

Prediction of early recurrence of hepatocellular carcinoma after resection based on Gd-EOB-DTPA enhanced magnetic resonance imaging: a preliminary study

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Background: Early recurrence (ER) after radical resection of hepatocellular carcinoma (HCC) affects the prognosis of patients. Gadolinium ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) can improve the detection rate of small HCC. This study innovatively introduces a new quantitative index combined with qualitative index to compare the differences in clinical and imaging characteristics between ER and non-ER groups and evaluate the feasibility of Gd-EOB-DTPA-enhanced MRI in predicting ER.

Methods: A total of 68 patients with HCC confirmed by operation and pathology in the Shandong Cancer Hospital and Institute were included retrospectively. All participants were examined by Gd-EOB-DTPA-enhanced MRI within 3 weeks before surgery. Regular follow-up was performed every 2 months within 1 year after operation. Among them, 18 cases with new lesions were in ER group, and 50 cases without new lesions were in non-ER group. The clinical and imaging data of the 2 groups were collected, and the differences of clinical data and preoperative MRI signs between the ER group and non-ER group were compared. The predictive factors of ER after HCC were analyzed by multivariate logistic regression.

Results: The quantitative parameter lesion-to-liver contrast enhancement ratio (LLCER) can predict the pathological grade of HCC (P=0.023). The results of univariate analysis between the ER group and non-ER group showed that there were significant differences in pathological grade (P=0.008), lesion morphology (P=0.011), peritumoral low signal intensity in hepatobiliary phase (HBP) (P<0.001), satellite nodules (P<0.001), and LLCER (P<0.001) between the 2 groups. Multivariate logistic regression analysis showed that HBP peritumoral low signal intensity [odds ratio (OR) =7.214, 95% confidence interval (CI): 1.230–42.312, P=0.029], satellite nodules (OR =9.198, 95% CI: 1.402–60.339, P=0.021), and parameter LLCER value (OR =0.906, 95% CI: 0.826–0.995, P=0.039) were independent predictors of ER of HCC after resection.

Conclusions: Preoperative Gd-EOB-DTPA enhanced MRI has important predictive value for early recurrence after radical resection of hepatocellular carcinoma.

Keywords: Hepatocellular carcinoma (HCC); early recurrence; gadolinium ethoxybenzyldiethylenetriaminepentaacetic acid (Gd-EOB-DTPA); magnetic resonance imaging (MRI); prediction

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Introduction

Hepatocellular carcinoma (HCC) is one of the main causes of cancer-related death and a serious threat to human health. For patients with HCC whose liver function is well preserved, radical resection is the main treatment (1). However, due to the dual blood supply of HCC from the hepatic artery and portal vein and the formation of collateral circulation, it is difficult to completely necrotize HCC (2), so there is a high risk of recurrence. Up to 70% of HCC patients relapse within 5 years after operation (3), and early recurrence (ER) within 1 year after radical resection of HCC is closely related to poor prognosis (4). Previous studies have identified some pathological factors to predict ER after HCC, such as microvascular invasion, histological grade, and intravascular tumor thrombus (5-7); however, these can only be evaluated by pathologic and histological examination after surgery, which makes it of limited value in preoperative evaluation and treatment planning.

Magnetic resonance imaging (MRI) has become an important non-invasive tool for the diagnosis of HCC. Gadolinium ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) is a hepatocyte-specific contrast agent of which intravenous injection can increase the contrast of MRI liver parenchyma (8). Therefore, it has the advantages of improving the detection rate of small and micro HCC lesions and assisting in the differentiation of HCC from other non-HCC lesions. In practical clinical work, however, the application of preoperative Gd-EOB-DTPA-enhanced MRI features and quantitative parameters to evaluate ER is still limited.

In this study, the parameter lesion-to-liver contrast enhancement ratio (LLCER) was creatively introduced to evaluate early postoperative recurrence, which compensated for these limitations. Based on this, the purpose of this study was to explore the value of preoperative Gd-EOB-DTPA-enhanced MRI imaging features and quantitative parameters in predicting the pathological grade of HCC and ER after operation of HCC. We present the following article in accordance with the STARD reporting checklist (available at https://jgo.amegroups. com/article/view/10.21037/jgo-22-224/rc).

