

ORIGINAL RESEARCH

Differences in the Diagnosis and Treatment of Patients with Early-Stage Hepatocellular Liver Cancer by Multi-Row Spiral CTMDCT and Gd-EOB-DTPA-Enhanced MRI

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ABSTRACT

Objective • The assessment of liver cancer lesion characteristics mainly relies on multi-row spiral computed tomography (MDCT) and magnetic resonance imaging (MRI). MDCT suffers from a series of problems, such as low soft tissue contrast and large tumor boundary errors, which lead to its limited practical application value in liver cancer. In contrast, Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MRI has better soft-tissue contrast than MDCT and increases the clarity of liver cancer lesions. To investigate the differences between MDCT and Gd-EOB-DTPA-enhanced MRI in managing patients with hepatocellular liver cancer.

Methods • A total of 80 patients diagnosed with hepatocellular carcinoma of the liver, who received treatment at our hospital between September 2020 and September 2022, were included in this study. These patients were evenly divided into two groups: the observation group and the control group, with 40 cases in each. The aim of this study was to compare the differences in signal indices of hepatobiliary stage between the two groups in patients with hepatocellular carcinoma.

Results • A total of 89 cancer nodules were detected in patients by MDCT, and 109 cancer nodules were detected in

patients by Gd-EOB-DTPA-enhanced MRI. When the number of nodules detected by both imaging modalities was statistically analyzed, the differences in the number of hepatocellular carcinoma (HCC) nodules detected by MDCT and Gd-EOB-DTPA-enhanced MRI were statistically significant ($P < .05$). Further analysis of the data by single cancer nodule, multiple cancer nodules, and cancer nodule size showed that the difference between the two imaging modalities was statistically significant ($P < .05$) in the diagnosis of patients with a single liver cancer nodule or multiple liver cancer nodules (94.8% vs.81.3%). The difference in the comparison was statistically significant ($P < .05$).

Conclusion • Gd-EOB-DTPA-enhanced MRI demonstrates superior diagnostic efficacy in detecting small hepatocellular carcinoma, offers improved staging capabilities for hepatocellular carcinoma, and provides more precise guidance for treatment planning. Consequently, Gd-EOB-DTPA-enhanced MRI exhibits exceptional diagnostic value and serves as a valuable tool for guiding treatment decisions in patients with hepatocellular carcinoma. (*Altern Ther Health Med.* 2024;30(1):31-35).

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a prevalent malignancy worldwide, often characterized by a subtle onset and absence of distinctive clinical manifestations during its

initial phases.¹ The majority of individuals affected by HCC tend to present with symptoms such as abdominal pain, jaundice, and ascites when the disease has progressed to intermediate or advanced stages.² The majority of these patients exhibit suboptimal treatment outcomes, unfavorable prognoses, and limited survival durations. Consequently, the timely identification and diagnosis of hepatocellular carcinoma, coupled with the implementation of suitable therapeutic approaches, are pivotal in enhancing patient treatment outcomes, extending their survival durations, and mitigating the likelihood of recurrence.³ MDCT is currently widely used to evaluate HCC and guide the selection of treatment options, but the sensitivity of these tests is still low for liver nodules ≤ 2 cm in diameter.⁴ Nevertheless, despite the implementation of aggressive therapeutic interventions, the

overall prognosis remains unsatisfactory primarily due to the occurrence of early intrahepatic recurrence resulting from the inaccurate evaluation of hepatocellular carcinoma during the initial treatment phase.⁵

