European Journal of Radiology 89 (2017) 234–241

Contents lists available at ScienceDirect

European Journal of Radiology

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

Evaluation of hepatocellular carcinoma tumor vascularity using contrast-enhanced ultrasonography as a predictor for local recurrence following radiofrequency ablation

Tomohiro Ishii[a], Kazushi Numata[a,*], Yoshiteru Hao[a], Nobutaka Doba[a], Koji Hara[a], Masaaki Kondo[b], Katsuaki Tanaka[a], Shin Maeda[b]

[a] Gastroenterological Center, Yokohama City University Medical Center, 4-57 Urafune-cho, Minami-ku, Yokohama, Kanagawa 232-0024, Japan
[b] Division of Gastroenterology, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama, Kanagawa 236-0004, Japan

ARTICLE INFO

Article history:
Received 2 April 2016
Received in revised form
21 November 2016
Accepted 19 December 2016

Keywords:
Radiofrequency ablation
Hepatocellular carcinoma
Contrast-enhanced ultrasonography
Computed tomography
Local recurrence

ABSTRACT

Purpose: The purpose of this study was to evaluate whether the hypervascularity of hepatocellular carcinomas (HCCs) on contrast-enhanced ultrasonography (CEUS) prior to radiofrequency ablation (RFA) is a significant risk factor for local recurrence after RFA.
Materials and methods: Institutional review board approval and informed consent were obtained. Overall, 208 patients (mean age, 71.7 years; range, 50–87 years; 137 men, 71 women) with 282 HCCs treated with RFA were analyzed retrospectively. The mean maximum tumor diameter was 15.7 mm. We compared the abilities of CEUS and contrast-enhanced computed tomography (CECT) to detect hypervascularity in HCCs. We then classified the HCCs into two groups according to the arterial-phase CEUS findings: a "hypervascular group" with whole or partial hypervascular areas within the lesions compared with the surrounding liver parenchyma, and a "non-hypervascular group" with isovascular or hypovascular areas within the lesions. We assessed the cumulative rate of local recurrence after RFA, and we also evaluated the risk factors for local recurrence using a univariate analysis.
Results: The detection rate for hypervascular HCCs was significantly higher using CEUS (78%, 221/282) than that using CECT (66%, 186/282) ($P < 0.001$). Using the CEUS findings, the cumulative rate of local recurrence was significantly higher in the hypervascular group (41.2%, 56/221) than in the non-hypervascular group (18.4%, 6/61) ($P = 0.007$). A univariate analysis revealed that hypervascularity on CEUS was an independent risk factor for local recurrence ($P = 0.010$).
Conclusion: Hypervascularity in HCCs as observed using CEUS is a significant risk factor for local recurrence after RFA.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and the seventh most common in women worldwide [1]. Since curative treatment can be performed only at an early stage (single or 3 nodules <3 cm, PS 0), the detection of HCCs at an early stage is still a prerequisite for improving the prognosis of patients with HCCs [2].

Even though several curative options are available for early-stage HCCs, surgical resection is the first choice [3,4]. On the other hand, percutaneous ablative therapy such as percutaneous ethanol injection (PEI) [5,6], microwave coagulation therapy (MCT) [7], and radiofrequency ablation (RFA) [2,8–10] are useful for unresectable small HCCs. Among these treatments, RFA is now used to treat HCCs, especially small HCCs, around the world. RFA is potentially curative, minimally invasive, and can be easily repeated in cases with recurrence [11].

However, the local recurrence rates after RFA have ranged from 4.5% to 22.0% at 10–33 months after RFA [10,12–16]. To improve local disease control and the outcome after RFA, several studies have analyzed the risk factors of local recurrence [17–20]. In general, vessels adjacent to HCCs, a tumor size of 2 cm or greater, and the absence of an ablative margin of 5 mm have been identified as the main risk factors for local recurrence after RFA [17–20]. In contrast, Park et al. reported that a high degree of arterial enhancement on contrast-enhanced computed tomography (CECT)

* Corresponding author.
E-mail address: kz-numa@urahp.yokohama-cu.ac.jp (K. Numata).

http://dx.doi.org/10.1016/j.ejrad.2016.12.018
0720-048X/

before RFA in HCCs larger than 2 cm is a significant risk factor for local recurrence after RFA; furthermore, arterial enhancement on CECT was the only independent significant risk factor for local recurrence [21]. This previous report has been the only study to describe a correlation between hypervascularity in HCCs on CECT and local recurrence after RFA [21]. Additionally, the correlation between hypervascularity in HCCs on the arterial phase of contrast-enhanced ultrasonography (CEUS) and local recurrence after RFA has not been reported.

In general, most investigators evaluate hypervascularity in HCCs using CECT. However, we previously reported that CEUS was more sensitive for the detection of hypervascularity in pathologically diagnosed early HCCs, compared with CECT, prior to RFA [22]. In the present study, we evaluated whether the hypervascularity of HCCs as observed using CEUS prior to RFA was a significant risk factor for local recurrence after RFA.

2. Materials and methods

2.1. Patients and tumors

Institutional review board approval and informed consent from all the patients were obtained for this retrospective study. At our institution, 289 consecutive chronic liver disease patients with 389 HCCs with a maximum diameter smaller than 30 mm underwent conventional US, CECT, contrast-enhanced magnetic resonance imaging (CE-MRI) with gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA; Primovist; Bayer Schering Pharma AG, Berlin, Germany), and percutaneous RFA under ultrasound guidance as a treatment between January 2009 and December 2012.