Methods

Patients

The study was conducted in accordance with the

Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Shandong Cancer Hospital and Institute (No. SDTHEC-2021008008). Individual consent for this retrospective analysis was waived. The data of patients who underwent radical resection of HCC in the Shandong Cancer Hospital and Institute from January 2016 to May 2020 were analyzed retrospectively. The inclusion criteria were as follows: (I) HCC was not treated with radiotherapy, chemotherapy, ablation, and embolization before radical resection, and was confirmed by pathology after operation; (II) Gd-EOB-DTPA-enhanced MRI scans were performed within 3 weeks before operation; and (III) regular followup was performed for at least 1 year after operation. The exclusion criteria were as follows: (I) comorbidity of other diseases that seriously affect patient survival time; (II) tumor invading portal vein or hepatic vein; (III) postoperative complication of other malignant tumors and/or distant organ metastasis; (IV) those with incomplete data. A total of 68 patients who underwent Gd-EOB-DTPA-enhanced MRI before surgery and were pathologically diagnosed with HCC were finally included by searching our organization's database according to the above criteria, of which 18 patients with ER comprised the ER group and 50 patients without ER comprised the non-ER group. Figure 1 shows the flow chart of the study.

The clinical data of the 2 groups were collected, including gender, age, Child-Pugh grade, alpha-fetoprotein (AFP) level, history of hepatitis B, and pathological grade. According to the Edmondson-Steiner pathological grading system (9), HCC was divided into grade I–IV, whereby nonpoorly differentiated (highly differentiated and moderately differentiated) HCC was grade I and II, and poorly differentiated HCC was grade III and IV.

All cases were followed up regularly every 2 months within 1 year after operation. Liver function, AFP level, and abdominal ultrasound were examined to monitor the recurrence. When the AFP level increased, or new lesions were detected by ultrasound, abdominal enhanced computed tomography (CT) or MRI evaluation was performed. Intrahepatic recurrence was defined as the occurrence of new lesions in the remnant liver, which was confirmed by puncture or secondary surgery and pathology, or had typical imaging features, showing enhancement in the hepatic arterial phase and reduced enhancement in the portal vein or delayed phase. The ER was defined as recurrence within 1 year after radical resection (10).



Figure 1 Flow chart included by the research team. HCC, hepatocellular carcinoma; ER, early recurrence; MRI, magnetic resonance imaging; Gd-EOB-DTPA, gadolinium ethoxybenzyl-diethylenetriaminepentaacetic acid.

MRI techniques

The Philips Ingenia 3.0T superconductive magnetic resonance scanner (Philips Healthcare, Eindhoven, Netherlands) was used and an 8-channel abdominal phased array coil was used to collect images. Conventional MRI scanning sequences included cross-sectional T1 weighted imaging (T1WI), fat-suppressing T2WI, and Dither scanning parameters were as follows: T1WI, repetition time (TR) 495 ms, time to echo (TE) 10 ms, field of view (FOV) 340 mm; fat suppressing T2WI, TR 4,213 ms, TE 120 ms; echo-planar imaging (EPI) technique, TR 7,099 ms, TE 5 ms, TE 5 ms, 800 s/mm, 340 mm, 0 mm, 0 mm, 0 mm, 120 ms, 5 ms, 5 ms, 5 ms, 5 ms, 7 ms, respectively, and 800 s/mm², respectively. For Gd-EOB-DTPAenhanced MRI, plain scan and enhanced arterial phase (20-35 s), portal venous phase (60 s), transition phase (3 min), and 20 min hepatobiliary phase images were obtained. Using enhanced T1 high-resolution isotropic volume excitation (e-THRIVE) sequence, the timing of arterial phase imaging was determined by MR fluoroscopic bolus injection technique. The contrast agent Gd-EOB-

DTPA (German Bayer Medical and Health Co., Ltd., Leverkusen, Germany, 10 mL/bottle, 181.43 g/L) was automatically injected intravenously at the speed of 2 mL/s through a high-pressure syringe. The total dose was 0.025 mmol/kg. Immediately after that, the catheter was flushed with 20 mL saline.

Image analysis

The images collected from all cases were transmitted to the Dutch Philips workstation, and the lesions were analyzed by 2 experienced diagnosticians (residents who had worked for 5 years and deputy chief physicians who had worked for 15 years). Both doctors knew that the lesions were HCC, but they did not know the clinical features, laboratory examination, pathological grade, and postoperative followup. The 2 investigators reached an agreement through consultation, and if there is any objection to the result, a final judgment was made by the third chief physician who had 30 years of work experience. The following indicators were observed: (I) lesion size: in the sequence with the most clearly defined edge of the lesion, the maximum