Gd-EOB-DTPA is a magnetic resonance contrast agent that exhibits specificity for hepatocytes. Following transvenous injection, approximately 50% of the contrast agent is absorbed by normal hepatocytes within approximately 20 minutes. This timeframe coincides with the peak enhancement of the liver parenchyma and concurrent visualization of the biliary system.⁶ Gd-EOB-DTPA-enhanced MRI has both dynamic imaging characteristics and liver-specific hepatobiliary phase images.⁷ Numerous contemporary studies have demonstrated that the utilization of Gd-EOB-DTPA-enhanced MRI exhibits enhanced sensitivity and accuracy in the diagnosis of hepatocellular carcinoma (HCC) when compared to MDCT. This imaging technique particularly proves advantageous in the detection of HCC lesions measuring ≤ 2 cm in diameter, as well as in the identification of liver nodules.⁸ Some recent studies have shown that adding Gd-EOB-DTPA-enhanced MRI to MDCT can change the BCLC staging of HCC and the choice of treatment options and improve the recurrence-free survival and overall survival of patients.⁹ Furthermore, the identification of tumor encapsulation on computed tomography (CT) or magnetic resonance imaging (MRI) not only aids in the characterization of hepatic nodules but also facilitates the formulation of suitable therapeutic strategies and serves as a reliable prognostic indicator following radical hepatocellular carcinoma (HCC) treatment.¹⁰

Recent studies have shown that Gd-EOB-DTPA-enhanced MRI can improve the diagnostic efficiency of HCC.¹¹ However, the existing literature remains limited in terms of investigating the potential enhancement of diagnostic value for hepatocellular carcinoma (HCC) through the utilization of Gd-EOB-DTPA-enhanced MRI. Consequently, our study aimed to ascertain the potential improvement in diagnostic value for early HCC by evaluating alterations in tumor envelope detection subsequent to the incorporation of Gd-EOB-DTPA-enhanced MRI in patients being evaluated for early HCC via MDCT.

PATIENTS AND METHODS

Study subjects

The clinical case data of 80 patients with hepatocellular liver cancer treated in our hospital from September 2020 to September 2022 were selected and divided equally into 40 cases, each in the observation and control groups. A total of 80 patients with an average age of 54 (19-79) years were included in our study, 65 of whom were males. Etiologically, there were 58 cases of hepatitis B virus infection, 8 cases of hepatitis C virus infection, and 14 cases of other causes. 63 cases of Child-Pugh liver function grade A and 17 cases of combined cirrhosis. In the initial MDCT examination, single nodal HCC accounted for 65 cases, 2 HCC nodules accounted for 15 cases, and the mean diameter of each nodule was about 3.0 (0.6-12) cm.

Inclusion and exclusion criteria of study subjects

Inclusion criteria: (1) confirmed diagnosis of primary hepatocellular carcinoma with proposed local treatment (surgery, radiofrequency ablation, TACE); (2) MDCT scan within 1 week; (3) age ≥ 18 years and < 70 years; (4) Eastern Cooperative Oncology Group physical status score of 0 or 1; (5) liver function Child-Pugh classification of grade A or B.

Exclusion criteria: (1) combination of other malignancies; (2) severe renal insufficiency, cardiovascular system disease or respiratory system disease; (3) allergy, or a history of Gd-EOB-DTPA contrast agent allergy; (4) metal foreign body in the body, not suitable for MRI; (5) in the period of pregnancy or lactation.

MDCT examination

Procedural steps: In the control group, MDCT was performed using a 64-row spiral CT (Philips), and the contrast agent for the enhancement scan was iopromide, which was injected intravenously with a contrast dose of 100 mL and a flow rate of 3 mL/s. The thickness of the scanned slice was 5 mm, the slice spacing was 2.5 mm, the arterial phase delay scan time was 35 s, the portal vein phase delay scan time was 60 s, and the equilibrium phase delay scan time was 180 s.

Gd-EOB-DTPA-enhanced MRI examination

Procedure: The MR examination was performed with Siemens 1.5T and United Imaging 3.0T MRI machines. The examination procedure was explained in detail to the patient, and breathing and breath-holding training was performed to obtain good cooperation. An 8-channel abdominal soft coil was used followed by an array spatial sensitivity encoding technique correction scan, followed by axial breath-hold 3DFSPGR, weighted imaging, axial breath-gated FSE-XL fat suppression T₂-weighted imaging and breath-gated SE/EPI diffusion-weighted imaging in the upper abdomen. Coronal and multi-angle left anterior oblique coronal MRCP were then performed. The contrast agent used for enhancement scans was Gd-EOB-DTPA at a dose of 0.025 mmol/kg and an injection rate of 1.0 mL/s, followed by an equal amount of saline. Liver acquisition was first performed in the upper abdomen at axial position PH, volume accelerated LAVA, TR/TE = 2.8 ms / 1.2~1.3 ms, excitation angle 11 bandwidth 83.33, FOV 40~48 cm, fat suppression, matrix 224 × 224, ASSET 3.00, 1 acquisition, breath hold 12-16 s, 2.6 mm layer thickness, ZIP512 × 512 reconstruction, using zero-fill interpolation algorithm) planar scans and dynamic enhancement scans, followed by hepatobiliary phase scans of the same sequence and orientation at 5, 10, 15, 20 min and 25 min after contrast injection.

