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Quantitative analysis of gadoxetic acid-enhanced magnetic resonance imaging predicts histological grade of hepatocellular carcinoma

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ABSTRACT

Objective: To confirm the histological grade of hepatocellular carcinoma (HCC) by gadoxetic acid-enhanced MRI.
Methods: Ninety-five HCC patients underwent gadoxetic acid-enhanced MRI before surgical intervention. The correlations among the signal absolute enhancement, contrast enhancement ratio (CER) and tumor histological grade were analyzed.
Results: The correlation between CER of tumor-to-liver and the grades of tumor differentiation is the most significant negative. The k-value for the CER of tumor-to-liver and histopathologic analysis is 0.62, which gives evidence of good agreement.
Conclusion: The quantitative analysis of gadoxetic acid-enhanced MRI can predict the histological grades of small HCCs.

1. Introduction

Primary liver cancer is the eighth most common malignant tumor type worldwide, and occurs commonly in patients with liver cirrhosis [1]. In 2012, approximately 782,500 new cases of liver cancer were diagnosed and 745,500 deaths occurred worldwide, and it was estimated that 50% of the total number of cases and deaths occurred in China [2]. According to global statistics, the major histological subtype of primary liver cancer is hepatocellular carcinoma (HCC) [3]. Early screening programs have been performed in patients at high risk of liver cancer, and generally patients with small HCCs are considered more suitable candidates for surgical intervention and have better prognoses than those with advanced HCCs. Because HCC histological grade is strongly associated with prognosis, we investigated the confirmation of histological grade via noninvasive imaging before surgery.

Magnetic resonance imaging (MRI) is becoming more and more suitable for the diagnosis of HCCs. Furthermore, the use of contrast agents in MRI has become increasingly common in the imaging of multifarious solid organs, especially the liver [4]. Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (gadoxetic acid disodium or Gd-EOB-DTPA; Primovist, Bayer Schering Pharma, Berlin, Germany) is a third-generation gadolinium-based contrast media for MRI. The agent is absorbed specifically by liver cells and excreted into the biliary system, due to distinctive pharmacodynamics [5,6]. Because Gd-EOB-DTPA is hydrophilic, paramagnetic, and highly water-soluble, it is suitable for T1-weighted MRI. Hepatocellular uptake and biliary excretion of Gd-EOB-DTPA has been evaluated by Gd-EOB-DTPA-enhanced MRI [7]. Some researchers have reported that both normal hepatocytes and partially functioning liver cancer cells take up Gd-EOB-DTPA, and the quantity of the agent absorbed in normal hepatocytes or hepatocyte-derived cancer cells is considered to reflect the functioning of these cells [8]. Furthermore, the uptake of Gd-EOB-DTPA is also influenced by the degree of differentiation of HCCs [9]. Therefore, evaluation of signal intensity (SI) in the hepatobiliary phase of gadoxetic acid-enhanced MRI is considered to indirectly reflect the functioning of hepatocytes and hepatocyte-derived cancer cells, and accordingly to indirectly reflect the histological grade of HCCs. Furthermore, the value of gadoxetic acid-enhanced MRI in the early detection and characterization of HCCs has been demonstrated [10].

To date, it remains controversial whether the degree of lesion enhancement in gadoxetic-enhanced MRI is relevant to the differentiation grade of HCCs [11,12]. In studies reporting that it is not, they have not considered HCC size or the homogeneity of the tissue inside HCCs. Some equations used in previous studies have given no consideration to the liver-to-lesion SI or enhanced-to-unenhanced conditions [13,14].

Given that large and very large HCCs elicit heterogeneous SI, we evaluated small HCCs, with diameters ≥1.5 cm but ≤5 cm, and no necrosis inside them, to investigate the prediction of histological grade via quantitative analysis of gadoxetic acid-enhanced MRI [15]. The aim

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was to investigate whether such HCCs could be accurately characterized before surgery via a noninvasive modality.

2. Materials and methods

2.1. Patients

This retrospective study was approved by the ethics committee of ZhuJiang Hospital of Southern Medical University, and all patients recruited to this study provided informed consent. This study reviewed patient data in our hospital database from January 2014 to April 2016, and analyzed all lesions that were ≥1.5 cm but ≤5 cm in patients who were found to have histologically proven HCC with no necrosis inside the tumor after surgical resection, and underwent preoperative gadoxetic acid-enhanced MRI. Exclusion criteria included history of prior regional or systemic chemotherapy, history of prior thermal ablation, history of prior cryosurgery, and presence of hemochromatosis or hemosiderosis, because these conditions may result in necrosis of HCCs and affect the functioning of hepatocytes. In this trial, all 101 liver lesions in 95 patients were removed by regular or irregular hepatectomy in our hospital. The clinicopathologic data of the patients are summarized in Table 1.

