CT versus MR Imaging of Hepatocellular Carcinoma: Toward Improved Treatment Decisions

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Detection, characterization, staging, and treatment monitoring are major roles of diagnostic imaging of liver cancers. Developments in multidetector-row computed tomography (MDCT) technology have increased the spatial and temporal resolution of CT to allow more precise evaluation of the hemodynamics of liver tumors and improve the diagnostic accuracy of dynamic MDCT. The high spatial and temporal resolutions of dynamic MDCT enable us to reconstruct 3-dimensional (3D) images that are very useful for pretreatment evaluation. Dynamic MR imaging with fast 3D T₁-weighted gradient echo imaging sequence using nonspecific contrast medium can be highly sensitive for detecting hypervascular HCC. However, the use of gadolinium ethoxybenzyl diethylenetriamine pentaaetic acid (Gd-EOB-DTPA), a contrast medium specific to hepatic tissue, offers greater diagnostic ability and, so, has become essential to liver imaging. MR imaging with Gd-EOB-DTPA may replace CT during hepatic arteriography and CT during arteriportography.

Keywords: Gd-EOB-DTPA, hepatocellular carcinoma, MRI

Introduction

Diagnostic imaging of hepatocellular carcinoma (HCC) is used to detect, characterize, and stage tumor and to evaluate anatomical information before treatment and determine treatment response. Less invasive examinations, such as computed tomography (CT) and magnetic resonance (MR) imaging, have recently undergone dramatic development. The wide availability of multidetector-row CT (MDCT) with more than 64 channels has led to liver imaging using dynamic MDCT with high spatial and temporal resolution, and CT has developed from 2-(2D) to 3-dimensional (3D) imaging. Advances have also been made in the research of functional imaging, such as analysis of tissue blood flow by perfusion CT and fast techniques for MR imaging. Dynamic MR imaging with 3D T₁-weighted gradient echo sequence and nonspecific contrast medium, such as gadopentetate dimeglumine (Gd-DTPA), is also reported useful. Moreover, the clinical availability of tissue-specific MR contrast media that accumulate in Kupffer cells by phagocytosis or in hepatic cell by hepatocytic function are reported to improve tumor detactability. The high diagnostic ability with use of gadolinium ethoxybenzyl diethylenetriamine pentaaetic acid (Gd-EOB-DTPA), a contrast medium specific to hepatic tissue, has made it essential in liver imaging. CT during hepatic arteriography (CTHA) and/or CT during arteriportography (CTAP) are more invasive but still believed reliable imaging techniques because of their high sensitivity in identifying hepatocellular carcinoma (HCC). Choice of imaging modality is important for correct diagnosis.

In this review, we describe the usefulness of CT and MR imaging for diagnosing HCC.

CT Imaging

Dynamic MDCT with bolus injection of contrast medium is essential for diagnosing liver tumor. In MDCT, progressively higher spatial and temporal resolutions have been achieved by increasing gantry rotation speed and number of detector rows. Advances in MDCT technology have enabled more precise evaluation of the hemodynamics of liver tumor and improved diagnostic accuracy. Scanning through the upper abdomen can be performed in less than 3 s by MDCT scanners with more than 64
channels, even when spatial resolution of 0.6 mm is employed for both longitudinal and short axes of the body (isotropic voxel volume imaging). Dynamic study with such high quality MDCT can reveal arterial enhancement of HCC and washout of contrast medium from the tumor in portal venous and equilibrium phase imaging, a typical finding of hypervascular HCC (Fig. 1). High quality 3D images can be reconstructed from isotropic voxel imaging data using multiplanar reconstruction (MPR), volume-rendering (VR), and maximum intensity projection (MIP) techniques (Fig. 2), and surgeons can use these 3D images for preoperative anatomical evaluation and patient education.2

CT versus MR Imaging

Similar to MDCT imaging, dynamic MR imaging is also useful for diagnosing liver diseases. Gd-DTPA is a nonspecific (extracellular) contrast medium widely used in dynamic MR imaging. Previously, we showed no significant difference in sensitivity between dynamic MDCT and dynamic MR imaging for detecting hypervascular HCC.4 We would consider cost and radiation exposure in choosing modalities, especially for follow-up studies in HCC.

Superparamagnetic iron oxide (SPIO) has been used for many years as a liver-specific contrast agent for further work-up of liver diseases than MDCT and dynamic MRI with Gd-DTPA.11 SPIO acts as a negative contrast agent because uptake of its particles by Kupffer cells in the reticuloendothelial system of the liver12,13 causes local magnetic field inhomogeneity and results in considerable T2* shortening.13 SPIO-enhanced MR is useful for detecting HCC14–16 and has higher sensitivity than dynamic MDCT for detecting hypervascular HCCs smaller than 10 mm in diameter.3 On dynamic

Fig. 1. Dynamic multidetector-row computed tomography (CT) of the liver. Hypervascular hepatocellular carcinoma (HCC) in chronic hepatitis C. The lesion shows hypoattenuation precontrast (A), hyperenhancement relative to the liver parenchyma in the arterial phase (B), and iso- or hypoattenuation due to washout of contrast medium in the portal venous (C) and equilibrium phases (D). Capsular enhancement can be also seen (D). These are characteristic enhancement patterns of hypervascular HCC. Nonenhanced region within the tumor indicates necrosis (arrow).