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diameter of each lesion on the axial plane; (II) lesion morphology: according to the edge outline of the lesion, it can be divided into quasi-circular and irregular shapes; (III) peritumoral low signal intensity in HBP: irregular wedgeshaped or flaming low signal area in the liver parenchyma located outside the edge of the hepatobiliary lesion (11); (IV) satellite nodules: lesions with MRI features similar to the main lesions and <2 cm, located within the 2 cm around the main lesions (12); (V) LLCER: the mean signal intensities (SI) of HCC and adjacent liver parenchyma was measured using the circular area of the region of interest (ROI). The ROI of HCC was placed within the range of lesions as much as possible, while the ROI of adjacent liver parenchyma was larger than 1.5 cm², and there was no focal signal change and the influence of large vessels. The LLCER = $[(SI_{Tpost}/SI_{LVpost}) - (SI_{Tpre}/SI_{LVpre})] / (SI_{Tpre}/SI_{LVpre}),$ $SI_{\rm Tpre},\,SI_{\rm Tpost},\,SI_{\rm LVpre}$ and $SI_{\rm LVpost}$ corresponded to the signal intensity of lesions and liver parenchyma on plain scan and HBP images, respectively. No obvious adverse events were reported in MRI examinations.

Statistical analysis

The software SPSS 24.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Measurement data conforming to normal distribution were expressed as mean \pm standard deviation, and the independent sample t-test was used for comparison between the 2 groups. Measurement data that did not conform to normal distribution were represented by the median (quartile) [M (P25–P75)], and comparison between the 2 groups was made by Mann-Whitney U test. The chi-square (χ^2) test was used to compare the count data between the 2 groups. Significant variables with P<0.05 in the univariate analysis were included in the multivariate logistic regression analysis to identify the independent risk factors of ER after HCC. A difference of two-sided P<0.05 was considered statistically significant.

Results

Prediction of pathological grade by quantitative parameter LLCER

A total of 68 patients who underwent radical resection for HCC were included, including 47 cases with non-poorly differentiated HCC and 21 cases with poorly differentiated HCC. For the parameter LLCER, the measured values in non-poorly differentiated HCC and poorly differentiated HCC were -20.287±12.141 and -27.581±11.374, respectively.

Comparison of clinical and imaging data between ER group and non-ER group

A total of 18 patients with HCC had ER after radical resection, and the time of ER was 2–12 months, with an average of 8 ± 8.9 months. There was no significant difference in gender, age, Child-Pugh grade, AFP level, history of hepatitis B, and lesion size between the 2 groups (P>0.05; *Tables 1,2*). There were significant differences in pathological grade, lesion morphology, peritumoral low signal intensity in HBP, satellite nodules, and parameter LLCER between the 2 groups, and the LLCER value in the ER group was lower than that in the non-ER group (P<0.05; *Tables 1,2*, *Figure 2*).

Multivariate logistic regression analysis of ER after operation of HCC

The pathological grade, lesion morphology, peritumoral low signal intensity in HBP, satellite nodules, and parameter LLCER values in the above analysis were taken as independent variables, and the occurrence of ER as a dependent variable, according to which multivariate logistic regression analysis was carried out. The results showed that peritumoral low signal intensity in HBP, satellite nodules, and parameter LLCER were independent predictors of early recurrence after HCC, and LLCER was negatively correlated with ER (*Table 3*).

Discussion

The ER of HCC is an important factor for poor prognosis after radical resection. Effective evaluation and prediction of ER of HCC before operation is of great significance to the adjustment of clinical treatment decision making and the evaluation of prognosis. Choi *et al.* (13) found that recurrence after HCC has nothing to do with the enhancement mode of the lesion in arterial phase and portal phase, but the level of HBP signal is the influencing factor of postoperative recurrence. Therefore, through the retrospective analysis of the clinical data, preoperative Gd-EOB-DTPA-enhanced MRI features and HBP quantitative parameters of patients after radical resection of HCC, it was found that some preoperative MRI features and HBP

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Table 1	Comparison	of clinical	characteristics	between ER	group and non-ER g	group
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Clinical characteristics	ER group (n=18)	Non-ER group (n=50)	χ^2/t	P value
Gender			0.094 ^ª	0.759
Male	16	41		
Female	2	9		
Age (years)	54.6±8.1	54.5±9.6	-0.052 ^b	0.959
Child-Pugh grade			0.141 ^ª	0.707
A	11	28		
В	7	22		
AFP (ng/mL)			0.106ª	0.744
<400	15	45		
≥400	3	5		
History of hepatitis B			0.822ª	0.365
Yes	14	45		
No	4	5		
Pathological grade			6.982 ^ª	0.008
Non-poorly differentiated	8	39		
Poorly differentiated	10	11		

ER, early recurrence; AFP, α -fetoprotein; a, χ^2 value; b, *t* value.

