

Magnetic resonance imaging of the cirrhotic liver: An update

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Author contributions: All authors have contributed equally to this work in form of literature review, manuscript writing/editing, and figure collection/illustration/annotation/captioning.

Conflict-of-interest: The authors declare that they have no competing interests.

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Received: August 30, 2014

Peer-review started: August 30, 2014

First decision: September 30, 2014

Revised: October 10, 2014

Accepted: December 3, 2014

Article in press: December 3, 2014

Published online: March 27, 2015

Abstract

Noninvasive imaging has become the standard for hepatocellular carcinoma (HCC) diagnosis in cirrhotic livers. In this review paper, we go over the basics of MR imaging in cirrhotic livers and describe the imaging appearance of a spectrum of hepatic nodules marking the progression from regenerative nodules to low- and high-grade dysplastic nodules, and ultimately to HCCs. We detail and illustrate the typical imaging appearances

of different types of HCC including focal, multi-focal, massive, diffuse/infiltrative, and intra-hepatic metastases; with emphasis on the diagnostic value of MR in imaging these lesions. We also shed some light on liver imaging reporting and data system, and the role of different magnetic resonance imaging (MRI) contrast agents and future MRI techniques including the use of advanced MR pulse sequences and utilization of hepatocyte-specific MRI contrast agents, and how they might contribute to improving the diagnostic performance of MRI in early stage HCC diagnosis.

Key words: Magnetic resonance imaging; Hepatocellular carcinoma; Hepatic nodules; Liver imaging reporting and data system; Dysplastic nodules; Regenerative nodules

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Core tip: Noninvasive imaging has become the standard for hepatocellular carcinoma (HCC) diagnosis in cirrhotic patients. Typical imaging features of HCC, including increased arterial enhancement and delayed washout, provide very high specificity and acceptable sensitivity in characterizing even very small nodules. Diagnostic limitations apply to detecting hypovascular HCCs and differentiating high-grade dysplastic nodules from early HCCs. New techniques such as diffusion-weighted images, T2*, and hepatocyte-specific magnetic resonance imaging contrast agents, are being currently evaluated, which might improve future detection and characterization of hepatic lesions when combined with the current standard imaging protocols with dynamic imaging.

Watanabe A, Ramalho M, AIObaidy M, Kim HJ, Velloni FG, Semelka RC. Magnetic resonance imaging of the cirrhotic liver: An update. *World J Hepatol* 2015; 7(3): 468-487 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v7/i3/468.htm>
DOI: <http://dx.doi.org/10.4254/wjh.v7.i3.468>

INTRODUCTION

Every year, hepatocellular carcinoma (HCC) is diagnosed in more than 500000 people worldwide; with approximately 20000 new cases in the United States^[1,2]. HCC is already the fifth most common neoplasm worldwide and is the third most common cause of cancer-related death, after lung and stomach cancers^[1].

HCC rarely occurs before the age of 40 years, reaching a peak at approximately 70 years of age, and is two to four times more prevalent in men^[3].

Most of the burden of disease (85%) occurs in developing countries, with the highest incidence rates reported in regions such as Southeast Asia and sub-Saharan Africa; where infection with hepatitis B virus (HBV) is endemic^[1]. On the other hand, HCC related to hepatitis C virus (HCV) infection and secondary cirrhosis has become the fastest-rising cause of cancer-related death in the developed countries^[2].

Patients diagnosed at an early stage are eligible for potentially curative therapies; including surgery (resection and liver transplantation) and locoregional ablative options (radiofrequency, microwave ablation, or ethanol injection). With this stage-driven strategies, 5-year survival rates range between 50%-70%^[4]. However, very poor prognosis is observed with advanced HCC.

Therefore, an effort to diagnose HCC at early stages is being taken with the implementation of screening programs that may lead to earlier implementation of treatment.

Correlation with alpha-fetoprotein levels may sometimes be useful; however, not all tumors express alpha-fetoprotein. Additionally, mildly elevated alpha-fetoprotein levels may be seen in patients with chronic liver disease or in patients with cirrhosis but no HCC^[5].

Ultrasound (US) is widely used, and represents the first imaging modality of screening by various international society consensus; essentially because of the ease of access, lack of ionizing radiation, and lower cost compared with computed tomography (CT) and magnetic resonance imaging (MRI). The role of gray-scale US in cirrhotic patients in clinical practice is screening and surveillance, rather than accurate diagnosis of HCC (Figure 1). According to the updated American Association for the Study of Liver Diseases (AASLD) guidelines^[6], the diagnostic algorithm of HCC starts from suspected nodules found on US surveillance. However, reported sensitivity and specificity is variable^[7] and studies have shown a significant lower detection rate of HCC compared with CT and MRI^[8]. Additionally, the technique is poor to detect small HCCs. At present, the real cost-effectiveness of US is not known, as it is common to find HCC in patients with prior negative US while receiving appropriate surveillance^[9,10].

The use of CT for the detection of HCC requires

intravenous iodinated-contrast administration and a minimum of a triphasic technique to evaluate the characteristic findings of increased arterial enhancement and late washout of typical HCCs. Several studies have shown higher sensitivities of gadolinium-enhanced MR imaging compared to CT for the detection of HCC of all sizes^[11], while other studies have suggested a lower sensitivity of CT for detecting dysplastic nodules, small HCCs, and diffuse HCC compared with MRI^[7,10].

The relatively short interval follow-up that is advocated for this patient population raises concern regarding the cumulative radiation dose and increased risk of worsening renal function due to the necessary repeated administration of intravenous contrast material^[12].

Recent technological development of MRI scanners allowed high-quality multiphase dynamic imaging of the entire liver^[13]. Additionally, the superb contrast resolution and development of liver specific contrast agents rendered MR an important imaging modality for assessing cirrhosis and its complications, especially HCC. However, despite being an optimal imaging technique for the comprehensive evaluation of the liver^[14,15], MRI has been used mainly as a problem solving technique^[14].

Several studies have demonstrated a trend to increased sensitivity and specificity of dynamic MRI over dynamic CT for the detection and characterization of HCC of all sizes with reported sensitivities of 76%, 61%, 90% and 77% for MRI vs 61%, 52%, 78% and 54% for CT, respectively^[11,16-18]. An optimized, dynamic T1-weighted gradient recalled echo (GRE) with individually tailored arterial phase timing, has shown very high sensitivity and specificity (> 90%-95%)^[19].

The MRI sensitivity vary with tumor size; however, it was estimated to be about 100% in HCCs larger than 2 cm^[20]. The detection of small tumors remains challenging, and MRI also outperforms CT in this area, with reported sensitivities for the detection of HCCs measuring 1-2 cm of 84% and 47% for MRI vs 85% and 68% for CT, respectively^[11,21].

To date, validated CT and MRI criteria for the diagnosis of HCC are based on the hemodynamic features of the nodules and include arterial hyper-enhancement and delayed washout^[22]. The most recent recommendations by the AASLD state that a diagnosis of HCC can be made if a nodule larger than 1 cm shows typical hemodynamic features of HCC on either dynamic CT or MRI^[6]. In our opinion, this reduces MRI and CT to a minimum common denominator; because despite the greater sensitivity of dynamic MRI for the detection of small HCCs; which might be explained by inherit superior contrast resolution of MRI and superior paramagnetic effect of intravenous gadolinium-based contrast agents, the diagnosis of HCC using only hemodynamic criteria is not without its limitation, as small HCCs frequently show atypical enhancement patterns^[23]. One study showed that the majority of

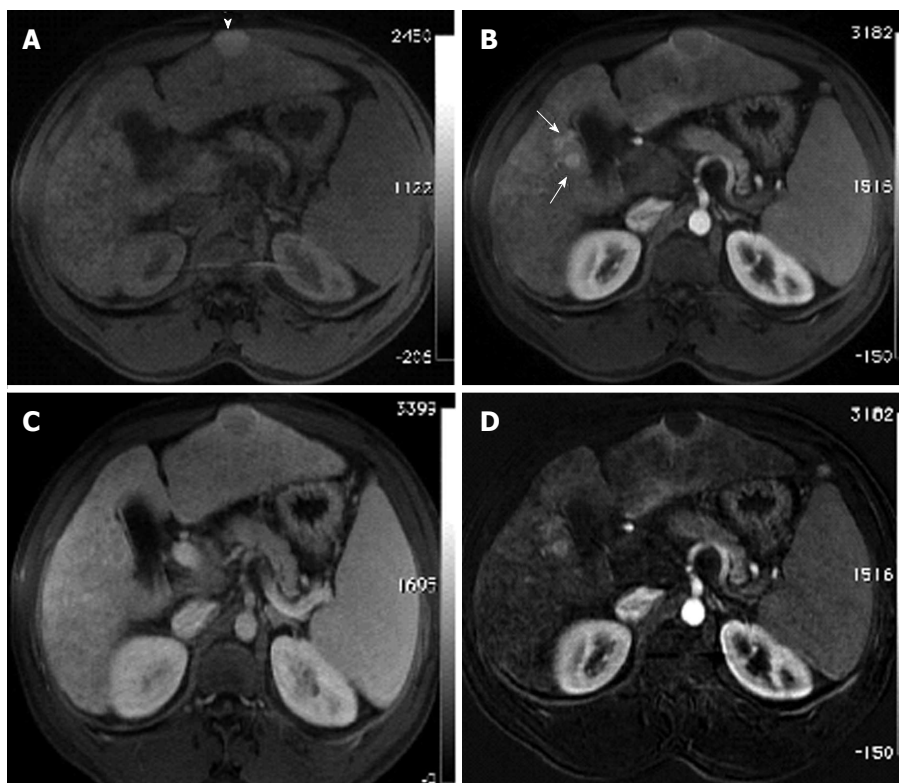


Figure 1 Incidentally discovered solitary left hepatic lobe nodule on screening ultrasound, referred as suspicious nodule for HCC, for MRI evaluation. A: Pre- and post-contrast fat-suppressed 3D-GRE T1-weighted images during the (B) late hepatic arterial and (C) delayed phases; D: Post-processed subtracted arterial image. The known left hepatic lobe nodule demonstrate increased intrinsic T1 signal (arrowhead, A), without appreciable increased arterial enhancement (B), confirmed on subtraction images (D), in keeping with a macro-regenerative nodule. However, the MRI reveals multiple small foci at hepatic segment #5 that show increased arterial enhancement (arrows, B) and delayed washout (D) in keeping with multiple small HCCs. HCC: Hepatocellular carcinoma; MRI: Magnetic resonance imaging; GRE: Gradient recalled echo.

HCCs less than 2 cm showed arterial hypervascularity regardless of washout^[24].

MRI provides multi-parametric data on anatomical abnormality with both T1- and T2-weighted sequences, and provides functional sequences such as diffusion-weighted images (DWI) and contrast uptake with the use of liver-specific hepatobiliary contrast agents, providing cellular information of the hepatocellular nodules that can improve lesion detection and characterization. Table 1 shows a summary of a wide-spectrum of lesions in cirrhotic liver and their imaging appearances on MRI.