Fig. 2. A cirrhotic patient with splenomegaly, thrombocytopenia, and recurrent variceal hemorrhage. Preoperative computed tomographic (CT) evaluation was performed for laparoscopic splenectomy. Coronal multiplanar reformatted (MPR) image shows displacement of the stomach and pancreas due to splenomegaly (A). Arterial-phase volume-rendering (VR) image (B) and portal venous VR image (C) demonstrate the meandering splenic artery and vein.
MDCT, arterial parenchymal enhancement due to arterioporal venous (AP) shunt may become a false positive lesion in the investigation of HCC. Washout pattern is useful to distinguish non-tumorous AP shunt from hypervascular HCC; both show focal arterial enhancement. Corresponding washouts in the portal and equilibrium phases indicate HCC, but when HCCs do not demonstrate washout, uptake of SPIO by the region allows diagnosis of AP shunt.

The combination of dynamic MDCT and SPIO-enhanced MR imaging has been reported capable of providing the same accuracy for diagnosing hypervascular HCC as that of CTHA and/or CTAP. However, CTHA and CTAP offer greater detection sensitivity for HCCs smaller than 15 mm in diameter.\textsuperscript{17,18} One previous paper reported that the combination of dynamic MR imaging and SPIO-enhanced MR imaging has shown diagnostic accuracy comparable to that of CTHA and CTAP.\textsuperscript{19} Gd-EOB-DTPA is another liver-specific contrast medium that works as a T\textsubscript{1}-shortening agent. Because it acts as both an extracellular and hepatocyte-specific contrast medium, we can use Gd-EOB-DTPA in dynamic MR imaging with T\textsubscript{1}-weighted fast imaging sequence to evaluate both hepatocyte function and the hemodynamics of liver tumor.\textsuperscript{20} Approximately 15 to 20 min after injection, hepatocytes take up Gd-EOB-DTPA in the hepatocytic phase via transporter of organic anion.

![Fig. 3. Gadolinium ethoxybenzyl diethylene triamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance (MR) imaging of hypervascular hepatocellular carcinoma (HCC) in chronic hepatitis C. (A) T\textsubscript{1}-weighted (in-phase) image, (B) T\textsubscript{1}-weighted (opposed-phase), (C) T\textsubscript{2}-weighted image, (D) precontrast 3-dimensional (3D) T\textsubscript{1}-weighted image, (E) arterial phase, (F) portal venous phase, and (G) hepatocyte phase. In-phase T\textsubscript{1}-weighted (A) and opposed-phase T\textsubscript{1}-weighted (B) images reveal no fat deposition in the tumor. The tumor shows high intensity on T\textsubscript{2}-weighted image (C). The tumor shows hypointensity relative to the liver parenchyma on the precontrast 3D-T\textsubscript{1}-weighted image (D), but enhancement of HCC can be seen in the arterial phase (E). The tumor shows hypointensity in the portal venous phase (F) and hypointensity in the hepatocytic phase, the most important phase for detection of tumor (G, arrow).]
transporting polypeptides 1B3 (OATP1B3).

Gd-EOB-DTPA works as a T1-shortening agent at the hepatocytic phase after injection so that malignant liver lesions, such as HCC and liver metastases, are spared from the contrast uptake that occurs in the surrounding liver parenchyma (Fig. 3).

Employing 3D fast imaging sequence with high spatial resolution of the longitudinal axis of the body, MR imaging using Gd-EOB-DTPA can detect more tiny nodules than that using SPIO. Gd-EOB-DTPA-enhanced MR imaging has been reported superior to both dynamic MDCT and dynamic MR imaging with Gd-DTPA in detecting HCC. Many small hypovascular HCCs can be detected only on hepatocytic phase images of Gd-EOB-DTPA-enhanced MR imaging; they show no arterial enhancement and only mild washout of contrast medium in the portal venous and equilibrium phases of dynamic MDCT and dynamic MR imaging with Gd-DTPA (Fig. 4). Moreover, detection may be low on SPIO-enhanced MR imaging because hypovascular HCC is usually well differentiated with Kupffer cells and often takes up SPIO and shows hypo- or isointensity relative to the liver parenchyma. On the other hand, Gd-EOB-DTPA-enhanced MR imaging can reveal HCC as a nodule hypointense relative to the liver parenchyma without depending on histological differentiation of the HCC (Fig. 5). Gd-EOB-DTPA-enhanced MR imaging shows higher detection sensitivity for hypo- and hypervascular HCC than either dynamic MDCT or dynamic MR imaging with Gd-DTPA. Compared with SPIO-enhanced MR imaging, Gd-EOB-DTPA-enhanced MR imaging also shows higher detection sensitivity for hypovascular HCC and the same detection sensitivity for hypervascular HCC.

