Research Article

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Non-hypervascular hepatobiliary phase hypointense nodules on gadoxetic acid-enhanced MRI: Risk of HCC recurrence after radiofrequency ablation

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Background & Aims: Hepatobiliary phase images (HBPI) of gadoxetic acid-enhanced MRI can depict borderline hepatocellular nodules that have the potential to progress into hypervascular hepatocellular carcinomas (HCCs), as non-hypervascular hypointense nodules. We retrospectively evaluated the impact of the presence of non-hypervascular hypointense nodules at HBPI of gadoxetic acid-enhanced MRI on the patient's prognosis after radiofrequency ablation (RFA) for early stage HCCs.

Methods: A total of 139 patients who underwent pre-procedural gadoxetic acid-enhanced MRI followed by RFA were included. After a mean follow-up of 44.6 ± 13.2 months, we compared the results of tumor recurrence as well as overall and recurrence-free survival (RFS) with the presence of non-hypervascular hypointense nodules on HBPI.

Results: The presence of non-hypervascular hypointense nodules on HBPI did not affect overall survival ($p = 0.136$). However, the estimated 5-year RFS rate was 71.3% in 29 patients without non-hypervascular hypointense nodules on HBPI compared to 27.9% in 110 patients with non-hypervascular hypointense nodules on HBPI, indicating a significant difference (hazard ratio = 2.84 [1.39–5.98], $p = 0.006$). When we classified recurrence into local tumor progression [LTP], intrahepatic distant recurrence [IDR], and extra-hepatic metastasis [EM], five-year cumulative incidences (CI) of IDR in patients with non-hypervascular hypointense nodules on HBPI were significantly higher than those in patients without non-hypervascular hypointense nodules on HBPI (17.9% *vs.* 67.5%, $p < 0.001$). Five-year CIs of LTP and EM showed no significant difference ($p > 0.05$).

Conclusions: The presence of non-hypervascular hypointense hepatocellular nodules on HBPI of gadoxetic acid-enhanced MRI taken prior to RFA is a significant predictive factor of recurrence after RFA of early stage HCCs, particularly IDR.

Cancer

Keywords: Hepatocellular carcinoma; Radiofrequency ablation; Non-hypervascular hypointense nodule; Gadoxetic acid-enhanced MRI; Risk of recurrence.

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Abbreviations: HCC, hepatocellular carcinoma; HBPI, hepatobiliary phase images; DN, dysplastic nodule; MRI, magnetic resonance imaging; RFA, radiofrequency ablation; RFS, recurrence-free survival; LTP, local tumor progression; IDR, intrahepatic distant recurrence; EM, extra-hepatic metastasis; CI, cumulative incidence; CT, computed tomography; OATP, organic anion transporting polypeptide; IRB, Institutional Review Board; CT, computed tomography; US, ultrasound; AASLD, American Association for the Study of Liver Disease; TSE, turbo spin echo; GRE, gradient recalled echo; DWI, diffusion weighted images; AP, arterial phase; PVP, portal venous phase; LDP, late dynamic phase; AFP, alpha fetoprotein; TACE, transarterial chemoembolization; PEIT, percutaneous ethanol injection therapy.

Introduction

Hepatocellular carcinomas (HCCs) most often occur in patients considered to be at high risk for this disease, such as those with underlying chronic liver disease or cirrhosis. HCCs develop through the multistep process of hepatocarcinogenesis, ranging from regenerative nodules to classic hypervascular HCCs [1,2]. Recent studies have demonstrated that 1) borderline hepatocellular nodules, such as early HCCs, or high grade dysplastic nodules (DN) can be considered to be precursors of progressed HCCs, and that 2) percutaneous radiofrequency ablation (RFA) may be effective in treating these high grade DNs and well-differentiated HCCs as vascular invasion or intrahepatic metastasis are exceedingly rare in the case of early HCCs [3–5]. Therefore, detection of borderline hypovascular hepatocellular nodules including DNs and early HCCs can play an important role in the management of patients with liver cirrhosis. Yet, until now, cross sectional imaging studies such as ultrasound, CT, or MRI have shown limited ability in the detection and characterization of these nodules [6–8].

