Hepatic tumors: pitfalls in diagnostic imaging

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Summary. On computed tomography (CT) and magnetic resonance imaging (MRI), hepatocellular tumors are characterized based on typical imaging findings. However, hepatocellular adenoma, focal nodular hyperplasia, and hepatocellular carcinoma can show uncommon appearances at CT and MRI, which may lead to diagnostic challenges. When assessing focal hepatic lesions, radiologists need to be aware of these atypical imaging findings to avoid misdiagnoses that can alter the management plan. The purpose of this review is to illustrate a variety of pitfalls and atypical features of hepatocellular tumors that can lead to misinterpretations providing specific clues to the correct diagnoses. (www.actabiomedica.it)

Keywords: CT, MRI, hepatocellular tumors, hepatocellular adenoma, focal nodular hyperplasia, hepatocellular carcinoma

Introduction

According to the classification of hepatocellular nodules by the International Working Party in 1995 and further elaboration by the International Consensus Group for Hepatocellular Neoplasia in 2009, hepatocellular nodules are divided into regenerative lesions including focal nodular hyperplasia (FNH), and dysplastic or neoplastic lesions, which comprise hepatocellular adenoma (HCA), dysplastic nodule (DN), and hepatocellular carcinoma (HCC) (1). Diagnostic imaging is a fundamental step for characterizing a wide range of pathologies (2-12), and in the abdominal field, we can take advantage of a multiparametric assessment through ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) (13–21). Typical imaging features of hepatocellular nodular lesions are well known (22). However, FNH, HCA, and HCC can show unusual findings or share an overlap in radiological characteristics leading to diagnostic challenges. Differentiation of benign from malignant lesions is essential for an appropriate management plan (23–25).

In this review, we profile both typical and atypical imaging features of hepatocellular tumors on CT and MRI for being aware of radiologic pitfalls and for achieving the correct diagnosis.

Focal Nodular Hyperplasia

FNH is the most common benign hepatocellular lesion (up to 8% of all liver neoplasms), occurs primarily in women of reproductive age (80% of cases), and is often discovered incidentally (26–28). FNH is thought to arise from a vascular anomaly leading to a hyperplastic response with disorganized growth of hepatocytes and bile ducts. As the FNH management is usually
conservative, a definitive diagnosis should be obtained by imaging in order to avoid biopsy. However, atypical imaging FNH presentations can occur so that diagnosis could be a challenge. Typical FNHs are solitary, non-capsulated with a central fibrous scar (53% of FNHs overall), and are usually smaller than 5cm (27). On non-enhanced CT, FNH is usually iso- or hypodense to the adjacent liver parenchyma. Thanks to its multiparametric properties, MRI is highly sensitive and specific for the characterization of focal liver lesions (29). On unenhanced MRI, FNH is typically iso- or moderate hypointense on T1-weighted images and iso- or moderate hyperintense on T2-weighted images (30). The central scar appears as a thin band hypointense on T1 and hyperintense on T2-weighted images (fig. 1) (31). On contrast-enhanced CT and MRI, FNHs typically undergo immediate, intense, homogeneous enhancement on arterial phase and enhancement similar to the liver on portal venous and delayed phases (fig. 1) (30). The central scar is characterized by a delayed enhancement due to fibrotic content (32, 33).

In literature, the prevalence of atypical FNHs varies from 10% to 50%, and a wide range of atypical imaging findings have been described (26). On T1-weighted images, FNHs can appear hyperintense due to intralesional steatosis, hemorrhage, copper accumulation, or peliosis (26). In 10-37% of cases, FNHs show a pseudocapsule that results from compression of the adjacent hepatic parenchyma leading to differential diagnosis with HCC (26).

