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Staging Hepatocellular Carcinoma with Gadolinium-Ethoxybenzyl Diethylenetriaminepentaacetic Acid -Enhanced Magnetic Resonance Imaging: A Comparison with Multi-Detector Row Computed Tomography

Jingjing Fu[1], **Jun Zhao**[2], **Xiaochun Zhang**[2], **Xuesong Li**[3], **Li Xiaoming**[2] **and Lin Zhang**[2*]

[1]*College of Nursing, Third Military Medical University, Chongqing, China*

[2]*Department of Radiology, Southwest Hospital, Third Military Medical University, Chongqing, China*

[3]*Institute of Hepatobiliary Surgery, Southwest Hospital, Third Military Medical University, Chongqing, China*

***Corresponding author:** Lin Zhang, Department of Radiology, Southwest Hospital, Third Military Medical University, 29 Gaotanyan St., District Shapingba, Chongqing, 400038, China, Tel: +86-23-6875-4425; Fax: +86-23-6546-3026; E-mail: linzhangswh@yahoo.com

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Abstract

Aim: To explore if gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA)-enhanced MRI provides more accurate information than multi-detector row computed tomography (MDCT) for staging hepatocellular carcinoma (HCC).

Methods: We retrospectively investigated 112 patients with HCC who underwent MDCT and Gd-EOB-DTPA-enhanced MRI within one month before treatment. Two experienced radiologists reviewed the size, number, and boundaries of the HCC lesions, portal invasion, and tumor metastasis on MDCT and MRI images in consensus. Then the performance of Gd-EOB-DTPA-enhanced MRI and MDCT on staging HCC lesions was compared through statistical analysis. The classification of the Barcelona Clinic Liver Cancer (BCLC) stage was also evaluated.

Results: HCC lesions in five patients were detected on Gd-EOB-DTPA-enhanced MRI only. Of the other 107 patients, 21 (19.6%) were in BCLC stage 0, 49 (45.8%) in BCLC stage A, 14 (13.1%) in BCLC stage B, and 23 (21.5%) in BCLC stage C on MDCT. On Gd-EOB-DTPA-enhanced MRI, 12 (11.2%), 48 (44.9%), 17 (15.9%), and 30 (28.0%) patients were classified as BCLC stages 0, A, B, and C, respectively. The two methods differed significantly in staging HCC patients (χ^2=16.444, P=0.006).

Conclusion: This study suggests that Gd-EOB-DTPA-enhanced MRI provides more accurate information than MDCT for characterizing and staging HCC which will help to choose accurate treatment strategy.

Keywords: Hepatocellular carcinoma; Gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid; Multidetector row computed tomography; Barcelona clinic liver cancer stage

Abbreviations:

BCLC: Barcelona Clinic Liver Cancer; MRI: Magnetic Resonance Imaging; HCC: Hepatocellular Carcinoma; LT: Liver Transplantation; MDCT: Multidetector Row Computed Tomography; RFA: Radiofrequency Ablation; TACE: Transarterial Chemoembolization

Introduction

Hepatocellular carcinoma (HCC) accounts for 85%–90% of primary liver cancers [1]. HCC-related mortality can be reduced by its early detection and the application of potentially curative treatments, including resection, liver transplantation (LT), and radiofrequency ablation (RFA) [2]. Various morphological factors need to be considered, including the type, nodular or infiltrative, the number of lesions, their size, their anatomical relationships and loco-regional and extra-hepatic extension [3]. Once HCC is diagnosed, the lesions are staged, together with the clinical condition of the patient, the most appropriate treatment strategy will be determined in each case [4].