The inclusion criteria for this study were as follows: (1) three or fewer HCCs detected using conventional US; (2) a platelet count of 5×10^4/L or more; and (3) no eligibility for surgical resection, or refusal of surgery. The exclusion criteria for this study were as follows: (1) HCCs with tumor thrombosis in the branches of the portal vein; (2) Child-Pugh grade C liver cirrhosis; (3) patients who were unable to undergo CECT or CE-MRI with Gd-EOB-DTPA because of a contraindication for the use of iodinated contrast agents (allergic reactions and impaired renal function); and (4) lesions located behind the portal vein because of the difficulty in RFA punctuation. Finally, 282 HCCs in 208 patients were eligible for inclusion in the present study.

2.2. Diagnosis of HCC

The diagnosis of typical HCC was made based on criteria recommended by the American Association for the Study of Liver Disease [2]. When tumors did not exhibit a typical enhancement pattern on CECT or CE-MRI with Gd-EOB-DTPA, a biopsy was performed to diagnose the tumor as a HCC. In total, 96 HCC lesions did not exhibit a typical enhancement pattern on CECT or CE-MRI with Gd-EOB-DTPA. Of the 96 HCCs, 44 were early HCCs (eHCCs), 47 were well-differentiated HCCs, and the remaining 5 were moderately differentiated HCCs.

2.3. Imaging methods

2.3.1. CT imaging

Before RFA, all the HCCs were examined using CECT. CECT imaging was performed using a 16-channel multidetector scanner (Aquilion 16; Toshiba Medical, Tokyo, Japan) with a tube voltage of 120 kV, a tube current set at the automatic milliampere exposure setting, a reconstruction section and interval thickness of 5 mm, a pitch of 15, and a gantry speed of 0.5 s per rotation. A nonionic contrast agent (iopamidol, Iopamiron 300, or Iopamiron 370; Bayer Healthcare, Osaka, Japan) was injected. Patients weighing less than 70 kg received 300 mg of iodine per milliliter, while those weighing 70 kg or more received 370 mg of iodine per milliliter. After a power injector (Dual Shot GX; Nemoto Kyorindo, Tokyo, Japan) was used to inject 100 mL of iopamidol at 3 mL/s through a catheter placed in the antecubital vein, the scanning time in the arterial phase was confirmed using an automatic bolus-tracking program (Real-Prep; Toshiba Medical). The trigger point for starting arterial phase scanning was set at an attenuation of 230 HU from the baseline attenuation of the abdominal aorta. Hepatic venous phase scanning was performed 70 s after the contrast agent injection, and equilibrium phase images were acquired 180 s after the injection. CT data were transferred to a computer workstation (Zio M900; Zio Software, Tokyo, Japan).

2.3.2. MR imaging

When the tumors did not exhibit a typical enhancement pattern on CECT, we performed CE-MRI using Gd-EOB-DTPA to detect the HCCs. MR imaging was performed using a 1.5-T whole-body imager (Avant; Siemens Medical System, Erlangen, Germany). At the same time as the arrival of Gd-EOB-DTPA in the celiac artery, a power injector (Spectris Solaris EP; MEDRAD, Bayer Schering Pharma AG, Berlin, Germany) was used to inject 0.1 mmol/kg of Gd-EOB-DTPA at 1 mL/s through a catheter placed in the antecubital vein, followed by flushing with 20 mL of sterile saline solution at 2 mL/s. Arterial phase scanning was performed 13 s after contrast injection, portal phase scanning was performed 70–85 s after contrast injection, delay phase scanning was performed 180 s after contrast injection, and hepatobiliary phase scanning was performed 20 min after contrast injection. The images were obtained using a fat-suppressed volumetric interpolated breath-hold examination (FS VIBE) with T1-weighted sequences (TR, 6.2 ms; TE, 3.15 ms; flip angle, 20°; band width, 260 Hz/pix; matrix, 166 × 320; acquisition time, 20 s) and a fast low-angle shot (FLASH) T1-weighted sequence (TR, 115 ms; TE, 4.76 ms; flip angle, 70°; band width, 260 Hz/pix; matrix, 192 × 256; acquisition time, 20 s ×3). In addition, turbo spin-echo (TSE) pace respiratory-triggered T2-weighted sequences and echo planar imaging (EPI) diffusion-weighted sequences were also obtained.

2.3.3. Conventional US images

We assessed the detection of HCCs using the LOGIQ E9 or LOGIQ7 ultrasound system (GE Healthcare, Milwaukee, WI, USA) with native tissue harmonic gray-scale imaging using a convex probe with a frequency of 2–5 MHz and a micro-convex probe with a frequency of 2–5 MHz (hereafter referred to as conventional US).

2.3.4. CEUS procedures

A 0.2 mL dose of Sonazoid was injected into an antecubital vein at 0.2 mL/s via a 24-gauge cannula followed by 2 mL of 5% glucose after the Sonazoid injection. CEUS images were acquired during three contrast phases, consisting of an arterial phase (10–50 s after injection), a portal phase (80–120 s after injection), and a post vascular phase (10 min after injection) [23].

2.3.5. Evaluation of vascularity in HCCs on CEUS

We evaluated the enhancement pattern of HCCs during the arterial phase, and the patients were classified into two groups according to the CEUS findings as follows: the “hypervascular group” had whole or partial hypervascular areas within the lesions compared with the surrounding liver parenchyma (Fig. 1), and the “non-hypervascular group” had isovascular or hypovascular areas within the lesions (Fig. 2). Finally, 221 HCCs were defined as belonging to the hypervascular group, and 61 HCCs were defined as belonging to the non-hypervascular group.