The primary differential diagnosis of the typical FNH includes HCA, which demonstrates a similar enhancement pattern. Usually, the diagnosis of FNH or HCA is possible thanks to characteristic lesion features such as the central scar in FNHs or the heterogeneous appearance due to intralesional hemorrhage in HCA (34). However, in up to 50% of cases, FNHs do not exhibit the central scar, especially in lesions smaller than 3cm, and, also, they can occasionally show heterogeneous signal on MRI (35). Therefore, hepatobiliary (HB) contrast-enhanced MRI is mandatory to differentiate FNHs from HCAs. MRI performed with HB contrast agent (the most common are Gd-BOPTA, MultiHance, Bracco, Milan, Italy and Gd-EOB-DTPA, Primovist; Bayer Schering Pharma, Germany) is considered the gold standard in imaging FNH (32, 34). Furlan A. et al., in their study on FNHs occurred after chemotherapy treatment, demonstrated that typical MRI

![Figure 1. FNH with the central scar on Gd-EOB-DTPA-enhanced MRI. The typical FNH shows a central scar (arrows) that appears as a hypointense band on T1 (A) and hyperintense on T2-weighted images (B). On contrast-enhanced MRI, FNH undergoes immediate enhancement on arterial phase (C) and enhancement similar to the liver on portal venous and late, delayed phases (D-E). In the hepatocyte phase, FNH shows isointensity with the central scar hypointense (F).](image-url)
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appearance might avoid unnecessary biopsy or surgery (36). A particular finding of FNHs is iso- or hyperintensity in the hepatocyte phase with the central scar hypointense (fig. 1) (37, 38). On the contrary, in HCAs, the failure uptake of HB contrast agents on hepatocyte phase leads to hypointensity relative to a background enhanced normal liver parenchyma (34, 35).

The central fibrous scar is not specific for FNH, and other lesions, such as haemangiomas and fibrolamellar HCCs, may show it (32). Fibrolamellar HCC is a variant that usually occurs in young adults without chronic liver disease. The clues to the correct diagnosis of fibrolamellar HCCs are features such as hypointensity of the central scar on both T1- and T2-weighted images and hypointensity on the HB phase, different from FNHs (38).

In the cirrhotic liver, especially in patients with alcoholic cirrhosis or in liver showing hemodynamic changes, such as Budd Chiari syndrome, hyperplastic nodules called FNH-like nodules (FNH-LNs) has been reported. These hypervascular lesions may mimic tumors such as metastasis, HCA, or HCC. FNH-LNs can show marked arterial enhancement or a wash-out and capsule appearance on CT or MRI, as HCC dose (39, 40). However, as FNH, FNH-LNs uptake HB contrast agents on hepatocyte phase showing iso- or hyperintensity (39).

Hepatocellular Adenoma

HCA is an uncommon benign tumor (annual incidence of 3-4/100000) that usually affects young females with a history of prolonged oral contraceptive use (41). Recent studies suggest obesity and metabolic syndrome as emerging risk factors for HCA, too (41). HCA is characterized by cords of well-differentiated hepatocytes separated by sinusoids lacking portal triad and interlobular bile ducts (27, 28).

The most common complication of HCA is bleeding with the risk of hemorrhagic rupture, while malignant degeneration occurs in a small subset of HCAs (around 4-5% of HCAs) (27).

According to 2010 WHO classification, four subtypes of HCA are described based on their genetic and pathologic features: inflammatory HCA (I-HCA), hepatocyte nuclear factor (HNF)-1α-inactivated HCA, β-catenin-mutated HCA (β-HCA), and unclassified HCA (U-HCA) (28, 37). These subtypes show noticeable differences in imaging features. The latest 2017 Genotype/Phenotype Classification of HCAs categorized HCAs into eight major subtypes. The four additional subtypes were previously within the U-HCA category, and they have not yet been associated with specific diagnostic imaging features (41).

MRI plays a crucial role in the diagnosis and subtype characterization of HCAs, helping to differentiate HCAs from HCCs and FNHs (41, 42). Bise S. et al. analyzed MRI features of 116 HCAs reporting that MRI can identify up to 88% of the two main HCA subtypes (I-HCA and HNF1α-HCA). However, they demonstrated that MRI cannot classify HCAs when necrotic/hemorrhagic changes cover > 50% of the lesion, HNF1α-HCAs does not show steatosis and when HCA subtype is β-HCA or U-HCAs (43).

