascular changes during hepatocarcinogenesis leads to arterialization and a lack of portal blood flow. Even if these imaging features make overt HCC distinguishable from all other lesions, portal and arterial supplies of DN (and RN) are variable and inconsistent to allow a correct differential diagnosis (Park and Kim, 2011; Choi et al., 2014b). So, considering overlapping of signal intensity in post-contrast phases, MRI and CT with extracellular contrast agents display insufficient radiological criteria to discriminate between lower-risk and premalignant nodules (Hanna et al., 2008; Park and Kim, 2011; Gatto et al., 2013).

Small hepatocellular carcinomas

Small HCCs are definitely HCC ≤ 2 cm in diameter: the most recent WHO guidelines divided small HCC into early HCC (eHCC) and small progressed HCC (spHCC) (Nagtegaal et al., 2020). These entities were previously named eHCC of the "vaguely nodular type" and eHCC of the "distinctly nodular type", respectively (Fung et al., 2021).

Histological-Radiological correlations

eHCC is an incipient form of malignant transformation: on a gross examination it is devoid of a capsule, so its margins are indistinct. It is well-differentiated, and the global architecture is very similar to the normal hepatic lobules, with the reticulin framework generally reduced or lost. Most eHCCs are 1–1.5 cm in diameter and seldom surpass 2 cm (Choi et al. 2014b). The vascular supply is slightly different from that of a dysplastic nodule, with few portal tracts and rare unpaired arteries. The distinction between eHCC and a HGDN can be challenging, the more useful feature being the stromal invasion. By definition, vascular invasion is not present in eHCCs (Kojiro and Roskams, 2005; Nagtegaal et al., 2020), since they have incomplete neoangiogenesis (Nagtegaal et al., 2020). This histological feature may explain why on contrast-enhanced MRI (and CT) sequences, the small and well-differentiated form of HCC, such as eHCC, typically display isointensity (Choi et al., 2014b) (Fig. 1).

spHCC, on the other hand, is an overt cancer of small size. Macroscopically it appears capsulated or with distinct margins. Histologically, it is a progressed HCC with an expansive/infiltrative growth pattern, a possible solid or macrotrabecular histologic architecture, and eventually a nodule-in-nodule growth. spHCC is usually moderately-to-poorly differentiated, without portal tracts, with a consistent number of unpaired arteries and sinusoidal capillarization. The stromal invasion is obvious, and it can also show vascular invasion, which implies that spHCC can already metastasize (Paradis,

2013; Nagtegaal et al., 2020).

Immunohistochemistry can be helpful in the differential diagnosis between small HCC and HGDN: the last WHO classification recommends the triad composed by heat shock protein 70 (HSP70), glypican-3 (GCP3) and glutamine synthetase (GS): positivity for at least two of these markers indicates HCC with high sensitivity and specificity. Ancillary stains are CD34, which stains the endothelial cells of unpaired arteries as well as pathological sinusoids, and CK7/CK19, which enhance the lack of biliary ductules around nodules of carcinoma.

Up to 60% of the small HCC harbor telomerase reverse transcriptase (TERT) promoter mutations, an event that occurs early in the pathogenesis, and there is also evidence of activation of MYC, an alteration shared with dysplastic nodules (Rebouissou and Nault, 2020). TERT promoter mutations are the most frequent mechanism of TERT overexpression in neoplastic hepatocytes, an event that leads to telomerase maintenance and which has a key role in the early promotion of carcinogenesis in a background of a cirrhotic liver. Telomere length preservation by telomerase reactivation enables neoplastic hepatocytes to avoid senescence and apoptosis and to undertake virtually endless proliferation, mimicking the stem cell activity of self-renewal (Nault et al., 2019). Studies of gene expression profiles revealed upregulation of HSP70 and cyclase-associated protein 2 (CAP2) in small HCC (Ueno et al., 2020).

