European Journal of Radiology 84 (2015) 1540–1545

Contents lists available at ScienceDirect

European Journal of Radiology

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

Efficacy of radiofrequency ablation for initial recurrent hepatocellular carcinoma after curative treatment: Comparison with primary cases

Takayuki Fukuhara, Hiroshi Aikata*, Hideyuki Hyogo, Yohji Honda, Kei Morio, Reona Morio, Masahiro Hatooka, Tomoki Kobayashi, Noriaki Naeshiro, Tomokazu Kawaoka, Masataka Tsuge, Akira Hiramatsu, Michio Imamura, Yoshiiku Kawakami, Kazuaki Chayama

Department of Gastroenterology and Metabolism, Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

ARTICLE INFO

Article history:
Received 23 January 2015
Received in revised form 16 April 2015
Accepted 21 April 2015

Keywords:
Hepatocellular carcinoma
Radiofrequency ablation
Recurrence
Prognostic factor

ABSTRACT

Objective: To determine the efficacy of radiofrequency ablation (RFA) for initial recurrence of small hepatocellular carcinoma (HCC; ≤3 nodules, each nodule ≤3 cm in diameter) after curative treatment and identify prognostic factors affecting therapeutic outcome, we compared clinical and outcome factors between patients with primary HCC and those with initial recurrent HCC who underwent RFA.
Methods: In this retrospective cohort study, 211 HCC patients who underwent RFA were enrolled and comprised two groups: primary group (n = 139) and initial recurrent group (n = 72). We compared local tumor progression, overall survival (OS), disease-free survival (DFS), and RFA safety between the groups.
Results: Median follow-up was 53 months. Local tumor progression rate was 5.8% in the primary group and 4.2% in the recurrent group. OS rates at 5 years and 10 years were 63.2% and 25.5% in the primary group and 54.5% and 33.4% in the recurrent group, respectively. Corresponding DFS rates were 30.7% and 14.6% and 19.2% and 11.0%. DFS was significantly shorter in the recurrent group (hazard ratio [HR] = 1.81; 95% confidence interval [CI], 1.27–2.57; P = 0.001). In the recurrent group, time from primary HCC development to recurrence was a determinant of OS (≤2 years; HR = 3.42; 95% CI, 1.52–7.72; P = 0.003).
Conclusion: Although local tumor control and OS were similar between the groups, the recurrent group had shorter DFS than the primary group. Time from primary HCC development to recurrence was a prognostic factor for recurrence of HCC.

1. Introduction

Japanese and American clinical practice guidelines recommend hepatectomy and radiofrequency ablation (RFA) as curative treatments for small hepatocellular carcinoma (HCC; ≤3 nodules and each ≤3 cm in diameter) [1,2]. However, intrahepatic recurrence is very common after such curative treatments; it occurs in 50–70% of patients within 5 years of hepatectomy because of undetected intrahepatic spread or multicentric tumor occurrence [3–5]. Treatment selection is therefore important for improved survival, but the algorithms recommended in the above-mentioned guidelines are for primary HCC not recurrent HCC.

Although repeat hepatectomy has been effective in treating recurrent HCC [6–9], additional hepatectomy is contraindicated in most patients. Deterioration of liver function reserve from repeat treatments for recurrent HCCs and/or progression of background liver disease restrict the treatment options available. Less invasive curative treatments than hepatectomy are desirable and RFA is suitable in this respect, but its effectiveness for recurrent HCC has not been established.

RFA is regarded as safe and effective for small HCC as a first-line treatment [10–15], and a small number of studies have found RFA to be promising for recurrent HCC [16–18]. However, prognosis remains to be fully evaluated for patients who received percutaneous RFA for recurrent HCC after curative treatment such as hepatectomy, percutaneous ethanol injection (PEI), microwave coagulation therapy (MCT), or percutaneous RFA.

This retrospective study sought to clarify the effectiveness of RFA for initial recurrent HCC after curative treatment and to identify prognostic factors affecting therapeutic outcome. We compared clinical and outcome factors following RFA treatment between patients with primary HCC and those with initial recurrent HCC.

* Corresponding author. Tel.: +81 82 257 5192; fax: +81 82 257 5194.
E-mail address: aikata@hiroshima-u.ac.jp (H. Aikata).

http://dx.doi.org/10.1016/j.ejrad.2015.04.020
0720-048X/

2. Materials and methods

2.1. Patients

The following inclusion criteria were used: (1) primary HCC or initial recurrent HCC after curative treatment, (2) ≤3 nodules and each ≤3 cm in diameter, (3) no vascular invasion and no extrahepatic metastasis, (4) Child–Pugh class A or B, and (5) prothrombin activity >40% and platelet count >50,000/μl. We reviewed 401 consecutive HCC patients treated with RFA between January 2001 and June 2013 at our hospital. Among them, 211 patients with 263 small HCCs who met the inclusion criteria were evaluated. Patients were divided into two groups: primary HCC group (n = 139) and initial recurrent HCC group (n = 72) (Fig. 1).

