

ARTICLE

MRI in detection of hepatocellular carcinoma (HCC)

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Abstract

Hepatocellular carcinoma (HCC) is the commonest malignancy of the liver and is usually due to cirrhosis. Early detection of HCC and the premalignant dysplastic nodules has implications on the management options of tumor ablation, liver resection and transplantation. Magnetic resonance imaging is useful for the detection and characterization of lesions, in the identification of dysplastic nodules and their malignant transformation into HCC.

Keywords: Cirrhosis; liver tumors; hepatocellular carcinoma; imaging; magnetic resonance imaging; computed tomography; ultrasonography; regenerative nodule; dysplastic nodule.

Introduction

HCC is the commonest primary malignancy of the liver accounting for one million deaths annually worldwide. The incidence of HCC in North America has almost doubled during the past 20 years, more significantly among younger people of 40–60 years^[1]. More than 80% of patients with HCC have underlying cirrhosis of varied etiology.

Cirrhosis of the liver is a progressive diffuse fibrosis with architectural distortion and nodular regeneration. Chronic viral hepatitis due to the Hepatitis B and Hepatitis C virus is the most important etiologic factor in North America followed by alcoholic liver disease. Other uncommon causes include hemochromatosis, hemosiderosis, Wilson's Disease, alpha1 antitrypsin deficiency, Budd–Chiari Syndrome, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, toxins like aflatoxin and cryptogenic etiology. All types of cirrhosis predispose to HCC.

Pathology of nodules in cirrhosis

Regenerative nodules represent focal proliferation of hepatocytes in response to various injurious stimuli.

They can be classified as micronodular (<5 mm) or macronodular (>5 mm). Their blood supply is from the portal vein and hence they show an enhancement pattern similar to the normal liver parenchyma. Some nodules may contain iron (siderotic nodules) and these have a greater propensity towards dysplasia.

Dysplastic nodules are premalignant and contain atypical hepatocytes without definite features of malignancy on histology. According to the severity of the cellular atypia, they can be low grade or high grade and can undergo malignant transformation in a short duration of 4 months^[2]. They receive their blood supply from the portal vein and are hypovascular. However, occasionally they can have increased arterial flow^[3].

HCC may be solitary, multifocal or diffusely infiltrative. Small HCC (<3 cm) are usually well differentiated whereas larger and diffuse HCC are poorly differentiated. They receive their blood supply mostly from the hepatic artery although rarely portal venous supply may be noted. Fibrous capsule and fat may be noted in well differentiated HCC thus differentiating them from dysplastic nodules. Fibrous septa, necrosis, hemorrhage and invasion of veins and bile ducts can also be present.

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Importance of early detection

Early detection and staging of HCC are necessary for the more effective triage of patients and in planning management strategies like resection, transplantation, tumor ablation (using radiofrequency, cryotherapy or percutaneous ethanol injection) and chemo-embolization. Although long term survival is poor, it is significantly increased following early diagnosis and treatment. The survival of cirrhotic patients undergoing transplantation with a solitary HCC of less than 2 cm is similar to that of patients transplanted for non-malignant disease^[4] whereas patients transplanted with up to three discrete lesions of less than 3 cm or a solitary 2–5 cm lesion have a 75% 4-year survival^[5]. The commonly used criteria for liver transplantation include a single tumor of less than 5 cm, fewer than three tumors (largest no greater than 3–4 cm), no invasion of major blood vessels and no lymph node or extra-hepatic site involvement. When patients fall outside these criteria, the survival rate is reduced. There is an advantage of liver transplantation over liver resection, even in potentially resectable HCC. In patients with cirrhosis and HCC, living donor liver transplantation yields superior results when the waiting time for a cadaveric organ exceeded 7 months^[6].

Diagnosis of HCC

Measurement of serum alpha fetoprotein (AFP) is used for the screening of patients with cirrhosis and rising serum AFP levels are diagnostic of HCC. However, it is neither sensitive nor specific if used alone. Moreover, with dysplastic nodules and small HCC, the level of AFP is usually in the normal range and imaging plays an important role in the early detection of dysplastic nodules and HCC.

