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MINIREVIEWS

Diagnostic value of imaging examinations in patients with primary hepatocellular carcinoma

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Abstract

Primary hepatocellular carcinoma (PHC) includes hepatocellular carcinoma, intrahepatic cholangiocarcinoma and other pathological types and is characterized by rapid progression. Most of the clinical diagnoses are made at late stage or when distant metastasis occurs, increasing the difficulty of treatment and resulting in a poor prognosis. Therefore, the early diagnosis of PHC plays an important role in timely treatment and the improvement of prognosis. The gold standard for the diagnosis of primary liver cancer is liver biopsy, but it has limitations as an invasive examination. Presently, imaging has become the first choice for the diagnosis of liver cancer. We here summarize the new methods and techniques of imaging in diagnosis and evaluation of primary liver cancer in recent years, including ultrasonography, computed tomography perfusion imaging, diffusion-weighted imaging technology-voxel incoherent motion, diffusion tensor imaging, iterative decomposition of water and fat with echo asymmetry and least squares estimation-iron quantification, dynamic enhanced magnetic resonance imaging and hepatocyte-specific contrast medium imaging. Imaging diagnosis can not only evaluate the degree of differentiation, blood supply and perfusion, and invasiveness of the lesion, but also predict the prognosis, evaluate liver function, and

provide references for clinical diagnosis and treatment.

Key words: Diagnosis; Imaging; Magnetic resonance imaging; Primary hepatocellular carcinoma; Diffusion-weighted imaging

Core tip: Primary hepatocellular carcinoma (PHC) is one of the most serious malignant tumors with high morbidity and mortality. It is the fifth leading cancer worldwide and third most common cause of cancer-related death. Early diagnosis of PHC plays an important role in timely treatment and improvement of prognosis. An ideal imaging technique should be chosen early and used promptly to make a qualitative diagnosis. The progress made in imaging techniques has offered new diagnostic methods for the study of liver cancer. This review outlines the diagnostic value of imaging in patients with PHC.

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INTRODUCTION

Primary hepatocellular carcinoma (PHC) is one of the most seriousmalignant tumors with high morbidity and mortality. It is the third most common cause of cancer death and fifth leading cancer worldwide[1-3]. According to cancer statistics, hepatocellular carcinoma (HCC) mortality has gradually increased, and the overall cure rate for HCC has not improved significantly over the past decade[4]. A few risk factors have been identified for PHC such as viral hepatitis, cirrhosis, aflatoxin, parasitic infection and genetic factors[5-9]. Due to its characteristic concealment, PHC has no specific early symptoms and rapidly progresses. Most of the clinical diagnoses are made at late stage or when distant metastasis occurs, increasing the difficulty of treatment and leading to a poor prognosis. Therefore, early diagnosis of PHC plays an important role in timely treatment and the improvement of prognosis.

The early diagnosis of PHC follows the guidelines of the American Association for the Study of Liver Diseases (AASLD)[10], European Association for the Study of Liver Disease (EASL)[11], Asia-Pacific Association Study of the Liver (APASL)[1] and EASL-EORTC Clinical Practice Guidelines[12]. Several imaging modalities have been identified for the clinical diagnosis of PHC, and this review outlines the diagnostic value of imaging in patients with PHC.

TRADITIONAL IMAGING DIAGNOSIS OF PHC

Traditional imaging methods of liver cancer, such as ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI), can provide information about lesions, including their location, size and nature. These methods can also make a clear diagnosis, assist staging, guide treatment and evaluate efficacy[13-15]. Liver cancer presents as a hypoechoic mass on ultrasonography, and color Doppler shows a star-spot and a short-line blood flow signal. Ultrasonography is radiation-free, is repeatable, occurs in real-time and is convenient in operation. However, the ultrasound field of vision is small, interference is large, single imaging can only observe one or several lesions, and the results are dependent on the operator's skill and experience. CT is a wide-coverage, high-speed and unique examination technique, but it has the side effects of radiation and the contrast agent. MRI uses no radiation and has high soft-tissue resolution. It can display multiple sequences and parameters, leading to the display of lesions in multiple ways-conventional-weighted images and dynamic-enhanced images, which are excellent for displaying anatomical structures. However, MR images do not provide functional information, the MR scanning speed is slow, the patient's breath holding requirement is high, and there are side effects of the contrast agent. The current guidelines vary among different societies for the diagnosis of liver cancer. Both AASLD and EASL recommended that the diagnosis should be based on the imaging findings and size of the lesions; APASL recommends that the diagnosis should be based on the blood supply only, regardless of the focus size and α-fetoprotein (AFP) level; the Japan Society of Hepatology recommends combining AFP and imaging findings and then making a diagnosis based on the characteristics of the blood supply of the lesion[16]. EASL guidelines show that contrast-enhanced ultrasonography is not as accurate as CT and MRI in detecting lesions. Dynamic-enhanced MRI and multiphase-enhanced CT are the most effective techniques to detect < 2-cm tumors, and approximately 25%-30% of cases are underestimated[17].

