British Journal of Medicine & Medical Research
11(1): 1-14, 2016, Article no.BJMMR.19597
ISSN: 2231-0614

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Hepatocellular Carcinoma in Cirrhotic Liver: New Perspectives in Diagnostic Imaging

Daniel Trabulo[1*], Pedro Santos[2], Afonso Gonçalves[2] and Isabel Távora[2]

[1]Department of Gastrenterology, Hospital de São Bernardo, Centro Hospitalar de Setúbal, Setúbal, Portugal.
[2]Department of Radiology, Hospital de Santa Maria, Centro Hospitalar de Lisboa Norte, Lisboa, Portugal.

Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2016/19597
Editor(s):
(1) Chan Shen, Department of Biostatistics, MD Anderson Cancer Center, University of Texas, USA.
Reviewers:
(1) Amal Ahmed Mohamed, National Hepatology and Tropical Medicine Research Institute, Egypt.
(2) Anonymous, Sunway Medical Center, Malaysia.
(3) Anonymous, Shanghai Jiao Tong University, China.
(4) Anonymous, University of Coimbra, Portugal.
Complete Peer review History: http://sciencedomain.org/review-history/11413

Review Article

Received 18th June 2015
Accepted 28th July 2015
Published 16th September 2015

ABSTRACT

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-relared death in the world. It incidence is expected to increase in the next decades. It is incrasingly being detected at an earlier stage, owing to the implementation of screening programs and regular follow-up imaging in high risk populations. Thus, it becomes essential to differentiate it from benign or pre-malignant nodules, as it has distinct therapeutic and prognostic implications. More recently, liver-specific contrast agents for magnetic resonance imaging (MRI) have become available, such as gadoxetic acid. They have improved lesion detection and characterization of liver injury, when compared to gadolinium-based contrast agents used in recent decades. The authors present a review of the imaging of hepatic nodules in the cirrhotic liver (regenerative, dysplastic and HCC), emphasizing the role of MRI and new contrast agents in the characterization of HCC and its differentiation from other focal lesions.

**Corresponding author: Email: danieltrabulo@yahoo.com;*

Keywords: Hepatocellular carcinoma; hepatic nodules; liver cirrhosis; magnetic resonance contrast agents.

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common malignant liver tumor, the fifth most common cancer in men (554,000 cases, 7.5% of the total) and the ninth in women (228,000 cases, 3.4%). HCC is the second most common cause of death from cancer worldwide [1]. It is estimated that the incidence will increase over the next two decades, mainly due to infection with hepatitis C and sunsequent cirrhosis [2]. Furthermore, the mortality due to HCC increased in 41% in the last twenty years [2]. Several studies have shown that patients with early stage HCC, defined by Milan criteria [4], treated with resection or transplantation, have a better prognosis than those with advanced disease, with a 40-75% survival rate at 5 years [2,3]. The presence of microvascular invasion - an independent factor of poor prognosis - is more likely in larger tumors [1]. Thus, early detection and accurate characterization of a focal lesion in a cirrhotic patient is essential for an appropriate treatment [2,5].

According to the most recent recommendations of the American Association for the Study of Liver Diseases (AASLD), the diagnosis of HCC can be performed when a liver lesion > 2 cm shows typical characteristics (hyper-vascularization in the arterial phase and washout in the venous phase) in computed tomography (CT) or magnetic resonance imaging (MRI) contrast, or a mass with 1-2 cm presents these characteristics in both exams [5].

There is a great need for early detection of small tumors, for which curative therapies are more effective. However, the most difficult imaging in cirrhotic livers puts on the characterization of hypervascular nodules smaller than 2 cm, which often have nonspecific and atypical imaging features.

Distinguishing an early stage HCC from a benign or pre-malignant nodule is essential, since the therapeutic approach is different and has implications for survival and quality of life. The gadoxetc acid (Gd-EOB-DTPA) is a relatively new MRI contrast agent, hepatocyte-specific, well tolerated and safe, allowing the acquisition of images in dynamic and hepatobiliary phases [2,6-9]. Its high uptake and biliary excretion improves the detection and characterization of lesions by increasing the differentiation between the liver and the lesion, in the hepatobiliary phase [2,6-9]. It has been shown that MRI with gadoxetic acid is superior to MRI and CT with other contrast agents for the detection and characterization of liver lesions [1].

The authors present a review of the imaging spectrum of liver nodules in cirrhotic liver (regenerative, dysplastic and HCC), highlighting the role of MRI with gadoxetic acid in the characterization of HCC and its differentiation from other nodular lesions. It is illustrated the imaging aspects of HCC and other lesions often found in the cirrhotic liver.

2. EVOLUTION IN LIVER MAGNETIC RESONANCE IMAGING (MRI)

MRI has become one of the modalities for the evaluation of focal and diffuse lesions of the cirrhotic liver. However, about 60% of small malignant nodules in cirrhotic liver are not diagnosed by MRI [2].

The diagnostic accuracy of MRI has been improved with the continuous perfectioning of the sequences as well as the appearance of contrast agents hepatospecific, which are only available for this exam [2,10,11].

The variety of sequences and multiphase post-contrast images provide new information on liver injury, allowing the elucidation of different signal strengths, which reflect the inherent properties of the composition of the lesion, as well as the blood flow dynamics, giving various characteristics to each type of lesion [2].

The extracellular contrast agents consisting of gadolinium have been used in clinical practice since twenty years ago, playing a key role in the detection and characterization of focal liver lesions, mainly based on assessment of its vascularization [10]. However, this evaluation is limited since some of the cirrhotic liver lesions may be associated with vascular disorders, while others may not have specific features with that evaluation [11].

Recently, hepatospecific contrast agents composed of gadolinium have been developed, as gadoxetic acid (Gd-EOB-DTPA or etoxibenzildietilenotriaminapentacetic acid with gadolinium, Primovist® and Eovist®) [10-12].

