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Original Article

Application of ultrasound combined with enhanced MRI by Gd-BOPTA in diagnosing hepatocellular carcinoma

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Abstract: Objective: This study aimed to probe into the diagnostic level and clinical value of ultrasound combined with enhanced MRI by Gd-BOPTA in hepatocellular carcinoma (HCC). Methods: A total of 58 suspected HCC patients in our hospital from January 2016 to November 2020 were collected as the research subjects, including 37 HCC and 21 non-HCC patients. The diagnostic results of ultrasound and enhanced MRI by Gd-BOPTA were compared, and the microvascular invasion in patients was assessed. The independent risk factors of microvascular invasion were analyzed by logistics regression, and the diagnostic value of these factors was tested by ROC. Results: The specificity, sensitivity and accuracy of enhanced MRI by Gd-BOPTA were 89.19%, 90.48% and 94.59%, respectively. The specificity, sensitivity and accuracy of ultrasound were 85.71%, 72.97% and 91.89%, and those of combined diagnosis were 76.19%, 97.30%, and 89.66%, respectively. The confirmation rate of microvascular invasion of enhanced MRI by Gd-BOPTA was dramatically higher than with ultrasound. Tumor diameter, comorbid cirrhosis and differentiation degree were independent risk factors of microvascular invasion, and ROC curve revealed that the area under the curve (AUC) of these risk factors was > 0.6. Conclusion: Enhanced MRI by Gd-BOPTA combined with ultrasound has good diagnostic value in HCC patients, and it can be widely used in early HCC diagnosis and clinical examination.

Keywords: Ultrasound, enhanced MRI by Gd-BOPTA, HCC

Introduction

Liver cancer (LC) is one of the most common malignancies in the world and the second most prominent malignancy occurring in China at present [1]. Thereinto, more than 80% cancer patients suffer from HCC [2]. The mortality rate is extremely high, ranking the third among all causes of cancer-related deaths in the world and the second in China [3]. The main causes are hepatitis B virus and hepatitis C virus infection, and over 60-80% can be attributed to hepatitis B virus infection [4]. The first-line treatment is hepatectomy. Early diagnosis of HCC in patients and understanding the pathological conditions of their lesions can improve patient outcomes. Moreover, HCC patients have high postoperative mortality and recurrence rates, so they need regular follow-ups, and imaging examination is one of the main means for accurate follow-up [5, 6].

Ultrasound is a familiar imaging tool for liver disease, it has a reasonable cost and rapid results [7]. Ultrasound also has good monitoring and diagnosis effects in HCC, and it can also predict some histological features and tumor differentiation [8, 9]. However, Jeong et al. [10] mentioned that the sensitivity of ultrasound detection for HCC was low, with some interference factors of patients also affecting the results of ultrasound examination; ultrasound also relies heavily on the experience of the operators, so it is best to use other imaging techniques to make up for these defects. Magnetic resonance imaging (MRI) has good resolution of soft tissue. It lacks ionizing radiation and has the function of multiplanar imaging. It is also widely used in diagnosing liver diseases, and its false positive rate is lower than that of ultrasound [11, 12]. Gd-BOPTA is a liver-specific contrast agent. Compared with conventional hepatobiliary MRI, enhanced MRI

by Gd-BOPTA has higher accuracy in many liver diseases, with higher accuracy in benign and malignant cases. CT and MRI have different diagnostic values in different types of LC [13].

In this study, we evaluated the diagnostic value of ultrasound and enhanced MRI by Gd-BOPTA in HCC to explore its clinical significance.

Materials and methods

Patient data

A total of 58 suspected cases of HCC in the Fourth Affiliated Hospital of Anhui Medical University and the Third Affiliated Hospital of Anhui Medical University from January 2016 to November 2020 were collected in this research. Among them, 37 patients were confirmed with HCC by surgery and pathology, and they were included into the HCC group, including 25 males and 12 females, with an average age of (48.7±6.5) years; while 21 were non-HCC patients, including 12 males and 9 females, (49.4±5.2) years old on average. We obtained the consent of the medical ethics committee of our hospital, and all patients were informed and they signed an informed consent form.

Inclusion and exclusion criteria

Inclusion criteria: All patients were pathologically determined to have HCC after operation. The diagnostic criteria were based on the diagnostic guidelines for HCC issued by the European Society for Medical Oncology (ESMO) [14]. They had no allergic reaction to the drugs used in the study, and their follow-up and clinical data were complete.

Exclusion criteria: Patients had contraindications of ultrasound and enhanced MRI; those who were complicated with other malignancies, or heart, lung, liver and kidney dysfunction; pregnant women or nursing mothers; those aged < 18 years old.