Ultrasonography

Sonography has variable sensitivity in the detection of HCC in the cirrhotic liver ranging from 33 to 96% with a high sensitivity of 80% if HCC is suspected clinically. However, there are no specific features to distinguish dysplastic nodules from HCC and it has low sensitivity for the detection of dysplastic nodules (0–1.6%) and also for small HCC less than 1 cm^[7]. Harmonic imaging and sonographic contrast agents may improve detection of the lesions^[8–10].

Computed tomography

Multiphasic dynamic helical computed tomography (CT) is useful in the evaluation of nodular lesions in the cirrhotic liver. Arterial phase imaging is most useful for the detection of HCC as its predominant blood supply is from the hepatic artery. However, it is less sensitive for the detection of small HCC and for

dysplastic nodules which appear isodense to the liver parenchyma due to their predominant blood supply from the portal vein^[11,12]. CT arterio-portography and CT hepatic arteriography are more sensitive for the detection of HCC but the false positive rate is high due to benign hypervascular lesions like arterioportal shunts^[13,14]. Multidetector CT has a higher sensitivity in the detection of HCC in patients with cirrhosis due to increased speed and improved spatial and temporal resolution. Double arterial phase imaging is useful for the evaluation of hepatic arterial anatomy which is essential in patients who are likely to undergo surgery as well as in improved detection of HCC.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is extremely useful in the detection and characterization of regenerating and dysplastic nodules and HCC (Table 1). Several studies have demonstrated the superiority of MRI in both lesion detection and characterization for focal hepatic lesions when compared to CT^[15,16].

Techniques

There are various new techniques that can be employed in the evaluation of HCC and nodular lesions of the liver. Non-contrast sequences include fast spin echo sequence with short and long echo times (T1 and T2 W images), in-phase and opposed phase T1 W gradient echo images and fat suppression with T2 W fast spin echo sequences.

The choice of sequence is generally dictated by field strength, gradient factors and patient cooperation. In general T1 weighted imaging is performed with the breath hold spoiled gradient echo (SGE) technique. The advantages of this sequence include fast data acquisition, avoidance of breathing artifacts and complete coverage of the liver in a single breath hold. Optimal parameters for this sequence include relatively long TR (100–150 ms) and flip angle of approximately 60–90 degrees. This sequence generates 14–22 sections in a 20-s breath hold period. The drawback of SGE is that it requires the patient to suspend respiration. In patients who cannot cooperate, spin echo techniques are effective if the breathing is regular, otherwise breathing independent techniques such as turbo FLASH are necessary. T2 weighted imaging is most frequently performed as echo train spin echo (FSE or TSE). Short tau inversion recovery (STIR) may also be used as a T2 weighted sequence and this can be modified to turbo STIR to save time. In-phase and opposed phase T1 W gradient echo images are useful for the evaluation of fatty infiltration of lesions.

Multiphasic dynamic gadolinium contrast enhanced T1 W images in hepatic arterial, portal venous and delayed phases improve the detection and characterization of lesions, particularly small HCC, and they

Table 1 MR features of focal liver lesions in cirrhosis

| Lesion | T1 W image | T2 W image | Contrast enhancement pattern | SPIO uptake | Other features |
|---------------------|---------------|--------------|-------------------------------------|-------------|---|
| Regenerative nodule | Variable | Hypointense | Enhances during portal venous phase | Present | Siderosis |
| Dysplastic nodule | Hyperintense | Hypointense | Enhances during portal venous phase | Present | Siderosis, nodule-in-nodule |
| HCC (small) | Hypointense | Hyperintense | Enhances during arterial phase | Absent | Nodule-in-nodule |
| HCC (large) | Heterogeneous | Hyperintense | Enhances during arterial phase | Absent | Fibrous capsule, satellite nodules, invasion, fat |
| Pseudolesion | Variable | Hypointense | Enhances during arterial phase | Absent | |

are superior to multiphasic helical CT^[17–19]. It is performed with a T1 weighted GRE sequence with the shortest possible TE and with a breath-hold technique. 3-D sequences are recommended as they provide both a higher signal to noise ratio and thinner effective slice thickness. Fat suppression is desirable because the conspicuity of contrast enhancement is improved. However, small HCC may not always be detected.