Typical imaging findings of HCA are heterogeneous signal intensity on T1- and T2-weighted images and heterogeneous iso or hypodensity on unenhanced CT due to the presence of hemorrhage, necrosis, or intralesional fat (fig. 2). On contrast-enhanced imaging, HCA typically demonstrates moderate to intense enhancement in the arterial phase and prolonged mild enhancement or washing out on the portal venous phase. On hepatocyte phase images of HB contrast-enhanced MRI, HCA typically appears hypointense compared to the adjacent liver parenchyma (35, 38).

I-HCA is the most common subtype representing 30%-50% of HCAs. The hallmark feature for I-HCA is the “atoll sign” on T2-weighted images described as a band of peripheral T2 hyperintense signal. I-HCA may show imaging features that overlap with FNH. They are hypervascular masses that demonstrate intense arterial enhancement with persistent enhancement on portal venous and delayed phases. Different from other adenoma subtypes, on HB phase I-HCAs can appear iso- to hyperintense compared to the background parenchyma probably due to retention of contrast material within dilated intratumoral sinusoids. The clue to differentiate I-HCA from FNH is the signal intensity on the HB phase not as homogeneous as FNH, and often the hyperenhancement is only peripheral (42). T2 signal hyperintensity associated with strong arterial phase enhancement and delayed persistent enhancement on
MRI enable diagnosis of I-HCA with a sensitivity of 85–88% and a specificity of 88–100% (41).

HNF1α-HCA is the second most common subtype, and histologically is characterized by intracellular fat deposition. Therefore, a signal dropout on opposed-compared with in-phase T1-weighted images had a reported sensitivity of 86% and a specificity of 100% for HNF1α-HCA (42).

β-HCA is less common (approximately 10% of all HCAs) and occurs more in men. This subtype has a higher risk of malignant transformation. The imaging features of β-HCA are not specific and mimic HCCs. On contrast-enhanced MRI, β-HCAs demonstrate homogenous or heterogeneous arterial phase hyperenhancement with possible wash-out on portal venous phase. Also, these tumors can show a capsule appearance as HCC. On diffusion-weighted imaging (DWI), the absence of restriction can be useful to distinguish benign lesions from HCC (fig. 2), although also HCA could sometimes show restricted diffusion (42). Besides, these tumors can show a vaguely demarcated central scar and appear iso- to hyperintense relative to the liver parenchyma on the HB phase, so that the differential diagnosis from FNH could be a challenge.

Finally, no specific imaging features have been described for unclassified HCA (41, 42).

In conclusion, in the absence of typical features of HCA on MRI, a tumor biopsy should be proposed to rule out malignancy (27).

**Figure 2.** β-HCA on Gd-BOPTA-enhanced MRI. β-HCA shows heterogeneous signal intensity on T1- (A) and T2-weighted (C) with a signal dropout on opposed-phase T1-weighted image (B) due to the presence of hemorrhage and intralesional fat. On contrast-enhanced imaging, β-HCA demonstrates moderate enhancement in the arterial phase (D) and prolonged mild enhancement on the portal venous phase (E). On hepatocyte phase (F), β-HCA appears hypointense compared to the adjacent liver parenchyma. The presence of a capsule appearance (arrows) leads to differential diagnosis from HCC. On DWI (G-H) the absence of diffusion restriction is useful to distinguish β-HCA from HCC.
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**Hepatocellular Carcinoma**

HCC is the most common primary hepatic malignant tumor and typically develops in a cirrhotic liver (42, 44). According to international guidelines, including those of the European Association for the Study of the Liver and the American Association for the Study of Liver Disease, HCC can be diagnosed noninvasively using contrast-enhanced CT or MRI based on its typical vascular pattern (37, 45). Imaging modalities also play a fundamental role in guiding interventional radiology procedures, as well as in surgical planning and follow-up (46-57). The hallmark imaging features of HCC are arterial phase hyperenhancement (wash-in) and hypoenhancement on portal or delayed phase images (wash-out) (42, 58, 59). However, approximately 40% of HCC nodules show atypical imaging features, so that diagnosis remains a challenge for radiologists (42).

