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Liver-specific contrast agents

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Abstract

In the patient with cancer, magnetic resonance imaging is increasingly used as a diagnostic tool for disease detection, lesion characterization, as well as the assessment of treatment response. Although non-contrast T1-weighted and T2-weighted imaging, together with low molecular weight extracellular gadolinium contrast-enhanced T1-weighted magnetic resonance imaging remain the cornerstone for liver assessment, there is increasing recognition of the benefits of liver-specific contrast agents for disease evaluation.

Keywords: *Contrast agents; liver specific; MR imaging.*

In the patient with cancer, magnetic resonance (MR) imaging is increasingly used as a diagnostic tool for disease detection, lesion characterization, as well as the assessment of treatment response. Although non-contrast T1-weighted and T2-weighted imaging, together with low molecular weight extracellular gadolinium contrast-enhanced T1-weighted MR imaging remain the cornerstone for liver assessment, there is increasing recognition of the benefits of liver-specific contrast agents for disease evaluation.

Liver-specific or liver-selective MR contrast agents have been a relatively recent development within the last decade; the basis for their hepatic effects and consequently their utilization varies between the different types of contrast agents. Broadly divided, liver-specific contrast agents are either Kupfer cell selective or hepatocyte selective.

Kupfer cell selective contrast agents are composed of small iron oxide particles (SPIO), which are phagocytosed by Kupfer cells in the liver and by cells of the reticuloendothelial system. The susceptibility effect of the iron particles results in signal reduction in normal liver on T2- or T2*-weighted MR imaging. Malignant lesions lack normal Kupfer cells and remain relatively high signal intensity post contrast on imaging[1,2]. For probable commercial reasons rather than a lack of diagnostic efficacy, SPIO contrast agents have largely been withdrawn from the market and they are no longer currently available for routine diagnostic use.

Hepatocyte selective contrast agents can be either manganese or gadolinium based. Magafodipir trisodium (MnDPDP) is a contrast agent that is administered by infusion, which is actively transported into hepatocytes. The contrast causes T1 shortening and signal enhancement in the normal liver, but not in non-hepatocellular focal liver lesions[3]. Unfortunately, MnDPDP has also been withdrawn from the market.

Hence, currently, the only commercially available hepatocyte-specific contrast media are gadolinium based. These include Gd-BOPTA (Multihance®) and Gd-EOB-DTPA (Primovist or Eovist®). Both are low molecular weight gadolinium chelates, which freely distribute within the vascular and extravascular spaces after contrast administration, but also undergo selective hepatocellular excretion. For this reason, these contrast media are sometimes also known as biphasic or combination contrast media. However, the relative percentages of hepatocellular excretions differ between Gd-BOPTA (3–5%) and Gd-EOB-DTPA (50%). Consequently, imaging in the hepatocellular phase of contrast enhancement is usually performed at about 1 h or more after Gd-BOPTA administration, but may be performed as early as 10–20 min

after Gd-EOB-DTPA administration[4]. Furthermore, signal enhancement of the normal liver is higher using Gd-EOB-DTPA compared with Gd-BOPTA[5,6].

Using Gd-EOB-DTPA, it has been shown that the uptake of contrast of hepatocytes is mediated by the organic anionic transporting polypeptides (OATPs), while the multi-drug resistant proteins (mrp) mediate the excretion of the contrast from the hepatocytes into the biliary system.

In oncological practice, using hepatocyte-selective contrast media in MR imaging has improved the detection of malignant disease, especially for demonstrating the presence, number, location and distribution of liver metastases (e.g. in colorectal cancer), which has a bearing for patient management (e.g. surgical versus non-surgical)[7,8]. When Gd-EOB-DTPA is administered, there is improved diagnostic accuracy for identifying hepatic lesions, which are 1 cm or less in size.

Another major advantage of using hepatocyte-selective contrast media is in the characterization of hepatocellular lesions. Using Gd-EOB-DTPA or Gd-BOPTA, focal nodular hyperplasia (FNH) show contrast uptake in the delayed hepatocellular phase, which is more signal intense than the surrounding liver parenchyma[9]. The enhancement may appear ring-like, due to non-enhancement of the central scar[10]. This improves the diagnostic confidence for FNH, especially if the lesion shows atypical features on conventional MR imaging. By contrast, hepatic adenomas are usually hypointense to the liver in the hepatocellular phase of Gd-EOB-DTPA imaging, but may show weak or heterogeneous enhancement[11,12]. One of the potential pitfalls of over-reliance on hepatocellular phase imaging is that haemangiomas are hypointense in this phase of enhancement, and may be mistaken for malignant disease.

In patients with liver cirrhosis, there is a growing amount of data to show the value of Gd-EOB-DTPA for detecting hepatocellular carcinoma (HCC). HCC typically are hypointense in the hepatocellular phase of imaging, although a small percentage of tumours may express OAPT1B3 receptors, and show T1 enhancement[13,14]. Furthermore, there can be overlap of imaging features between early HCC and dysplastic nodules. However, Gd-EOB-DTPA has been shown be useful for distinguishing transient hepatic arterial enhancement from true hepatic lesions in the cirrhotic population[12].

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