At imaging, American guidelines (Heimbach et al., 2018) stated that the diagnosis of HCC can be made only for nodules greater than 1 cm and with characteristic vascular patterns on CT or MRI; on the contrary, nodules smaller than 1 cm should undergo a follow up every three months by using the same diagnostic method. On unenhanced sequences, generally, HCC signal intensity varies greatly depending on dimensions, grade and biological features. Small (early and small progressed) HCCs have variable behavior on both T1 and T2-weighted sequences. However, on T2-weighted sequences, malignant lesions, such as spHCC, are frequently significantly enhanced (Hanna et al., 2008). After the contrast agent's injection, most cases of eHCCs have iso or hypointensity, while arterial hyper-enhancement and "wash out" on vascular sequences are typical of spHCC (Hanna et al., 2008; Kudo, 2009).

The detection of hypervascularization in the arterial phase is of paramount importance not only for the diagnostic phase but also in the treatment evaluation and in the decision of making re-treatment such as chemoembolization (Golfieri et al., 2014; Terzi et al., 2014b; Tovoli et al., 2018; Granito et al., 2021a). In fact, although chemoembolization could be standardized and performed by an expert interventional radiologist, it represents a treatment that exposes both patients and operators to x-rays with the consequent stochastic and non-stochastic effects and, therefore, it could be utilized only when arterialization is confirmed (Compagnone et al., 2012; Terzi et al., 2014a; Renzulli et al., 2021a).

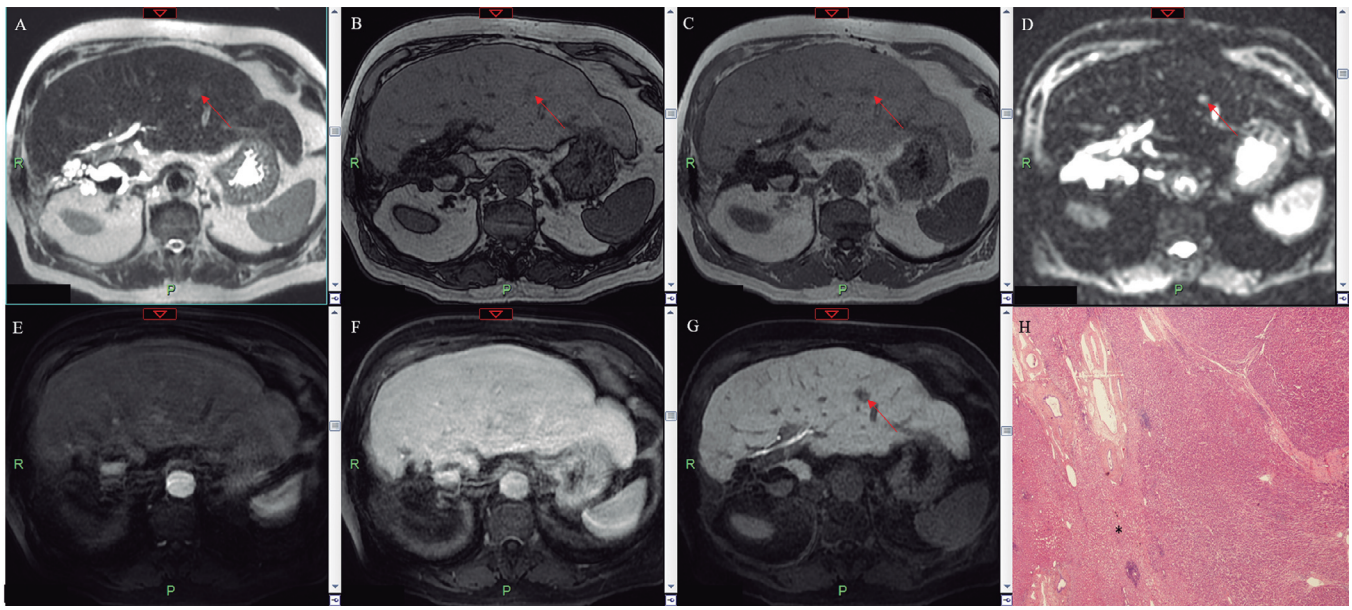

Fig. 1. Early hepatocellular carcinoma (HCC) on MR images and histological specimens. MRI images demonstrating a nodule in the liver segment III, which appears hyperintense on T2-weighted image (arrow in **A**), slightly hypointense on T1-weighted images, both in out-of-phase (arrow in **B**) and in-phase (arrow in **C**). DWI (arrow in **D**) demonstrates evident diffusion restriction of the lesion. The lesion is not visible in arterial and portal phase (**E and F**, respectively) but during the HBP, it appears markedly hypointense compared to the surrounding parenchyma (arrow in **G**). **H.** A low-magnification (4x) picture of the lesion, with low grade, microtrabecular architecture, and indistinct margins (black asterisk on not neoplastic liver).