In this article, we provide an overview of the basic MRI techniques used for assessment of cirrhotic nodules. We also shed some light on liver imaging reporting and data system (LI-RADS), and the role of different MRI contrast agents and future MR imaging techniques including the use of advanced MR pulse sequences and utilization of hepatocyte-specific MRI contrast agents, and how they might contribute to improving the diagnostic performance of MRI in early stage HCC diagnosis.

PROTOCOL

An adequate imaging protocol has to be standardized

to allow repeatability and consistency. The standard imaging techniques are based on dynamic fat-suppressed post-contrast T1-weighted 3D GRE sequences, combined with fat-suppressed and non fat-suppressed T2-weighted sequences. T2-weighted images are usually acquired with single-shot fast spin-echo (SSFSE) technique due to its robustness to motion. Chemical shift imaging is acquired with breath-hold dual-echo spoiled GRE. Additional sequences may be added to the protocol (see below).

Since detection of HCC relies on dynamic fat-suppressed post-contrast T1-weighted 3D GRE sequences and proper timing of the arterial phase is critical for optimizing sensitivity for HCC detection (Figure 2). We routinely use real time bolus-triggering method in order to consistently achieve adequate arterial phase images. An optimal arterial phase is recognized when contrast is present in the portal veins and absent in the hepatic veins; referred to as late-hepatic arterial phase or hepatic-arterial dominant phase. Post-processed subtraction arterial imaging may be utilized and may carry an additional value for detecting subtle early enhancement; which can be observed in cases of nodules with increased intrinsic signal on T1-weighted images, nodules with microscopic fat (Figure 3), or small lesions in a

Table 1 Summary of a wide-spectrum of lesions in cirrhotic liver and their imaging appearances on magnetic resonance imaging

Imaging sequences	RNs	Siderotic nodules (RNs or LGDNs)	LGDNs ¹	AP Shunts ²	HGDNs	HCCs
T1-weighted images	Iso- or hyperintense ³	Hypointense ⁴	Iso- or hyperintense	Isointense	Iso- or slightly hyperintense	Ranging from hypo- to hyperintense
T2-weighted images	Iso- or hypointense	Hypointense	Iso- or hypointense	Isointense	Isointense	Iso- to mildly hyperintense
DWI	Isointense	Hypointense	Iso- or hypointense	Isointense	Isointense	Iso- to hyperintense ⁵
Post-Gadolinium Dynamic images (arterial and delayed images)	Iso-enhancement on the hepatic arterial phase, and no delayed washout	Iso-enhancement on the hepatic arterial phase, and no delayed washout	Iso-enhancement on the hepatic arterial phase, and no delayed washout	Hyper-enhancement on the arterial phase, and no show delayed washout ⁶	Usually hyper-enhancement on the arterial phase and can be mistaken for HCC. These nodules do not show delayed washout	Usually hyper-enhancement on the arterial phase and delayed washout (hypointense), with or without pseudocapsule enhancement ⁷
Hepatobiliary phase images	Iso- to slightly hyperintense	Hypointense	Iso- to slightly hyperintense	Isointense	Isointense	Hypointense ⁸

¹RNs and LGDNs tend to be indistinguishable on MRI; ²AP shunts might be indistinguishable from HGDNs and small, early HCCs. Relying on additional features and short-term follow-up can help in making this distinction; ³The exact cause for this hyperintensity is believed to be due to the presence of binding proteins; ⁴These nodules show lower signal intensity on longer TE T1-weighted GRE sequences, due to susceptibility artifact; ⁵Usually hyperintense, especially if > 2 cm; ⁶AP shunts are usually easy to differentiate from other hypervascular lesions when they show a triangular or linear configuration. When AP shunts show round configuration, they can be indistinguishable from HGDNs and HCCs; ⁷HCCs ≤ 1.5 cm are frequently isointense on T1- and T2-weighted images and are detected only on the arterial phase. Early stage HCC, especially tumors ≤ 2 cm, may also appear isointense, or less likely, hypointense on the arterial phase; ⁸Some HCCs may appear isointense or hyperintense on the hepatobiliary phase; especially well-differentiated and moderately-differentiated HCCs. LGDNs: Low-grade dysplastic nodules; AP: Arterio-portal; HGDNs: High-grade dysplastic nodules; HCCs: Hepatocellular carcinomas; RNs: Regenerative nodules; DWI: Diffusion weighted images.

background of heterogeneous background hepatic parenchymal enhancement.

of a problem with the new advancement in developing faster and motion robust sequences.

HEPATOGENESIS

In cirrhotic liver the stepwise development of cancer from areas of regeneration to overt development of HCC is called "multistep hepatocarcinogenesis" and is the widely accepted main mechanism of hepatocarcinogenesis. *De novo* hepatocarcinogenesis also is presumed to occur as an alternative pathway. Even in such cases, later progression to overt HCC takes place in a multistep fashion^[25]. Accepted imaging diagnosis of HCC is primarily based on sequential changes in the intra-nodular blood supply during hepatocarcinogenesis; regenerative nodules (RN) show similar blood supply to normal liver, borderline lesions such as dysplastic nodules (DN) or early HCCs show wide variations of blood supply, and advanced HCCs are supplied by abnormal arteries alone^[25,26].

High-grade DN is a lesion with strong malignant potential, being recognized as a precursor of HCC. DN and early HCCs are recognized as lesions in the "gray zone"^[27] as although usually being hypervascular they tend to show no washout on late phases, hindering the diagnosis^[24].

Another source of HCC misinterpretation is on iso-enhancement of HCC on arterial phase images due to the iso or hypovascularity of the lesion^[28] (Figure 4). Additionally, misdiagnosed HCCs on MRI may be due to poor patient compliance, especially from the inability to suspend respiration, which is becoming less

MRI FEATURES OF CIRRHOTIC NODULES

Dominant nodules are frequently identified during an imaging surveillance program in patients with liver cirrhosis. The change in vascularity observed in hepatic nodules during the multistep hepatocarcinogenesis correlates with the development of malignancy and determines their distinguishing imaging characteristics.

RN

RNs consist of proliferating normal liver cells surrounded by a fibrous stroma^[29]. A RN is described as containing one or more portal tracts located in a liver that is abnormal whether because of cirrhosis or other disease^[30]. The blood supply of a RN continues to be largely from the portal vein, with minimal contribution from the hepatic artery^[31]. This explains why there is no hyper-enhancement on the hepatic arterial phase on MR images. Because of their histopathological nature, as described above, RNs are often indistinct on T1- and T2-weighted images. However, they can have higher T1 signal intensity compared to background liver tissue. The explanation for this increase in signal is not exactly known; it has been proposed to be due to the presence of metal-binding proteins, proteins *per se*, or lipid^[32,33] (Figure 5). RNs may occasionally contain iron (siderotic nodules), which will show decreased T1- and T2 signal intensities due to susceptibility effects^[34].

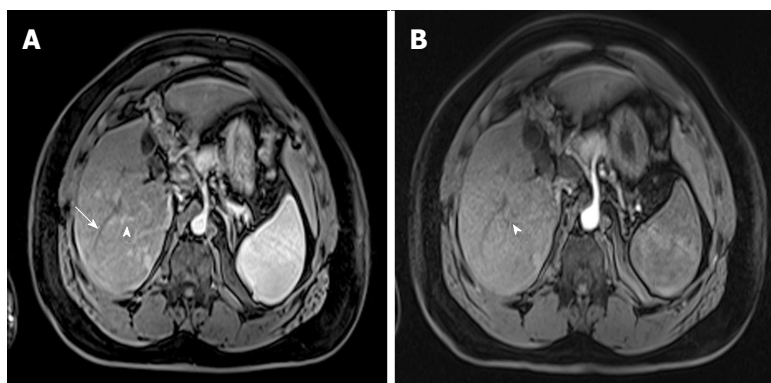


Figure 2 Value of proper timing for detecting hypervascular hepatic lesions. A-B: Post-contrast fat-suppressed 3D-GRE T1-weighted images acquired 4 mo apart. A: Initial scanning shows contrast in the portal vein branches (arrowhead, A), without opacification of the hepatic veins (arrow, A), suggesting late hepatic arterial phase timing; the optimal time for detecting hypervascular pathologies, with demonstration of multiple lesions; B: A subsequent scan acquired 4 mo later shows contrast in the hepatic artery without opacification of the portal vein branches (arrowhead, B), suggesting an early arterial timing, without evidence of hypervascular lesions. A subsequent scan was acquired (not shown); which confirmed the persistence of these hypervascular lesions. GRE: Gradient recalled echo.