Gd-EOB-DTPA is a liver-specific hepatocyte magnetic resonance (MR) T1-enhanced agent that allows lesion characterization and the definition of the tumor–vascular relationship [5]. To date, Gd-EOB-DTPA-enhanced MR imaging (MRI) has been shown to be largely superior to unenhanced MRI, computed tomography (CT), and other types of contrast agents for the detection and characterization of liver lesions [6,7], especially small HCCs [8]. However, little research has compared the effects of Gd-EOB-DTPA-enhanced MRI and multi-detector row computed tomography (MDCT) in staging HCC [9,10], with few data available on the differences between Gd-EOB-DTPA-enhanced MRI and MDCT in identifying BCLC stages B and C. In this article, we will explore the difference in staging of HCC between Gd-EOB-DTPA-enhanced MRI and MDCT according to BCLC stages.

Patients and Methods

Patients

This study was conducted with the approval of The Institutional Review Board of southwest hospital. Informed consent was not required for this retrospective study. Patient records/information was anonymized and de-identified prior to analysis. Between January 2012 and November 2013, 119 patients who were initially diagnosed with

HCC at our hospital were consecutively enrolled in this study. All lesions in the patients' livers were evaluated with MDCT and Gd-EOB-DTPA-enhanced MRI (Figure 1).

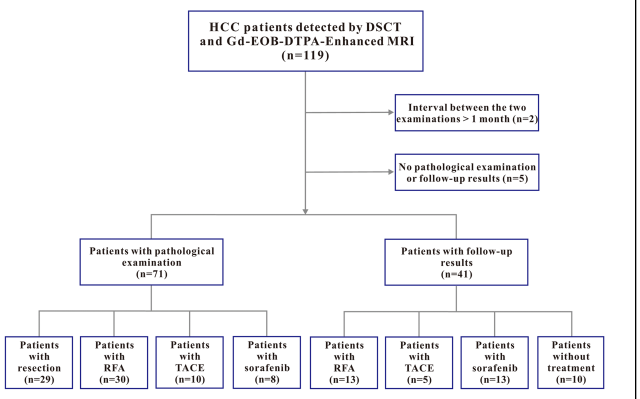

Figure 1: Flow diagram of the inclusion and exclusion of patients in the study. (six hepatocellular carcinoma [HCC] patients were treated with both resection and radiofrequency ablation [RFA]).

Of these 119 HCC patients, two were excluded because the interval between the two examinations exceeded one month. Five patients were excluded because there were no results for the pathological examination or adequate follow-up. Finally, 41 patients (92 HCC lesions) with follow-up results and 71 HCC patients (165 HCC lesions) with pathological examination results were enrolled in the study. The follow-up period was between 6 months and 2 years. 92 lesions seen in follow up met the American Association for the Study of Liver Diseases (AASLD) guideline in follow up examination [11,12]. All the HCC lesions were confirmed to correspond to identify by previous CT or MRI.

MDCT Image Acquisition

Multiphase CT scanning was acquired with a MDCT scanner (Somatom Sensation 16, Siemens, Munich, Germany). The scanning parameters were as follows: 120 kVp, 240 mAs, 5 mm slice thickness with an increment (overlap) of 2.5 mm, table speed of 26.5–39.37 mm/rotation (pitch, 0.828–1.07), and a single-breath-hold helical acquisition of 14–16 s. Hepatic arterial phase scanning began 30–40 s after the injection of 80– 100 mL of a nonionic iodinated contrast agent (iopromide injection 370mg l/ml; Bayer Schering Pharma AG, Berlin, Germany) at a rate of 3–5 mL/s with a bolus-triggered technique (120 kVp; 40–60 mA; monitoring frequency from 12 s after the injection of 100 HU of contrast agent into the abdominal aorta; delay from trigger to initiation of scan, 18 s). The contrast agent was administered through the antecubital vein with a power injector (ulrich medical USA® Missouri editon 094). The portal and equilibrium phases of scanning began 70 s and 180 s after the injection of the contrast agent, respectively.