Even if the signal intensity characteristics of DN and small HCCs are quite similar, differential diagnosis can be reached considering that LGDN and HGDN are rarely hyperintense on T2-weighted imaging and lack a real capsule (Choi et al., 2014b). On the other hand, eHCC shows a capsule as a thin circumferential ring around the nodule, which thickens as the size of the nodule becomes larger. Nevertheless, DN and RN can show exceptional hyperintensity in ischemic nodules which suffer hepatic hypoperfusion episodes. So, infarcted lesions may be hard to distinguish from hypovascular HCC on MRI (Choi et al., 2014b).

However, using HCM proved to be the main diagnostical tool for differential diagnosis. HCM has shown high sensitivity and specificity (96.6% and 86.6%) for the distinction of RN and LGDN from higher risk lesions (Nault et al., 2019). In fact, the hypointensity in HBP supports the diagnosis of HGDN (or early HCC) over LGDN (or other cirrhotic nodules), since hepatocyte function starts to gradually and valuably decline from HGDN (Hanna et al., 2008; Lee et al., 2011; Gatto et al., 2013; Choi et al., 2014b; Merkle et al., 2016; Chen et al., 2016). Exceptions consist of some well-differentiated HCCs which enhance during HBP, due to residual functioning hepatocytes (Gheonea et al., 2015).

The usual imaging sequence of a liver MRI includes even DWI, as a functional imaging approach. Since limited diffusion in water molecules represents tissue hypercellularity, the presence of restricted diffusion promotes the diagnosis of malignancy and aids in the differentiation of HCCs from DN (Park et al., 2017).

Progressed hepatocellular carcinoma

HCC is defined as a primary malignancy of the liver composed of epithelial cells showing hepatocellular differentiation (Nagtegaal et al., 2020).

On gross examination, HCC shows a capsule of fibrotic tissue and it has got three main patterns of growth, each with prognostic implications: the nodular (or expanding) pattern, the infiltrative pattern, and the diffuse pattern (Paradis, 2013). The presence of one dominant, well-defined nodule together with other multiple lesions characterizes the nodular type, whereas the infiltrative pattern is represented by a single scarcely delimited mass that substitutes hepatic parenchyma; furthermore, the diffuse growth pattern manifests as numerous small nodules that nearly completely replace the organ (Paradis, 2013; Gheonea et al., 2015). Diffuse tumour pattern is microscopically composed of atypical hepatocytes –identified by morphology and/or immunohistochemistry– arranged in an aberrant architecture that shows loss of portal tracts, loss of reticulin framework, sinusoidal capillarization and unpaired arterioles.

There are four histological growth patterns (trabecular, macrotrabecular, solid and pseudoglandular), with a high percentage of resected tumours showing a mixture of them. Tumour grade identifies the degree of differentiation in comparison with the mature benign hepatocyte and it predicts patient prognosis. Although a