Superparamagnetic iron oxide (SPIO) or Ferumoxide particles are taken up by Kupffer cells and result in decreased signal intensity on T2 W images. Uptake of SPIO occurs in benign hepatocellular lesions but not in HCC, thus improving the detection of small HCC and also helping in the differentiation of HCC from regenerative and dysplastic nodules, both of which show SPIO uptake. Hypovascular HCC not seen on a dynamic Gd-contrast study may be detected on SPIO images. Double contrast MR imaging using gadolinium and SPIO is found to be highly sensitive (92%) in the diagnosis of HCC larger than 1 cm and better than either of them alone. However, the sensitivity for the detection of subcentimeter lesions (38%) is still poor^[20–22].

Tissue or liver specific MR contrast agents like Mangafodipir (MnDPDP), Gadobenate (Gd-BOPTA) and Gadoxetic acid (Gd-EOB-DTPA) may be useful in the detection of hepatocellular tumors. However, they are not superior to gadolinium and are not useful in the differentiation of well-differentiated HCC from benign nodules^[23–25].

Imaging characteristics

Regenerative nodules

These have variable intensity on T1 W images, are hypointense on T2 W images with an enhancement pattern similar to normal liver parenchyma and without abnormal enhancement during the arterial phase. They also take up SPIO^[26–28]. Siderotic nodules appear hypointense on T1 and T2 W gradient recalled echo images. However, siderosis can also be noted in dysplastic nodules.

Dysplastic nodules

Due to the gradual change of a regenerative nodule to a dysplastic nodule and then to HCC, it may not

always be possible to differentiate one from the other. Dysplastic nodules appear hyperintense on T1 W and hypointense on T2 W images (Fig. 1). They enhance in the portal venous phase and appear iso/hyperintense to liver parenchyma. Uptake of SPIO and the presence of siderotic foci may also be noted. Malignant change appears as nodule-within-a-nodule with hyperintense foci within a hypointense nodule on T2 W images. However, the nodule-within-nodule appearance can also occur in small HCC. The absence of a fibrous capsule, fat, arterial phase enhancement and hyperintensity on T2 W images help in differentiating dysplastic nodules from HCC. However, occasionally, dysplastic nodules can enhance during the hepatic arterial phase^[29,30].

HCC

Most HCC are characteristically hypointense on T1 W and hyperintense on T2 W images with intense enhancement during the hepatic arterial phase of a dynamic gadolinium contrast study (Fig. 2). However, the intensity on T1 W images can be variable due to hemorrhage and the presence of copper, protein, lipid and glycogen. HCC show no uptake of SPIO.

Small HCC, in addition may have nodule-within-a-nodule appearance. Large HCC may have certain characteristic features including: (a) a fibrous capsule that appears hypointense on T1 W and T2 W images with enhancement during the portal venous or delayed phases of a dynamic contrast study, depending on the extent of vascularity^[31,32]; (b) a mosaic appearance due to areas of necrosis and hemorrhage; (c) extra capsular extension into adjacent parenchyma and vessels; (d) satellite nodules; (e) lymph nodal and distant metastases.

Diffuse type HCC is an extensive, ill-defined, infiltrative, heterogeneous tumor with variable intensity on T1 W and heterogeneous hyperintensity on T2 W images and variable enhancement on the early phase of dynamic contrast study^[33].

There are certain benign lesions like focal fibrosis, hemangioma, arterio-portal shunts and other pseudolesions of unknown etiology which can be mistaken for HCC on imaging. However, the different techniques of MR are useful in differentiating them from HCC. A multi-phasic dynamic contrast study helps in differentiating HCC from focal fibrosis which enhances only during