MR Image Acquisition

Gd-EOB-DTPA-enhanced MRI (3.0 tesla MRI; Trio Tim, Siemens, Munich, Germany) was performed using the liver-specific hepatocyte-directed MRI contrast agent Gd-EOB-DTPA (Primovist; Bayer Schering Pharma AG, Berlin, Germany). Briefly, Gd-EOB-DTPA solution (0.1 mL/kg bodyweight) was injected at a speed of 1–2 mL/s through an intravenous line placed in the antecubital vein with a power injector (Medrad®, Indianola, PA, USA), followed by a flush with 20–30 mL of 0.9% normal saline. A multiphasic dynamic study was performed using three-dimensional T1-weighted gradient-echo (TR/TE/FA: 3.42 ms/1.25 ms/9°; matrix size: 224 × 168; field of view: 400 mm). Care bolus was used for the dynamic enhancement of MRI in the arterial phase. When the contrast agent reached the level of the aorta abdominalis segment, each patient was asked to hold breath and arterial phase scanning was conducted. Portal- and equilibrium-phase images were also obtained at 50–80 s and 180 s after injection, respectively. T1-weighted images with fat suppression were repeated 20 min after injection, as the hepatobiliary-phase images.

Image Analysis and BCLC staging

The size, number, and boundaries of the HCC lesions, portal invasion, and tumor metastasis on the MDCT, Gd-EOB-DTPA-enhanced MRI images were all reviewed by two radiologists followed by a consensus reading. Both (L.Z. and X.Z.) had at least ten years of professional experience at interpreting abdominal CT and MR images, and both were blinded to the clinical histories and final diagnoses. Image interpretation was conducted in two sessions: During session 1, the CT images of all patients were analyzed. During session 2, the MRI images of all patients were analyzed. More than 1 week of time interval was set between the reading sessions of CT and MR images to reduce recall bias. The sizes of the tumor lesions detected with MDCT or Gd-EOB-DTPA-enhanced MRI were recorded as the literature reports [13]. The diagnostic criteria for HCC on MDCT were applied according to the most recent AASLD guideline, updated in 2011 [14]. The diagnostic criteria for HCC on Gd-EOB-DTPA-enhanced MRI were any three of four imaging findings (arterial-phase hyperintensity, portal or delayed washout, hyperintensity on T2-weighted images, and hepatobiliary-phase hypointensity) proposed in a previous study [15].

All patients were staged carefully according to the BCLC staging system, which has been approved by the European Association for the Study of the Liver and the AASLD [16,17]. After MDCT images analysis was performed, two radiologists and one surgeon (X.L. with ten years' clinical HCC surgeon experience) assessed the stage of each HCC patient accorded with the BCLC staging system. The second decision was made in the same way after Gd-EOB-DTPA-enhanced MRI [18-20]. More than 1 week of time interval was set between the reading sessions of CT and MR images to reduce recall bias.

Statistical Analysis

Differences between categorical variables and staging methods were analyzed with a paired χ^2 test. The differences in the total lesion numbers, lesion sizes, and single or multiple lesions were analyzed statistically with a χ^2 test (means of the Wilcoxon signed-rank test, Fisher's exact test, or a paired χ^2 test). A value of $P<0.05$ was considered statistically significant. The software used for all analyses was SPSS (version 13; SPSS, Inc., Chicago, IL, USA).

Results

Baseline characteristics of patients

The baseline characteristics of the 112 patients were summarized in Table 1. There were 100 (89.3%) males and 12 (10.7%) females in the study. The median patient age was 50.5 years (range, 27–74 years). Of the 112 patients enrolled, 93 patients (83.0%) were Child–Pugh class A, 18 (16.1%) were Child–Pugh class B, and only one (0.9%) patient was Child–Pugh class C. The median α-fetoprotein concentration in the cohort was 58.0 ng/mL (range, 1.1–16.7 × 10^4 ng/mL). Fourteen (12.5%) patients had no history of hepatitis, 95 (84.8%) patients had hepatitis B, and three (2.7%) patients had hepatitis C. Half the 112 patients had a history of liver cirrhosis.