Ultrasonic inspection methods

A GE Logiq9 color ultrasound diagnostic instrument was used for ultrasound detection, and the probe frequency was 3.5 MHz. The subjects had to fast for 6 h. The size, location, boundary, internal echo and blood flow of liver lesions were evaluated by two-dimensional ultrasound images, and the blood flow parameters of the hepatic artery and portal vein were detected by color Doppler ultrasound. The test was completed by two experienced sonographers, and when there were different opinions about the tissue, results were discussed with a third physician to solve any contradictions.

MRI examination methods

A GE Discovery MR 750 3.0T MR scanner was used for MRI, and the receiving coil was an 8-channel phased array coil. The subjects had to fast for 4 h, and the entire liver was scanned with the liver as the positioning center. The scanning sequence was as follows: T2WI (TR/TE: 6528 ms/79 ms, layer thickness 5 mm, matrix: 320×224, bandwidth: 240 Hz/pixel), positive and negative phases (TR/TE: 133 ms/6.2 ms, layer thickness 5 mm, matrix: 320×224, bandwidth: 280 Hz/pixel), HASTE (TR/TE: 1400 ms/91 ms, flip angle: 90, matrix: 320×256, bandwidth: 506.4 Hz/pixel), T2-weighted sequence of breath-holding multi-beat with contraction factor of 2 or 4 (TR/TE: 2161 ms/70 ms, layer thickness 5 mm, matrix: 320×224, bandwidth: 446 Hz/pixel), VIBE (TR/TE: 3.9 ms/1.4 ms, layer thickness 3 mm, matrix: 320×224, bandwidth: 400 Hz/pixel). All patients were intravenously injected with 0.2 ml/kg Gd-BOPTA contrast agent manually at 2 ml/sec. Twenty-five seconds later, they underwent enhanced scanning, dynamic scanning in arterial phase, portal vein phase and equilibrium phase, and images of hepatobiliary phase were obtained 2 h after injection.

Outcome measures

Main outcome measures: The results of the two diagnostic methods on HCC positive and negative classification between the two groups were compared, the judgment of ultrasound and MRI on vascular invasion was observed and compared, and the diagnostic value formula of each index was shown in **Table 1**.

Secondary outcome measures: The clinical data of patients in both groups was observed, the risk factors of vascular invasion of HCC patients was assessed via multivariate analysis, and the diagnostic value of these risk factors in vascular invasion was analyzed by ROC curve.

Table 1. Diagnostic value formula

Indexes	Formula
Specificity	True negative number/(true negative number + false positive number) ×100%
Sensitivity	True positive number/(true positive number + false negative number) ×100%
Accuracy	(True positive number + true negative number)/(true positive number + true negative number + false positive number + false negative number) ×100%

Table 2. Clinical data table

	HCC group (n=37)	Non-HCC group (n=21)	t/X^2	P
Gender			0.630	0.427
Male	25 (67.57)	12 (57.14)		
Female	12 (32.43)	9 (42.86)		
Age (years)	48.7±6.5	49.4±5.2	0.601	0.549
Lesion site			0.475	0.789
Left lobe	13 (35.14)	9 (42.86)		
Right lobe	21 (56.76)	11 (52.38)		
Bilateral lobes	3 (8.10)	1 (4.76)		
Child-pugh grading			0.535	0.765
Grade A	29 (78.38)	18 (85.72)		
Grade B	6 (16.22)	2 (9.52)		
Grade C	2 (5.40)	1 (4.76)		
AFP level			5.754	0.016
< 25 ng/ml	8 (21.62)	11 (52.38)		
≥ 25 ng/ml	29 (78.38)	10 (47.62)		
Comorbid hepatitis B	34 (91.89)	19 (85.71)	0.551	0.459
Comorbid cirrhosis	27 (72.97)	14 (66.67)	0.257	0.612
Tumor diameter (cm)	5.12±2.46			
Degree of differentiation				
Highly differentiated	4 (10.81)			
Moderately differentiated	26 (70.27)			
Poorly differentiated	7 (18.92)			

Statistical methods

All data were calculated by SPSS 20.0 (SPSS Inc., Chicago, IL, USA), and the rate comparison was made by Chi-square test, expressed by X^2. When the number of samples was ≥ 40 and the theoretical frequency was < 1, it was assessed via Fisher's test. All the measurement data were in line with normal distribution and analyzed through independent-samples T test. The diagnostic value of risk factors of vascular invasion was evaluated by ROC curve, and pictures were illustrated with GraphPad Prism 7 (GraphPad Software, Inc., San Diego CA, USA). $P < 0.05$ was considered to be statistically significant.

Results

Clinical data of patients

Comparing the two groups, we found that there was no statistical difference in gender, age, lesion site, comorbid hepatitis B or cirrhosis, but there was statistical difference for Child-pugh grading and AFP level between groups (**Table 2**).