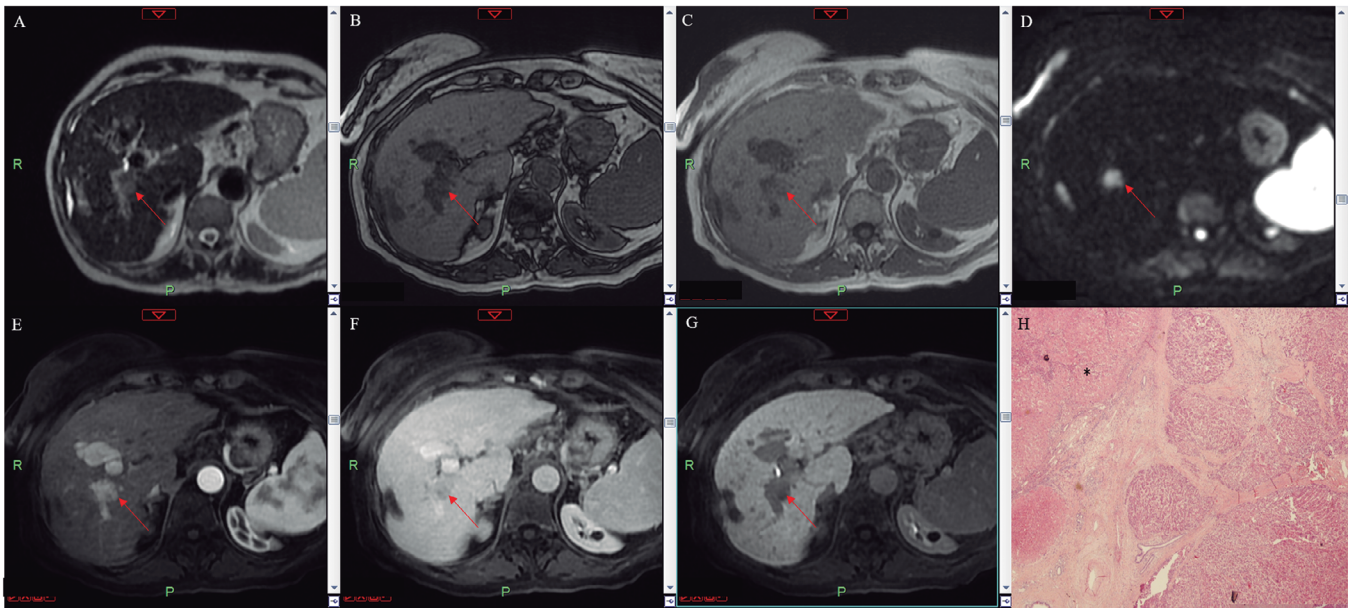

Fig. 2. MRI and histological views of a progressed hepatocellular carcinoma (HCC). T2-weighted image (arrow in **A**) shows an hyperintense nodule near the right portal branch, which appears as hypointense on T1-weighted "out of phase" and "in phase" images (arrows in **B and C**, respectively), with evident diffusion restriction on DWI (arrow in **D**). The lesion demonstrates arterial hyperenhancement on the arterial phase (arrow in **E**) and washout appearance on transitional phase (arrow in **F**). On the HBP (arrow in **G**) the lesion appears as markedly hypointense. **H.** A low-magnification (4x) picture of the lesion, trabecular architecture, and with a thick capsule infiltrated by neoplastic nests (black asterisk on non neoplastic liver).

unique grading system is lacking, two major systems are in use, the four-tiered modified Edmondson and Steiner system (Edmondson and Steiner, 1954) and the proposed WHO three-tiered system (Nagtegaal et al., 2020).

Typical radiological features of overt HCC include hypointensity on T1 weighted sequences, variable hyperintensity on T2 weighted images (caused by intralesional necrosis, fat or hemorrhage), and peculiar behavior after gadolinium injection: arterial hyperenhancement, "wash out" on delayed phases and hypointensity on HBP (Hanna et al., 2008; Choi et al., 2014a; Gheonea et al., 2015). A minority of cases may be isointense on vascular sequences, which leads to a false negative, or may show as hypovascular nodules, which need a biopsy for correct diagnosis. Besides, HCC usually presents restricted diffusion which appears as a high signal on DWI images and a low signal on ADC map (Gheonea et al., 2015) (Fig. 2).

The presence of a tumour capsule on imaging is highly indicative of advanced HCC. About 70% of progressed HCCs develop tumour capsules and fibrous septa. Meanwhile, cirrhotic nodules, dysplastic nodules, and early HCCs lack these features. Despite the capsule appearance in MRI sequences, it does not necessarily correlate to the presence of a real histologic capsule made of thick collagen deposition (Kim et al., 2018). Its development may be related to either passive thickening of the liver stroma in response to the lesion's growth pressure or to the surrounding parenchyma which limits the tumour expansion by activating mesenchymal cells (Choi et al., 2014b; Kim et al., 2018).