This agent combines selective perfusion properties of hepatocytes in order to evaluate liver function, in addition to the vasculature, overcoming some of the limitations of pure extracellular contrast agents for the detection and characterization of lesions in the cirrhotic liver [2,10,13].

In fact, several studies have shown that MRI with gadoxetic acid has a higher accuracy and diagnostic sensitivity in the detection of HCC in cirrhotic liver (88 to 91.4%) when compared to biphasic spiral CT or multidetector CT (69 to 71.6%). This superiority also occurred in the detection of lesions smaller than 1.5 cm [7-9,13].

3. PHARMACOKINETIC AND PHARMA-CODYNAMIC PROPERTIES OF GD-EOB-DTPA

Gadoxetic acid was approved for use in Europe in 2005 at a concentration of 0.25 mol/L and dose of 0.025 mmol/Kg [10]. After its intravenous bolus administration, 50% of the injected dose is captured by normal functioning hepatocytes (unlike extracellular agents) through the OATP transporter 1 (organic anion transporting polypeptide 1), the same bilirubin transporter located in the basolateral membrane of hepatocyte [10,11]. The underlying cellular mechanisms of this high percentage of contrast enhancement can be explained by the lipophilic property of the gadoxetic acid [2]. The contrast agent is then eliminated through the bile duct via MRP2 (multidrug resistance protein 2) [2,10,11]. Biliary excretion depends on overall liver function. This process occurs after 10 to 20 minutes after the infusion and lasts for about 2 hours, allowing the acquisition of the hepatobiliary specific late phase in addition to the usual dynamic early phase, with a test time of about 35 min [2]. This phase improves the diagnostic accuracy, since hepatocytes do not capture dysfunctional contrast, appearing more darker (hypointense) than the surrounding liver [2].

Gadoxeic acid is excreted in equal amounts in urine and bile, which makes it particularly useful in patients with renal failure [2,10,11].

4. ROLE OF GADOXETIC ACID AND MRI HEPATOBILIARY PHASE IN THE CHARACTERIZATION OF LESIONS IN THE CIRRHOTIC LIVER

Acquisition of an arterial phase is particularly important in cirrhosis, since the lesion vascularity is an essential feature for the detection of HCC and for their differentiation from benign nodules [11].

However, conventional MRI criteria based only on vascularization can lead to false-negative for false positive findings [11]. Acquisition of a hepatobiliary phase may be useful in the detection of iso or hypovascular HCC as well as in the characterization of non-specific hyperenhancing lesions detected in dynamic vascular phases [11]. Indeed, in the conventional dynamic phases, a large percentage of initial stage HCC can be vascularised by the portal vein and appear hypo- or isointense (not showing the typical contrast uptake in the arterial phase) and, thus, not being detected or even mistaken for benign nodules in arterial phase [11]. On the other hand, benign lesions with abnormal vascularity may show contrast uptake and thus may be confused with HCC. Furthermore, in a cirrhotic liver, it can be difficult to assess the presence or absence of washout of small lesions (<2 cm) that capture contrast in the arterial phase, difficulting the diagnosis [11].

The interpretation of the images in the hepatocytic phase should be taken in conjunction with the dynamic phases and without contrast (T1, T2 and diffusion), taking into consideration the size of the lesion, its cellular composition and the appearance of the surrounding parenchima [11].

Table 1. Gadoxetic acid characteristics 1

Plasma half-life	56 min.
Contrast enhancement	Organic anion transporters of hepatocytes
% contrast enhancement	50%
Acquisition of hepatobiliary phase	10-45 min. after contrast administration
Duration of hepatic uptake	2h
Depuration	Biliary excretion 50%, renal excretion 50%
Recommended dosage	0.025 mmol / kg bolus injection of 2 mL / sec
Limitations	Possibility of capturing in well-differentiated HCC

Unlike normal parenchyma, which is typically homogeneous and hyperintense on hepatocytic phase, cirrhotic liver has a variable appearance in this phase [10,11]. Thus, the patients with compensated or initial cirrhosis capture gadoxetic acid is preserved and the liver parenchyma appears hyperintense but heterogeneous due to the presence of nodules of variable size, interspersed with fibrosis septa [11].

Moreover, in patients with advanced or decompensated cirrhosis, there is a delay in the contrast uptake and a decrease in the signal intensity in the parenchyma and bile ducts, [10,11]. The reason for this delay is related with the inadequate capture of gadoxetic acid from the extracellular space to the hepatocytes, mediated by OATP1, and a subsequent decrease of biliary excretion by MRP2, due to a reduction of functioning hepatocytes or dysfunction of these transporters in patients with cirrhosis [2,10-13]. Consequently, there is a decrease in contrast in the liver parenchyma, with subsequent difficulty in differentiating between parenchyma and lesion. Moreover, unlike patients without cirrhosis in which the intensity of the vascular signal quickly decreases after the peak of the contrast agent, in patients with advanced cirrhosis, the hepatic elimination pathway is altered, resulting in a slower blood clearance. Thus, in these patients, there is a prolonged plasma half-life of the contrast (*pooling*), and the blood vessels appear hyperintense for a longer period. Concomitant renal failure may worsen the extension of this time [2,10,12,13].

While in normal livers, a 20 minute delay is suitable for image acquisition in the hepatobiliary phase, in cirrhotic livers it may be beneficial to extend this time [10,12,13].

For evaluation of vascular permeability or residual/ recurrent disease after chemoembolization or radiofrequency or in patients with bilirubin> 3 mg/dL, gadoxetic acid is not recommended, and conventional extracellular contrast agents should be used [10].

5. IMAGING CHARACTERISTICS OF CIRRHOTIC NODULES

The development of HCC in the cirrhotic liver is a process of progressive increase of size and cell density, which begins with the regenerative nodules (resulting from chronic inflammation and cell regeneration, composed of normal liver cells), through dysplastic nodule and culminating in HCC. A key feature of this process is the gradual change in the blood supply of the various nodules in cirrhotic liver, through the formation of new tumor vessels (neoangiogenesis). As a result, there is a decrease of the portal blood supply and an increase in arterial irrigation, making vascularization characteristics quite useful for early detection of HCC and its characterization in imagiologic studies. The changes in intranodular hemodynamics that occur during hepatocarcinogenesis are shown in Fig. 1.