Diagnostic criteria

The diagnostic imaging criteria for diagnosing HCC by MDCT are enhancement in the lesion's arterial phase, and rapid elution in the portal or regressive phase. Diagnostic imaging criteria for the diagnosis of HCC by disodium cetate-enhanced MRI: AASID guidelines or at least 3 of the

following 4 imaging features: 1) high signal in the arterial phase of enhancement: 2) rapid enhancement in the portal or regressive phase: 3) high signal on T2-weighted images: 4) low signal in the hepatobiliary phase.

Image analysis

The size, number, and imaging performance of the detected liver nodules found were counted from the patients' MDCT images and Gd-EOB-DTPA-enhanced MRI images of the patients. The medical history and findings of each patient were masked during image analysis, and image analysis was performed in two steps: MDCT images of all patients were analyzed in the first step, and Gd-EOB-DTPA-enhanced MRI images of all patients were analyzed in the second step, and the two image analysis steps were performed at an interval of 2 weeks, and the image order of each patient was different for the two image analyses. This reduces manual errors due to memory bias. Two radiologists read the images, and the results were decided after a discussion of the divergent images. Statistics of nodules were found in both images. A nodule was diagnosed as an HCC nodule if it showed a typical "fast-in-fast-out" pattern of a nodule in the arterial phase with significant or uniform enhancement and a nodule in the portal and/or parenchymal equilibrium phase with significantly weaker or reduced enhancement on MDCT. If the nodule in the Gd-EOB-DTPA enhancement MRI showed the above "fast-in-fast-out" pattern on Gd-EOB-DTPA enhancement MRI, or if the nodule showed a low signal in the hepatobiliary phase showed low signal, the nodule was diagnosed as HCC nodule.

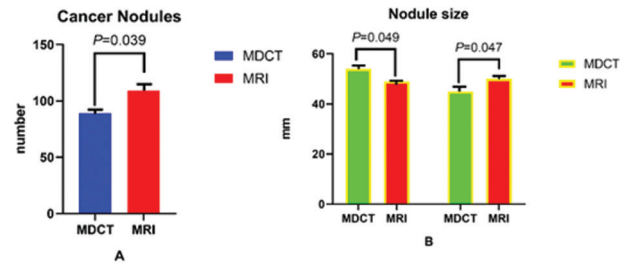
Data processing

Two or more attending physicians performed data processing independently, and any disagreement was discussed and resolved. The signal intensity of the liver parenchyma before and after or to the left and right of the lesion was measured at each point in the hepatobiliary stage and the mean value was calculated. The signal intensity of the lesion was measured, and the ratio of the signal intensity of the liver parenchyma to that of the lesion was calculated, and the one-way repeated measures ANOVA test was used to compare the differences of this ratio at different time points. The signal intensity of liver cancer lesions at the above time points was evaluated visually and classified into three grades: significantly low signal, low signal, equal or slightly low signal, and the differences in signal intensity of liver cancer lesions in patients with different Child-Pugh classifications were observed.

Statistical Analysis

All statistical data in this study were entered into Excel, and Statistic Package for Social Science (SPSS) 28.0 (IBM Corp., Armonk, NY, USA). Was used for statistical calculation. Measurement data conforming to the normal distribution were expressed as Mean ± SD, independent samples *t* test was used, count data were compared by chi-square test, and rank data were compared by rank sum test. *P* < .05 was considered statistically significant.