Table 2 Comparison of Gd-EOB-DTPA enhanced MR	I characteristics between ER group and non-ER group
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MRI characteristics	ER group (n=18)	Non-ER group (n=50)	$\chi^2/Z/t$	P value
Lesion size, M (P25–P75)	35.5 (22.75–47.75)	29 (19.75–46.25)	-0.793ª	0.428
Lesion morphology			6.395 ^b	0.011
Quasi-circular	12	47		
Irregular shape	6	3		
Peritumoral low signal intensity in HBP			18.234 ^b	<0.001
Yes	12	7		
No	6	43		
Satellite nodules			22.835 ^b	<0.001
Yes	15	10		
No	3	40		
LLCER, mean ± SD	-0.34±0.08	-0.18±0.11	5.36°	<0.001

Gd-EOB-DTPA, gadolinium ethoxybenzyl-diethylenetriaminepentaacetic acid; MRI, magnetic resonance imaging; ER, early recurrence; M, median; HBP, hepatobiliary phase; LLCER, lesion-to-liver contrast enhancement ratio; SD, standard deviation; a, Z value; b, χ^2 value; c, *t* value.

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Figure 2 A 58-year-old male with poorly differentiated HCC in the right lobe of the liver was found to have recurrence 6 months after resection. Before the resection, the right lobe of the liver showed an irregular mass. (A) DWI (b=800 s/mm²) showed high signal; (B) irregular ring enhancement around the lesion in the arterial phase; (C) hepatobiliary specific phase showed low signal around tumor (yellow arrow); (D) hepatobiliary specific phase showed low signal around tumor (yellow arrow) and satellite nodules (red arrow). HCC, hepatocellular carcinoma; DWI, diffusion-weighted imaging.

Table 3 Multivariate logistic regression analysis of early recurrence of hepatocellular carcinoma after resection

Variables	Regression coefficient	Standard error	Wald	P value	OR (95% CI)	
Pathological grade	1.526	0.896	2.905	0.088	4.602 (0.795–26.620)	
Lesion morphology	0.418	1.011	0.171	0.680	1.518 (0.209–11.015)	
Peritumoral low signal intensity in HBP	1.976	0.903	4.793	0.029	7.214 (1.230–42.312)	
Satellite nodules	2.219	0.960	5.346	0.021	9.198 (1.402–60.339)	
LLCER	-0.098	0.048	4.279	0.039	0.906 (0.826–0.995)	

OR, odds ratio; CI, confidence interval; HBP, hepatobiliary phase; LLCER, lesion-to-liver contrast enhancement ratio.

quantitative parameters could evaluate the ER of HCC, which has rarely been reported in previous literature. In addition, this study analyzed the relationship between the enhancement degree of HCC lesions in HBP and pathological grade, and found that the parameter LLCER value could predict the pathological grade of HCC.

Prediction of ER after operation of HCC by imaging features of Gd-EOB-DTPA enhanced MRI

The solution of Gd-EOB-DTPA is a hepatobiliary specific MRI contrast agent, which shows low signal intensity because the focus does not ingest the contrast medium in the hepatobiliary phase. The uptake of contrast medium in

normal liver tissue shows high signal, which increases the detection rate of small and micro liver cancer (14). Previous studies have shown that preoperative Gd-EOB-DTPAenhanced MRI is helpful to predict early postoperative recurrence of HCC (9,15-17). In this study, it was found that peritumoral low signal intensity in HBP and satellite nodules were independent predictors of ER after radical resection of HCC. A possible mechanism of peritumoral low signal on HBP is that the tumor invades microvessels and causes peri-tumor perfusion changes, which affects the function of organic anion transporter and reduces Gd-EOB-DTPA uptake by peritumoral hepatocytes (15). Satellite nodules are small lesions around the main focus, and their presence represents an increased risk of tumor spread and intrahepatic metastasis in HCC (18). Wei et al. (1), through the study of ER risk stratification after radical resection of HCC, found that peritumoral low signal intensity in HBP and satellite nodules can be used to assess the risk of ER after preoperative stratified hepatectomy. Ahn et al. (9) found that peritumoral low signal intensity in HBP was a predictor of ER of HCC. Plessier et al. (19) reported that 7 of 28 HCC patients with satellite nodules relapsed, while none of the 41 patients without satellite nodules relapsed (P<0.001). Xu et al. (20) reported that satellite nodule is an independent risk factor for recurrence after HCC. These results suggest that the presence of peritumoral low signal intensity in HBP and satellite nodules promotes tumor progression and recurrence, which is consistent with the results of this study, so peritumoral low signal intensity in HBP and satellite nodules can be used to evaluate ER after HCC before operation.