The tumour capsule normally presents hypointensity on unenhanced T1- and T2-weighted imaging, even if an outer lamina, hyperintense on T2-weighted sequences, is a common finding in capsules thicker than 4 mm (Hanna et al., 2008; Fung et al., 2021). Appearance on extracellular contrast-enhanced MRI consists of a typical peripherical and progressive rim enhancement around lesions owing to gadolinium deposition in the fibrotic tissue. Nevertheless, the absence of hepatocytes in fibrotic tissue and the contrast agent's rapid removal from the extracellular space result in hypointensity on HBP (Kim et al., 2018). Intratumoural fibrous septa are fibrous strands that connect HCC subnodules between each other or regions of necrosis to tumour tissue (Choi et al., 2014b).

Histological subtypes of progressed hepatocellular carcinomas: Histological-Radiological correlations

About one third of HCC can be subclassified into specific subtypes that represent discrete entities with prognostic implications. Some of them are peculiar at the point of being radiologically identifiable.

Steatohepatitic HCC

The steatohepatitic subtype of HCC is a tumour characterized by conspicuous fatty deposits and an overall appearance reminiscent of non-alcoholic steatohepatitis (NASH) (Low et al., 2019) such as inflammatory infiltrates and cell ballooning. This subtype is strongly associated with an underlying metabolic syndrome and livers affected by steatohepatitis (Salomao et al., 2012). The phlogistic microenvironment of steatohepatitic HCC, compared to classical HCC, enhances the JAK/STAT signaling pathway. The overall molecular profile is similar to normal liver, lacking Wnt/beta-catenin pathway activation (Calderaro et al., 2017, 2019) and leading to a form with a relatively good prognosis (Ueno et al., 2020).

On MRI, steatohepatitic HCCs typically are smaller than other forms and they display diffuse or focal intralesional fat content appearing as a loss of signal on the out-of-phase sequences. As discussed before, fat metamorphosis represents a typical feature of premalignant lesions, and it reaches a peak in the early HCC. Nevertheless, this process may continue to be a feature of the tumour in both the early and progressed stages (Balci et al., 2009). In a background of hepatic parenchyma steatosis, distinguishing this subtype of HCC from the surrounding liver may be challenging for radiologists. Moreover, larger steatohepatitic HCCs should not be misdiagnosed with other fat-containing tumours, such as angiomyolipoma and adenoma, that simulate it on opposed-phase sequences, or with fat-containing eHCC (Balci et al., 2009; Loy et al., 2022). Finally, the presence of fat in mass may not be enough to consistently predict a steatohepatitic HCC, since the fat-in-mass sign can be founded in other HCC subtypes. Thus, radiological preoperative diagnosis of steatohepatitic HCC form should be considered only in individuals that present a fat-containing malignant lesion synchronously to a non-alcoholic fatty liver disease or alcoholic liver disease (Cannella et al., 2021).

Scirrhous HCC

The scirrhous HCC subtype shows dense intratumoural fibrosis in >50% of the mass, and it often shows intratumoural septa with a central scar, without necrosis. Most scirrhous HCC has been found immunoreactive for CK7 and CK19 (Murtha-Lemekhova et al., 2021). Gene expression studies found activation of transforming growth factor beta (TGF beta) pathway, TSC1 and TSC2 mutations and epithelial-to-mesenchymal transition with overexpression of VIM, SNAIL, SMAD4 and TWIST (Calderaro et al., 2019). There is no consensus about the prognostic implications of this subtype.

On MRI, the exuberant fibrous stroma and the rich vascularization are reflected in specific radiological findings. On T2-weighted images, the scirrhous type does not show typical hyperintensity of progressed HCC and a low signal is usually found. In the arterial and portal venous phases, scirrhous HCC exhibits peripheral enhancement followed by gradual and persistent

concentric enhancement of the core section in the equilibrium phase (Loy et al., 2022; Yoon et al., 2022). Moreover, abundant central fibrosis and high cellularity determine so-called "targetoid" appearance on HBP images, with the tumour exhibiting peripheral hypointensity relative to central contrast filling, and on DWI images with an outer high signal relative to a hypointense central zone (Low et al., 2019; Yoon et al., 2022).