Figure 1. Statistical analysis of liver cancer nodule data



Note: Comparative data on daily living self-care scores were entered using Epidata and then statistically processed using SPSS 28.0. The data needs to be entered into a computer database. And then use SPSS 28.0 for statistical processing of the data. The data needs to be entered into a computer database by two people, expressed as mean ± standard deviation, two people, expressed as mean ± SD and independent samples are carried out. *t* test showed that the number of liver cancer nodules detected by MDCT and Gd-EOB-DTPA enhanced MRI was significantly different (*P* < .05). Further analysis of the data according to single cancer nodules, multiple cancer nodules, and the size of cancer nodules showed a statistically significant difference between the two imaging methods in the diagnosis of single or multiple liver cancer nodules in patients (*P* < .05).

RESULTS

Statistical analysis of liver cancer nodule data

Statistical results showed that a total of 89 cancer nodules were detected by MDCT and 109 cancer nodules were detected by Gd-EOB-DTPA-enhanced MRI in patients. Analyzing the number of nodules detected by the two imaging methods, it was found that the difference in the number of liver cancer nodules detected by MDCT and Gd-EOB-DTPA-enhanced MRI was statistically significant (*P* < .05). Further analysis of the data according to single cancer nodules, multiple cancer nodules, and cancer nodule size revealed statistically significant differences between the two imaging methods in diagnosing patients with a single or multiple liver cancer nodules (*P* < .05). See Figure 1.

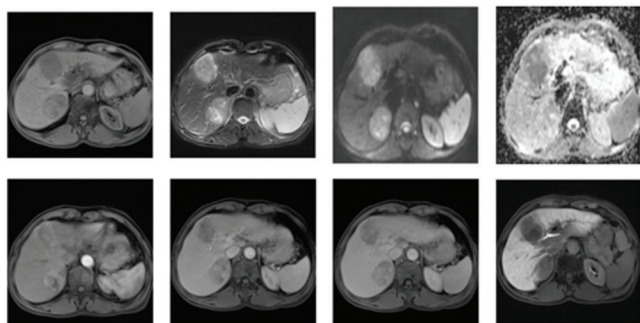
Diagnostic results of MRI and MDCT

A total of 116 HCC nodules were eventually detected in 80 patients by surgical pathological examination and follow-up confirmation, of which 86 HCC nodules were detected in 51 postoperative pathological confirmations, and 30 HCC nodules were detected in 29 patients by follow-up confirmation. The sensitivity of Gd-EOB-DTPA-enhanced MRI for the detection of HCC nodules was higher than that of MDCT (94.8% vs. 81.3%), and the difference in comparison was statistically significant (*P* < .05). Still, there was no statistically significant difference in the positive predictive values of Gd-EOB-DTPA-enhanced MRI and MDCT. After adding Gd-EOB-DTPA-enhanced MRI, additional HCC nodules were found in 11 patients.

Typical case

Male patient, 68 years old, suffered from hepatitis B for more than 10 years. Gd-EOB-DTPA-enhanced MRI of the upper abdomen was performed due to physical examination findings that accounted for the liver lesions for 13 days. See Figure 2.

Figure 2. Hepatobiliary stage 10, 15, and 25-minute images with two small nodular hepatocellular carcinoma lesions in the liver parenchyma and left outer lobe at each time point.



Note: The contrast between the two signals was significant, and the lesions showed a significantly low signal. Both MDCT and Gd-EOB-DTPA-enhanced MRI showed a typical HCC nodule of about 3.0 cm in diameter in segment VI of the liver, but Gd-EOB-DTPA-enhanced MRI additionally found a nodule of approximately 0.9 cm in diameter was found in segment I of the liver on Gd-EOB-DTPA-enhanced MRI. The nodule in segment IV of the liver showed enhancement in the arterial phase, the slightly low signal in the portal phase, the low signal in the hepatobiliary phase, and a high signal in the T2 and DWI phases on Gd-EOB-DTPA-enhanced MRI, which was finally pathologically confirmed as HCC. The BCLC stage increased from stage A to stage B after the additional Gd-EOB-DTPA-enhanced MRI.