Diagnostic value of HCC

We observed and compared the positive and negative diagnosis of HCC by ultrasound and enhanced MRI by Gd-BOPTA, and found that the specificity, sensitivity and accuracy of the latter were higher than those of the former. Ultrasound combined with enhanced MRI by Gd-BOPTA dramatically improved the diagnostic sensitivity (**Table 3**).

Diagnostic value of microvascular invasion

We measured the microvascular invasion of HCC patients, and found that 13 patients had microvascular invasion and 24 didn't. We compared their positive and negative diagnosis of microvascular invasion by ultrasound and enhanced MRI by Gd-BOPTA, and discovered that the sensitivity of the joint detection was markedly increased (**Table 4**).

Analysis of risk factors of vascular invasion

Clinical data were collected and assessed through univariate analysis. It was found that tumor diameter, hepatitis B, cirrhosis and differentiation degree were unfavorable factors. Logistics multivariate regression analysis iden-

Table 3. Diagnostic value of HCC

	HCC group (n=37)	Non-HCC group (n=21)	Specificity	Sensitivity	Accuracy
Ultrasound			85.71%	72.97%	77.59%
Positive	27 (72.97)	3 (14.29)			
Negative	10 (27.03)	18 (85.71)			
Enhanced MRI by Gd-BOPTA			89.19%	90.48%	89.66%
Positive	33 (89.19)	2 (9.52)			
Negative	3 (8.11)	19 (90.48)			
Joint detection			76.19%	97.30%	89.66%
Positive	36 (97.30)	5 (23.81)			
Negative	1 (2.70)	16 (76.19)			

Table 4. Diagnostic value of vascular invasion

	Microvascular invasion (n=13)	No microvascular invasion (n=24)	Specificity	Sensitivity	Accuracy
Ultrasound			95.83%	84.62%	91.89%
Positive	11 (84.62)	1 (4.17)			
Negative	2 (15.38)	23 (95.83)			
Enhanced MRI by Gd-BOPTA			95.83%	92.31%	94.59%
Positive	12 (92.31)	1 (4.17)			
Negative	1 (7.69)	23 (95.83)			
Joint detection			91.67%	100.00%	94.59%
Positive	13 (100.00)	2 (8.33)			
Negative	0 (0.00)	22 (91.67)			

Table 5. Cox regression analysis

Factor	Single factor			Multiple factors		
	HR	*P* value	HR (95% CI)	HR	*P* value	HR (95% CI)
Gender (male VS female)	0.758	0.458	0.365-1.575			
Age (< 55 years VS ≥ 55 years)	0.509	0.071	0.245-1.058			
Sites of lesions (left and right lobes and bilateral lobes)	1.062	0.485	0.523-1.946			
Child-pugh grading (A, B and C)	3.518	0.232	1.265-4.124			
AFP level (< 25 ng/ml VS ≥ 25 ng/ml)	2.746	0.064	1.868-4.103			
Tumor diameter (< 5 cm VS ≥ 5 cm)	0.689	0.032	0.535-0.912	0.681	0.018	0.512-0.908
Comorbid hepatitis B (yes VS no)	3.765	0.043	2.346-4.427	4.029	1.032	2.306-6.082
Comorbid with cirrhosis (yes VS no)	0.436	0.013	0.356-0.821	0.469	0.021	0.314-0.672
Degree of differentiation (poor, moderate and high)	2.341	0.024	1.834-2.701	2.327	0.016	1.876-2.728

tified that tumor diameter, comorbid cirrhosis and differentiation degree were independent risk factors of microvascular invasion (**Table 5**).

Predictive value of risk factors

We detected the diagnostic value of tumor diameter, comorbid cirrhosis and differentiation degree in patients with microvascular invasion by ROC curve, and found that the AUCs were 0.752, 0.610 and 0.684 respectively, all of which had certain diagnostic value (**Figure 1**).

Discussion

At the moment, there are more and more patients with viral hepatitis. With the gradual damage of liver function, the disease will gradually develop into cirrhosis, and some patients will eventually develop HCC [15]. Therefore, regular examination of patients with hepatitis B, hepatitis C and cirrhosis can improve the screening and diagnosis rate for HCC, treating them early and improving their prognosis and quality of life [16]. AFP is a serological indicator