Considering these promising results, traditional imaging faces enormous challenges. First, according to a report[18], among 243 cases of HCC confirmed by pathology, only 137 cases (56.4%) showed typical enhancement and 106 cases (43.6%) showed atypical enhancement, including equal or low enhancement in the arterial phase and no contrast elution in the equilibrium phase. At the arterial stage, 53 cases showed equal or low enhancement, and 53 cases were not eluted by a contrast agent in the balanced phase. Atypical HCC is not uncommon, posing a challenge for a definite diagnosis. Second, for the diagnosis of borderline lesions (early HCC and high heteromorphic hyperplasia nodules),

most of the lesions are not enhanced in the arterial phase and show a low signal in the venous phase and delayed phase. They are not distinguishable on imaging. Third, for patients with arteriovenous fistula, the arterial phase is obviously enhanced, and the venous phase and equilibrium phase are isointense, similar to the enhancement of focal nodular hyperplasia and adenoma; thus, it is difficult to differentiate[18]. How to address this challenge requires continuous development of imaging.

PROGRESS IN CT DIAGNOSIS

CT perfusion imaging is a noninvasive functional imaging method to evaluate the perfusion status of organs and tissues. Typical CT perfusion imaging of liver cancer is characterized by increased blood flow, increased blood volume, increased hepatic artery perfusion, decreased portal vein perfusion, and an increased hepatic artery perfusion index[19]. CT perfusion imaging can be used to evaluate the efficacy of transcatheter arterial chemoembolization. After lipiodol embolization, tumor survival can be determined by perfusion if CT enhancement does not reveal the area of residual tumor with abnormal enhancement. After perfusion, a small region of high blood flow around the edge of the lesion, a small blood volume area, increased hepatic artery perfusion, decreased portal perfusion, and increased hepatic artery perfusion index indicate tumor survival[20].

PROGRESS IN MR DIAGNOSIS

In recent years, due to the advancement of MR hardware, new quantitative techniques regarding functional and metabolic directions have emerged and include diffusion-weighted imaging (DWI)-intravoxel incoherent motion imaging (IVIM), diffusion tensor imaging (DTI), iterative decomposition of water and fat with echo asymmetry and least squares estimation-iron quantification (IDEAL-IQ), MR spectroscopy, MR elastography, MR perfusion imaging and hepatocyte-specific contrast agent imaging. These new technologies can provide information on metabolism, such as glycogen, fat, iron metabolism, as well as information on the density of hepatocytes, structural disorder and phagocytosis of Kupffer cells in terms of structure and cell function.

DWI

DWI is based on the principle of the diffusion of water molecules. Due to various reasons, the gap between cells is narrowed, and the movement of water molecules is restricted. Abnormal proliferation of tumor cells leads to a decrease in the extracellular space, and the diffusion of tissue fluid located between cells is more limited than that of normal cells. Conventional DWI can be used to judge the degree of tumor differentiation. Nakanishi *et al*[21] have shown that, in HCC confirmed by surgery, the degree of differentiation is different: the degree of differentiation is high with a higher apparent diffusion coefficient (ADC) value, and the degree of differentiation is low with a lower ADC value. The ADC value in the necrotic area was significantly higher than that in the tumor area[21]. Studies have shown that, when the b value is 1000, the ADC value of HCC with different degrees of differentiation is significantly lower than that of highly differentiated HCC[22,23]. Conventional DWI can also be used to judge microvascular invasion, and Xu *et al*[24] showed that the ADC value of lesions with microvascular invasion was lower than that without microvascular invasion.