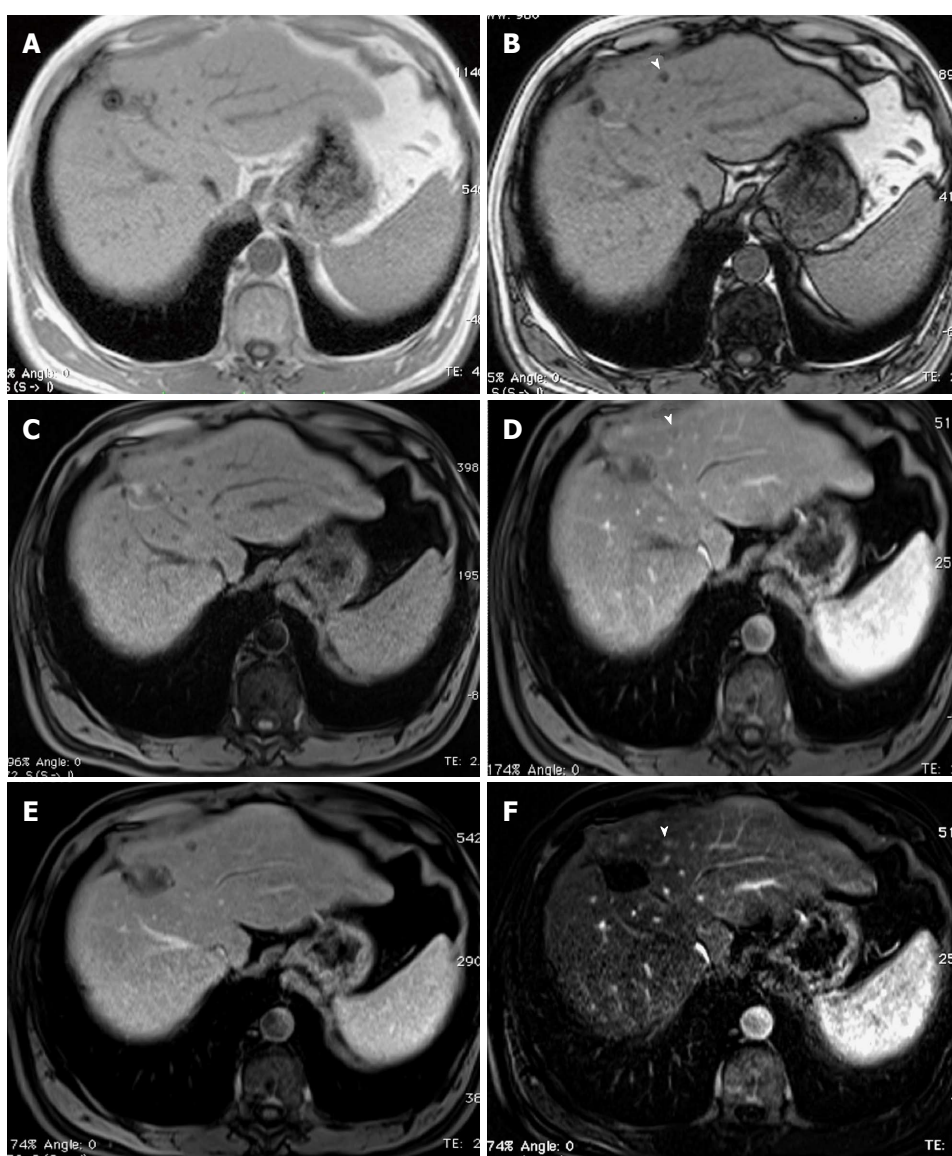


Figure 3 Small fat-containing hepatocellular carcinoma; the value of subtraction images. A: In-phase; B: Opposed-phase GRE T1 weighted images; C-E: Pre- and post-contrast fat-suppressed 3D-GRE T1-weighted images during the (D) late hepatic arterial and (E) delayed phases; F: Post-processed subtractions arterial phase image. There is a small left hepatic nodule, which demonstrates drop of signal intensity on opposed-phase (arrowhead, B) and pre-contrast images (C) compared to the in-phase images (A), suggesting the presence of fat, with possible minimal increased arterial enhancement (arrowhead, D), confirmed on subtraction images (arrowhead, F), and washout on delayed images (E) in keeping with a small fat-containing hepatocellular carcinoma. GRE: Gradient recalled echo.

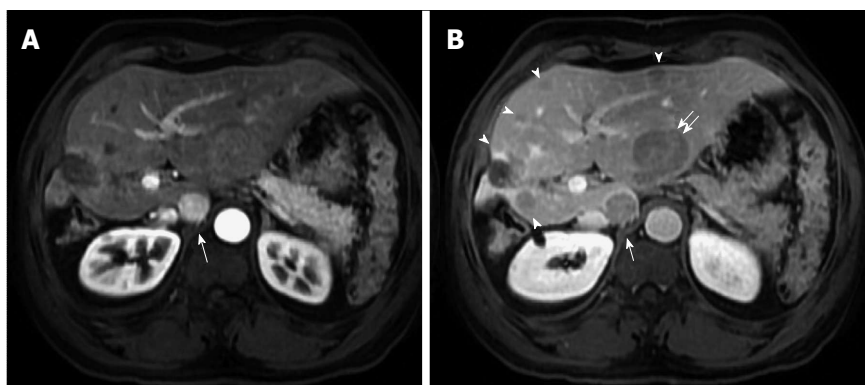


Figure 4 Hypervascular and non-hypervascular hepatocellular carcinomas. Post contrast fat-suppressed 3D-GRE T1-weighted images during the (A) late hepatic arterial and (B) delayed phases. There is a focal hepatic lesion medial to the inferior vena cava, which demonstrates intensely increased arterial enhancement (arrow, A) and washout on delayed images (arrow, B) in keeping with a hypervascular HCC. Additionally, there are multiple foci of delayed washout throughout the liver (arrowheads, B), the largest of which is seen at the left hepatic lobe (double-arrow, B), with variable degrees of arterial enhancement, in keeping with multiple hypo- and iso-vascular HCCs. Of note are the hypertrophic changes of the left hepatic lobe as well as atrophic and post-interventional changes of the right hepatic lobe. HCC: Hepatocellular carcinoma; GRE: Gradient recalled echo.

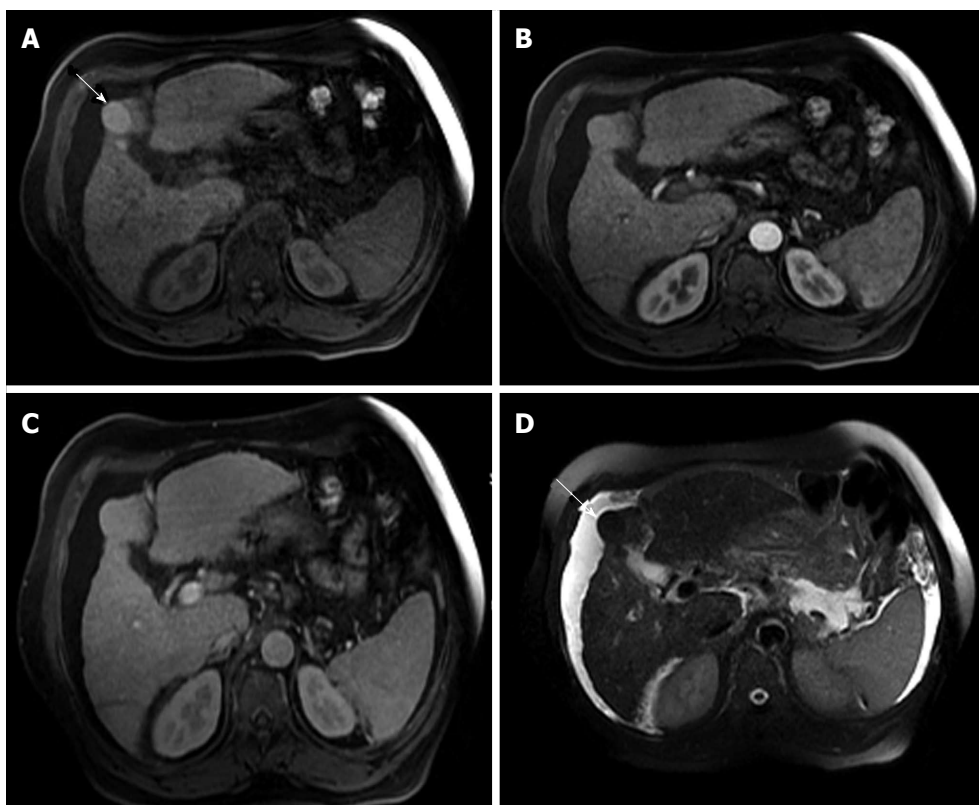


Figure 5 Dominant regenerative hepatic nodule. A-C: Pre- and post-contrast fat-suppressed 3D-GRE T1-weighted images during the (B) late hepatic arterial and (C) portal venous phases; D: Fat-suppressed SSFSE T2-weighted image. There is a subcapsular, partially exophytic nodule at hepatic segment #5, which demonstrates increased intrinsic T1 signal on pre-contrast images (arrow, A) and isosignal intensity to background liver parenchyma on post-contrast images (C), without appreciable increased arterial enhancement (B) or increased T2 signal intensity (arrow, D) in keeping with a dominant regenerative nodule. GRE: Gradient recalled echo; SSFSE: Single-shot fast spin-echo.

Chemical shift imaging aids in the characterization of hyperintense T1-weighted nodules. Fatty nodules show drop of signal intensity on the opposed-phase T1-weighted sequence, due to destruction of the magnitude vector within the same voxel, exerted by fat and water molecules having opposite directions and resulting in decreased signal intensity; indicative of intracellular (microscopic fat).

Chemical shift imaging aids also in the diagnosis of siderotic nodules, showing drop of signal on the sequence with the longer echo-time (TE), which could be during the in-phase or opposed phase, depending on the MR machine used for imaging and its field strength, due to susceptibility effects resulting from proton de-phasing exerted by the presence of iron (Figure 6).

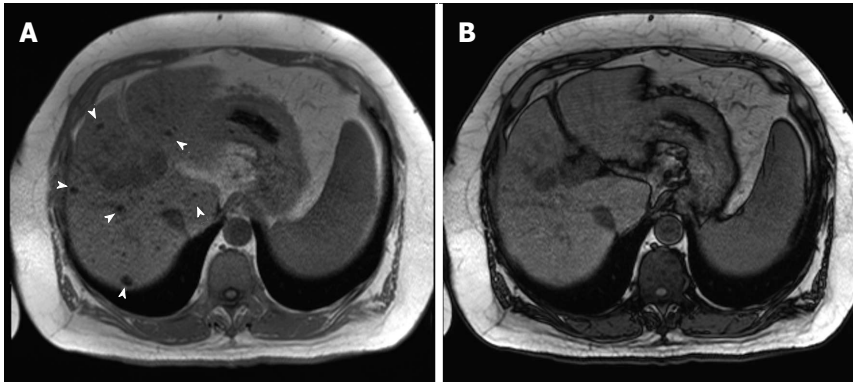


Figure 6 Multiple siderotic hepatic nodules. In-phase (TE = 4.9 ms) (A) and opposed-phase (TE = 2.4 ms) (B) GRE T1 weighted images. There are multiple small nodules seen through out the liver, which demonstrate isosignal intensity on the in-phase images (arrowheads, A), without corresponding abnormalities on the opposed-phase images in keeping with Multiple siderotic hepatic nodules. GRE: Gradient recalled echo.

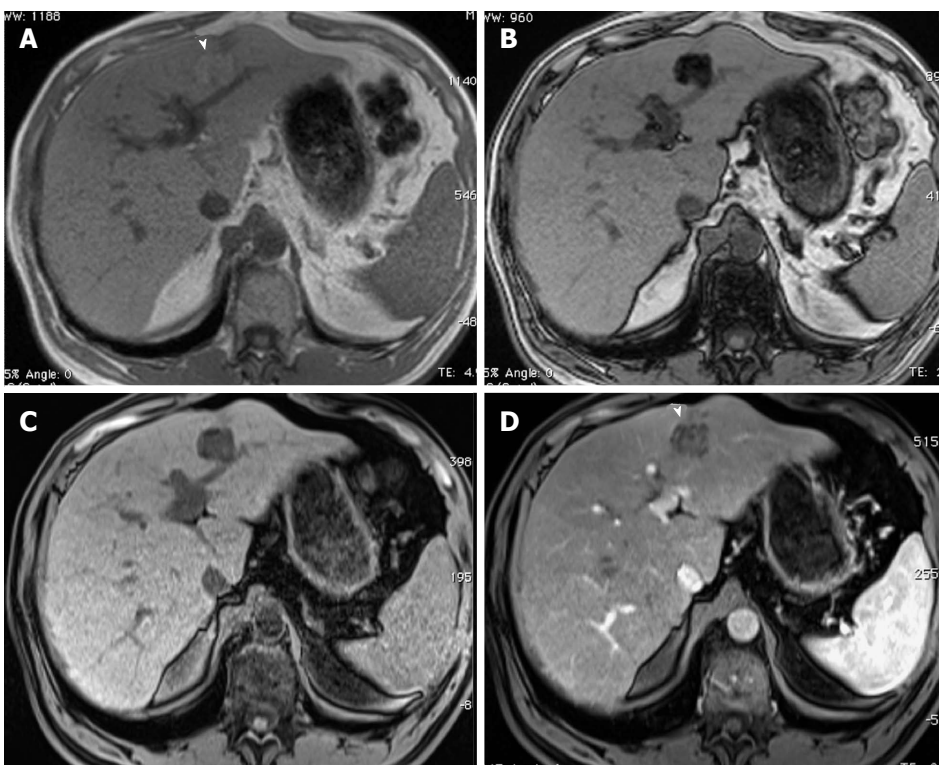


Figure 7 Large, fat-containing hepatocellular carcinoma. In-phase (A) and opposed-phase (B) GRE T1 weighted images. Pre- (C) and post-contrast fat-suppressed 3D-GRE T1-weighted images during late hepatic arterial phase (D). There is a prominent left hepatic nodule, which demonstrates minimally increased intrinsic T1 signal on the in-phase images (arrowhead, A) and low signal intensity on the opposed-phase (B) and pre-contrast images (C), indicating the presence of fat. The lesion demonstrates heterogeneous mildly increased arterial enhancement (arrowhead, D) in keeping with a fat-containing HCC. HCC: Hepatocellular carcinoma; GRE: Gradient recalled echo.