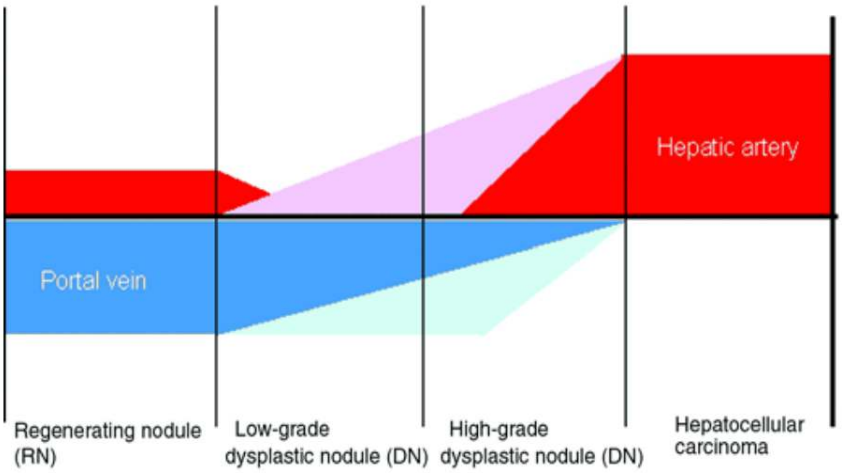

Fig. 1. Changes in intranodular hemodynamics during hepatocarcinogenesis in the cirrhotic liver [11]

5.1 Regenerative Nodules

Regenerative nodules represent a region of focal hepatocyte proliferation in response to various stimuli (necrosis or changes in blood circulation), being present in all cirrhotic livers. They are surrounded by fibrosis septa and its pattern can be classified as micronodular (≤ 3 mm) macronodular (> 3 mm) or mixed, generally having dimensions less than 2 cm. These nodules have invariably portal venous blood supply, with a minimum contribution of the hepatic artery, thus presenting similar characteristics to the vascularization of the remaining liver parenchyma [2,10,13].

In CT, they appear isodense in the arterial and portal phase, being difficult to notice. In MRI, they are usually isointense in T1 and T2, without enhancement in the arterial phase. The thick septa of fibrosis surrounding the regenerative nodules can enhance in late stages. In the hepatobiliary phase of MRI, there is normal uptake and excretion of gadoxetic acid (with signal intensity similar to the remaining parenchyma) due to preservation of hepatocellular function and transporter molecules [2,10,12,13].

Rarely, regenerative nodules may have modest enhancement in the arterial phase, thus imposing the differential diagnosis with HCC. These often arise in the context of liver injury without cirrhosis, as in Budd-Chiari syndrome and sinusoidal disease. They appear as well defined lesions not surrounded by fibrosis (unlike the regenerative cirrhotic nodules), and may contain a central scar. Thus, it is essential to know the medical history of the patient to the correct diagnosis [13].

5.2 Dysplastic Nodules

A dysplastic nodule develops from a regenerative nodule and consists of atypical hepatocytes with at least 1 cm in diameter and no histologic criteria of malignancy [10]. They are found in 15-25% of cirrhotic livers [14] and are classified as nodules with low or high-grade dysplasia. The latter are considered premalignant, and there are reports of transformation into a HCC in a 4 months period [15].

Although the blood supply is usually made at the expense of the portal vein, the nodules with high-grade dysplasia can develop arterial hypervascularization [10,13]. In fact, during hepatocarcinogenesis, there is loss of portal areas with arterial neoangiogenesis, which becomes the dominant source of blood supply in large dysplastic nodules and small HCC. Furthermore, the number of transporter molecules in dysplastic nodules decreases, reducing the capture capacity of gadoxetic acid, with implications in their imaging characteristics.

In dynamic CT study, dysplastic nodules arise isodense in the arterial and portal phase. In MRI, they show a great variability in their imaging characteristics, although the most frequent pattern is hyperintensity in T1 (due to the presence of glycogen and/or copper) and hypointensity and T2, compared to the liver parenchyma. The imaging characteristics of these nodules in the arterial phase will depend on the degree of differentiation: well differentiated lesions (low-grade) does not have uptake in the arterial phase; lesions less differentiated (high-grade) may show some uptake of contrast in the arterial phase, becoming more isointense in a later phase [13].

In hepatobiliary phase, dysplastic nodules that retain the ability to capture gadoxetic acid (but not to excrete) arise hyperintense due to intracellular cholestasis. These nodules thst lost the ability to capture (less differentiated or high-grade) appear hypointense, resulting in overlap with early stages of HCC, making the diagnosis difficult in these borderline cases [13]. In fact, Battaglia et al. suggest that a significant proportion of hypointense nodules in the hepatobiliary phase are nodules with high-grade dysplasia and, therefore, this does not constitute a specific characteristic of HCC [16].

Siderotic nodules (with high iron content) appear hypointense on T1 and T2 in MRI 2. Although previous studies suggest that the presence of iron in large nodules is a risk factor for HCC or dysplastic changes [17], recent studies seem to confirm that iron content in regenerative or dysplastic nodules is primarily a marker of disease activity and not a direct cause of carcinogenesis [3,18].

Rarely, a dysplastic nodule with a HCC focus can arise with the feature of "*nodule within nodule*" in MRI, which is the earliest sign of differentiation loss, obliging to a more interventionist attitude. In these cases, there is a focus of hyperintense signal on T2 (corresponding to the HCC component) in a dysplastic nodule with hypointense signal in T2 [3,13].

Figs. 2 to 5 illustrate the imaging aspects of dysplastic nodules in MRI with gadoxetic acid.