Recently, gadoxetic acid (Gd-EOB-DTPA, Primovist or Eovist, Bayer Healthcare, Berlin, Germany), which is a hepatocyte-specific contrast agent, has been increasingly used for the evaluation of liver diseases, particularly in Asian countries where the prevalence of HCC is high. Gadoxetic acid is known

to be taken up by organic anion transporting polypeptide (OATP) B1/8 transporters into the hepatocyte, while OATP B1/8 expression gradually decreases during the process of hepatocarcinogenesis [9,10]. Therefore, hepatobiliary phase images (HBPI) of gadoxetic acid-enhanced MRI may potentially provide improved detection of progressed HCCs, as well as borderline hepatocellular nodules that could appear as non-hypervascular hypointense nodules on HBPI owing to the decrease in or lack of OATP B1/8 expression [9,10]. Despite difficulties in differentiating high grade DNs from early HCCs among hypointense nodules, there are several reports of pre-existing, non-hypervascular, hypointense nodules that could be detected on HBPI of gadoxetic acid-enhanced MRI and developed into hypervascular HCCs during follow-up [11–15]. Nevertheless, the biological behavior of these non-hypervascular hypointense nodules, as well as their clinical significance, have yet to be determined.

As for the treatment of patients with early stage HCCs, RFA has emerged as an effective curative local treatment option [16–18]. With more active surveillance using ultrasound of patients at high risk of developing HCCs, such as those with cirrhosis, there has also been an increased detection of small HCCs, which in turn has resulted in the increased use of RFA for treatment of HCCs [19]. Concurrently, with advances in high spatial and temporal resolution T1-weighted imaging, in liver specific MR contrast media, as well as in diffusion weighted imaging [20,21], liver MR imaging has also seen increased use for the accurate assessment of HCCs and for the planning of RFA treatment. Indeed, a recent study has demonstrated that HBPI of gadoxetic acid-enhanced MRI may provide several advantages for RFA, including a high tumor-to-liver contrast and good depiction of intrahepatic vascular structures as well as intrahepatic bile ducts [22]. Furthermore, although HBPI of gadoxetic acid-enhanced liver MRI frequently demonstrates borderline hepatocellular nodules as hypointense nodules [8,10], whether the presence of non-hypervascular hypointense hepatocellular nodules on HBPI can affect the prognosis of patients with HCC after RFA treatment has not been fully investigated. Therefore, the purpose of this study is to retrospectively evaluate whether the presence of non-hypervascular hypointense nodules on HBPI of gadoxetic acid-enhanced liver MRI is a risk factor that can predict recurrence after RFA of early stage HCCs.

Patients and methods

Patients

Our Institutional Review Board approved this study and the requirement for written informed consent was waived. Between January 2009 and December 2010, 226 consecutive patients with HCC were referred to our department for RFA as a first-line treatment option. The detailed indications for RFA of HCC at our institute are as follows: we considered RFA as the first-line treatment modality in patients with a single nodular HCC less than 2 cm in diameter. When the patients had a single nodular HCC larger than 2 cm in diameter or two or three HCCs, we considered hepatic resection as the first-line treatment modality. However, when surgical resection candidates showed clinically significant portal hypertension (i.e., presence of varices or splenomegaly associated with thrombocytopenia), we recommended RFA as an alternative modality for hepatic resection according to current practice guidelines [23]. In addition, some hepatic resection candidates preferred RFA over surgery for their HCC lesions despite of the strong recommendations for surgery by the clinicians, and thus RFA was done for these patients. The inclusion criteria for this study were as follows: patients with a) early stage HCCs defined as a single HCC $\leqslant$5 cm in diameter, or 2–3 HCC nodules all $\leqslant$3 cm in diameter without extra-hepatic metastasis or macro-vascular invasion [17,18]; b) well-compensated Child-Pugh class A or B liver cirrhosis; c) absence of a bleeding tendency defined as a prothrombin activity >40% and a platelet count >5 $\times$ 10^9/L; and d) those who underwent gadoxetic acid-enhanced liver MRI within 3 months prior to RFA treatment for HCC. Among the 226 patients, 87 patients were excluded from the study for the following reasons: (a) size of the largest tumor $\geqslant$5 cm in diameter (n = 1); (b) more than three HCC nodules (n = 3); (c) presence of extra-hepatic metastasis (n = 1); and (d) absence of pre-procedural MRI (n = 82). The remaining 139 patients with 178 HCCs (mean size, 25.9 ± 7.9 mm; range, 9–50 mm; median size, 20 mm) finally comprised our study population (Fig. 1). The baseline characteristics of all of the study patients are summarized in Table 1.