The main challenge for radiologists is the differential diagnosis with non-HCC malignant lesions containing fibrous stroma, in particular intrahepatic cholangiocarcinoma (ICC) (Renzulli et al., 2021b). In fact, scirrhous HCC and ICC share gradual hyperenhancement on delayed phased and targetoid appearance. However, in a recent study, Choi et al. (2018) hypothesized that an arterial hyperenhancement >20% of the tumour diameter can help differentiate scirrhous HCC from ICC.

Macrotrabecular massive HCC

Macrotrabecular massive HCC (MTM-HCC) amounts to about 5% of HCC subtypes, but it is well known for its poor prognosis since studies enlightened early tumour relapse and scarce overall survival. It is histologically organized in macrotrabeculae (≥10 hepatocytes in thickness) surrounded by vascular spaces: this is a unique microvascular pattern known as a "sinusoid-like microvascular pattern, having an inadequate microvascular density that determines hypoxic microenvironment and frequent necrosis, common histopathologic traits (Rhee et al., 2021; Loy et al., 2022). Neoangiogenesis is conspicuous in MTM-HCC because of the high expression of angiopoietin 2 and vascular endothelial growth factor (VEGF). Previous results from our group showed immunoreactivity for Nestin in the endothelial cells surrounding the macrotrabecolae: this peculiar neoangiogenesis of MTM-HCC leads to specific imaging features, with hypointensity in the portal, late and HB phases (Vasuri et al., 2019).

MTM-HCC frequently shows satellite nodules, high α-fetoprotein serum levels and vascular invasion. Analysis frequently demonstrated a progenitor phenotype, with a positive stain for CK19 on immunohistochemistry (Calderaro et al., 2017). The aggressiveness of this subtype is confirmed also by the high incidence of TP53 mutations, often together with FGF19 amplification (Calderaro et al., 2019).

Compared with other subtypes, macrotrabecular HCC is greater in size. Some of its histological traits such as hypoxia, necrosis and vascular invasion may translate into radiology (Loy et al., 2022). In fact, due to neoangiogenesis factors activation, tumour-in-vein (TIV, i.e. presence of hyper-enhanced soft tissue in vein) and infiltrative appearance are specific characteristics (Loy et al., 2022). Besides, severe ischemia, necrosis and highly frequent intra or extrahepatic metastasis, quite common radiological findings, may be linked to the unique microvascular pattern (Rhee et al., 2021).

The main radiological feature of this form is the low enhancement during the arterial phase, which is probably caused by the hypoxia/neoangiogenesis-related genes activation and the low microvascular density. Nevertheless, this feature alone has not enough specificity to be diagnostic for the macrotrabecular type. Thus, Rhee et al. (2021). suggested two criteria for a correct preoperative diagnosis avoiding biopsies: 1) ≥ 20% arterial phase hypovascular component; 2) ≥50% hypovascular component and 2 or more ancillary findings (intratumoural artery, arterial phase peritumoural enhancement, and non-smooth tumour margin) (Rhee et al., 2021). On DWI images, macrotrabecular HCC shows marked diffusion restriction (Loy et al., 2022).

Other HCC subtypes

Other subtypes of HCC have been recently recognized in the last WHO classification, but unfortunately, our knowledge regarding their radiological behavior is still scarce.

Clear cell HCC

Clear cell HCC (CCHCC) is an HCC with clear cell morphology in >80% of the tumour mass, due to glycogen accumulation. It is often well-differentiated, with low rates of vascular invasion. The hepatocytes can enlarge from glycogen storage up to ballooning and they often contain Mallory-Denk bodies. The prognosis is better than conventional HCC, so much that some authors claim CCHCC is an intermediate stage in the pathogenesis of HCC rather than a variant (Bannasch et al., 2017). Clear cell HCC enters in differential diagnosis with metastasis of clear cell carcinomas from other organs, the kidney and the ovary above all (Torbenson, 2017).