DISCUSSION

The conventional imaging diagnosis of HCC is based on its multivessel nature. Most guidelines recommend criteria based on the typical enhancement pattern of HCC, i.e., lesions in the background of cirrhosis or chronic liver disease with significant enhancement in the arterial phase and clear gallery in the portal or extended regression phase.¹² Early detection and timely treatment of HCC is the key to improving patient prognosis and survival.¹³ Recent studies have shown that Gd-EOB-DTPA-enhanced MRI has advantages in diagnostic sensitivity and accuracy compared with MDCT, especially in improving the detection of HCC \leq 2 cm in diameter.¹⁴

Gd-EOB-DTPA is a hepatocyte-specific MRI contrast agent.¹⁵ Hepatocytes take up up to 50% of Gd-EOB-DTPA via the organic anion transfer polypeptides OATP1B1 and OATP1B3 on the sinusoidal gap membrane of hepatocytes.¹⁶ In contrast, tissues other than hepatocytes, which cannot take up Gd-EOB-DTPA, show low signal, highlighting liver lesions, which is the mechanism of Gd-EOB-DTPA as a liver-specific contrast agent.¹⁷ Many studies in recent years have demonstrated the advantages of Gd-EOB-DTPA-enhanced MRI for the diagnosis of HCC: high signal enhancement in the arterial phase, low signal in the portal or equilibrium phase, low signal in the hepatobiliary phase, and circumferential enhancement of the lesion.¹⁸ In addition, high signal T2-weighted images is also considered helpful in the diagnosis of HCC, but there is no consensus on the diagnostic criteria for hepatocellular carcinoma, and further studies are needed to help develop appropriate diagnostic criteria that may further improve the diagnostic value of Gd-EOB-DTPA-enhanced MRI.¹⁹ Many publications have

reported using Gd-EOB-DTPA for the diagnosis and differential diagnosis of HCC and the assessment of liver function.²⁰⁻²³ Since it functions as both a conventional MRI contrast agent and a specific contrast agent, it can be used as an effective validation and adjunct to MRI plain and dynamic enhancement. It is also considered by many publications to be of high value in identifying atypical hyperplastic nodules in the liver and early hepatocellular carcinoma.²⁴⁻²⁸ The timing for obtaining hepatobiliary phase images has been investigated in the literature. Gd-EOB-DTPA uptake by hepatocytes initiates approximately 1.5 minutes after injection and reaches its maximum intensity around 20 minutes. Some researchers argue that acquiring hepatobiliary phase images prior to the 20-minute mark may result in diminished contrast between liver and spleen signals. Conversely, a larger number of scholars contend that images obtained with a delay of 20-30 minutes in the hepatobiliary phase offer greater diagnostic accuracy for liver diseases.²⁹⁻³¹

This study is subject to certain limitations. Firstly, it is important to note that our study adopted a retrospective approach and employed stringent inclusion criteria, which consequently led to a reduced number of cases included in the study and the potential for selection bias. Secondly, it is worth mentioning that not all lesions underwent final pathologic confirmation of hepatocellular carcinoma (HCC), which may potentially impact the evaluation of the diagnostic efficacy of both screening methods. The results of our study indicate that Gd-EOB-DTPA-enhanced MRI exhibits higher accuracy in the early staging of hepatocellular carcinoma (HCC) and detection of the mantle. Nevertheless, it is important to note that the resection criteria employed in our research are more stringent compared to the clinical reality. Further investigation is required to determine whether the utilization of this imaging technique can enhance the prognosis of patients.

In conclusion, Gd-EOB-DTPA, a hepatobiliary-specific MRI contrast agent, offers the ability to assess both the hemodynamic characteristics of liver lesions and provide functional information on the hepatobiliary stage. This information is highly valuable for the diagnosis and differential diagnosis of hepatocellular carcinoma (HCC). Additionally, Gd-EOB-DTPA-enhanced MRI surpasses MDCT and extracellular space contrast-enhanced MRI in terms of providing more comprehensive and accurate staging prior to treatment. Consequently, this advanced imaging technique aids in treatment plan selection and ultimately improves patient prognosis. As Gd-EOB-DTPA-enhanced MRI becomes more widely used in clinical practice, its efficacy and utility are expected to further improve.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

KW and XZ designed the study and performed the experiments, XJ and JZ collected the data, XJ, JZ, and ZW analyzed the data, KW and XZ prepared the manuscript. All authors read and approved the final manuscript.

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