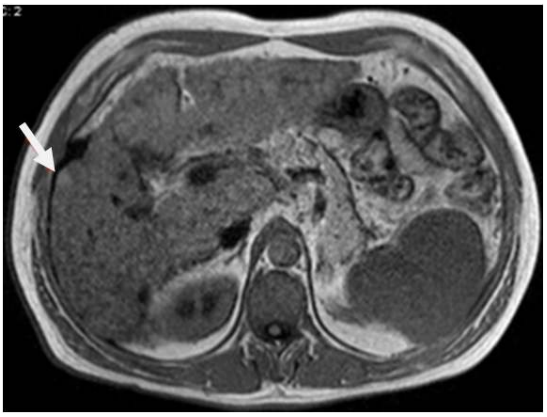

Fig. 2. Dysplastic nodule – MRI axial T1: nodular lesion in the periphery of the right lobe, with slight hyperintensity compared to the adjacent parenchyma in a cirrhotic liver

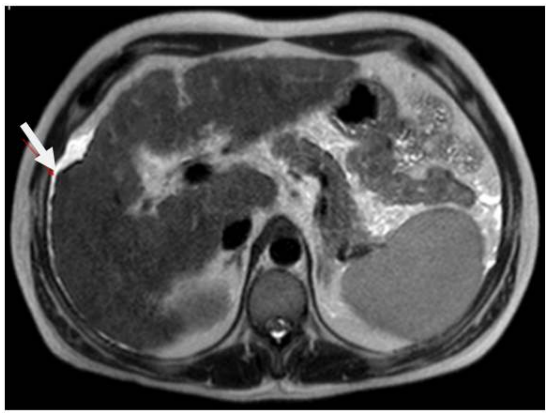

Fig. 3. Dysplastic nodule – MRI axial T2 The same lesion shows slight hypointensity on T2 TSE. It is also evident the presence of perihepatic fluid

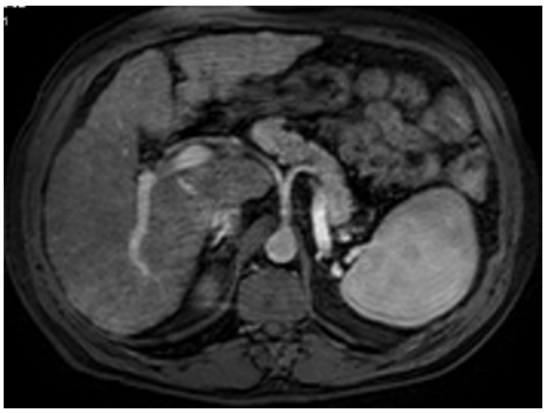

Fig. 4. Dysplastic nodule - MRI - T1 SPAIR (fat suppression) Axial contrast-enhanced, arterial phase. It is impossible to identify any lesion at this location

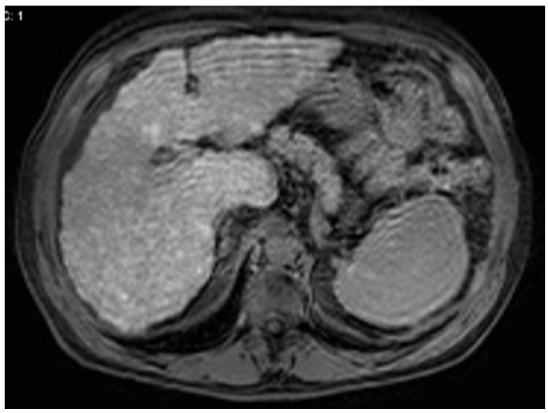

Fig. 5. Dysplastic nodule – MRI - T1 SPAIR (fat suppression) Axial contrast-enhanced hepatobiliary phase. It is not clear any change in the topography previously described

5.3 HCC

From the pathological point of view, HCC is classified macroscopically as solitary in 50% of cases, multifocal (multiple scattered nodules) in approximately 40% or diffuse (indistinct multiple dispersed tiny nodules) in less than 10% of cases [10].

The vascular supply of HCC is mostly arterial (resulting from neoangiogenesis process) with reduced or absent portal supply [10].

In the pre-contrast phase, small HCC nodules (≤ 2 cm) appear homogeneous, with variable intensity signal on T1 and moderate hyperintensity on T2 (unlike dysplastic nodules that appear hypointense). Large HCC nodules (> 2 cm) have several characteristic features: Hyperintense in T2; variable intensity signal areas and heterogeneous in T1 and T2 (confluent nodes separated by fibrous septa and areas of necrosis - mosaic pattern); tumor capsule with hyposignal; necrosis; intralesional fat; extracapsular extension with formation of satellite nodes; and vascular invasion. Such as regenerative nodules or especially dysplastic, HCC can show hyperintense on T1 when it contains fat, glycoproteins or copper [3,10,13].

The most typical imaging characteristic of HCC consists of hypervascularization in the arterial

phase, after the injection of gadoxetic acid (resuting from the neoangiogenesis process), which occurs in the vast majority of these lesions (80-90%) [10]. In addition, the presence of washout in the venous and late phases with lower signal strenght than the remaining parenchima is also very characteristic and necessary for the diagnosis [10].

However, some hypervascular HCC may not have washout, a characteristic which makes it difficult to notice in the late stages. A peripheral ring of contrast can be observed within 5 minutes following injection of contrast [10]. Moreover, a minority of HCC (corresponding to approximately 10-20%) are hypovascular (with loss of arterial and portal irrigation, associated with the absence of neoangiogenesis), presenting lower intensity signal than the surrounding parenchyma, in the arterial phase, and appearing as isointense or hypointense nodules [10]. These HCCs, which can be incorrectly diagnosed as benign lesions (regenerative or dysplastic nodules), are typically small tumors (≤ 2 cm) in an initial and well-differentiated stage and are best viewed in the portal phase [13].