Several studies have shown that nodules with high signal intensity on T1-weighted images are in most cases benign. In younger patients with numerous macro-nodules, almost all of these lesions follow a benign course^[35]. In patients with cirrhosis, small hyperintense hepatic lesions on T1-weighted images without hyper-enhancement on the arterial-phase images usually show no interval growth or disappear during serial imaging^[36]. Regardless of their intrinsic signal features, a reliable finding of RNs is the absence of enhancement on the arterial phase, compared with the background hepatic parenchyma.

A notable exception are fat-containing, large size (> 1.5 cm) nodules (hyperintense on T1-weighted in-phase images with drop of signal on the opposed-phase T1-weighted images), which strongly suggest malignancy (Figure 7). Otherwise, the presence of numerous nodules < 1 cm suggests benignity^[37].

DNs

DNs are defined as regenerative nodules containing atypical cells with nuclear crowding and architectural derangement and a variable number of unpaired arterioles or capillaries without definite histologic

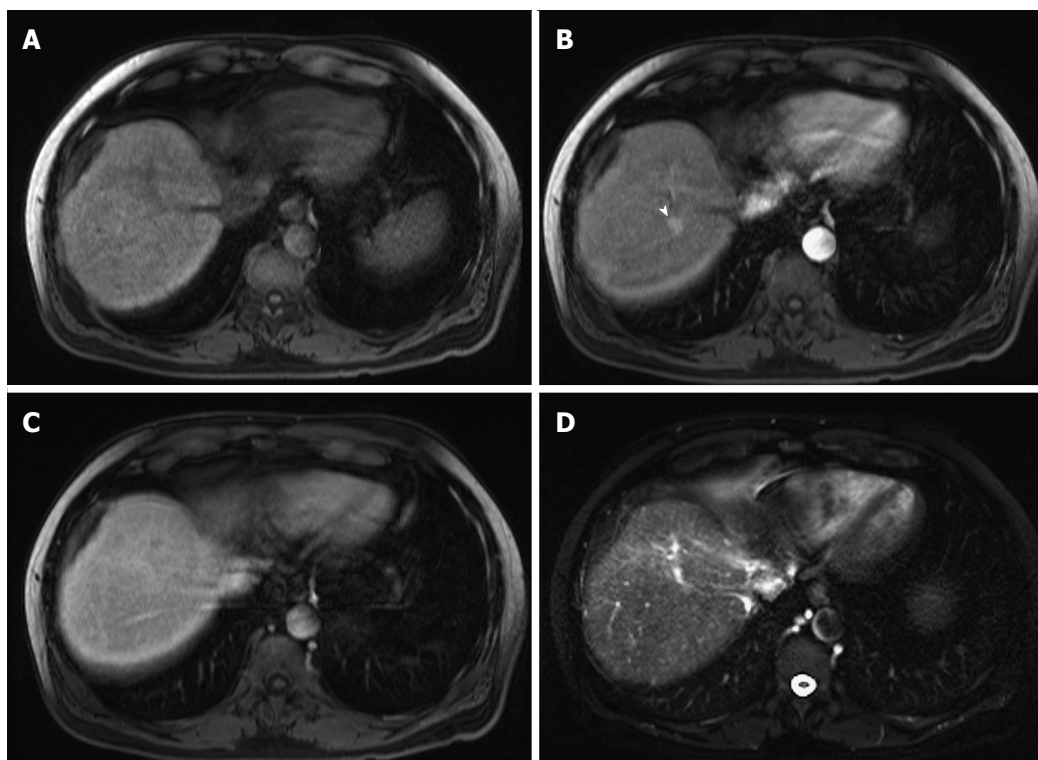


Figure 8 High-grade dysplastic nodules. Pre- (A) and post-contrast fat-suppressed 3D-GRE T1-weighted images during the (B) Late hepatic arterial; and (C) Delayed phases; (D) Fat-suppressed SSFSE T2-weighted image. There is a nodule at hepatic segment #7, which demonstrates iso T1 signal intensity (A), increased arterial enhancement (arrowhead, B), without definite washout or corresponding T2 signal abnormality in keeping with a HGDN. However, early HCC cannot be totally excluded and short-term follow-up should be recommended, especially in patients with hepatitis C infection. HGDN: High-grade dysplastic nodules; HCC: Hepatocellular carcinoma; GRE: Gradient recalled echo; SSFSE: Single-shot fast spin-echo.

signs of malignancy^[38]. High-grade dysplastic nodules (HGDNs) display at least moderate atypia and occasional mitosis^[30]. DNs primarily display T1 and T2 isointensity to the background liver parenchyma, but T1 hyperintensity is also possible as described above with RNs^[39]. Low-grade dysplastic nodules (LGDNs) primarily display enhancement characteristics similar to that of the background liver parenchyma on all dynamic phases; because they remain mainly supplied by the portal circulation. LGDNs are not considered premalignant lesions. As lesions progress, their blood supply becomes more arterialized, giving the typical hypervascular features of HCC^[40]. Unfortunately, the portal and arterial supply to LGDNs and HGDNs is variable and inconsistent^[39]. They may even be associated with increased alpha-fetoprotein despite not being malignant^[41].

HGDNs are considered premalignant lesions^[30] and tend to show intense early enhancement after gadolinium injection and fade to isointensity^[42], without washout (Figure 8), because supply from the portal venous system remains comparable with the background liver^[43,44].

The development of HCC within a DN has been reported within as short as 4 mo^[45]. Usually it is seen as an increase in size and development of washout on delayed imaging, allowing definite diagnosis of HCC (Figure 9). Early studies have also reported DNs with

“a nodule within a nodule” appearance. This classic MR description is a focus of increased T2 signal intensity within a T2 low-signal-intensity nodule, which may or may not demonstrate arterial hyper-enhancement on dynamic MR images^[46].

According to the latest guidelines from the EASL and AASLD practice guidelines, DNs should not be treated or managed as cancers^[47]. In our clinical practice, we advise more frequent surveillance imaging (usually 3 mo) as there is an increased risk of progression to HCC.

ARTERIOPORTAL SHUNTS

Arterioportal (AP) shunts usually demonstrate enhancement on the arterial phase and mostly fade back to isointensity on the portal venous or delayed images (Figure 10). They are sometimes easily distinguished from HGDNs/early HCCs by their subcapsular location and wedge- or comma shaped configuration. However, they may sometimes become main mimickers of HGDN/early HCCs; posing as a potential differential diagnosis when they are round or oval in configuration^[48].

HCC

The EASL and AASLD have proposed and validated

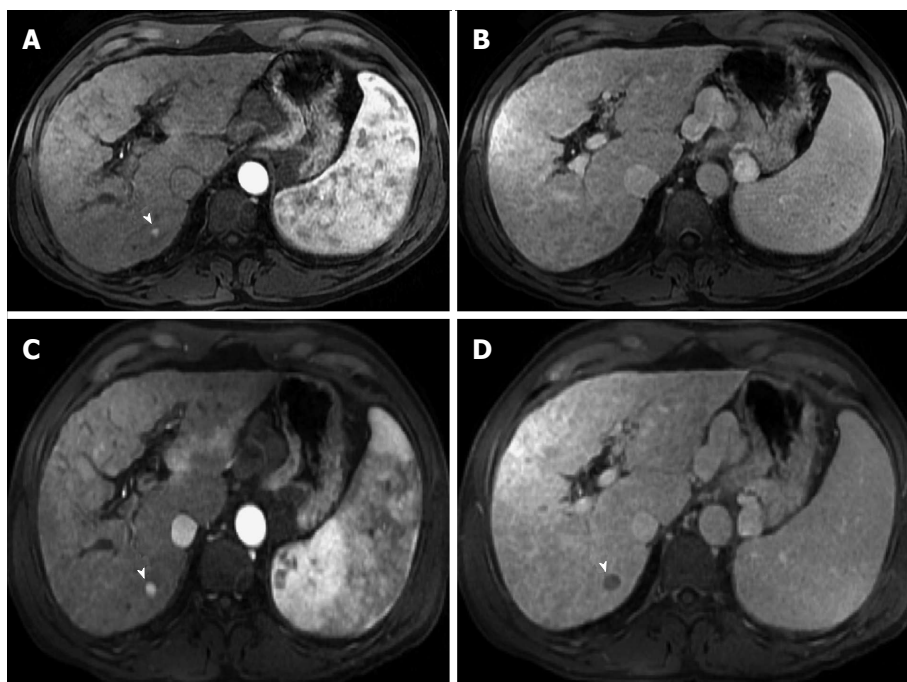


Figure 9 Dysplastic nodule progressing into an hepatocellular carcinoma. Post-contrast fat-suppressed 3D-GRE T1-weighted images during the late hepatic arterial (A and C) and delayed phases (B and D). There is a small right hepatic lobe nodule, which demonstrates increased arterial enhancement (arrowhead, A) and fades out on the delayed images (B) on the initial examination. On the 4-month follow-up study, there is evidence of interval growth (arrowhead, C, D) and development of clear delayed washout (arrowhead, D) both of which are signs of progression into HCC. HCC: Hepatocellular carcinoma; GRE: Gradient recalled echo.