With further study of DWI, it was found that, if multi-b-value imaging is used, the tissue signal decreases with the increase in the diffusion-weighted b value. The characteristics of the diffusion signal are described in the IVIM double-exponential model; one part comprises the water molecule diffusion signal, and the other part comprises the microcirculation perfusion signal in the capillary. A low b value is generally considered $\leqslant$ 200, including diffusion and perfusion effects, but mainly the perfusion effect, and a high b value (> 200) reflects the true dispersion effect. IVIM-derived parameters contain the perfusion fraction (f), pseudodiffusion coefficient (D*) and pure diffusion coefficient (D) values. The f value is the perfusion fraction that is linked to the microcirculation. D* is the perfusion parameter that represents the perfusion-related incoherent microcirculation, and D is the diffusion coefficient representing true molecular diffusion[25]. Woo *et al*[26] showed that the ADC and D values were correlated with the clinical grade of Edmondson, but the ADC, F, D and D* values were not correlated with the enhancement of the arterial phase (no blood supply enhancement, no blood supply or no enhancement). The D value was superior to ADCs in differentiating high-grade and low-grade HCC, and the f value was significantly correlated with the percentage of arterial enhancement[26].

DTI is also a DWI technique that provides additional information on anisotropy diffusion and total diffusion orientations, which can obtain the diffusion degree in multiple dimensions using at least six or more gradient directions[27,28]. Fractional anisotropy (FA) can be calculated by DTI in addition to the ADC value, which is a scalar value describing the anisotropy degree of the diffusion of extracellular water molecules[29]. The malignant cells contain more membranes, organelles and complicated fibers, causing the cells in PHC to be densely packed. However, it remains unknown whether diffusion in PHC is isotropic or anisotropic; moreover, no study has explored the feasibility of DTI for the PHC diagnosis. Therefore, our previous study evaluated the feasibility of distinguishing HCC from healthy liver using FA and ADC values, and we found that both FA and ADC could be used as indexes to differentiate HCC from healthy liver[30].

IDEAL-IQ sequence

For liver magnetic resonance scans, t fast spoiled gradient recalled echo with antiphase imaging was used to diagnose hepatic steatosis. Using the same window and wide window, if the liver signal is high in the same phase image and low in the inverse phase image, then liver fatty degeneration is considered[31,32]. However, this method cannot be applied to patients with liver iron overload because iron sinks in the liver to accelerate the phase acceleration of the hydrogen protons so that, in the same phase image as that with a low signal, the reversed phase image shows a high signal, greatly interfering with the diagnosis whether or not the patient has liver fat degeneration. Thus, using IDEAL-IQ, a single scan can generate a pure water image, a pure fat image, an in-phase image, and an inverse phase image. The ratio of fat to fat is similar to the R2* relaxation rate of six groups of images to determine whether the liver has fatty degeneration and iron overload[33]. It was reported that the presence of intratumoral fat is up to 19.6% in HCCs on MRI[34], and Siripongsakun *et al*[35] claimed that fat-containing HCC, compared with nonfat-containing HCC on MRI, may predict a more favorable prognosis. Therefore, we predict that IDEAL-IQ exhibits great value to distinguish fat-containing HCC from nonfat-containing HCC.

DYNAMICENHANCED MRI

With the application of the LAVA sequence in high-field MRI, the detection rate of small HCC has been significantly improved by DWI combined with dynamic contrast-enhanced MR. The smallest lesion diameter of 0.4 cm could be detected[36]. The enhancement of LAVA could better capture the arterial blood supply of the tumor, and the contrast between the enhancement of the lesion at the arterial stage and surrounding normal hepatic parenchyma was optimal, being helpful to distinguish small liver cancer from the new vessels in the tumor and increase the detection rate of small HCC inliver cirrhosis . However, LAVA enhancement is difficult to detect small liver cancer with a lack of a hepatic artery blood supply[37].