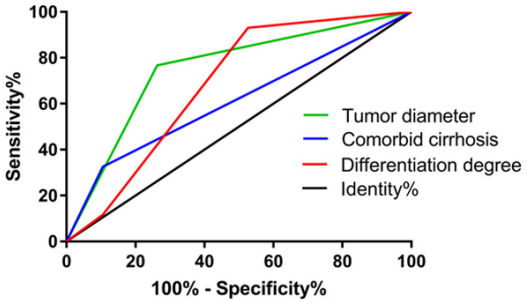

Figure 1. Diagnostic value of microvascular invasion. AUC, 95% CI, specificity and sensitivity, and Youden index of tumor diameter are 0.752, 0.615-0.889, 73.68% and 76.74%, and 50.42%. AUC, 95% CI, specificity and sensitivity, and Youden index of comorbid cirrhosis are 0.610, 0.465-0.756, 89.47% and 32.56%, and 22.03%, respectively. AUC, 95% CI, specificity and sensitivity, and Youden index of differentiation degree are 0.684, 0.615-0.889, 47.37% and 93.02%, and 40.39%.

widely used in clinical practice for HCC, but its diagnostic ability is insufficient. Ma et al. [17] pointed out that the sensitivity and specificity of AFP in diagnosing HCC were 74.42% and 55.63%, respectively, and the serum AFP level of some patients with HCC does not increase.

With the development of imaging technology, the diagnostic value of imaging has gradually exceeded the value of serology in HCC [18]. According to research reports, radical resection of liver tumors, preoperative CT, laparoscopic ultrasound and preoperative MRI can eliminate suspicious tissues as early as possible and effectively improve the surgical results [19]. MRI and ultrasound have their own advantages and disadvantages in clinical application, and the application of a single diagnostic method may lead to mis-diagnosis or diagnostic errors [20]. Ultrasound has wide accessibility and low cost, so it is recommended for patient monitoring, but its sensitivity is considered to be greatly influenced by imaging scheme, equipment, patient characteristics and operator experience [21]. Gd-BOPTA, is an extracellular space contrast agent, it can reveals uniform enhancement in liver tissue; but because there are no normal hepatocytes ingesting Gd-BOPTA in tumors, it presents a low signal which does not facilitate diagnosis. Many studies also show that the diagnostic efficiency of enhanced MRI by Gd-BOPTA is higher than that of conventional MRI [22, 23].

In HCC diagnosis and screening, the diagnostic accuracy of enhanced MRI by Gd-BOPTA is higher than that of ultrasound, which is consistent with our research. We found that the specificity, sensitivity and accuracy of enhanced MRI by Gd-BOPTA were 89.19%, 90.48% and 94.59%, respectively; those of ultrasound were 85.71%, 72.97% and 91.89%. Gd-BOPTA contrast agent can shorten the paramagnetism of T1 relaxation time, reflect the hemodynamic and blood supply characteristics of the lesions in the dynamic phase, and reflect whether there is liver cell uptake and bile excretion in the hepatobiliary phase, and enhance the sensitivity and specificity of MR scanning diagnosis [24]. Furthermore, we compared the results of ultrasound combined with MRI, and found that the combined diagnosis did not improve the specificity of patients, but increased the sensitivity to 97.30%, which indicated that ultrasound combined with enhanced MRI by Gd-BOPTA could better diagnose HCC in patients and further reduce the missed diagnosis rate of HCC. Meanwhile, we also observed the vascular invasion of HCC in patients, among which 13 patients had microvascular invasion. Microvascular invasion will lead to higher recurrence risk and worse survival prognosis of patients. The ability to identify preoperative imaging features related to vascular invasion has crucial prognostic significance, and even facilitates the relevant stratification of patients [25]. This study found that the specificity, sensitivity and accuracy of enhanced MRI by Gd-BOPTA in diagnosing microvascular invasion were 95.83%, 92.31% and 94.59%, and the sensitivity was improved to 100.00% after combined diagnosis. Finally, through logistics regression analysis, we found that tumor diameter, comorbid cirrhosis and differentiation degree were independent risk factors for microvascular invasion. McIntyre et al. [26] also mentioned that some elderly patients with HCC and hyperlipidemia or coronary artery disease had no obvious increased risk factors. The diagnostic ability of these risk factors to microvascular invasion was analyzed by ROC. It was found that the AUSs of tumor diameter, comorbid cirrhosis and differentiation degree were 0.752, 0.610 and 0.684, respectively, all of which were > 0.6, with certain diagnostic value.

This research also has some limitations. Firstly, it is inevitably biased, so the results do not rep-

resent all types of LC. Secondly, we have not included patients' individual treatment plans. It is not clear whether enhanced MRI by Gd-BOPTA and ultrasound will affect the treatment efficacy. Finally, although the radioactive detection method has good detection ability, it needs to be improved, and it is hoped that some non-invasive serological tests can be introduced in the future to enhance the diagnosis efficacy.

To summarize, enhanced MRI by Gd-BOPTA combined with ultrasound has good diagnostic value in determining HCC in patients, and it can be widely used in early clinical HCC diagnosis and examination.

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Disclosure of conflict of interest

None.

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