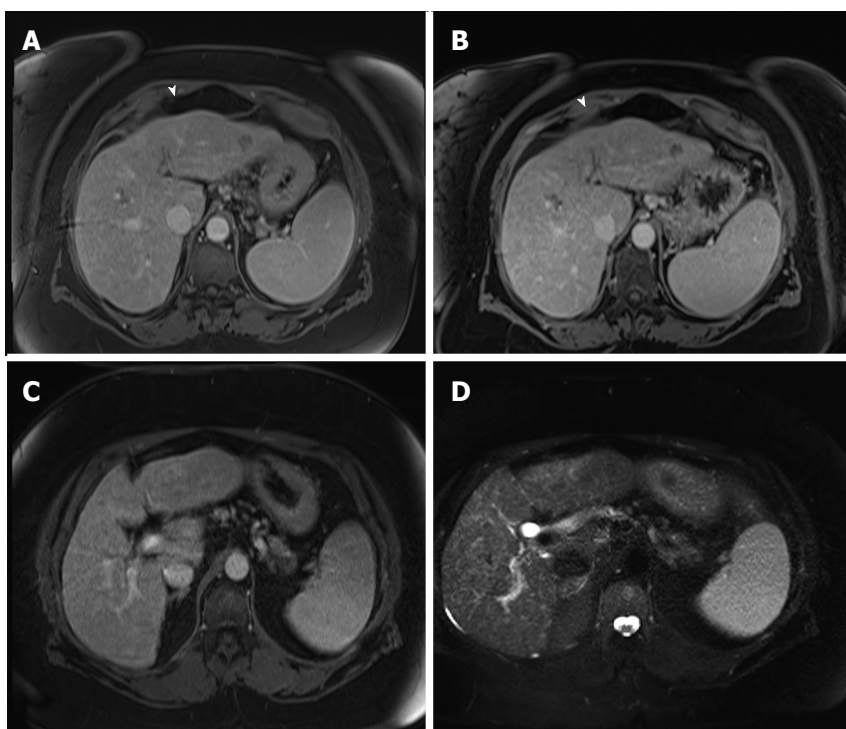


Figure 10 Arterioportal shunt. Post-contrast fat-suppressed 3D-GRE T1-weighted images during the late hepatic arterial (A and B) and delayed phases (C); D: Fat-suppressed SSFSE T2-weighted image. There is a convoluted linear area of increased arterial enhancement with a vessel leading to it (arrowhead, A, B), which does not demonstrate delayed washout (C), or corresponding T2 signal abnormality in keeping with an AP shunt. SSFSE: Single-shot fast spin-echo; GRE: Gradient recalled echo.

imaging criteria for the diagnosis of HCC in cirrhotic patients, which correspond to the typical HCC features including arterial hyper-enhancement and delayed

washout^[49] (Figure 11). HCCs may show a variety of MR imaging features; reflective of the variable characteristics of the tumor's architecture, grading,

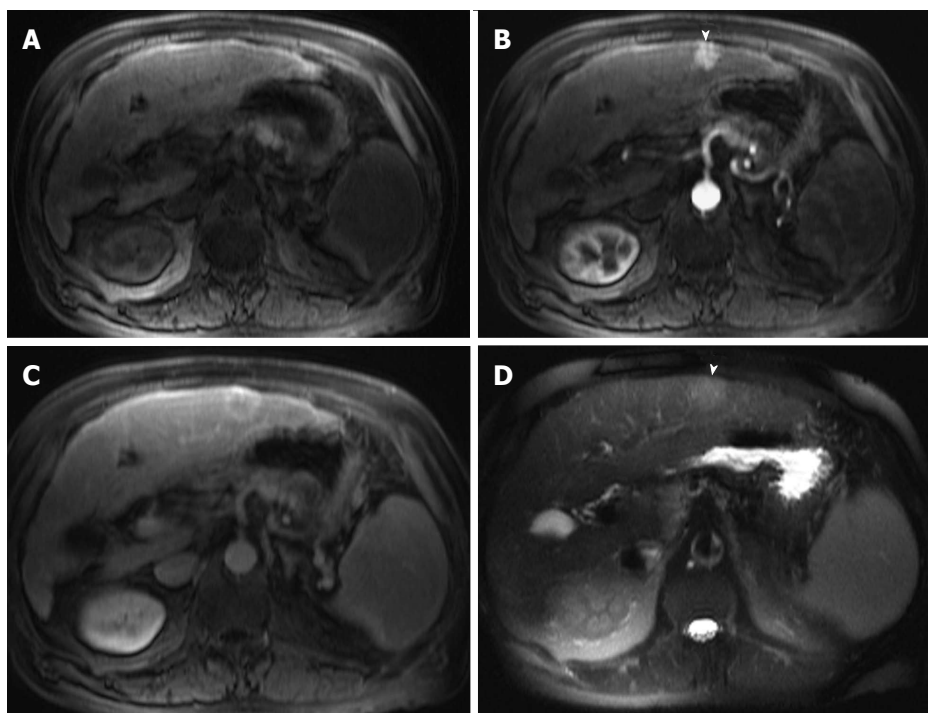


Figure 11 Classical hepatocellular carcinoma. A: Pre- and post-contrast fat-suppressed 3D-GRE T1-weighted images during the late hepatic arterial (B) and delayed phases (C); D: Fat-suppressed SSFSE T2-weighted image. There is a peripheral well defined left hepatic lobe nodule, which demonstrates iso T1 signal intensity (A), increased arterial enhancement (arrowhead, B), delayed washout and pseudocapsule enhancement (C), and mildly increased T2 signal (arrowhead, D) in keeping with classical features of HCC. HCC: Hepatocellular carcinoma; GRE: Gradient recalled echo; SSFSE: Single-shot fast spin-echo.

stromal components, and intracellular content^[22].

Arterial hyper-enhancement is the most common and important imaging finding in the diagnosis of HCC^[50]. While considered a reliable feature, it can be seen in HGDNs and AP shunts. Arterial hyper-enhancement can also be seen in a variety of benign and malignant hepatic lesions, including hemangiomas and focal nodular hyperplasia and hypervascular metastases. However, these liver lesions are infrequent in the setting of hepatic cirrhosis^[51].

Because arterial hyper-enhancement can be observed with other lesions and nodules, additional imaging criteria are needed to decrease the false-positive rate and increase sensitivity, while maintaining high specificity for the diagnosis of HCC^[49]. Therefore, delayed washout, among other secondary features, is used for this purpose.

The key distinguishing feature of HCC is the development of delayed "washout"; defined as arterially enhancing nodules becoming hypointense compared to the background liver on the delayed phase imaging (not to be confused with "fade out", which is defined as arterially enhancing nodules becoming isointense to background liver on delayed phase imaging).

HCCs greater than 2 cm in size tend to show washout^[52,53], which explains the high diagnostic sensitivity for tumors this size. However, for HCCs smaller than 2 cm the sensitivity is lower. This is not due to hypovascular HCCs, which are uncommon, but rather to hypervascular HCCs that do not show

washout on delayed images^[24,49,54] (Figure 12). In one series of 60 HCCs, smaller than 2 cm, 85% of these lesions were hypervascular, and only 61.7% of which showed washout^[24]. Similarly, in another series, 51 out of 131 HCCs showed arterial hyper-enhancement without clear wash-out on delayed images^[54].

Delayed pseudo-capsule enhancement of hepatic nodules aids in the diagnosis of HCC, and can be helpful in lesions that do not show classical features of HCC on dynamic imaging (Figure 13).

Since it is extremely difficult to perform biopsy of small nodules that are only visible on arterial phase images, we usually prefer close follow-up. Generally we advocate that lesions measuring 1-2 cm are re-imaged at a 3-mo interval to assess for lesion interval growth or development of washout. The lack of interval growth on short-term follow-ups does not exclude the possibility of malignancy, as HCC may demonstrate slow growth. Therefore, only nodules that are stable for 2 years are considered benign^[14]. However, it is worth emphasizing the value of direct comparison and lesion measurement between both the current and older prior examination to demonstrate undetected subtle changes in size on short-term followups; which is indicative of slow growth, a feature of early well-differentiated HCC (Figure 14).

MORPHOLOGIC HCC SUB-TYPES

HCCs can manifest as different morphologic types including focal (nodular), massive, and diffuse/

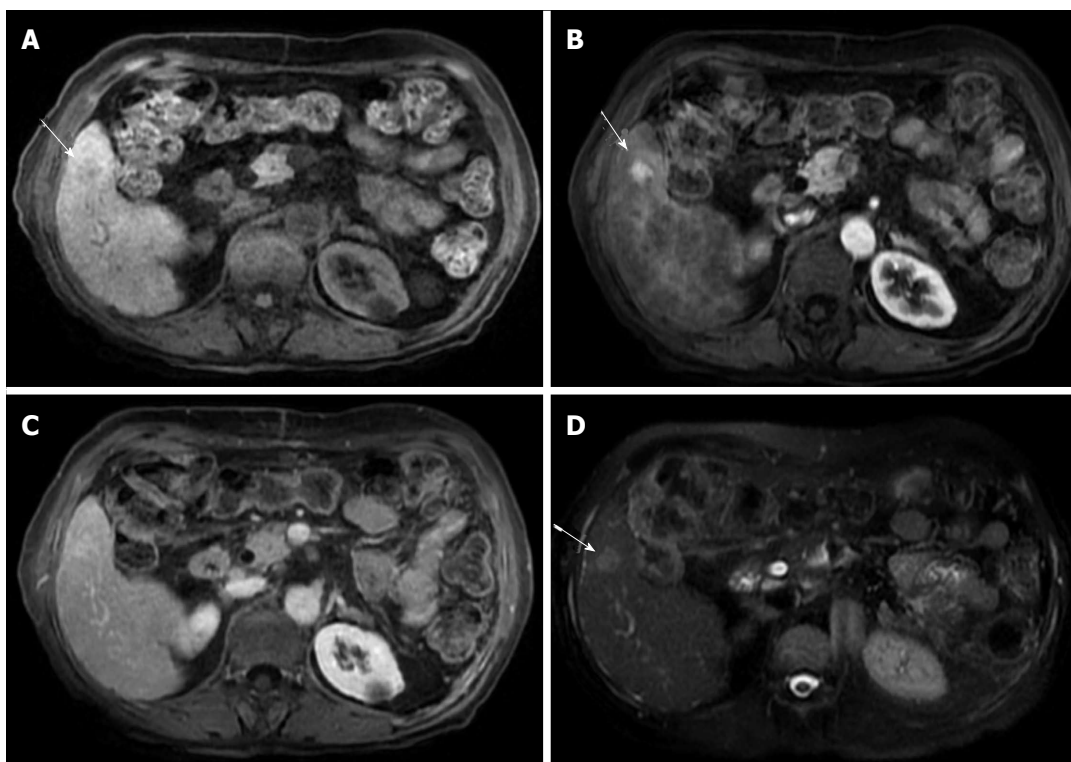


Figure 12 Small, non-washing-out hepatocellular carcinoma. A: Pre- and post-contrast fat-suppressed 3D-GRE T1-weighted images during the late hepatic arterial (B) and delayed phases (C). D: Fat-suppressed SSFSE T2-weighted image. There is a small nodule at hepatic segment #5, which demonstrates minimally decreased T1 signal on pre-contrast images (arrow, A) and increased arterial enhancement (arrow, B). The nodule demonstrates iso to slightly increased signal on the delayed phase images, without clear washout (C), but mildly increased T2 signal intensity (arrow, D) in keeping with an HCC. Note that T2 signal alteration increased the accuracy of diagnosing HCC in this patient, despite the lack of delayed washout (also see Figure 17). HCC: Hepatocellular carcinoma; GRE: Gradient recalled echo; SSFSE: Single-shot fast spin-echo.

infiltrative^[55,56].