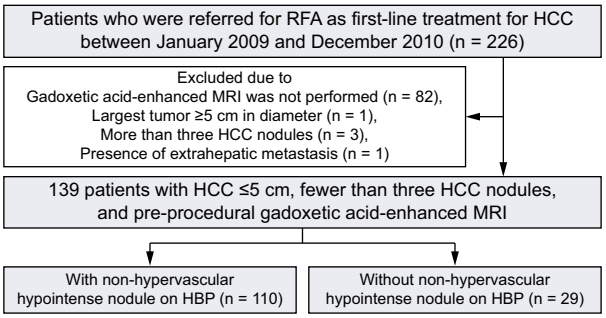

Fig. 1. Flow diagram summarizing the patient enrollment process of this study.

Diagnosis of HCC before RFA

Prior to RFA treatment of the HCCs, all patients underwent imaging studies including gadoxetic acid-enhanced liver MRI and contrast-enhanced, multi-phase computed tomography (CT). The diagnosis of HCC was made using the non-invasive criteria defined by the American Association for the Study of Liver Disease (AASLD) recommendations, consisting of arterial hyperenhancement with washout on portal or delayed phase images in 125 patients [19]. In the remaining 14 patients who did not meet the non-invasive diagnostic criteria, HCC diagnoses were made through liver biopsies with pathologic confirmation.

Acquisition of gadoxetic acid-enhanced liver MR imaging

Gadoxetic acid-enhanced liver MRI was performed prior to RFA (mean time before RFA: 11.5 days [range: 0–74 days; median: 8 days]) for the diagnosis and staging of HCCs in all patients. MR images were performed on either a 1.5T (Signa HDx, GE Medical Systems, Milwaukee, WI, USA, n = 59) or on a 3T (Signa Excite, GE Medical Systems, n = 49; Verio, Siemens Medical Solutions, Erlangen, Germany, n = 13; Trio, Siemens Medical Solutions, n = 18) superconducting system using either an 8-channel (Signa HDx, Excite), or a 32-channel (Verio, and Trio) phased-array coil. Our gadoxetic acid-enhanced liver MRI protocol consisted of a breath-hold fat-saturated T2-weighted fast spin echo or turbo spin echo (TSE) sequence, a breath-hold T1-weighted dual-echo (in-phase and opposed-phase) gradient-echo (GRE) sequence, dynamic 3D fat-saturated T1-weighted GRE sequences, and free-breathing diffusion weighted imaging (DWI) using a single-shot echo planar imaging sequence. Dynamic 3D fat-saturated T1-weighted GRE sequences were performed both before and after administration of contrast media (Primovist®; Bayer Healthcare, Berlin, Germany). All patients received a rapid bolus of 1 ml/10 kg body weight (0.025 mmol/kg) of gadoxetic acid (Primovist®) at a rate of 1.5 ml/s, immediately followed by a 30 ml saline flush through an antecubital venous catheter, using a power injector (Spectris Solaris® EP, MEDRAD Inc., Warrendale, PA, USA). After contrast administration, scanning delay times for arterial phase imaging were determined with real-time MR fluoroscopic monitoring. The arterial phase (AP) was scanned seven seconds after the contrast media had arrived at the distal thoracic aorta, and the portal venous phase (PVP), late dynamic phase (LDP), and hepatobiliary phase were subsequently scanned 50 s, three minutes, and 20 min, respectively, after starting contrast-medium injection. In order to evaluate the enhancement of the nodules on postcontrast T1-weighted images, subtraction images were obtained by subtracting precontrast scans from postcontrast scans [24,25]. Detailed scanning parameters of the MR equipment used are summarized in the Supplementary data.