The imaging characteristics of CCHCC are similar to those of common HCC and, therefore, could be useful for differentiating these from other liver tumours including hepatic metastases. Compared to common HCC, however, CCHCC is more prone to form pseudo capsules (Liu et al., 2011; Park et al., 2019; Loy et al., 2022).

Chromophobe HCC

Chromophobe HCC is made of cells with light cytoplasm and mainly bland atypia, except for scattered cellular elements showing striking nuclear pleomorphism, and it shows microscopic pseudocysts. In comparison with conventional HCC, chromophobe HCC has a higher prevalence in females (Khang et al., 2021). It is associated with alternative lengthening of the telomere, a telomerase-independent mechanism allowing telomere length maintenance (Wood et al., 2013; Calderaro et al., 2019). Overall survival and Recurrence-free survival are similar between chromophobe HCC and

classical HCC (Kang et al., 2021).

The imaging characteristics of chromophobe HCC are poorly described in the literature. Wood et al. (2013) published a case series where only 6 of the 13 cases had a preoperative MRI or CT. On MRI this rare form typically appears lightly hypointense on T1-weighted and hyperintense on T2-weighted images, showing a pseudocapsule and being characterized by the classical hyperenhancement in the arterial phase and the washout appearance on the delayed phase; only one case displayed a progressive enhancement during the portal phase, with a large central necrotic area (Wood et al., 2013).

Neutrophil-rich HCC

Neutrophil-rich HCC is a rare subtype of HCC (<1%) that produces G-CSF and is characterized by numerous and diffuse neutrophils. Focal areas of sarcomatoid dedifferentiation can be present (Torbenson, 2017). Patients can receive a misdiagnosis of inflammatory/infectious disease, due to the elevated white blood cell count and high serum levels of C-reactive protein and IL-6. There are limited data on molecular biology. Compared to conventional HCC, neutrophil-rich HCC has a worse prognosis (Nagtegaal et al., 2020).

According to the scarce published cases on the imaging appearance of neutrophil-rich HCC, this subtype seems to be comparable to conventional HCC on both CT and MRI (Joshita et al., 2010; Kohno et al., 2013; Sakamoto et al., 2018). However, an atypical appearance of nodular cystic morphology within mural enhanced components has been reported by some authors (Aita and Seki, 2006; Nagata et al., 2016).

Lymphocyte-rich HCC

Lymphocyte-rich HCC is an equally rare subtype, characterized by a great number of lymphocytes. Some authors identified lymphocyte-rich HCC as a lymphoepithelioma-like carcinoma (LEL-C), a neoplastic entity of the upper aero-digestive tract defined by a prominent immune microenvironment (Chan et al., 2015; Calderaro et al., 2019). LEL-C are well known in various organs, but while there is an association with Epstein-Barr virus in a significant percentage of extra-hepatic LEL-C, this has not been found in LEL-C HCC. Besides, other authors consider lymphocyte-rich HCC and LEL-C of the liver as two separate entities (Torbenson, 2017). The immunophenotype of the lymphocyte population shows a predominance of cytotoxic CD8+ and increased expression of PD1 and PD-L1. There are no conclusive data on recurrent transcriptomic signs or gene mutations. This subtype has a better prognosis than classic HCC (Chan et al., 2015; Calderaro et al., 2019).

Rare published cases of lymphocyte-rich HCC documented common HCC imaging features on both MRI and CT (Shinoda et al., 2013; An et al., 2015; Yuan et al., 2015; Sweed et al., 2022).

Fibrolamellar HCC

Fibrolamellar HCC is a rather peculiar subtype of HCC, different from conventional HCC. It accounts for 1% of HCC and it occurs in young patients (median age of 25 years) without cirrhotic background. These characteristics, along with the lack of specific symptoms and the lack of elevation of serum alpha-fetoprotein, explain the usual great dimension of the mass (>10 cm) and the frequently advanced stage at the time of diagnosis (Lin and Yang, 2018). Macroscopically, it appears as an obvious and well-circumscribed mass, generally with a central scar and calcifications. On histology, it is composed of large eosinophilic, oncocytic cells with prominent nucleoli, arranged in trabeculae and cords surrounded by a variable amount of lamellar fibrosis. It is well to moderately differentiated and it usually shows aspecific but characteristic pale bodies and hyaline bodies.