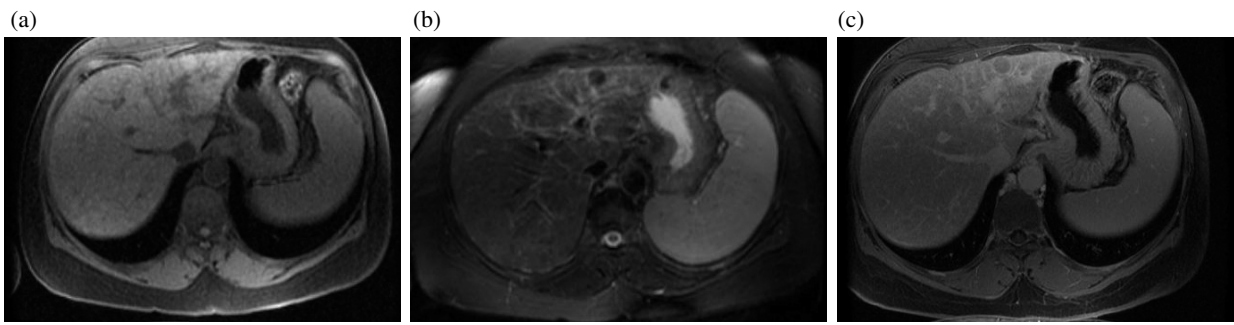


Figure 1 MRI of the dysplastic nodule. (a) T1 weighted image showing a hyperintense dysplastic nodule in the left lobe of the liver. (b) Nodule is characteristically hypointense on T2 weighted image. (c) Non enhancing after IV gadolinium administration.

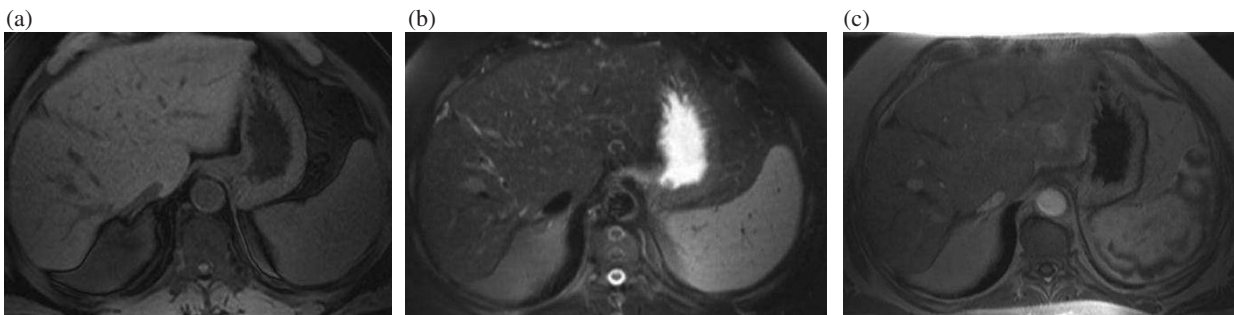


Figure 2 Small HCC in segment 8 of the liver. (a) T1 weighted image showing a small hypointense nodule adjacent to the right hepatic vein. (b) Nodule is characteristically hyperintense on T2 weighted image. (c) Enhancement during arterial phase after administration of IV gadolinium.

the portal venous and delayed phases. Hemangiomas show peripheral enhancement during the early arterial phase with complete intense enhancement during the delayed phase, unlike HCC which enhances completely during the early arterial phase^[34,35]. MRI with blood pool contrast agent Code 7227 has also been found to be useful in differentiating HCC from hemangiomas^[36]. Diffusion weighted MRI, though not routinely performed, may also be useful in the differentiation of HCC from other focal lesions like metastases and hemangiomas, as their mean ADC values are different^[37]. Other lesions that enhance during the early arterial phase, like arterio-portal shunts and other pseudolesions of unknown etiology, can be differentiated from HCC by the signal intensity on T2 W images; pseudolesions are of variable signal intensity on T1 W images and hypointense on T2 W images, whereas HCC is hyperintense^[38,39].

Dynamic MRI is also useful for the evaluation of the effect of chemoembolization on HCC as it shows enhancement on the hepatic arterial phase but only in the viable tissue^[40-42].

Conclusion

The various techniques of MRI are useful and more sensitive than other modalities in the early detection

and characterization of HCC in the cirrhotic liver and in differentiating it from dysplastic nodules and pseudolesions.

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