Variable	Total
Sex (male/female), n (%)	100/12 (89.3/10.7)
Age (years)[a]	50.5 (27–74)
History of hepatitis, n (%)	
No/B/C	14/95/3 (12.5/84.8/2.7)
Liver cirrhosis (yes/no), n (%)	56/56 (50.0/50.0)
α-Fetoprotein (ng/mL)[a]	58.0 (1.1–16.7 × 104)
ALT (IU/L)[a]	43 (10–624)
AST(IU/L)[a]	44 (19–898)
Albumin (g/L)[a]	43 (23.5–87.7)
Total bilirubin (μmol/l)[a]	18 (6.7–516.6)
Creatinine (mg/dL)[a]	73 (14.2–146.0)
Prothrombin time (INR)[a]	12.6 (10.5–17.7)
Child-Pugh Class, n (%)	
A/B/C	93/18/1 (83.0/16.1/0.9)
PST, n (%)	
0/1/2	34/70/8(30.4/62.5/7.1)
ALT: Alanine Transaminase; AST: Aspartate Transaminase; INR: International Normalized Ratio; PST: performance status. [a]Median (range)	

Table 1: Baseline clinical characteristics of 112 patients with HCC.

Characteristic HCC lesions detected with MDCT and Gd-EOB-DTPA-enhanced MRI

According to the statistical analysis, the total numbers of HCC lesions detected by the two imaging tests were significantly different (χ^2=59.093, P<0.001). The two imaging methods differed significantly in the size of the HCC lesions detected (χ^2=17.429, P<0.001). They also differed significantly in detecting whether the lesions were single or multiple (χ^2=17.152, P<0.001). The enhancement patterns of the HCC lesions detected with the two imaging methods were also significantly different (χ^2=53.706, P<0.001, Table 2). Six HCC lesions in five patients were detected with MRI but not with MDCT, and the mean diameter of these six lesions was 12.4 mm (range, 7–15 mm).

Variable	MDCT	Gd-EOB-DTPA-enhanced MRI	χ^2	P value
Lesion number (n)	204	257	59.093	0.000*
Lesion number in each patient (n)			21.333 (17.152)	0.000* (0.000*)
Single lesions	70 (70)	45 (45)		
Multiple lesions	37 (134)	62 (212)		
Size (lesions, n)			9.577 (17.429)	0.002* (0.000*)
<15 mm	22 (26)	53 (74)		
≥ 15 mm	106 (178)	106 (182)		
Enhancement pattern (lesions, n)			53.706	0.000*
Wash in/out	204	198		
No wash in/out	0	59		
*Statistically significant results (P<0.05). (The five patients without HCC lesions on MDCT were not included in Table 2).				

Table 2: Characteristics of HCC lesions detected with MDCT and Gd-EOB-DTPA-enhanced MRI.

Changes in BCLC stages after Gd-EOB-DTPA-enhanced MRI versus MDCT

The five (4.46%) patients who were not diagnosed with HCC on MDCT were found to have HCC on Gd-EOB-DTPA-enhanced MRI; four of them were classified as BCLC stage 0 and one as BCLC stage A on MRI. Of the remaining 107 patients, 21 (19.6%) were classified with BCLC stage 0, 49 (45.8%) with BCLC stage A, 14 (13.1%) with BCLC stage B, and 23 (21.5%) with BCLC stage C on MDCT. However, after they were evaluated with Gd-EOB-DTPA-enhanced MRI, 12 (11.2%), 48 (44.9%), 17 (15.9%), and 30 (28.0%) patients were classified with BCLC stages 0, A, B, and C, respectively. The staging of HCC with the two imaging methods differed significantly on paired χ^2 test (χ^2=16.444, P=0.006; five patients without HCC on MDCT were not included).

After combining the characteristics and staging of the patients (Table 3), we found that MDCT and Gd-EOB-DTPA-enhanced MRI differed significantly in evaluating BCLC B patients with multiple lesions (χ^2=9.464, P=0.002). They also differed significantly in staging BCLC B patients with lesions of <15 mm (χ^2=5.783, P=0.016) and BCLC C patients with lesions of 15 mm (P=0.034). However, the two imaging methods did not differ significantly in evaluating HCC patients with single lesions (P>0.05).