HEPATOCYTE-SPECIFIC CONTRAST AGENTS

There are two types of hepatocyte-specific contrast agents: Gd-DTPA and Gd-EOB-DTPA. On the one hand, Gd-DTPA and Gd-EOB-DTPA can shorten the tissue T1 relaxation time and can produce a similar dynamic enhancement effect to traditional MR contrast agents to observe the conventional multiphase dynamic enhancement mode and performance of liver lesions. On the other hand, the liver parenchyma that contains normal liver cells is enhanced, and double information of the liver specific phase can be obtained. Therefore, hepatocyte-specific contrast agents can provide dual information on the liver dynamic phase and specific phase. Regarding Gd-EOB-DTPA, 50% is excreted through the liver, and 50% is excreted by the kidneys. Regarding Gd-DTPA, 2%-4% is excreted by the liver, and the remainder is excreted by the kidneys. Thus, the specificity of Gd-DTPA is lower than that of Gd-EOB-DTPA. Gd-EOB-DTPA application for 3 min was used, the normal hepatocytes began to ingest, and the dynamic phase was mixed with dual information, whereas the Gd-DTPA uptake started later, so Gd-DTPA could provide a pure dynamic phase. Hepatocyte-specific contrast agents can help radiologists to detect early liver cancer and some small lesions, and the detection rate of liver lesions is higher than that of conventional MR contrast agents[38,39]. Presently, Gd-BOPTA is widely used in clinical practice.

The experts from the radiology branch of the Chinese Medical Association have reached a consensus on the application of Gd-EOB-DTPA. For atypical HCC, especially in the early stage, Gd-EOB-DTPA-enhanced MR can also be performed, which will help to improve the diagnostic accuracy[40-43]. For patients with progressive elevation of AFP, especially with high-risk factors (such as hepatitis B- or hepatitis C-associated cirrhosis) and other patients with negative imaging examination (on ultrasonography or Gd DTPA-enhanced MRI), Gd-EOB-DTPA-enhanced MRI is recommended[44]. Contrast-enhanced CT in the decision of HCC surgery, if the detection of additional small lesions (maximum diameter $\leqslant$ 2.0) may change the established treatment plan, will help to improve the radical treatment of tumors and reduce postoperative recurrence and metastasis. In the diagnosis of HCC by Gd-DTPA-enhanced MR, no definite nodules, such as abnormal perfusion and early small HCC, were found in other hepatic lobes and in the preoperative evaluation of donors and recipients before liver transplantation, especially in the selection of recipients. The evaluation of the donor bile duct showed its superiority[45-48].

GD-EOB-DTPA can detect more liver lesions, likely changing the treatment plan. Some studies have shown that approximately 10% of HCC are found only in the GD-EOB-DTPA phase, and approximately 90% of HCC show low expression of OATP8 and a low signal of the liver-specific phase in the early stage[49,50]. Therefore, the detection rate of MR liver-specific phase imaging for early HCC with an oligoblood supply is very high. Ariizumi *et al*[51] found that the nonsmooth boundary of hepatocyte-specific lesions was closely related to portal vein invasion and intrahepatic metastasis and was significantly associated with recurrence within 1 year after HCC. Some studies have shown that the changes in liver cell membrane function were earlier than those of the neovascularization/blood supply in nodules[52,53]. Yamashita *et al*[54] and other studies showed that the expression of OATP1B3 and level of AFP were negatively correlated with the high expression level of OATP1B3. The low-expression cells came from stem cells/progenitor cells, and the differentiation was poor, resulting in the

increase in the T1 value of liver tissue in patients with liver cirrhosis and decrease in the hepatic parenchymal signal in the hepatobiliary phase[54]. Therefore, GD-EOB-DTPA is expected to assist in the diagnosis and differential diagnosis of liver function and to evaluate liver function at the segmental level.

BOLD-fMRI

BOLD-fMRI is a new MRI imaging technology. Using endogenous hemoglobin as the contrast agent, the blood oxygen content of tissues is measured by the tissue hemoglobin content. The content of blood oxygen in tissue depends on the relative changes in the perfusion oxygen supply and metabolic oxygen consumption. Therefore, the content of blood oxygen can reflect the changes in the hemodynamics, structure and function of the tissue. It has a certain value in the diagnosis, and clinical stage and curative effect evaluation of the tumor[55]. Choi *et al*[56] found that liver cancer chemoembolization and postoperative R2 changed significantly. Therefore, BOLD functional MRI has the potential value in the diagnosis of small HCC, but large samples are needed for further study.

CONCLUSION

An ideal diagnostic imaging technique for the diagnosis of liver cancer should be chosen early and used promptly to make a qualitative diagnosis[57-59]. Imaging progress has brought new opportunities for the study of liver cancer. The diagnosis can be established based on the presence or absence of a focus, lesion location, size, and nature including the degree of differentiation, blood supply and perfusion, and invasion of the lesion, and the imaging can also be used to assess the prognosis and liver function, making the diagnosis more accurate and providing more information for clinical treatment.

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