Nodular type is the most common encountered type and usually presents as encapsulated focal nodule with well-defined margins. Nodular type can be further classified as solitary or multi-focal.

Massive tumors are well-defined tumors large enough to often render these patients non-eligible for loco-regional ablative therapies or hepatic transplantation.

Multi-focal nodular subtype is an advanced type and shows similar features to solitary nodular subtype on conventional and dynamic MRI. Additional features that are not commonly seen with solitary focal lesions, but are noted with multi-focal HCC and other aggressive subtypes include portal venous thrombosis and intrahepatic metastases^[26].

Diffuse HCCs are usually large and have ill-defined boundaries without clear demarcation. They usually present with very high alpha-fetoprotein levels and are almost always associated with portal venous thrombus; which can be bland or most of the time tumoral in nature; based on the presence of neovascularity on the arterial imaging. Diffuse HCCs can be extremely subtle, and therefore difficult to demonstrate by imaging alone as they can blend with the background cirrhotic parenchyma; preventing early diagnosis and leading to advanced disease at presentation with often

distant metastatic disease.

One study by Kneuert *et al.*^[56] evaluated 147 patients with advanced HCCs (75 with infiltrative disease and 72 patients with multi-focal disease). In that study, failure to display a discrete mass was observed in 42.7% of patients, low signal on T1-weighted images was observed in 55.7%, high signal on T2-weighted images was observed in 80.3% of patients. They also demonstrated mild miliary pattern of enhancement on arterial phase imaging in 16.4% of patients, with delayed washout in 50.8%.

Diffuse HCCs can be difficult to differentiate from areas of confluent fibrosis on CT. However, the combined additive advantage of T2-weighted imaging, DWI, and delayed imaging can be used to enhance the diagnostic accuracy of diagnosis on MRI, which display more distinct lobulated margins, with poorly defined amorphous infiltration surrounding thrombosed portal veins, and clearly depict internal reticulation throughout the tumor^[57,58].

Additionally, post-contrast delayed imaging demonstrates heterogeneous washout^[59], allowing differentiation between confluent fibrosis as this shows increase enhancement over time. Another distinctive feature from confluent fibrosis is the presence of regional tumor thrombus that is almost invariably present in patients with diffuse HCC^[57,60,61] (Figure 15).

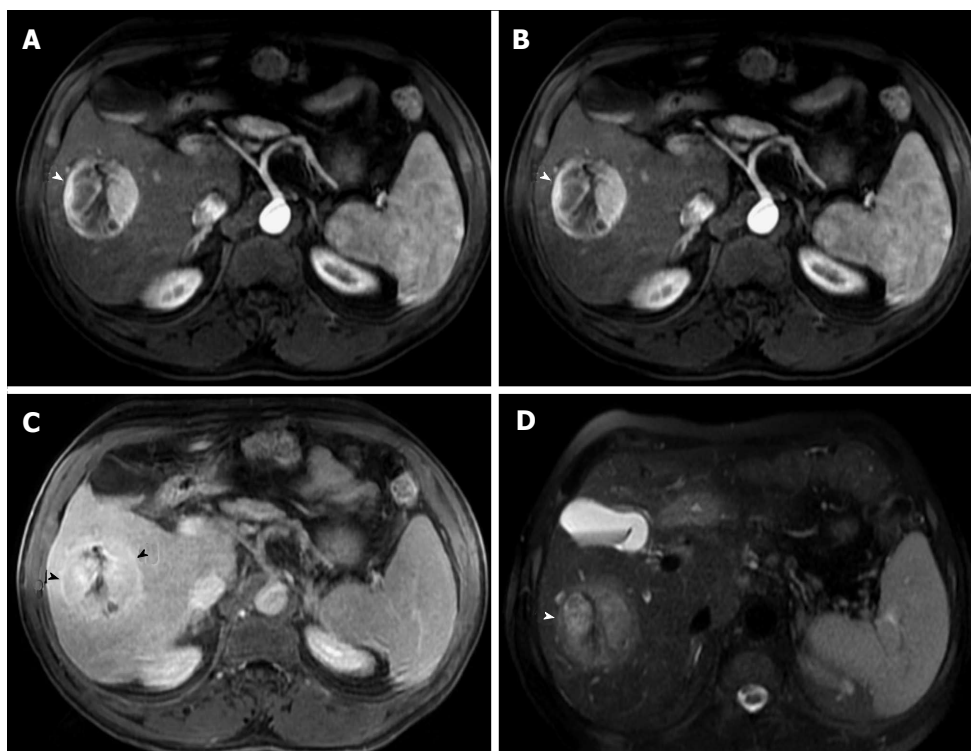


Figure 13 Large hepatocellular carcinoma with delayed pseudocapsule enhancement but no intralesional washout. Post-contrast fat-suppressed 3D-GRE T1-weighted images during the (A) late hepatic arterial, (B) portal venous, and (C) delayed phases; D: Fat-suppressed SSFSE T2-weighted image. There is a large right hepatic lobe mass, which demonstrates heterogeneous, intensely increased arterial enhancement (arrowhead, A) with progressive fading throughout the subsequent images (B), but no clear washout (C). The lesion demonstrates delayed pseudocapsular enhancement (black arrowheads, C) and mildly increased T2 signal intensity (arrowhead, D) in keeping with a large HCC. HCC: Hepatocellular carcinoma; GRE: Gradient recalled echo; SSFSE: Single-shot fast spin-echo.

Multiple small satellite nodules associated with the main tumor or multiple small recurrent tumors of moderate or poor differentiation are regarded as intrahepatic metastases^[62]. The clinical significance about intrahepatic metastases is that they require immediate curative or palliative interventions even when smaller than 1 cm; as such lesions are likely to display aggressive behavior, unlike single or multicentric primary tumors of the same size^[63].

A rare variant of nodular morphologic subtype is lesions with rim-enhancement on arterial imaging on initial MRI (Figure 16) has been described in the literature^[64], suggesting a more progressive behavior with rapid interval growth and disease worsening; therefore, requiring prompt therapy and short-term follow-up.

FUTURE DIRECTIONS

T2-weighted imaging

The appearance of HCC on T2-weighted images is variable. Early reports suggested that HCC displayed high or equivalent signal intensity compared to the liver parenchyma on T2-weighted images^[65,66].

Other researchers reported that both non-enhanced T1- and T2-weighted sequences may contribute in the characterization of cirrhotic nodules; however, minimally increasing the detection rate^[67].

More recent studies have shown that the addition

of T2-weighted imaging to gadolinium-enhanced T1-weighted 3D-GRE dynamic imaging improves the diagnostic performance of MRI in the detection of HCC compared to dynamic MR imaging alone. This is especially true for lesions smaller than 1 or 2 cm (Figure 12), which may show hypervascularity but might not display any washout, distinguishing them from HGDNs^[54,68-70] (Figure 17).

HCCs tend to show minimal to mildly increased signal intensity on T2-weighted images, as opposed to intra-hepatic cholangiocarcinoma or mixed HCC-cholangiocarcinoma; both of which are increasingly being reported in patients with cirrhosis, and tend to show moderately increased signal intensity on T2-weighted images with evidence of increased vascularity on arterial phase imaging and progressive contrast enhancement throughout subsequence phases. Such distinction is clinically important as those lesions are associated with a poor prognosis and a high rate of tumor recurrence after liver transplantation, and have higher risk of nodal and distant metastatic disease^[71].

T2-weighted imaging is also helpful in the detection of lymphadenopathy in patients with focal hepatic lesions^[70].

Diffusion-weighted imaging

The possibility of performing functional imaging sequences is an additional advantage of MRI over CT^[72]. With technological advances in hardware and

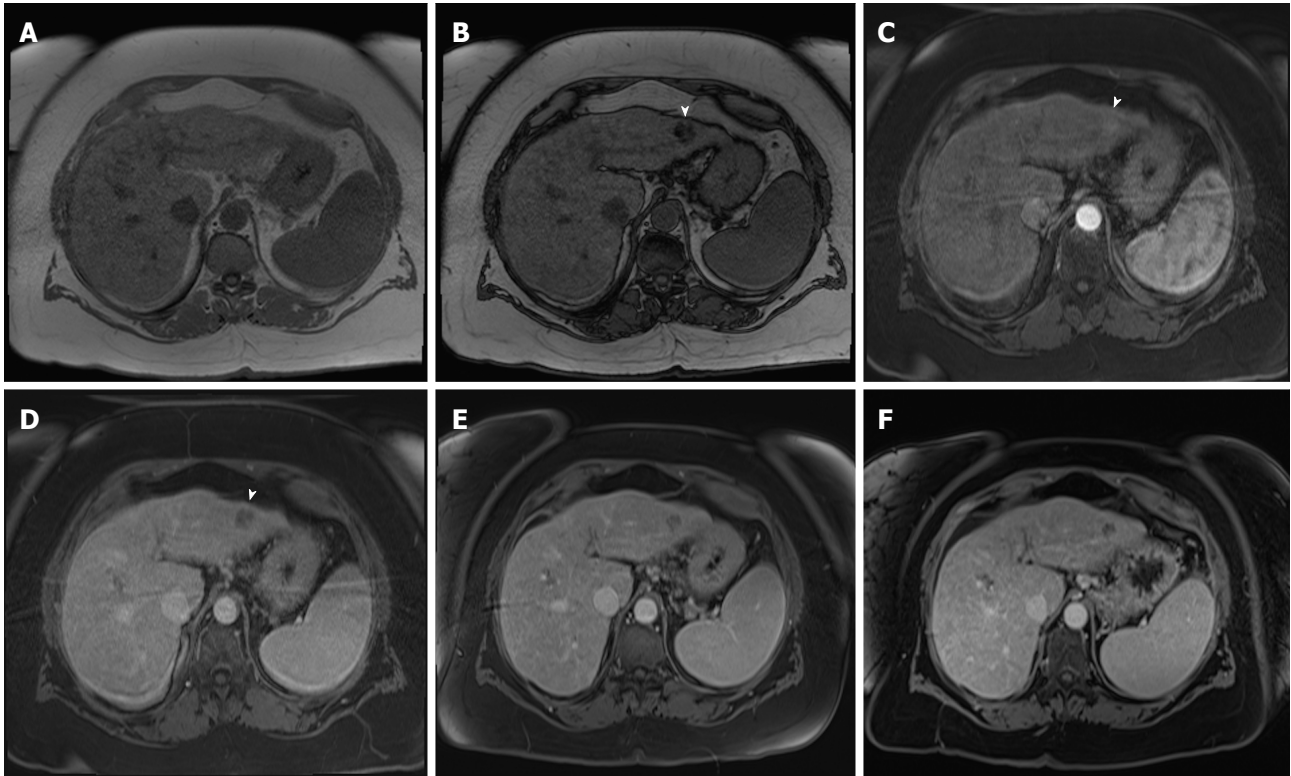


Figure 14 Slow growing, well-differentiated, fat-containing, small hepatocellular carcinoma. In-phase (A) and opposed-phase GRE T1 weighted images (B); Post-contrast fat-suppressed 3D-GRE T1-weighted images during the late hepatic (C) arterial and delayed phases (D). E, F: Post-contrast fat-suppressed 3D-GRE T1-weighted delayed images from prior examinations performed 1 and 2 years prior, respectively. The is a small left hepatic lobe nodule, which demonstrates drop of signal on the opposed-phase image (arrowhead, B) compared to the in-phase image (A), increased arterial enhancement (arrowhead, C), and delayed washout (arrowhead, D). The lesion does not demonstrate significant change in size from the immediate prior examination (E). However, when compared with a more remote examination (F), substantial interval growth can be appreciated consistent with a slow growing, well-differentiated, fat-containing, small HCC. HCC: Hepatocellular carcinoma; GRE: Gradient recalled echo.

software, DWI can be readily applied to liver imaging with improved image quality. DWI is an imaging technique based on differences in the Brownian motion (diffusibility) of water molecules within tissues. In highly cellular tissues such as tumors, the diffusion of water protons is restricted. Therefore, both qualitative and quantitative variables reflect tissue cellularity and cellular membrane integrity^[49,73-75]. DWI is useful for detecting small focal liver lesions in general^[49,73-75].