Changes in therapeutic decisions after Gd-EOB-DTPA-enhanced MRI

After MDCT (Figure 2), five (4.7%) of the 107 HCC patients were considered eligible for surgical resection, 55 (51.4%) for LT, nine (8.4%) for RFA, 15 (14.0%) for TACE, and 23 (21.5%) for sorafenib. However, the second round of imaging with Gd-EOB-DTPA-enhanced MRI resulted in marked changes in the therapeutic decisions.

Three (60.0%) of the five patients eligible for surgical resection became eligible for LT because additional HCC lesions were detected in these patients (Figure 3). Fifty-five patients were considered eligible for LT on MDCT, but the therapy recommended was altered for eight (14.5%) of them after the second round of imaging: seven (87.5%) for TACE, one (12.5%) for sorafenib because portal invasion or extrahepatic metastasis was detected.

The number of patients who were eligible for RFA on MDCT decreased from nine to three (33.3%) after the second round of imaging; of the six (66.7%) remaining patients, four (66.7%) became eligible for TACE (Figure 4) and two (33.3%) for sorafenib. The 15 patients eligible for TACE on MDCT decreased to nine (60.0%) after the second round of imaging; RFA was suitable for one (16.7%) patient and sorafenib for five (83.3%) patients. Of the 23 patients considered eligible for sorafenib on MDCT, only one (4.3%) became eligible for TACE after Gd-EOB-DTPA-enhanced MRI. On paired χ^2 tests, the therapeutic decisions made after each detection method differed significantly (χ^2=17.467, P=0.015).

Variable	MDCT	Gd-EOB-DTPA-enhanced MRI	χ^2	P value
Single				
BCLC 0	21	12	0.149	0.700
BCLC A	42	28	0.057	0.812
BCLC C	7	5	0.000	1.000
Multiple				
BCLC A	8 (18)	20 (43)	1.292 (2.653)	0.256 (0.103)
BCLC B	13 (56)	17 (55)	0.653 (9.464)	0.419 (0.002*)
BCLC C	16 (60)	25 (114)	0.081 (2.659)	0.775 (0.103)
< 15 mm				
BCLC 0	1 (1)	1 (1)	—	0.503 (0.454)
BCLC A	1 (1)	12 (12)	2.402 (1.624)	0.121 (0.203)
BCLC B	11 (15)	15 (23)	3.232 (5.783)	0.072 (0.016*)
BCLC C	9 (9)	25 (38)	0.246 (2.163)	0.620 (0.141)
≥ 15 mm				
BCLC 0	20 (20)	11 (11)	3.060 (3.083)	0.080 (0.079)
BCLC A	48 (55)	48 (59)	0.000 (0.096)	1.000 (0.757)
BCLC B	15 (45)	17 (33)	0.147 (2.710)	0.701 (0.100)
BCLC C	23 (58)	30 (79)	1.233 (4.471)	0.267 (0.034*)
*Statistically significant results (P<0.05).				

Table 3: HCC stages according to MDCT and Gd-EOB-DTPA-enhanced MRI.

The treatments for the five patients without HCC on MDCT were altered to accord with the change in their BCLC stages after Gd-EOB-DTPA-enhanced MRI: three were eligible for resection and two for LT. Though the actual treatment therapy differed with the BCLC therapeutic decisions to some extent.