2.2. Gadoxetic acid-enhanced MRI

For imaging, the same commercially available 3-T MRI work station (Achieva 3.0 T, Philips Healthcare) and the same protocol were used for all 95 patients, and gadoxetic acid was used as a contrast agent. Preoperatively (mean 11.1 ± 4.3 days, range 4–21 days before surgery), gadoxetic acid-enhanced MRI was conducted to characterize all HCCs and assess stage. The scanning protocol utilized the following sequence: T1-weighted imaging (repetition time/echo time = 3.0–10.0/1.0–2.0 ms, flip angle 10–15 degrees, slice thickness 4.0 mm, matrix 192 × 256); fat-suppressed 3D SPGR T1-weighted imaging (repetition time/echo time = 3.0–10.0/1.0–2.0 ms, flip angle 10–15 degrees, slice thickness 4.0 mm, matrix 192 × 256). A dose of 10 mL Primovist was injected intravenously with an infusion rate of 2.0 mL/s, followed by a 30-mL saline chaser. Twenty minutes after these procedures (the hepatobiliary phase of gadoxetic acid-enhance MRI), imaging was repeated.

2.3. Analysis of absolute signal enhancement and contrast enhancement ratio of gadoxetic acid-enhanced MRI

A region of interest (ROI) was drawn on unenhanced and hepatobiliary phase images. SI in the tumor and surrounding liver parenchyma were measured. The ROI of each lesion was a round or oval area containing the largest possible part of the lesion. Next, the SI of surrounding hepatic parenchyma at the same level of the lesion measurement was measured in a round or oval ROI. Necrotic areas, blood vessels, and bile ducts were excluded in the ROIs. The average size of the lesion ROIs was 552.9 ± 277.6 mm^2 (range 91.2–1221 mm^2). Tumor-to-tumor absolute contrast enhancement, tumor-to-tumor contrast enhancement ratio (CER), and tumor-to-liver CER were calculated by a radiologist who did not measure the SI of the lesions or surrounding liver. Representative images showing the characteristic radiological features of HCCs with different differentiation grades are shown in Figs. 1-A, B, 2-A, B, 3-A, B, 4-A, and B.

Absolute contrast enhancement was calculated via the equation $SI_{th} - SI_{tu}$, where SI_{th} represents the SI of the lesion in the hepatobiliary phase, and SI_{tu} represents the SI in the unenhancement phase. After measurement of SI_{th} and SI_{tu}, the equation $SI_{th} - SI_{tu}/SI_{tu}$ was used to calculate tumor-to-tumor CER. The equation $SI_{th} - SI_{tu}/SI_{lh} - SI_{lu}$ was used to calculate tumor-to-liver CER, where SI_{lh} represents the SI of the background liver in hepatobiliary phase, and SI_{lu} represents the SI of background liver in the unenhancement phase. Thus, the equation simultaneously incorporated liver-to-lesion SI and enhanced-to-unenhanced SI.

2.4. Histopathologic analysis

The diagnostic reference standard was histology. Formalin-fixed, paraffin-embedded liver sections and hematoxylin-eosin (H-E) staining were used in this study, and histological HCC specimens and the surrounding liver parenchyma from surgical resection were reevaluated. The diagnoses of HCCs were made in accordance with the International Working Party criteria [16]. Two experienced liver pathologists who were not privy to any clinical or radiological information pertaining to the patient populations in the study diagnosed each lesion via the Edmondson Steiner grading system [17]. The characteristic histological features of HCCs with different differentiation grades are shown in representative images in Figs. 1-C, 2-C, 3-C, and 4-C.

2.5. Statistical analysis

The statistical software package SPSS19 (SPSS Inc., Chicago, IL) was utilized for all statistical analyses in this study. One-way analysis of variance (ANOVA) was used to evaluate differences in mean absolute contrast enhancement and CER for different histological grades. Coefficients of determination (R^2) for three analyzed methods of SI and histological grades were tested. We used Spearman coefficients to determine the correlation between the degree of enhancement and differentiation grade. The determinations of the best cut-off values for the CER of tumor-to-liver for different histological grades were calculated via receiver operating characteristic (ROC) curves. The degree of agreement between the CER of tumor-to-liver and histopathologic analysis was calculated by Kappa statistics, and was assigned to categories as follows: k-values of 0.81–1.00 indicated excellent agreement; 0.61–0.80 indicated good agreement; 0.41–0.60 indicated moderate agreement; 0.21–0.40 indicated low agreement; and 0.00–0.20 indicated little or no poor agreement [18]. The results were expressed as mean ± standard deviation, and $p < 0.05$ was deemed to indicate statistical significance.

Table 1
The clinicopathologic characteristics of all 101 lesions.

Differentiation grade[a]		I	II	III	IV	Total
Number of tumors		20	37	32	12	101
Resected tumor size (mm)	Mean (range)	29.8 ± 7.45 (19–45)	36.9 ± 10.8 (15–50)	39.9 ± 8.6 (19–50)	39.4 ± 6.4 (29–49)	36.7 ± 9.7 (15–50)
Age (years)	Mean (range)	50.4 ± 12.4 (28–78)	59.2 ± 13.1 (34–82)	57.2 ± 13.1 (36–81)	53.7 ± 11.4 (28–79)	56.1 ± 13.0 (28–81)
Sex	Male, Female	M12, F8	M22, F15	M19, F13	M8, F4	M61, F40
Background liver tissue	Liver cirrhosis	5	19	25	11	60
	Others	15	18	7	1	41
Child-Pugh	A	18	34	31	8	91
	B	2	3	1	4	10

[a] Edmondson Steiner grading system.