Tissue Specific MR Contrast Media Role in the Differential Diagnosis of Cirrhotic Liver Nodules

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Abstract

State-of-the-art magnetic resonance (MR) imaging using tissue specific contrast media facilitates detection and characterization in most cases of hepatic nodules. According to the currently used nomenclature, in liver cirrhosis there are only two major types of hepatocellular nodular lesions: regenerative lesions and dysplastic or neoplastic lesions. The purpose of this clinical imaging review is to provide information on the properties of tissue-specific MR contrast agents and on their usefulness in the demonstration of the pathologic changes that take place at the level of the hepatobiliary and reticuloendothelial systems during the carcinogenesis in liver cirrhosis.

Keywords

Liver cirrhosis – carcinogenesis – magnetic resonance imaging – tissue specific contrast media.

Introduction

The development and progression of a hepatocellular carcinoma (HCC) in liver cirrhosis (hepatocarcinogenesis) is a long-term and multistep process. Morphologically, this process is associated with the presence of distinct nodular lesions in the liver that could be named preneoplastic lesions [1]. The characterization of nodular lesions and demonstration of HCC in the cirrhotic liver by imaging modalities, especially by magnetic resonance (MR), represent a challenging issue. Our purpose is to provide an overview on the properties, clinical development and application of hepatobiliary and reticuloendothelial MR contrast agents.

Histology

The concept of the “hepatic functional unit” has been revised, and has been focused on biliary excretory function [2]. It represents the smallest mass of liver tissue vascularized by a single terminal portal venule and drained by a single hepatic vein, accounting for the smallest group of cells and sinusoids performing the metabolic (endocrine) functions of the liver [1, 2]. The hepatic cell is characterized by two poles: the sinusoidal pole, which faces the sinusoid and the perisinusoidal space, and the biliary pole, bounding that part of the intercellular space that constitutes the bile canaliculus. Kupffer cells are hepatic macrophages and are present in the lumen of hepatic sinusoids [2]. Their primary functions include removal by ingestion and degradation of particulate and soluble material from the portal blood and the discrimination between “self” and “non-self” particles [3].

Histopathology

In cirrhotic liver, hepatocellular nodules are represented by hyperplastic lesions such as large regenerative nodule (LRN) and neoplastic lesions such as low-grade dysplastic nodule (LGDN), high-grade dysplastic nodule (HGDN), well-differentiated HCC, dedifferentiated HCC [2, 4, 5].

Hepatobiliary function. In LRN the hepatobiliary function is preserved [1, 4]. In LGDN the biliary domain of the cells is preserved, and bile ducts are present in portal areas [3]. In a HGDN, biliary function can only be partially impaired [2, 6, 7-11]. In well-differentiated HCC bile canaliculi are nearly always present between cells, and bile pigment may be found in tumor cells or in dilated canaliculi [2, 6-12]. The organization of portal areas is completely lost and bile ducts are absent, causing the inefficient biliary drainage from the HCC [2]. When tumor dedifferentiation takes place, biliary function is lost by tumoral cells, and therefore bile is rarely present in poorly differentiated HCC [4, 7, 9]. Undifferentiated cell populations may be difficult to distinguish from tumors of nonhepatocellular origin [9].

Reticuloendothelial function. Regarding the Kupffer cell population, as compared to cirrhotic parenchyma,
histopathological studies have shown that dysplastic lesions in cirrhosis possess an identical or sometimes slightly increased number of Kupffer cells [13]. In well-differentiated HCC, Kupffer cells may be present [13]. In these small tumors endothelial cells morphologically resemble normal sinusoidal endothelial cells, giving an environment similar to that of normal hepatic parenchyma [13-15]. The number of Kupffer cells in cancer tissues decreases as tumor size increases and as grading of the tumor increases [4, 7].

**Tissue specific MR contrast media**

**Hepatobiliary MR contrast agents.** Hepatobiliary contrast agents are paramagnetic compounds that are partially taken up by functioning hepatocytes and excreted in the biliary tract [13]. In our country, two hepatobiliary agents are available in clinical usage: gadobenate dimeglumine (Gd-BOPTA- MultiHance) and gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA, Primovist). Hepato-specific phase imaging can be performed at 20 min after the injection of Gd-EOB-DTPA and at 90-120 min after the injection of Gd-BOPTA. Focusing on biliary excretion, these contrast agents can be divided in compounds with high biliary excretion (Gd-EOB-DTPA up to 50% of the administered dose) and compounds with low biliary excretion (Gd-BOPTA up to 5% of the administered dose).

**Reticuloendothelial system (RES)-targeted contrast agents.** Reticuloendothelial agents target the RES, particularly the liver and spleen. In clinical use, RES-targeted contrast agents are superparamagnetic particles of iron oxide (SPIO) that produce distortions of the local magnetic field resulting in signal loss on T2-weighted images [14, 16]. Once injected intravenously, these agents are rapidly removed from the circulation by the RES. Ferucarbotran is a SPIO agent that can be injected as a bolus, which enables dynamic T1 MR imaging to be performed during different vascular phases than we are accustomed to in liver imaging with extracellular contrast agents [14-17]. In the accumulation phase, 10 min after the injection, when the SPIO particles are taken up by the Kupffer cells of normal liver parenchyma or by Kupffer cells located in liver lesions, T2 and T2* are used in lesion detection and characterization [16, 17].