Prediction of ER and pathological grade after operation of HCC by quantitative parameter LLCER

Kitao *et al.* (21) revealed that the signal intensity of hepatobiliary phase was related to the expression level of OATP8, an organic anion transport peptide on the membrane of hepatocytes which can take up Gd-EOB-DTPA. The expression level of OATP8 decreases significantly during the formation of HCC, so with the development of HCC, HBP signal decreases gradually (22). At the same time, some studies have shown that the enhancement degree of tumors after injection of Gd-EOB-DTPA is related to pathological grade. The higher the pathological grade is, the more obvious the difference of liver function between tumor and normal liver tissue is, the less the number of normal hepatocytes is, and the lower the signal is (21,23). Choi et al. (13) believe that the time of postoperative tumor recurrence in HCC with equal or high signal intensity on HBP images is much longer than that in HCC with low signal intensity, and it is an important prognostic factor. However, in practice, most HCC lesions show low signal intensity on HBP and equal or high signal intensity on HBP is very rare (24), so the clinical significance of this qualitative index is not great. Thus, the emergence of some quantitative parameters will reflect greater value in predicting ER after HCC surgery. Some studies have shown that the tumor contrast enhancement ratio (CER), the quantitative parameter of Gd-EOB-DTPA enhanced MRI, is related to the pathological grade of HCC (21,24). However, the parameter CER value ignores the difference in the functional state of hepatocytes in the surrounding liver tissue, so there are some defects, and the parameter LLCER value can reflect the situation of HCC lesions and surrounding liver tissue. Analysis with the LLCER quantitative parameter has been used to evaluate benign liver lesions, and it has high sensitivity and specificity in differentiating focal nodular hyperplasia and hepatocellular adenoma (25). Mulé et al. (26) believe that quantitative analysis of HBP tumor enhancement in Gd-BOPTAenhanced MRI by LLCER can accurately predict the pathological grade of HCC and recurrence-free survival rate after surgical resection. However, as far as we know, the value of the parameter LLCER in predicting ER after HCC has not been reported. Our study showed that the parameter LLCER of poorly differentiated HCC (III-IV grade) is significantly lower than that of non-poorly differentiated (I-II grade), which is consistent with the results reported by Mulé et al. (26). In multivariate analysis, the parameter LLCER value was negatively correlated with early postoperative recurrence, that is, with the decrease of LLCER value, the ER rate increased, so the parameter LLCER value can be used to evaluate early postoperative recurrence of HCC.

Prediction of ER after operation of HCC by pathological grade and lesion morphology

Shimada *et al.* (27) found that the degree of pathological differentiation of HCC is an independent factor affecting long-term survival and recurrence within 10 years. The higher the degree of malignancy and formation of new blood vessels, the more likely to invade the surrounding liver parenchyma, leading to recurrence (28). However, a previous study suggested that pathological grade cannot

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predict postoperative recurrence (29). The shape of the lesion is an important risk factor for the ER of HCC. Previous studies have shown that when the shape is irregular, which represents a more invasive biological behavior, the ER rate is increased (30,31). In this study, although there were significant differences in pathological grade and lesion morphology between the 2 groups in univariate analysis, the results of multivariate analysis were not independent predictors of early recurrence. We speculated that it may be due to the small sample size in the ER group or other predictive factors. Therefore, the pathological grade of HCC and the evaluation of morphological characteristics of MRI lesions before operation are still factors worthy of attention, and larger sample size research is needed in the future.

The deficiency of this study

The limitations of this study are as follows: first, this study was a single-center retrospective study with a small sample size and selective bias, which needs to be further confirmed by a large sample; second, the signal intensity of plain scan and HBP of HCC was measured on the largest cross section of the lesion, not in the whole tumor. Whole tumor analysis can not only evaluate the LLCER measurement of heterogeneous tumors more accurately, but also improve the repeatability, which is our future research direction.

Conclusions

The ER after radical resection of HCC is related to many factors, such as peritumoral low signal intensity in HBP, satellite nodules, and parameter LLCER value of HBP. The combined application of the above factors has a certain value in predicting ER after operation of HCC.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-224/rc

Data Sharing Statement: Available at https://jgo.amegroups. com/article/view/10.21037/jgo-22-224/dss *Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups. com/article/view/10.21037/jgo-22-224/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Shandong Cancer Hospital and Institute (No. SDTHEC-2021008008). Individual consent for this retrospective analysis was waived.

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