The typical enhancement pattern of HCCs is due to a multistep process of arterialization of the nodule. During the multistep process of hepatocarcinogenesis, a sequential decrease in the portal blood supply and development of neoangiogenesis with an increase in the hepatic arterial blood supply occurs (58, 60). The imaging features of HCC vary significantly with the histological classification and with the size of the lesion. Typically HCCs are hypointense on T1-weighted images and hyperintense on T2-weighted images. However, early HCCs (defined as a well-differentiated tumor <2 cm in size) can show iso- or hyperintensity on T1-weighted images because of the accumulation of fat, glycoproteins, or copper (42, 60, 61). Large HCCs may have a mosaic pattern with areas of variable signal intensities on T1- and T2-weighted images and heterogeneous enhancement on contrast-enhanced images during the arterial phase (60). Poorly differentiated and undifferentiated HCCs may show a tumor capsule that appears hypointense on both T1- and T2-weighted images. The tumor capsule appears as a peripheral rim enhancement on the portal venous phase that has to be differentiated from arterial rim enhancement, which is common in intrahepatic cholangiocarcinoma (ICC) or metastases from adenocarcinoma (42, 60, 62).

Early HCCs are hypovascular nodule due to decreased portal venous blood supply and insufficient neovascularization. As a result, 10-20% of HCCs do not show typical arterial phase wash-in and are detected only in the portal venous or delayed phase as hypoenhancing nodules (fig. 3). The differential diagnosis of hypovascular HCC from DN is a challenge, but several studies have reported that features as hypointensity on T1-weighted imaging, hyperintensity on T2-weighted imaging, and diffusion restriction on DWI help in distinguishing early HCCs from DNs (42, 58, 63). Several studies have demonstrated that HB contrast agents represent useful tools for the detection and characterization of atypical HCC nodules, such as hypovascular HCC (64). HB contrast agents are transported into the hepatocytes through the molecular transporter organic anion-transporting polypeptide 8 (OATP8) that are downregulated in HCC nodules. Therefore, hypointensity on the HB phase is strongly suggestive of almost all HCCs and some high-grade DNs (58, 64). Recent studies reported that the decreased expression of OATP8 precedes the neoangiogenesis among these nodules demonstrating that hepatobiliary phase imaging improves the diagnosis of HCCs (58). Galia M. et al. analyzed 69 indeterminate hepatocellular nodules demonstrating that hepatobiliary phase hypointensity is weakly associated with

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**Figure 3.** Atypical HCC on Gd-BOPTA-enhanced MRI. Hypovascular HCC does not show typical arterial phase wash-in (A), but it is detected in the portal venous (B) and delayed phase (C) as a hypoenhancing nodule (circle). On the hepatobiliary phase, hypovascular HCC appears hypointense (D)
HCC development (65). In this setting, the Asian Pacific Association for the Study of the Liver and the Korean Liver Cancer Study Group and the National Cancer Center guidelines suggest hypointensity on hepatobiliary phase as an alternative sign to wash-out on the portal venous phase (42). Nevertheless, a minority of HCCs (approximately 5–12%) appears iso or hyperintense relative to background parenchyma in the hepatocyte phase for increased expression of OATP8 in well- or moderately-differentiated lesions (35, 37, 66). Iannicelli E. et al., in their study on 120 suspected hepatic nodules in patients with chronic liver disease, reported two lesions appearing hyperintense in the hepatobiliary phase images; these nodules were well-differentiated HCCs at histological examination (58). Radiologists need to be familiar with this diagnostic pitfall to differentiate atypical HCCs from FNHs (67). The clues to the correct diagnosis of HCCs may be ancillary features such as a hypointense rim on the HB phase and absence of a central scar (fig. 4) (42).