Fibrolamellar HCC enters into differential diagnosis to conventional HCC and cholangiocarcinoma. A useful diagnostic tool is the immunohistochemistry stains for HepPar-1, CK7 and CD68, all positive in 85 to 90 % of fibrolamellar HCC (Graham, 2018).

This HCC subtype has a diagnostic molecular sign, the DNAJB1-PRKACA gene fusion, which leads to overexpression and activation of protein kinase alpha (PKA). PKA activation is recurrent in fibrolamellar HCC, while it is very rare in conventional HCC and cholangiocarcinoma (Hirsch et al., 2020).

On imaging, the fibrolamellar subtype appears as a well-defined solitary mass with low signal on unenhanced CT images and hypo- and hyperintensity on T1-weighted and T2-weighted images on MRI, respectively (Ichikawa et al., 1999; Chung et al., 2009). After contrast administration, heterogenous enhancement is typical both on MRI and CT. In addition, a central scar and intralesional calcifications can also be frequently found (Mulazzani and Alvisi, 2019; Loy et al., 2022).

Differential diagnosis between fibrolamellar HCC and focal nodular hyperplasia (FNH) is crucial for radiologists since both lesions display early arterialization and central scar. However, FNH stromal tissue component exhibits hyperintensity in T2-weighted images, whereas typical calcification and greater fibrous part of fibrolamellar HCC scar show low signal on the same sequences (Loy et al., 2022). Moreover, during the hepatobiliary phase, the central scar of fibrolamellar HCC has a low signal while the one of the FNH reaches maximum enhancement (Palm et al., 2018).

Molecular classification of progressed hepatocellular carcinomas: Histological-Radiological correlations

HCC subtypes recognized by the last WHO

classification are based on histology solely, but new classifications based on molecular findings and integrated morphological-molecular classifications have been recently proposed and they are likely to become clinically useful soon. An interesting proposal came from a French research group, which determined six molecular subclasses and found an association between molecular alterations and HCC phenotype (Calderaro et al., 2017). Activating mutations of the CTNNB1 gene, leading to Wnt/beta-catenin pathway activation and chromosomal stability, seems to characterize well-differentiated, low proliferative and generally cholestatic HCC, lacking inflammatory infiltrates. The cholestatic feature was associated by other authors with a high expression of organic anion transporter polypeptide (OATP) 1B3, which directly correlates with a different gadoxetic acid-enhanced MRI appearance. In fact, while conventional HCC is typically hypointense in the hepatobiliary phase, this molecular subtype appears hyperintense. Patients with hyperintense HCC show a lower recurrence rate and longer survival after surgical resection than patients with hypointense HCC (Kitao et al., 2020). On the other hand, there are poorly differentiated, highly proliferative HCCs, with angiogenesis activation and a higher tendency to vascular invasion, characterized by TP53 mutations. This molecular profile is strongly correlated with the macrotrabecular-massive subtype of HCC, the poor prognosis of which has been explained above. Moreover, TP53 mutations were found in the so-called progenitor HCC, a HCC defined by the immunohistochemical expression of CK19 in more than 5% of neoplastic cells (Calderaro et al., 2019). It remains unclear whether this progenitor phenotype arises from the malignant transformation of a hepatic progenitor cell, or is the result of the differentiation of neoplastic hepatocytes. There is also a challenging differential diagnosis between this HCC and a mixed primary liver carcinoma (Nagtegaal et al., 2020). Progenitor HCC has been significantly associated with radiologically hypovascular appearance (Chung et al., 2012).

Conclusions

CT and, especially, MRI are fundamental for the correct characterization of both pre-malignant and HCC nodules as they guarantee early detection, thus improving the clinical outcome of cirrhotic patients. Histology still plays an important role in doubtful and challenging cases with atypical imaging features. A close interplay and a constant interaction between pathologists and radiologists are increasingly necessary, as the molecular and histological characteristics of HCC subtypes and precursors often find a correspondence in their imaging features.

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