Therefore, it appears more clear the role of MRI with gadoxetic acid, in an attempt to increase the diagnostic accuracy of HCC, especially in atypical cases. Thus, in the hepatobiliary phase, HCC shows the typical lower intensity signal in comparison with the surrounding parenchyma, as a result of its inability to uptake the contrast, enabling a clear delineation of the tumor margins not visualized in dynamic phases [10]. However, about 2.5 to 8.5% of CHCs may also have paradoxical capture of gadoxetic acid in the hepatobiliary phase, arising iso- or hyperintense in comparison with the surrounding parenchyma [19].

In summary, we can set up three patterns of HCC in MRI with gadoxetic acid, in dynamic and hepatobiliary phases, depending on the expression of the carrier molecules OATP1 and MRP2 in their membranes:

(1) hypervascular lesion in the arterial phase with washout in the late phase in 3 minutes and hypointense in hepatobiliary phase in 10-20 minutes, as a result of absence of functioning hepatocytes – most characteristic feature [2,10];

(2) isointense or hyperintense lesion in the hepatobiliary phase in 10-20 minutes (by overexpression of OATP1 carriers in well or moderately differentiated HCC, resulting in uptake of the contrast agent) - 10-20% of cases [2,10];

(3) hypointense lesion in the hepatobiliary phase without arterial hypervascularization or hyperintensity on T2 (lack of neoangiogenesis) - 10% of cases [2,2,6, 10].

Portal vein thrombosis, which occurs by direct invasion, is also an important feature of HCC, occurring in about 5 to 44% of patients with HCC and emerging as hyperintense on T2. However, in a smaller number of cases (0.65 to 15.8%), cirrhotic patients may also develop portal vein thrombosis secondary to portal hypertension and venous stasis, although) [2,10].

The distinction between dysplastic nodules and HCC can be easier if the following features suggestive of malignancy are present: larger than 2 cm, hyperintensity on T2, washout in the late stage, hypointensity in the hepatobiliary phase, delayed enhancement of tumor capsule and rapid growth interval (Figs. 6 to 10).

6. LESIONS THAT CAN SIMULATE HCC

Although arterial uptake is the most consistent feature of HCC, it may also occur in non-malignant lesions, which can be found in cirrhotic liver. This is particularly relevant in lesions with dimensions of less than 2 cm, which may explain the high incidence of false positives.

6.1 Hemangioma

Hemangiomas are relatively rare in advanced cirrhosis[3]. However, small hemangiomas (< 2 cm) may exhibit marked enhancement in the arterial phase (*flash filling*), imposing differential diagnosis with HCC. However, they usually show enhancement in the later stages, while HCC exhibits a rapid washout of contrast, being iso or hypodense in comparison with the surrounding parenchyma. In addition to these features, they show a marked hyperintensity on T2, while HCC tends to arise isointense or slightly hiperintense [3,13] (Figs. 11 to 15).

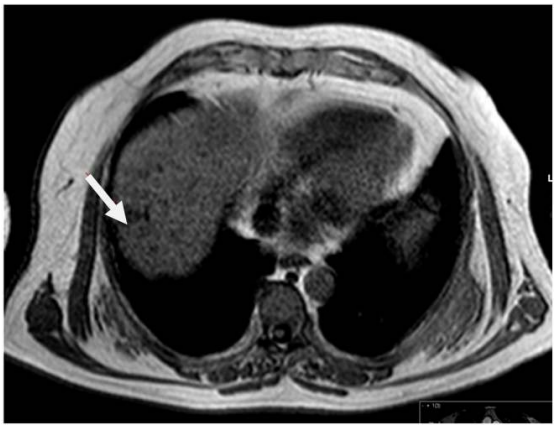

Fig. 6. HCC - MRI, axial T1. Nodular lesion slightly hypointense compared to the adjacent parenchyma in a patient with chronic liver disease

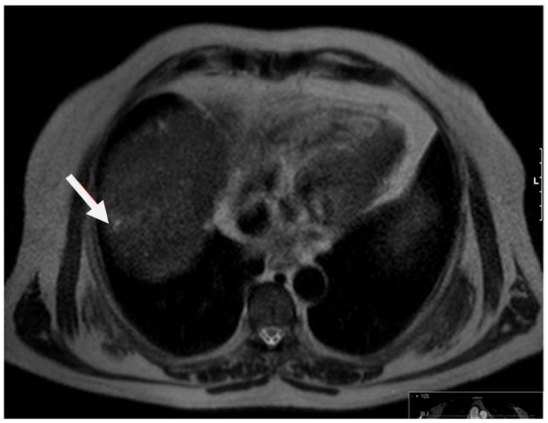

Fig. 7. HCC - MRI, axial T2 TSE. Nodular lesion slightly hyperintense compared to the adjacent parenchyma in a patient with chronic liver disease

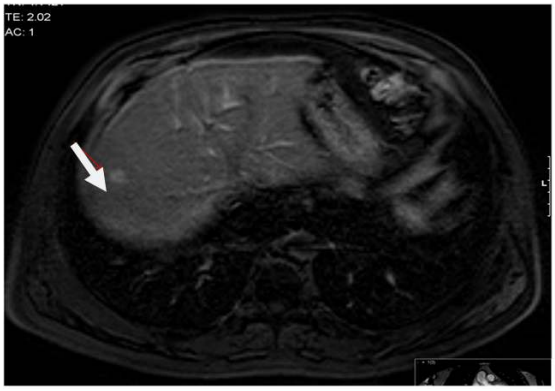

Fig. 8. HCC – MRI, T1 SPAIR (fat suppression) Axial contrast-enhanced, arterial phase: The lesion presents contrast uptake in the arterial phase

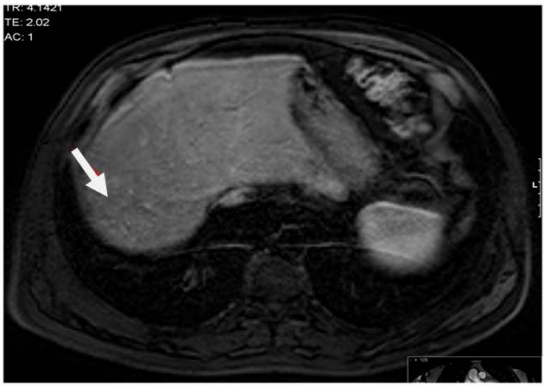

Fig. 9. HCC - T1 SPAIR (fat suppression) Axial post-contrast, parenchymal phase: The lesion keeps discrete contrast uptake in the parenchymal phase - not characteristic of CHC