A limited number of small studies have shown encouraging results suggesting that DWI has a good diagnostic performance in the detection of HCC in patients with chronic liver disease and equivalent to conventional contrast-enhanced for lesions greater than 2 cm in size^[49,76]. Currently, the limitation of DWI is primary lesion characterization rather than lesion detection^[49,76].

The greatest benefit relies on the combined use of DWI with conventional dynamic MRI; providing higher sensitivities than dynamic MRI alone in the detection of small HCC lesions in patients with chronic liver disease^[77,78] (Figure 18). Therefore, an additional acquisition of DWI is being implemented in abdominal protocols^[77].

In a recent study a new MRI criteria was proposed, combining the features of lesions after gado-

linium-based contrast agents administration and hyperintensity on DWI^[49]. This significantly increased the sensitivity for the diagnosis of HCC compared to conventional hemodynamic criteria, irrespective of tumor size. However, further larger prospective studies are still needed to establish its definitive role for detecting HCC in patients with chronic liver diseases.

T2*-weighted imaging

The performance of liver MRI is highly dependent on gadolinium administration^[79]. The revised recommendations refrain from the utilization of intravenous gadolinium-based contrast agents in patients with poor renal function^[80]. One recent report has suggested that T2*-weighted MRI may offer the potential for diagnosing HCC in patients with liver cirrhosis^[81].

The proposed mechanism for the visualization of HCC on the T2*-weighted sequence is attributed to the combination of the high sensitivity of this sequence to the presence of iron and iron differential deposition in the hepatic parenchyma. On T2*-weighted MRI, hepatic iron causes progressive signal loss with longer TEs, whereas HCCs demonstrate only slight signal loss^[81].

One limitation of this sequence is the appearance of lesions after chemoembolization, which potentially

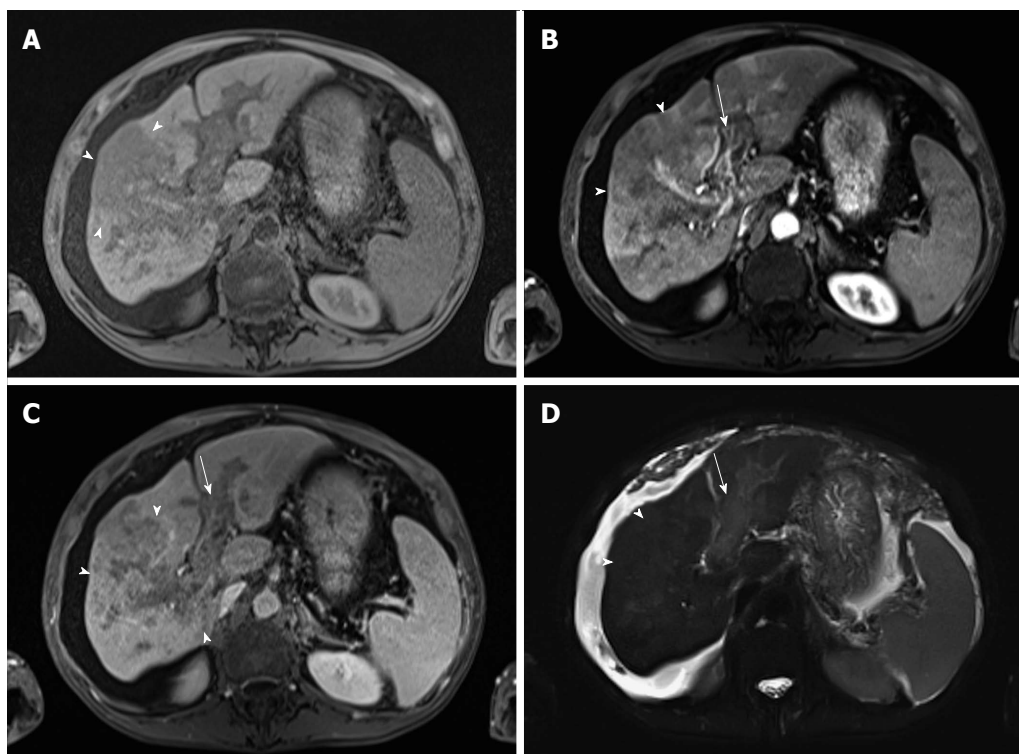


Figure 15 Diffuse hepatocellular carcinoma associated with tumor thrombus. (A) Pre- and post-contrast fat-suppressed 3D-GRE T1-weighted images during the (B) late hepatic arterial and (C) delayed phases; (D) Fat-suppressed SSFSE T2-weighted image. There is a large ill-defined area involving the right hepatic lobe, which shows decreased T1 signal in pre-contrast images (arrowheads, A), heterogeneous mildly increased arterial enhancement (arrowheads, B), and heterogeneous delayed washout with permeative appearance (arrowheads, C), and heterogeneous mildly increased T2 signal (arrowhead, D) in keeping with HCC. There is also evidence of expansion of the portal vein branches, abnormal increased arterial enhancement (arrow, B), lack of opacification and washout on the delayed images (arrow, C), and mildly increased T2 signal (arrow, D) simulating the behavior of the primary tumor in keeping with diffuse tumor thrombus, a finding almost invariably associated with diffuse HCC subtype. Also of note is the mild to moderate ascites and omental hypertrophy secondary to portal hypertension. HCC: Hepatocellular carcinoma; GRE: Gradient recalled echo.

reduces the diagnostic performance of the sequence^[82].

The addition of a T2*-weighted sequence to a routine liver MRI protocol might lead to additional improved specificity^[83], although future studies are likely indicated to determine the full diagnostic performance of T2*-weighted MRI in a larger patient population.

MRI CONTRAST AGENTS

Contrast agents used in cirrhosis-associated hepatic nodules MR evaluation are divided into three types: extracellular Gadolinium-based contrast agents (GBCAs), super-paramagnetic iron-oxide (SPIO) particles, and Gadolinium-based hepatobiliary contrast agents.

Extracellular GBCAs are paramagnetic contrast agents that generate T1-shortening and provide information about tissue vascularity^[38]. SPIO particles and hepatobiliary agents are liver-specific contrast agents. SPIO particles are taken up by Kupffer cells within the reticuloendothelial system (RES), and the hepatobiliary agents are taken up by hepatocytes and are excreted *via* the bile ducts^[84].

Despite early promising results of SPIO particles for diagnosing HCC, later evidence reveal that is less

efficient than dynamic MRI using conventional extracellular GBCAs in the detection and characterization of HCC^[85]. Additionally, there are currently no commercially available intravenous SPIO particles contrast agents in the market.

More recently, two hepatobiliary agents; gadobenate dimeglumine and gadoxetic acid were introduced to the market, combining extracellular properties with liver-specific properties, allowing both dynamic and hepatobiliary imaging. Gadoxetic acid is more highly liver-specific; approximately 50% of the injected dose is taken up by functioning hepatocytes and is excreted in bile, allowing delayed uptake imaging within 20 min from the time of injection, compared with an uptake of 3%-5% for gadobenate dimeglumine, which allows for delayed uptake imaging within two hours^[13].

The hepatocyte uptake manifests as an increased signal in the hepatic parenchyma on T1-weighted images resulting in improved lesion-to-liver contrast as less well-differentiated HCCs contain hampered functioning hepatocytes. HCCs exhibit hypointensity on hepatobiliary phase images (Figure 18), except for some well-differentiated HCCs that may retain the contrast agent. Nevertheless, characterization of liver lesions depicted with hepatobiliary phase imaging must be performed in conjunction with routine dynamic

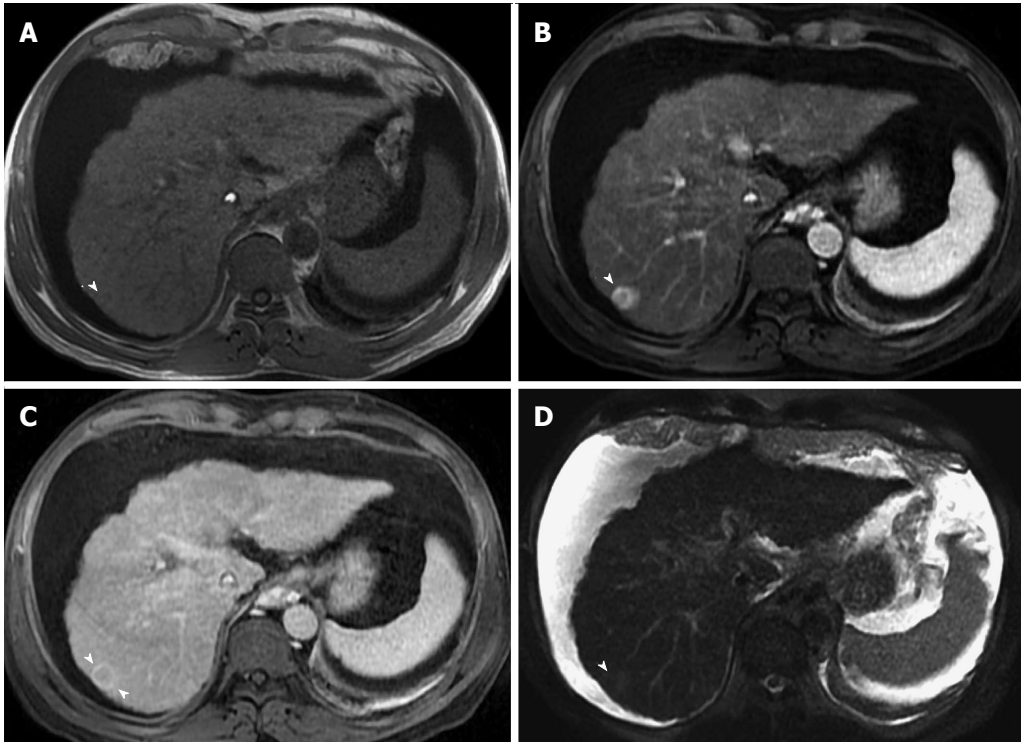


Figure 16 Ring-enhancing hepatocellular carcinoma, indicative of a more aggressive course. A: In-phase GRE T1 weighted image; B: Post-contrast fat-suppressed 3D-GRE T1-weighted images during the (B) late hepatic arterial and (C) delayed phases; (D) Fat-suppressed SSFSE T2-weighted image. There is a small nodule at hepatic segment #7, which demonstrates iso to slightly low T1 signal (arrowhead, A), heterogeneous increased arterial enhancement, predominantly peripheral (arrowhead, B), washout and pseudocapsule enhancement on delayed images (arrowhead, C), and mildly increased T2 signal intensity (arrowhead, D) in keeping with ring-enhancing HCC. HCC: Hepatocellular carcinoma; GRE: Gradient recalled echo; SSFSE: Single-shot fast spin-echo.

sequences to improve accuracy^[86].