The high detection sensitivity of CTAP and/or CTHA make them still the most reliable imaging methods for deciding treatment strategy for HCC, but they are used less frequently for diagnosing HCC. Gd-EOB-DTPA-enhanced MR imaging has been reported to have the same detection sensitivity for both hyper- and hypovascular HCC as CTAP.
Fig. 5. Superparamagnetic iron oxide (SPIO)-enhanced and gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance (MR) imaging of the liver. Hypovascular hepatocellular carcinoma (HCC) in chronic hepatitis C. (A) SPIO-enhanced T2-weighted image, (B) SPIO-enhanced T2*-weighted image, (C) arterial phase on Gd-EOB-DTPA-enhanced MR imaging, and (D) hepatocytic phase on Gd-EOB-DTPA-enhanced MR imaging. Hypovascular well differentiated HCC with Kupffer cells often takes up SPIO and shows isointensity relative to the liver parenchyma on SPIO-enhanced MR imaging (A, B), resulting in low detection sensitivity. On the other hand, Gd-EOB-DTPA-enhanced MR imaging can reveal hypovascular HCC (C) in liver segment 3 as a nodule hypointense relative to the liver parenchyma in the hepatocytic phase (arrow) (D).

Management of Small Nodules Seen Only on Gd-EOB-DTPA-enhanced MR Imaging

When we employ Gd-EOB-DTPA-enhanced MR imaging to screen patients with high risk for HCC, we sometimes encounter tiny hypovascular nodules smaller than 15 mm in diameter that can only be detected as hypointense nodules on hepatocytic phase images (Fig. 4). Biopsy or CTAP and CTHA may show useful clinical information, but use of these invasive examination methods is neither clinically realistic nor cost efficient to evaluate these tiny nodules. There have been reports of hypovascular tiny nodules with doubling time of less than 400 days that show hypervascularization of the tumor at a high rate during follow-up evaluation (Fig. 4). Follow-up study with Gd-EOB-DTPA-enhanced MR imaging that includes evaluation of doubling time of these tiny hypovascular nodules can be very useful and avoid invasive examination methods.

Pitfall of Gd-EOB-DTPA-enhanced MR Imaging

About 50% of Gd-EOB-DTPA is taken up by hepatocytes via OATP1B3 transporter and excretes into the bile duct via transporter multidrug resistance-associated protein (MRP). The other half excretes into the renal pelvis. Thus, liver enhancement depends on hepatocyte function. Gd-EOB-DTPA enhancement of the liver in patients with severe liver dysfunction may be insufficient to show good tumor-to-liver contrast. Nevertheless, though the insufficiency of contrast enhancement may be a problem for detecting liver tumor, the fact that liver enhancement depends on hepatocyte function may be useful for assessing liver function.

As mentioned, the absence of transporter of OATP1B3 in malignant liver lesions, such as HCC and liver metastases, spares them from Gd-EOB-DTPA uptake, which occurs in the surrounding liver parenchyma in the hepatocytic phase. However, some HCCs show hyperenhancement relative to the liver parenchyma in the hepatocytic phase that resembles the enhancement of focal nodular hyperplasia. This seemingly paradoxical enhancement of HCC has been observed in well or moderately differentiated hypervascular HCC. Some HCC tumor cells have been reported to express the hepatocellular transporters, including OATP1B1 and/or OATP1B3 and MRP2. The degree of expression of these transporters in tumor cells may affect the kinetics of gadoxetic acid in tumors.

Conclusion

Gd-EOB-DTPA-enhanced MR imaging is essential for liver imaging because it offers higher detection sensitivity for hyper- and hypovascular HCC than either dynamic MDCT or dynamic MR imaging with Gd-DTPA. However, dynamic MDCT with high spatial and temporal resolution enables 3D imaging that is very useful for pretreatment evaluation.
Fig. 6. A patient with chronic hepatitis B. Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance (MR) imaging (A–E) and computed tomographic (CT) angiography (F and G) detected hypervascular hepatocellular carcinoma (HCC) in liver segment 4 (arrows). Note that hepatobiliary phase imaging clarified the whole profile of the nodule-in-nodule HCC. Fat-suppressed T2-weighted image shows polygonal hyperintensity (A). Precontrast 3-dimensional (3D) T1-weighted image does not depict the nodule (B). Arterial phase Gd-EOB-DTPA-enhanced MR imaging shows heterogeneous enhancement of the nodule (C). Portal venous phase imaging does not visualize apparent washout (D). Hepatocytic phase image depicts well defined round-shaped nodule in liver segment 4 (E). Other nodules visualized in this phase were considered dysplastic because they showed no arterial enhancement or washout. CT arteriopography (CTAP) shows portal perfusion defect (F), and CT hepatic arteriography demonstrates hyperattenuating area in a part of the nodule (G). The findings indicated the heterogeneity in HCC, which was histologically confirmed by liver segmentectomy.

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