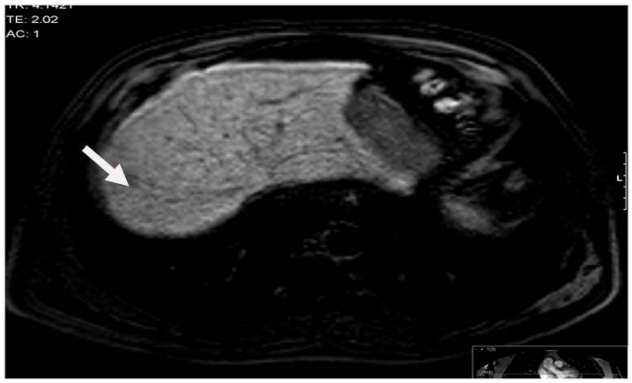

Fig. 10. HCC - T1 SPAIR (fat suppression) Axial contrast-enhanced, hepatobiliary phase (15 min.): The lesion presents contrast uptake on hepatobiliary phase, confirming the diagnosis of HCC

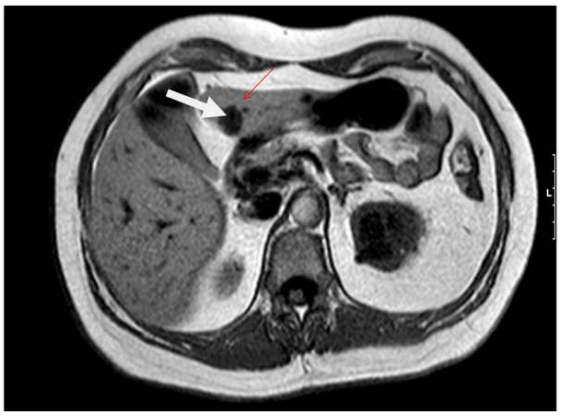

Fig. 11. Hemangioma - axial T1: Nodular lesion presents hypointense in comparison to the adjacent parenchyma.

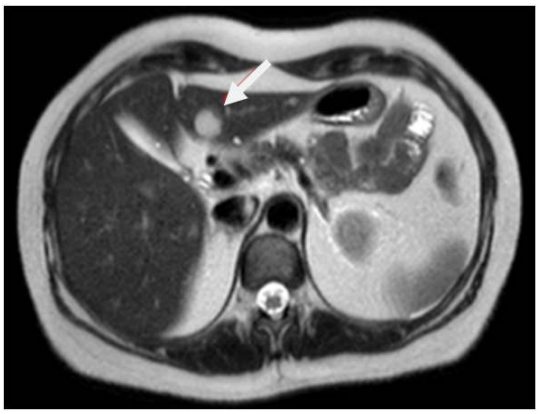

Fig. 12. Hemangioma - axial T2 TSE: The lesion is hyperintense in comparison to the adjacent parenchyma

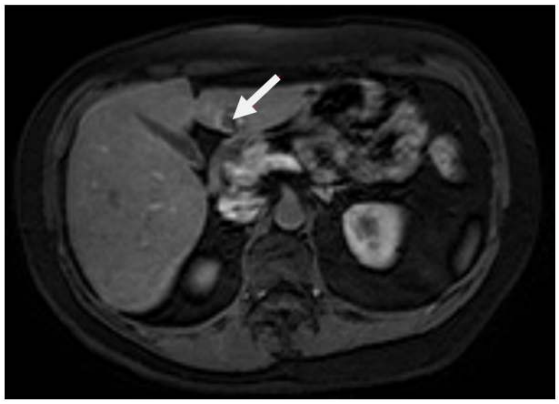

Fig. 13. Hemangioma - T1 SPAIR (fat suppression) Axial contrast-enhanced, arterial phase: The lesion has peripheral contrast uptake in the arterial phase

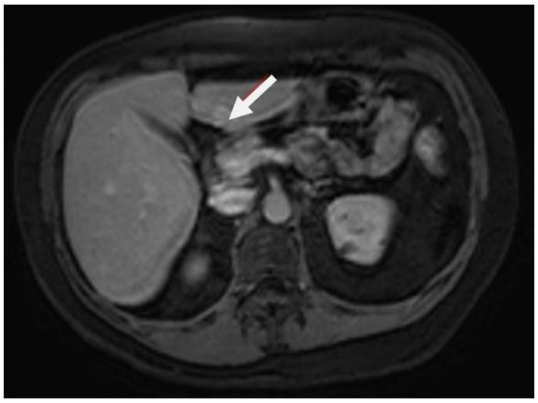

Fig. 14. Hemangioma - T1 SPAIR (suppressing fat) contrast-axial, parenchymal phase: Centripetal progression of contrast, feature consistent with the diagnosis of hemangioma

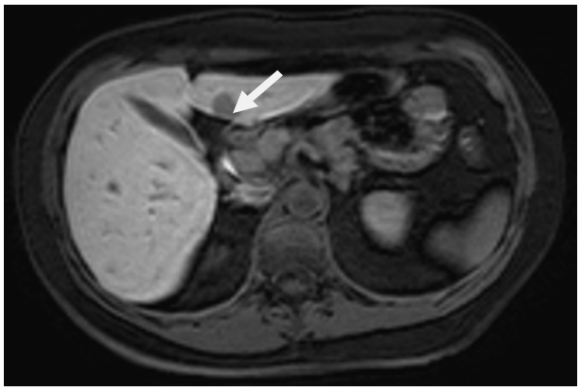

Fig. 15. Hemangioma - T1 SPAIR (suppressing fat) contrast-axial, hepatobiliary phase (15 minutes): Hypointense lesion in comparison to adjacent parenchyma (feature that does not allow the differential diagnosis with HCC)