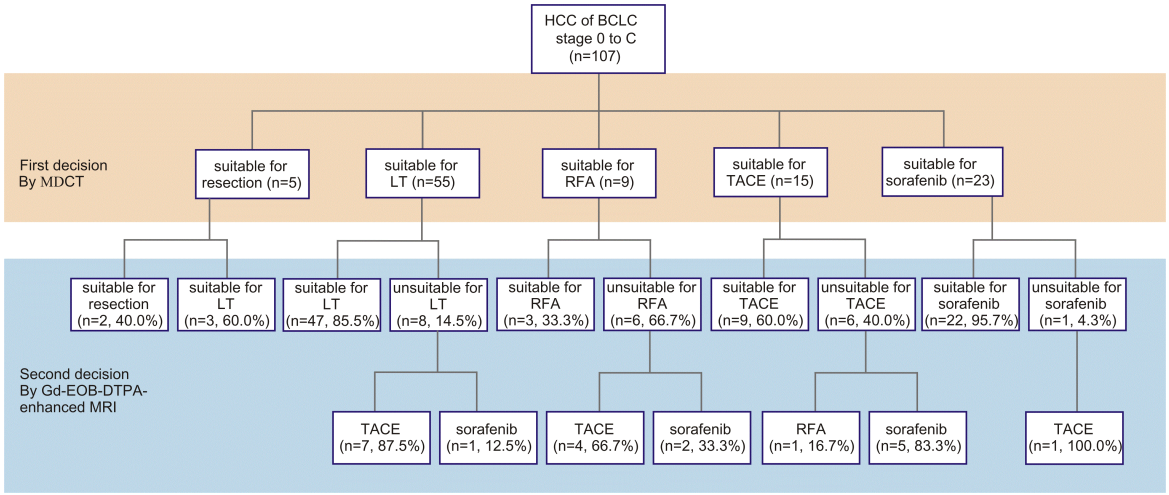

Figure 2: Changes in the therapeutic decisions by different imaging methods. Changes in the therapeutic decisions for hepatocellular carcinoma (HCC) in very early stage (BCLC 0), early stage (BCLC A), intermediate stage (BCLC B), and advanced stage disease (BCLC C).

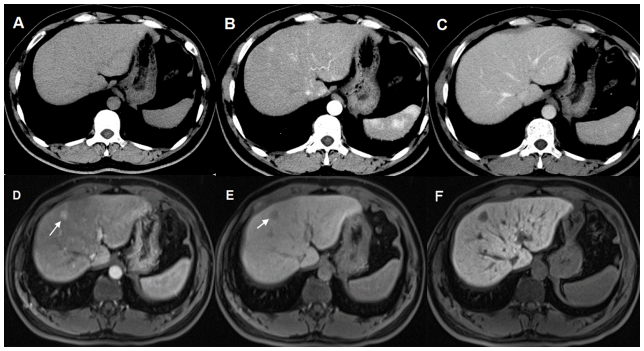

Figure 3: Staging changed from BCLC 0 to BCLC A. A 36-year-old man with a hepatocellular carcinoma (HCC) lesion of around 1.5 cm in segment II (figure not shown). No lesion was detected in segment IV on unenhanced CT (A), arterial-phase CT (B), or equilibrium-phase CT (C). On gadolinium-ethoxy benzyldiethylenetriaminepentaacetic acid (Gd-EOB-DTPA)-enhanced MRI, a lesion of about 1.8 cm was detected in segment IV. It showed obvious enhancement (arrow) on the arterial phase (D), a slight hypointense signal (arrow) on the equilibrium phase (E), and a hypointense signal (arrow) on the hepatobiliary phase (F). The lesion was finally pathologically confirmed as a moderately differentiated HCC. Therefore, the stage of the patient was changed from BCLC 0 to BCLC A.

