European Journal of Radiology 103 (2018) 25–31

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

T_1 mapping on gadoxetic acid-enhanced MR imaging predicts recurrence of hepatocellular carcinoma after hepatectomy

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ARTICLE INFO

Keyword:
T_1 mapping
Magnetic resonance imaging
Hepatocellular carcinoma
Recurrence
Hepatectomy

ABSTRACT

Purpose: Our purpose was to demonstrate the prognostic significance of T_1 mapping on gadoxetic acid-enhanced MR imaging in prediction of recurrence of single HCC after hepatectomy.

Materials and methods: One hundred and seven patients with single nodular HCC (≤3 cm) who underwent preoperative gadoxetic acid-enhanced MRI were included in the study. T_1 mapping with syngo MapIt was obtained on a 1.5 T scanner. Radiological features and reduction rate of T_1 relaxation time (Δ%) of tumors were assessed by two radiologists. Cumulative recurrence rates were compared between groups of low and high reduction rate of T_1 relaxation time. A further classified cumulative recurrence rate of the overall cohort was based on the numbers of independent predictive factors.

Results: Reduction rate of T_1 relaxation time ($P = 0.001$) and non-hypervascular hypointense nodules ($P = 0.042$) in preoperative gadoxetic acid-enhanced MRI were independently related to recurrence of HCC after hepatectomy. Patients of lower reduction rates group had higher cumulative recurrence rates ($P < 0.0001$) than patients of higher reduction rates group. A combination of the two risk factors in patients with single HCC had significantly higher recurrence rates compared to those with either or none of the two risk factors.

Conclusions: Reduction rate of T_1 relaxation time combined with non-hypervascular hypointense nodules can be reliable biomarkers in the preoperative prediction of recurrence of HCC after hepatectomy.

1. Introduction

The incidence of hepatocellular carcinoma (HCC) continues to rise while the prognosis for HCC is still poor worldwide despite some geographic and population barriers [1–3]. Unfortunately, the recurrence rate remains high after curative resection [1]. Study showed that early and late recurrences were related to various risk factors and different mechanisms [4], suggesting different treatment options.

Recently some MR imaging features are considered as potential biomarkers associated with biological behavior of HCC [5]. Gadoxetic acid (Gd-EOB-DTPA, Primovist or Eovist, Bayer Healthcare, Berlin, Germany) is a hepatobiliary-specific contrast medium, not only showing more accuracy for tumor staging compared with dynamic CT or dynamic MRI with non-specific gadolinium contrast agent [6,7] but also providing prognostic information for HCC. Studies showed that presence of non-hypervascular hypointense nodules on hepatobiliary phase images (HBPI) on preoperative gadoxetic acid-enhanced MRI was a risk factor for tumor recurrence [8–11], mainly due to multicentric recurrence. Furthermore, both quantitative assessment of the signal intensity (SI) [12–14] and qualitative measurement of enhancement ratio of the HCCs on HBP images [15] can be useful imaging biomarkers associated with tumor aggressiveness and clinical outcome.

However, several confounding technical factors and the mismatch between the signal intensity of lesions and the concentration of gadoxetic acid may limit the reliability for evaluating the degree of HBPI enhancement [16]. T_1 relaxation measurement on parametric mapping has direct correlation with the concentration of gadoxetic acid, which may be more reliable compared with direct signal intensity measurement [16,17]. Previous studies demonstrated that gadoxetic acid enhanced MR imaging using T_1 mapping was feasible for evaluating the

Abbreviations: ADC, apparent diffusion coefficient; AFP, alpha-fetoprotein; BCLC stage, Barcelona Clinic Liver Cancer stage; CT, computed tomography; DW, diffusion-weighted; EM, extrahepatic recurrence; HBPI, hepatobiliary phase imaging; HCC, hepatocellular carcinoma; IDR, intrahepatic distant recurrence; MR, magnetic resonance; NAR, non-anatomic resection; OATP, organic anion transporting polypeptide; PET, positron emission tomography; ROI, region of interest; SI, signal intensity; TTR, time to tumor recurrence

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https://doi.org/10.1016/j.ejrad.2018.03.027
Received 25 November 2017; Received in revised form 22 March 2018; Accepted 27 March 2018
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severity of liver function and liver fibrosis [18,19], quantitatively distinguishing hepatic hemangiomas from metastatic tumors [20] and predicting the degree of differentiation in hepatocellular carcinoma [21]. To our knowledge, few study has reported the relationship between T_1 mapping on gadoxetic acid enhanced MR imaging and prognosis of HCC after hepatectomy.

Therefore, our study was aimed to clarify whether T_1 mapping on gadoxetic acid enhanced MR imaging can be a prognostic imaging biomarker in the preoperative prediction of recurrence after hepatectomy of HCC.

2. Materials and methods

2.1. Patients

The retrospective study was approved by the institutional review board and the requirement for the informed consent was waived. Between January 2013 and December 2015, 275 patients were initially diagnosed as HCC by ultrasound or CT with a further preoperative gadoxetic acid-enhanced MRI examination in Zhongshan Hospital, Fudan University, Shanghai, China. All HCC patients received anatomic resection rather than non-anatomic resection (NAR). The inclusion criteria (Fig. 1) for this study were as follows: (a) Barcelona Clinic Liver Cancer (BCLC) stage of 0 or A HCC; (b) a single HCC ≤ 3 cm in diameter without any oncologic treatment; (c) availability of T_1 mapping before and after contrast enhancement; (d) MRI performed within 2 weeks prior to resection; (e) liver function of Child-Pugh Class A. Among the 275 patients, 168 patients were excluded for: (a) tumors larger than 3 cm in diameter (n = 65); (b) patients with more than one HCC (n = 43); (c) lack of T_1 mapping images (n = 4) (d) MRI performed more than 2 weeks prior to resection (n = 13) (e) patients with Child-Pugh Class B or C (n = 12) (f) less than 12 months of follow-up (n = 31). A total of 107 patients with histopathologically diagnosis of HCC were included in the study.