Gadoxetic acid-enhanced MRI has several advantages in imaging the cirrhotic liver including: (1) higher sensitivity for the diagnosis of HCC, especially for lesions ≤ 2 cm^[86-91]; (2) improved characterization of arterially enhancing lesions without definite washout on subsequent imaging^[89,92]; (3) distinguishing arterially enhancing pseudo-lesions from HCC^[92,93]; and (4) detection of lesions that are isointense to the background hepatic parenchyma on all sequences, apart from the hepatobiliary phase, that are at high risk of transforming to hypervascular HCC^[94,95].

However, some limitations to the use of gadoxetic acid-enhanced MRI in the liver cirrhosis have been proposed, especially pertaining to the fact that some patients with cirrhosis can show less optimal lesion-to-liver contrast on early dynamic imaging and poor venous enhancement, which may hamper the diagnosis of HCC and assessment of the porto-spleno-mesenteric venous system patency^[86].

Despite the recognized potential advantages of combined morphological and functional analysis of the liver, the inclusion of hepatobiliary contrast agents in international guidelines, besides the Japan Society of Hepatology, is still pending. Recently updated guidelines from the EASL^[47] and the AASLD^[6] make no contrast agent recommendations.

Overall, continued investigations with more direct comparative analysis between gadoxetic acid and

other extracellular agents are warrant.

LI-RADS

LI-RADS was developed by the American College of Radiology^[96]; with the aim of standardizing terminology and criteria for interpreting and reporting findings of CT and MRI examinations of the liver in patients with cirrhosis or increased risk of HCC; by using use a carefully chosen and agreed-on vocabulary, or lexicon, that differentiates hepatic histologic entities. It has been developed to provide a framework for assigning degrees of concern on imaging findings^[97]. The LI-RADS classifies lesions to five categories ranging from definitely benign to definitely HCC. It uses arterial hyper-enhancement, washout, capsule, and interval growth as ancillary findings^[96]. It currently, however, does not apply to hepatobiliary gadolinium-based agents^[97].

CONCLUSION

Noninvasive imaging has become the standard for HCC diagnosis in cirrhotic patients. Typical imaging features of HCC such as increased arterial enhancement and delayed washout provide very high specificity and acceptable sensitivity even in nodules ranging from 1-2 cm in diameter. However, limitations apply specifically to hypovascular HCCs and in the differentiating HGDNs

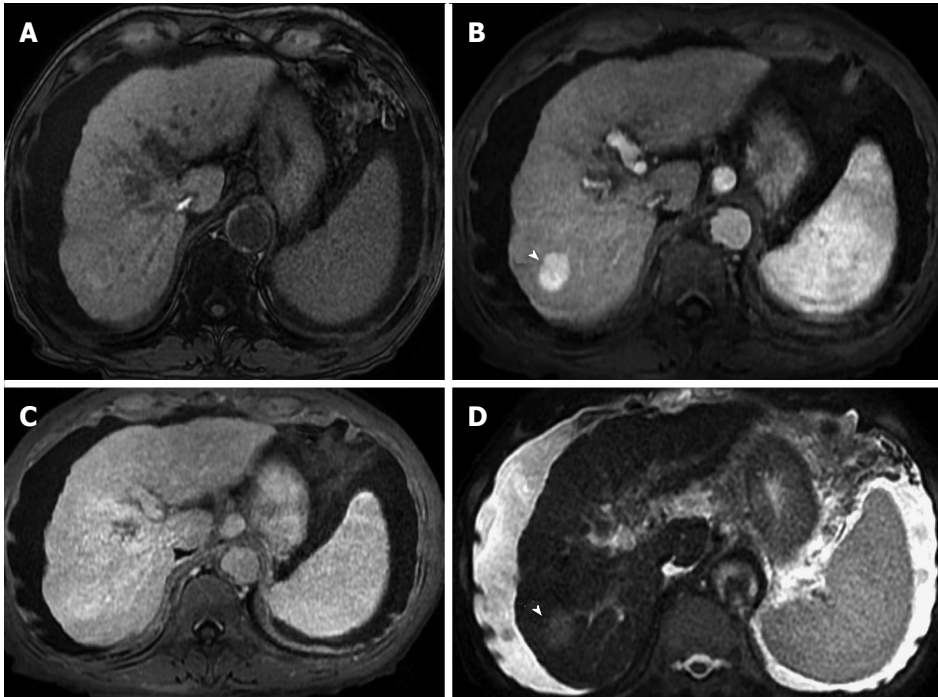


Figure 17 Large, non-washing-out hepatocellular carcinoma. A: Pre- and post-contrast fat-suppressed 3D-GRE T1-weighted images during the (B) late hepatic arterial and (C) delayed phases; D: Fat-suppressed SSFSE T2-weighted image. There is a sizable right hepatic lobe nodule, which demonstrates iso T1 signal intensity on pre-contrast images (A); increased arterial enhancement (arrowhead, B); becomes iso to slightly hyperintense compared to background liver, without definite washout, on the delayed images (C); and demonstrates mildly increased T2 signal intensity in keeping with HCC. Note that T2 signal alteration increased the accuracy of diagnosing HCC in this patient, despite the lack of delayed washout (also see Figure 12). HCC: Hepatocellular carcinoma; GRE: Gradient recalled echo; SSFSE: Single-shot fast spin-echo.

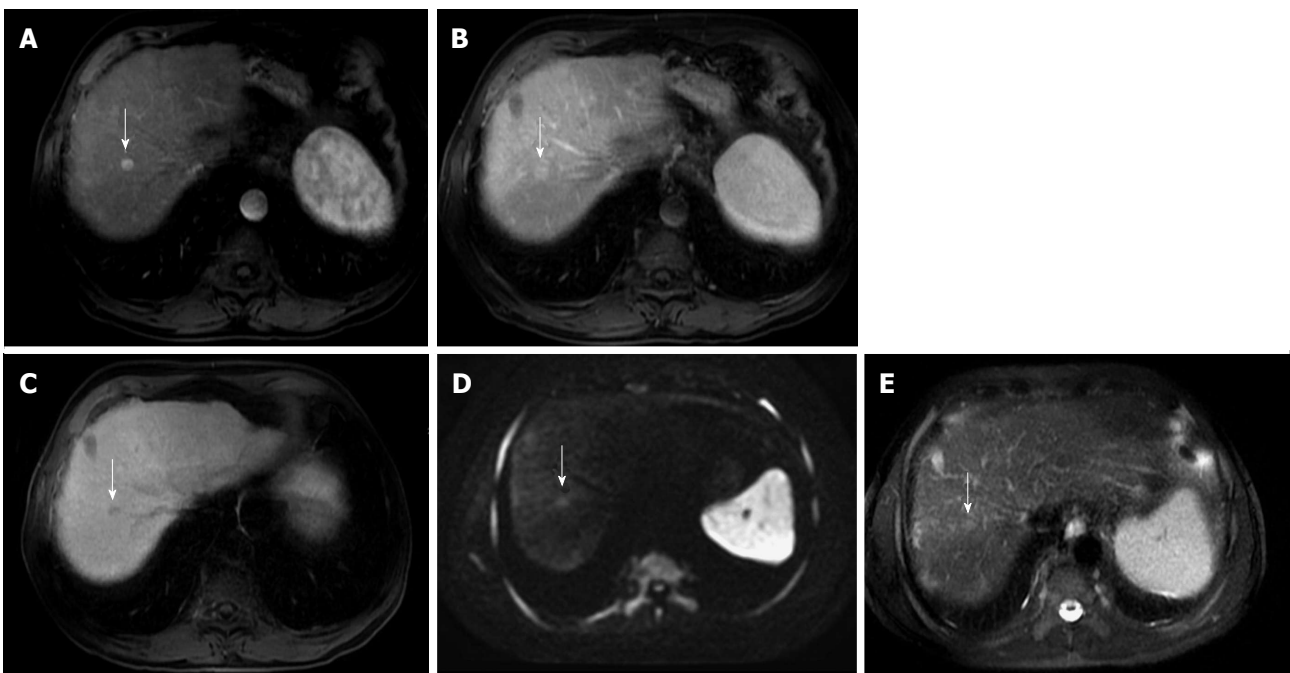


Figure 18 Small hepatocellular carcinoma showing the value of diffusion weighted image and hepatocyte-specific agents. A: Post-contrast fat-suppressed 3D-GRE T1-weighted images during the (A) late hepatic arterial, (B) delayed, and (C) hepatobiliary phases; D: Diffusion weighted image (DWI) ($b = 50$); E: Fat-suppressed SSFSE T2-weighted image. There is a small right hepatic lobe nodule, which demonstrates increased arterial enhancement (arrow, A), fading out on the delayed images (arrow, B), and demonstrates significantly decreased uptake on the hepatobiliary phase (arrow, C). The lesion also demonstrates clear increased signal on DWI (arrow, D) and subtle increased T2 signal (arrow, E). The constellation of findings is consistent with HCC. The decreased uptake on the hepatobiliary phase and increased signal on DWI increased the accuracy of HCC diagnosis in this patient with a small hypervascular nodule. HCC: Hepatocellular carcinoma; GRE: Gradient recalled echo; SSFSE: Single-shot fast spin-echo.

from early HCCs. In this review paper, we went over the basics of MR imaging of cirrhotic livers and

described future directions, including the addition of new techniques such as DWI, T2*, and hepatocyte-

specific MRI contrast agents, in order to improve HCC detection rate in conjunction with the reference standard of optimized dynamic GRE T1-weighted imaging, with individually tailored arterial phase timing.

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P- Reviewer: Kaya M, Lee YYV **S- Editor:** Tian YL **L- Editor:** A
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