2.2. Imaging and confirmation of diagnosis

Before RFA treatment, all patients underwent imaging studies including abdominal ultrasonography (US), contrast-enhanced dynamic CT or magnetic resonance imaging (MRI), and angiography combined with CT during arterial portography and hepatic arteriography. In 155 patients, HCC was diagnosed based on the following classic imaging manifestations: (i) early enhancement at the arterial phase and hypoattenuation at the portal venous phase or equilibrium phase on contrast-enhanced dynamic CT or MRI; and (ii) hyperattenuation on CT during hepatic arteriography and hypoattenuation on CT during arterial portography [19,20]. HCC was diagnosed in the remaining 56 patients by pathology.

2.3. RFA procedure

All RFA procedures were performed percutaneously under ultrasonographic guidance with patients under conscious sedation with pentazocine (5–10 mg, Pentagin; Sankyo, Tokyo, Japan) and midazolam (1–4 mg, Dormicum; Astellas, Tokyo, Japan) administered intravenously. We used a Cool-tip RF Ablation System (Covidien, Boulder, CO) with a 17-gauge cool-tip electrode. A 2-cm exposed tip (for nodules <1.5 cm in diameter) or a 3-cm exposed tip (for nodules measuring 1.5–3.0 cm) was inserted into the center of the nodule. In 172 patients (82%) with hypervascular HCC nodules confirmed on CT during hepatic arteriography, TACE was performed an average 3 days before RFA. TACE was performed through the femoral artery using the technique of Seldinger under local anesthesia. An angiographic catheter was inserted selectively into the hepatic feeding artery of a segment or subsegments containing the target tumor. Cisplatinum (Randa; Nippon Kayaku, Tokyo, Japan) was mixed with iodized oil (Lipiodol; Nihon Schering, Tokyo) at a concentration of 10 mg/ml and injected at a dose of 10–40 mg/body. The selected dose was based on tumor size. Injection was discontinued upon full accumulation of iodized oil in the tumor vessels.

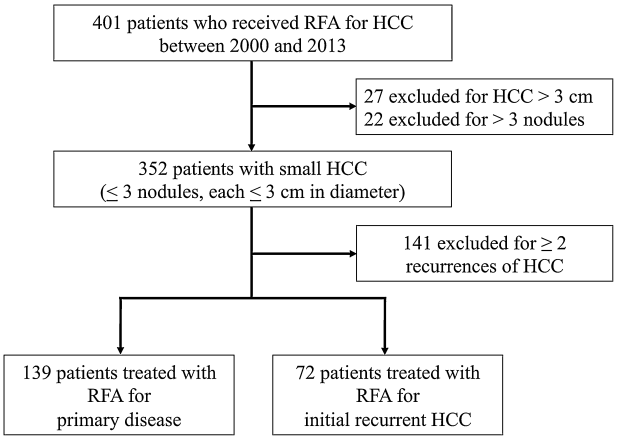

Fig. 1. Flow chart of patients treated by radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC).

RFA data assessment was performed in accordance with the Society of Interventional Radiology Technology Assessment Committee and the International Working Group on Image-Guided Tumor Ablation [22].

2.4. Assessment of therapeutic efficacy of RFA

Contrast-enhanced dynamic CT was performed 1–3 days after the RFA treatment session. On CT images, the non-enhancing area was measured as the ablated area. A complete effect was defined as disappearance of tumor enhancement with surrounding non-enhancing areas of ≥5 mm [22]. An incomplete effect was defined as a necrotic area diameter closely similar to that of the tumor without the ablation margin or partial enhancement of the tumor; in such case, additional RFA sessions were performed at 3- to 5-day intervals later until a complete effect was achieved. RFA outcome was evaluated on CT images 3–4 weeks after the final RFA session.

2.5. Follow up

All patients received follow-up examinations including US or contrast-enhanced dynamic CT or MRI every 3–4 months. Serum HCC-specific tumor markers including α-fetoprotein (AFP), its lectin fraction 3, and des-γ-carboxy prothrombin (DCP) were measured every 1–2 months.

Local tumor progression was defined as the reappearance of tumor enhancement around the ablated zone. Distant recurrence was defined as the appearance of new HCC in the untreated liver or extrahepatic sites. Early recurrence was defined as that occurring within 2 years and late recurrence as that occurring after more than 2 years.

Survival analysis was performed on a patient-by-patient basis. Disease-free survival (DFS) was defined as survival time from RFA to last follow-up, local tumor progression, occurrence of new HCC in the liver, distant metastasis, or death, whichever occurred first.

2.6. Complications

Complications after percutaneous RFA were evaluated using Society of Interventional Radiology grading criteria [21]. Major complications were defined as those requiring treatment or additional hospitalization or resulting in permanent adverse sequelae. All other complications were considered minor. Complications were assessed for each ablation session.

2.7. Statistical analysis

Rates of local tumor progression and primary and secondary effectiveness were determined by counting tumor number. Rates of local tumor progression, overall survival (OS), and DFS were estimated by the Kaplan–Meier method, and differences between the curves were determined using the log-rank test. Prognostic factors affecting OS and DFS survival rates after RFA for initial recurrent HCC were determined using Cox's proportional hazard model. Chi-square and Mann–Whitney U tests were used to compare differences in clinical features between the groups. P values <0.05 were considered significant. Data processing and analysis was performed with commercially available software (SPSS for Windows, version 9.0; SPSS, Chicago, IL).