2.2. Gadoxetic acid-enhanced MRI

All patients were scanned on a Siemens 1.5T scanner (MAGNETOM Aera, Siemens Healthcare, Erlangen, Germany). DWI was acquired prior to gadoxetic acid injection with the following parameters: TR/TE, 3200/56 ms; slice thickness, 5.5 mm; matrix size, 84 × 128; field of view (FOV), 380–400 × 300–324 mm; b values, 0 and 500 s/mm2. Dynamic T_1-weighted three-dimensional (3D) gradient-recalled echo imaging with fat suppression was performed after the intravenous injection, with the parameters as follows: repetition time (TR)/echo time (TE):3.47/1.36 milliseconds (ms), flip angle 10°, matrix of 320 × 195, slice thickness 3 mm. After the contrast administration, the arterial phase, the portal venous phase, transition phase and HBPI were subsequently scanned 20–30 s, 70–80 s, 180 s and 20 min, respectively. A dual flip-angle 3D gradient-echo sequence with VIBE was performed before and at 20 min after gadoxetic acid administration to obtain T_1 mapping with syngo MapIt. The parameters were as follows: TR = 4.38 ms; TE = 1.93 ms; flip angle, 2° and 12°; FOV, 380–400 × 300–324 mm; matrix, 216 × 288; slice thickness, 5 mm. In all patients, 0.025 mmol/kg body weight of Gd-EOB-DTPA was injected at a rate of approximately 1 ml/sec through a 20-gauge intravenous catheter. A parallel imaging technique (R = 2) was performed using generalized autocalibrating partially parallel acquisition (GAPPA). The T_1 maps and ADC maps were derived automatically on a voxel-by-voxel basis.

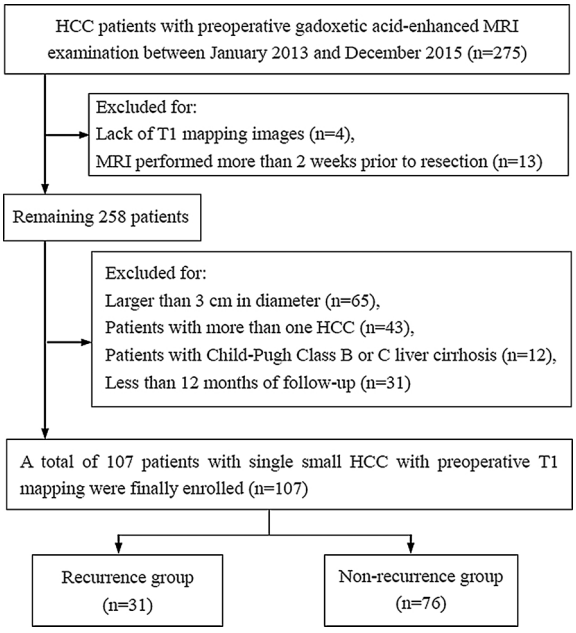

Fig 1. Flowchart of the study population.
HCC, hepatocellular carcinoma.

2.3. Imaging analysis

The morphologic features were analyzed by one experienced radiologist. Tumor size and location were assessed on HBP images. Compared with the SI of the surrounding liver parenchyma, HBP signal intensity of tumor was qualitatively classified as hypointensity and iso- to hyperintensity. Non-hypervascular hypointense nodule was defined as hypointense nodules on the hepatobiliary phase images without relative enhancement on the arterial phase during the dynamic imaging [9–12]. Quantitative measurement of MR images were performed by two radiologists who were blinded to each results and clinical data. Freehand region of interests (ROIs) were outlined around the boundary of the tumor on the high flip angle (12°) images and b value (500 s/mm^2) DW images and then copied onto the corresponding T_1 maps and ADC maps, respectively. Freehand ROIs covered the whole tumor area of each consecutive slice. T_1 relaxation time and ADC values were averaged to obtain the mean T_1 relaxation times and mean ADC values. Reduction rate (Δ %) of T_1 relaxation time was calculated as follows: Δ % = 100% × (pre T_1 value − post T_1 value)/pre T_1 value, where pre T_1 and post T_1 values were the T_1 relaxation times of the tumor before and after Gd-EOB-DTPA injection.

2.4. Follow up and assessment of recurrence

After resection, follow-up screening US, dynamic enhanced CT or MRI were performed every 3 months during the first 2 years, and every 6 months thereafter. Regular laboratory tests (including a-fetoprotein tests, blood count and so on) were monitored at a routinely 3-month interval. Chest CT or ^{18}F-fluorodeoxyglucose positron emission tomography (PET)/CT was performed to confirm extrahepatic recurrence. All patients were followed for at least 12 months until the end of March of 2017. Types of recurrence were classified as follows: intrahepatic distant recurrence (IDR), hypervascularization and extrahepatic recurrence (EM). Hypervascularization is defined that the recurrence tumors which showed hypervascularity in arterial phase with washout during the portal venous phase were developed from preoperative non-hypervascular hypointense nodules during follow-up [22]. The recurrent tumors were confirmed by pathologic reports after repeated hepatic resection or typical imaging findings according to the clinical guidelines of the American Association for the study of Liver Diseases [23].

2.5. Statistical analysis

Differences in continuous values with a normal distribution were

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