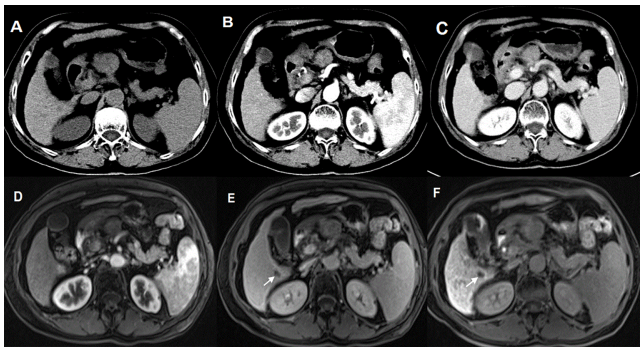

Figure 4: Staging changed from BCLC A to BCLC B. A 69-year-old woman with hepatitis B for over 28 months. On multidetector row computed tomography (MDCT), the lesion showed low density without obvious enhancement (A–C). On gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA)-enhanced MRI, the lesion was hyperintense on an arterial-phase contrast-enhanced T1-weighted image (D), hypointense(arrow) on a delayed-phase image (E) in segment VI, and showed a clear hypointense signal(arrow) on the hepatobiliary phase (F). The lesion was then confirmed to be a hepatocellular carcinoma (HCC). Both MDCT and Gd-EOB-DTPA-enhanced MRI had detected an HCC lesion of about 5.2 cm in segment IV. The Barcelona Clinic Liver Cancer (BCLC) stage of the patient changed from A to B.

Discussion

Our study showed that MDCT and Gd-EOB-DTPA-enhanced MRI differ significantly in the staging of HCCs. For patients with multiple lesions, more lesions were detected with Gd-EOB-DTPA-enhanced MRI than with MDCT in nearly all stages, especially in BCLC stage B, in which the difference was significant. This may be because Gd-EOB-DTPA-enhanced MRI detected more lesions in most patients. Consequently, early- or very-early-stage patients with single lesions were reclassified as intermediate- or advanced-stage patients with multiple lesions. For patients with lesions of <15 mm, there was also a significant difference between the two imaging methods in correctly evaluating BCLC stage B. For patients with lesions >15 mm, the staging of BCLC stage C differed significantly with the two imaging methods. Gd-EOB-DTPA-enhanced MRI tended to find more small and multiple lesions, therefore classifying the patients to a later stage.

Disease staging is particularly important in the management of HCC because it helps to predict prognosis and determine appropriate treatment options [21]. Several recent studies [9,10] have considered whether Gd-EOB-DTPA-enhanced MRI is better than MDCT in differentiating stages BCLC 0 and BCLC A in HCC patients eligible for curative treatments. In this study, patients with stages BCLC B and BCLC C were also included. The addition of Gd-EOB-DTPA-enhanced MRI after MDCT was also essential for the accurate evaluation of patients with BCLC stage B and BCLC stage C.

The current European Guidelines endorse the BCLC algorithm for treatment decisions [22]. Generally speaking, surgical treatment is the gold standard for tumors of small dimensions and patients with a good functional liver reserve while liver transplantation is indicated for patients with a compromised hepatic function [23]. Patients who are inoperable due to the presence of comorbidities and insufficient liver function reserve can be considered candidates for percutaneous ablation [24]. The treatment therapy of HCC depends on the tumor stage, patient performance status, liver function reserve, life expectancy and other realistic factors. So the final treatment decisions for the individual patient should be reached by an interdisciplinary team [22]. In China, patients develop HCC mainly on the basis of hepatitis B cirrhosis with poor liver function, and the degree of liver cirrhosis is high. Besides, HCC patients often drop out the treatment of liver transplantation due to the scarcity of donors. Therefore, the treatment therapy for HCC patients may not strictly follow the BCLC algorithm, RFA or TACE may be chosen more frequently instead.

This study had some limitations. Although the BCLC system obviously offers guidelines, the final decision must be made based on each patient's specific clinical condition [25]. So we didn't care for the final treatment decisions compared with the two imaging methods. Another limitation is that the number of the patients enrolled in the study was small and it was performed retrospectively, which was likely to contain bias. Besides, further study of the long term outcome/follow-up of the patients that had changed in staging is also limited. To our knowledge, there has been no predictive study comparing the efficacy of Gd-EOB-DTPA-enhanced MRI and MDCT in staging HCC. Therefore, a prospective study with a larger number of patients is required to verify our results.

This study suggests that Gd-EOB-DTPA-enhanced MRI not only evaluates the stages of early HCC more reliably than MDCT, but also differed in the staging of intermediate and advanced HCC which will help the clinical to choose more accurate therapeutic decisions for HCC patients.

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