**MR imaging**

**Hepatobiliary function and MR imaging.** Gd-BOPTA is routinely used in imaging the cirrhotic liver as an extracellular-interstitial contrast agent [13]. Using the delayed phase imaging of Gd-EOB-DTPA or Gd-BOPTA-enhanced MR imaging contributes to improved detection of small metastases in several studies [7, 13, 18, 19]. An increase of liver parenchymal enhancement does not necessarily increase the conspicuity or detection and the characterisation of hepatocellular lesions such as dysplastic nodule (Fig.1) and HCC because residual hepatocyte biliary polarization might influence the degree of uptake of the contrast media and therefore the tumoral enhancement [13, 20-24]. It has been demonstrated that there is a direct correlation between the histological differentiation of HCC and the degree of enhancement on delayed phase, well or moderately differentiated HCCs enhance more than poorly differentiated, because they retain sufficient hepatocyte activity to take up Gd-BOPTA of the former lesions [13, 19, 21]. In contrast, poorly differentiated HCC cells are not able to take up the contrast media at all (Fig.2).

**Reticuloendothelial function and MR imaging.** SPIO-enhanced imaging has been found to be more sensitive than unenhanced imaging in the detection of HCC (25, 30). In the study of Lim et al. [15] the conspicuity of nodular lesions in the liver after the administration of SPIO correlated well with the difference in the number of Kupffer cells between the hepatic parenchyma and the nodular lesions (Fig.3). Thus, moderately or poorly differentiated HCCs...
have high signal intensity (SI) (Fig.4), and all dysplastic nodules containing nearly the same number of Kupffer cells as the surrounding cirrhotic hepatic parenchyma may not be depicted on the postcontrast T2-weighted MR images. Dysplastic nodules or well-differentiated HCCs which contain the same number or even more Kupffer cells than the surrounding parenchyma are depicted as having a slightly lower SI than the surrounding liver, standing out as a nodule [16, 17]. Lower sensitivity in HCC detection of ferumoxide-enhanced MR imaging could be explained by the presence of reticular fibrosis of cirrhotic liver parenchyma that shows high SI and can obscure small HCCs [28, 29]. Several authors have reported that by using combined contrast MR methods, combined gadolinium-enhanced and ferumoxide-enhanced MR imaging (Fig.5), compared with single contrast-enhanced imaging, the diagnosis of HCC is improved [25-27, 30].

Pitfalls. Cirrhosis with severe liver dysfunction may result in poor SPIO uptake, which would limit the utility of the agent [30]. Depending on the indication, the acquisition time may have to be increased to compensate [7, 25]. Signal intensity loss in the liver also may lead to obscuration of the intrahepatic bile ducts by blooming artifacts. Accordingly, MR cholangiopancreatographic sequences should be performed before SPIO particles accumulate in the liver [30].

![Fig 2. Large hepatocellular carcinoma. Arterial phase T1wi after the administration of Gd-BOPTA: (a) the mass appears as heterogeneously hyperintense while in portal venous phase; (b) it is heterogeneously hypointense with a well-defined hyperintense pseudocapsule (arrowheads); (c) in the delayed hepatobiliary phase the lesion is hypointense due to the lack of contrast medium uptake by the malignant lesion.](image1)

![Fig 3. Cirrhotic liver with multiple regenerative nodules and fibrotic bands. No evidence of malignant lesions. a) before Resovist T2wi; b) after Resovist T2wi.](image2)
Clinical role of tissue-specific enhanced liver MR imaging

The correct detection and characterisation of any hepatic nodule in liver cirrhosis and the number of the malignant nodules are essential for the proper clinical management of the patient (Table 1), particularly in orthotopic liver transplantation, surgical resection and ablation. The diagnosis of HCC is presently restricted to nodules that show hypervascularity in the arterial phase and wash-out.

Table 1. Tissue specific MR contrast media used in the detection and characterisation of cirrhotic liver nodules

<table>
<thead>
<tr>
<th>Type of contrast media</th>
<th>Hepatobiliary agents</th>
<th>Reticuloendothelial agents</th>
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<tr>
<td>Prototype compound</td>
<td>Gd-BOPTA</td>
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<tr>
<td>Pharmacokinetics</td>
<td>Taken up by hepatocytes and excreted in bile</td>
<td>Gd-EOB-DTPA</td>
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<td>Mechanism of contrast effect</td>
<td>T1 shortening</td>
<td>T1 shortening</td>
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<tr>
<td>Excretion</td>
<td>Renal 95-98% Biliary 2-5%</td>
<td></td>
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<tr>
<td>Preferred MR imaging sequences</td>
<td>T1 wi 2D or 3D FSPGR</td>
<td>T1 wi 2D or 3D FSPGR</td>
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<tr>
<td>Timing</td>
<td>Late hepatic arterial phase (30 seconds) Hepatobiliary phase (90-120 minutes)</td>
<td>Dynamic T1 acquisition Hepatobiliary phase at 20 minutes</td>
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of contrast media in portal/delayed phases at two dynamic studies, in the presence of nodules 1–2 cm in diameter, or at one dynamic study for nodules >2 cm in diameter even if some overlap exists in the diagnosis of well-differentiated HCC and HGDN (Fig 6). Clinical follow-up studies have proved that a considerable proportion of HGDNs progress to a HCC within a few years [28, 29]. When the nodules with impaired biliary or reticuloendothelial functions are multiple and spread in liver parenchyma, the potential evolution towards multifocal HCC has to be taken into consideration [16, 30].

Conclusion

Cirrhotic and noncirrhotic livers may contain a number of benign, premalignant, and malignant hepatocellular nodules. The detection and characterisation of focal liver disease is significantly improved using tissue specific MR contrast media compared to unenhanced MRI, MRI with unspecific contrast agents and contrast-enhanced CT evaluation.

References


Fig 6. Macronodular hepatocellular carcinoma. T2 wi (a) and T1 after Primovist in arterial (b) and delayed phase (c) the macronodule is heterogeneous with a well defined peripheric capsule; in the delayed hepatobiliary phase the lesion is predominantly hypointense due to the lack of contrast medium uptake by the malignant lesion.