6.2 Arterioportal Shunts

Arterioportal shunts emerge in response to the reduction in portal blood supply. They can mimic hypervascular HCCs in conventional dynamic contrast studies (CT and MRI), and are more prevalent in the cirrhotic liver [2]. They appear as peripheral areas, with a wedge-shaped morphology, ranging from 5 to 20 mm, enhancing in the arterial phase (*flash filling*). Portal branches with early filling may or may not be observed in its interior [21,22]. They are usually subcapsular, without mass effect, being not visible in other phases [3,22]. In MRI, there are usually isointense in T1 and T2 compared with the adjacent parenchyma (unlike CHC, which shows increased signal intensity on T2); rarely, they appear hyperintense on T2 [3,10,13,22]. Hepatobiliary phase with gadoxetic acid is useful for their distinction with HCC, as they appear isointense in comparison to the surrounding parenchyma (wich contain functioning hepatocytes) [21] - Figs. 16 to 18.

Arteriovenous shunts and pseudoaneurysms may occur after liver biopsy and en hance similarly to the blood pool, appearing hypointense in hepatobiliary phase [3,10,13,22].

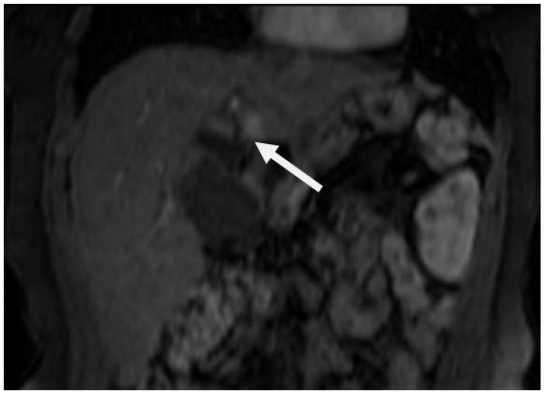

Fig. 16. Vascular shunt - T1 SPAIR (fat suppression) Axial contrast-enhanced, arterial phase: lesion with contrast uptake in the periphery of the left lobe; this change was not visible in T1 or T2 TSE prior to contrast administration

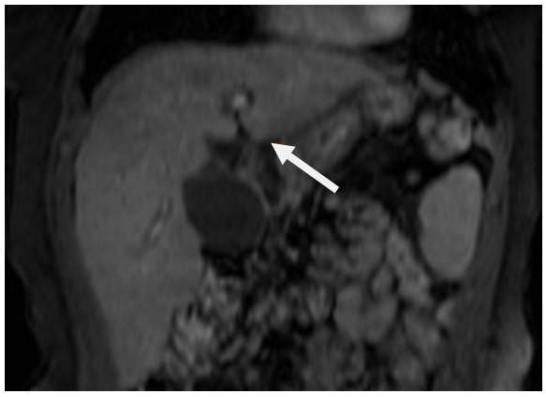

Fig. 17. Vascular Shunt - T1 SPAIR (fat suppression) Axial post-contrast, parenchymal phase: it is not possible to identify the previously described lesion; this area becomes isodense in comparison to adjacent parenchyma

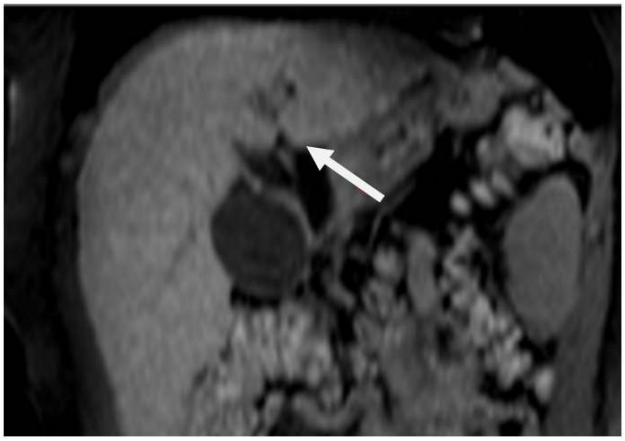

Fig. 18. Vascular Shunt - T1 SPAIR (suppressing fat) contrast-axial, hepatobiliary phase: i tis not possible to detect any focal lesion in this topography, feature consistente with the diagnosis of vascular shunt