When MRI is performed with gadoxetate disodium (Eovist Bayer HealthCare; Primovist, Bayer Schering Pharma) as HB contrast agent, the radiologist must pay attention to the “pseudo-washout” phenomenon (68). When this HB contrast agent is used, hemangiomas appear hypointense compared to the surrounding parenchyma in the equilibrium phase due to rapid contrast uptake by the adjacent normal parenchyma. This is known as the “pseudo-washout” phenomenon and lead to differentiate especially high-flow hemangioma from hypervascular hepatic tumors, such as HCC (68, 69). The keys to differentiate hemangiomas from malignant lesions are very high signal on T2- and heavily T2-weighted images and no restriction on DWI. Finally, the diagnosis can be confirmed with CT or with MRI performed with an extracellular contrast agent (35, 63, 68).

Small HCCs often do not show portal or delayed phase wash-out at dynamic CT or MR images appearing isointense. This atypical enhancement pattern causes difficult differential diagnoses with non-neoplastic arterial-enhancing pseudolesions commonly found in cirrhotic liver, such as arterioportal shunts. DWI and MR hepatobiliary contrast agents may be helpful because arterioportal shunts usually show no diffusion restriction and are isointense on hepatobiliary phase, instead of HCC. The nodule-in-nodule is another atypical radiologic feature of HCC. It is defined as a tumor focus within a high-grade dysplastic nodule. On enhanced CT o MR images, the central HCC focus appears as

![Figure 4](image-url). Well-differentiated HCC on Gd-BOPTA-enhanced MRI. HCC (circle) shows a slight hypointensity on T1-weighted image (A), slight hyperintensity on T2-weighted image (B), and typical arterial wash-in (C) and wash-out on portal phase (D). HCC appears hyperintense relative to background parenchyma in the hepatocyte phase (E) with a hypointense peripheral rim.
a focus of arterial phase hyperenhancement inside a less enhancing nodule. On T1-weighted images, the background nodule often has a higher signal intensity, while on T2-weighted images the inner focus of HCC is hyperintense. The inner HCC focus shows diffusion restriction on DWI (42, 63).

Approximately 7-13% of HCCs do not appear as a nodule but as a mass with ill-defined and invasive borders, and they are called infiltrative HCCs. Portal vein tumor thrombosis is often a primary imaging feature of these atypical HCCs and can affect the hemodynamics of the tumor so that infiltrative HCCs may not exhibit the hallmark imaging features of wash in and wash-out. In this setting, the correct diagnosis is difficult, and the differential diagnosis should include ICC. Multidisciplinary discussion and laboratory data, such as elevated alpha-fetoprotein levels, may help diagnose infiltrative HCCs correctly (42).

Among the HCC variants, those with targetoid appearance include scirrhous HCCs and large HCCs (≥5 cm) with central necrosis/ischemia. The enhancement pattern of scirrhous HCCs is determined by central fibrosis within the tumor. On dynamic CT and MRI, scirrhous HCCs show peripheral rim enhancement on the arterial phase with a delayed enhancement of the central region. Also, scirrhous HCCs often showed the targetoid appearance on the HB phase, defined as peripheral hypointensity. Therefore, it is critical to differentiate scirrhous HCCs from ICCs characterized by the targetoid appearance on dynamic or HB imaging as well as on DWI. Ancillary features such as heterogeneous hyperintensity with central dark area on T2-weighted images or a capsule are more favorable for scirrhous HCCs in comparison with ICCs. On the contrary, the absence of the wash-out appearance, surface retraction, and presence of bile duct dilatation is helpful features in distinguishing ICCs from scirrhous HCCs. According to the Liver Imaging Reporting and Data System (LI-RADS), hepatic tumors with arterial rim enhancement should be categorized as probably or definitely malignant but not HCC specific, and liver biopsy is warranted for a confirmative diagnosis (42).

In conclusion, a definitive diagnosis of HCC cannot be made with dynamic CT or MRI without the hallmark features. Therefore the majority of international guidelines recommend liver biopsy in atypical HCC nodules larger than 1 cm (65).

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