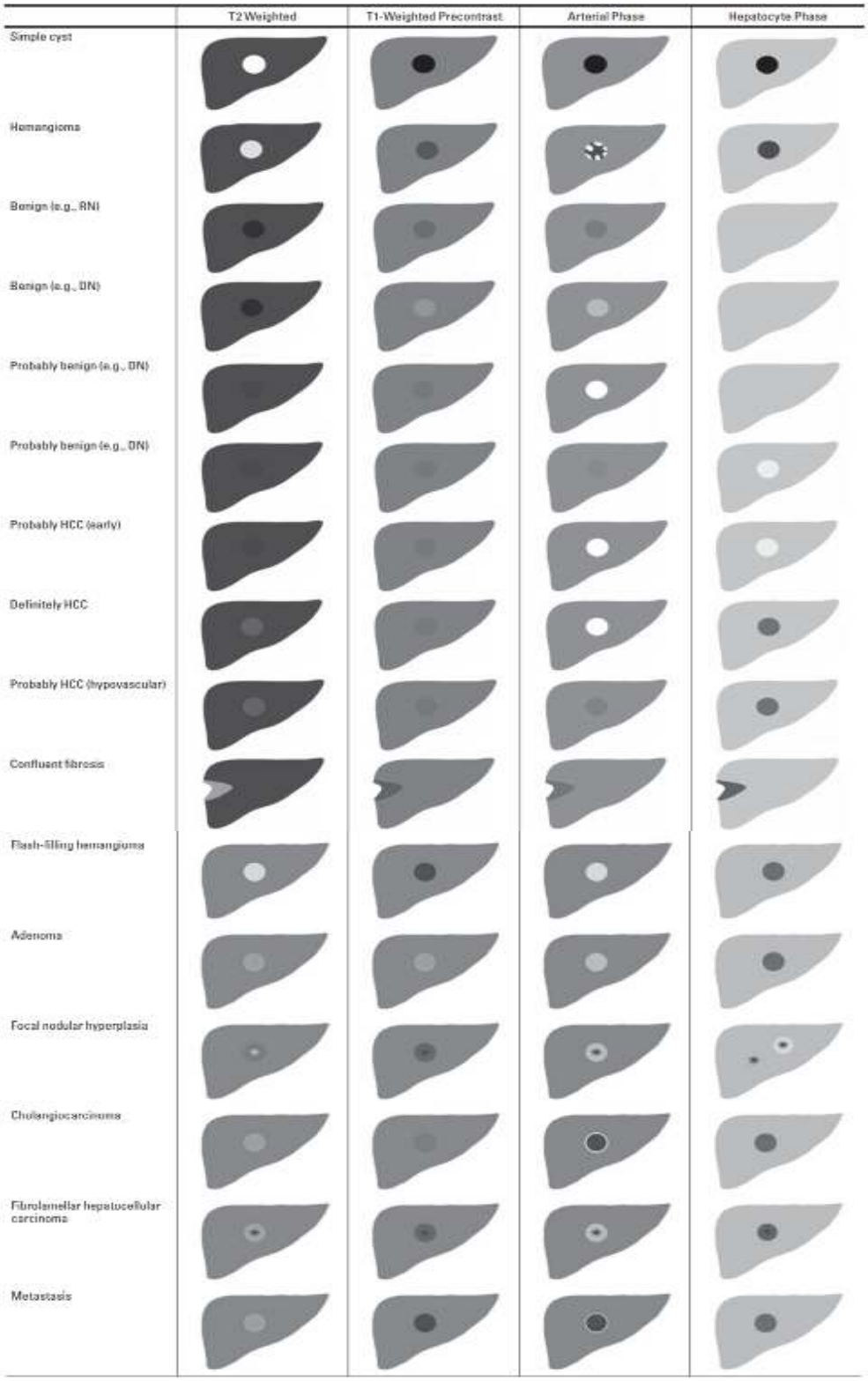

Fig. 19. Imagiologic features of focal liver lesions with gadoxetc acid

6.3 Aberrant Venous Drainage

The presence of aberrant drainage veins (cystic, right gastric or capsular) that drain systemic venous blood directly to liver sinusoids, can cause perfusion changes, with areas of enhancement in the arterial phase, mimicking small HCC. They are usually located in the peri-vesicular area, before the portal confluence and in the subcapsular area [3,22].

6.4 Confluent Fibrosis

Confluent fibrosis is characterized by the presence of focal areas of fibrosis in cirrhotic liver, which can mimic tumoral nodules. They have a linear or wedge-shaped morphology, radiating from portal confluence to the capsule. Parenchymal atophy and concomitant capsular shrinkage are often present. This finding aids in the differential diagnosis with HCC [3,10,13]. They usually are located in the segment IV and right anterior segments [3,10,13]. In CT they arise hypo/isodense. In MRI, they present hyposignal in T1, hyperintensity in T2 and hypointensity in the hepatobiliary phase (like HCC), since it does not contain hepatocytes [3,13]. However, their morphology, the lack of uptake in the arterial phase and the enhancement in the late phase are crucial in the differential diagnosis with HCC [10].

6.5 Focal Nodular Hyperplasia (FNH)

FNH is the second most common benign tumor, consisting of normal liver tissue involved in fibrous septa. It is, however, relatively infrequent in cirrhotic livers [2,13]. Generally, they show contrast uptake in the arterial phase, and in about half of the cases, they present a "*central scar*". After administration of gadoxetic acid, ithey arise as a iso- or hyperintense lesion in the hepatocytic phase due to the presence of functioning normal hepatocytes and bile canaliculii, which is considered a typical feature. In most cases, histological characterization is not required.

6.6 Adenoma

Hepatic adenoma is a relatively rare benign liver tumor, which predominantly affects women taking oral contraceptives, men taking anabolic steroids or patients with glycogen storage diseases type [2]. As FNH, adenomas are typically hypervascular in the arterial phase, though they do not present any "*central scar*" [13,23]. In hepatobiliary phase, adenomas do not uptake gadoxetic acid, unlike FNH. However, few reports describe hyperintensity in the hepatobiliary phase, but currently there are little published data to confirm the predominant pattern in adenomas [2,10,23].

6.7 Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma usually presente with a peripheral ring uptake in the arterial and venous phases with progressive and concentric filling of contrast in the late phase (atypical pattern for HCC). It can also display dilated intrahepatic biliary ducts distal to the tumor (obstruction) and capsule retraction [3].

Fig. 19 summarizes the major imagiologic features of focal liver lesions in studies with gadoxetic acid.

7. CONCLUSION

Cirrhotic liver is associated with a broad spectrum of nodular lesions, including regenerative nodules, low-grade dysplastic nodules, high-grade dysplastic nodules (pre-malignant) and HCC.

Knowledge of how cirrhotic nodules and other focal lesions can mimic HCC can improve its diagnosis and characterization in imaging studies with CT or MRI.

On MRI, imaging characteristics suggestive of malignancy are size > 2 cm, slow washout, hyperintensity on T2, hypointensity in the hepatobiliary phase, delayed enhancement of tumor capsule and rapid growth interval.

MRI with gadoxetic acid has several advantages over other imaging modalities for the detection and characterization of HCC in the cirrhotic liver, since it provides information about the blood supply and hepatocellular function. Hepatobiliary phase may assist in differentiating benign nodules (regenerative and dysplastic) from HCC nodules. This may potentially be the preferred diagnostic method if an increase of its overall application and experience is provided.

CONSENT

All authors declare that ‘written informed consent was obtained from the patient (or other approved

parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
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http://sciencedomain.org/review-history/11413