CME

*Open*

# Radiofrequency Ablation for Hepatocellular Carcinoma: 10-Year Outcome and Prognostic Factors



Shuichiro Shiina, MD, PhD[1], Ryosuke Tateishi, MD, PhD[1], Toru Arano, MD[1], Koji Uchino, MD[1], Kenichiro Enooku, MD, PhD[1], Hayato Nakagawa, MD, PhD[1], Yoshinari Asaoka, MD, PhD[1], Takahisa Sato, MD, PhD[1], Ryota Masuzaki, MD, PhD[1], Yuji Kondo, MD, PhD, Tadashi Goto, MD, PhD[1], Haruhiko Yoshida, MD, PhD[1], Masao Omata, MD, PhD[1] and Kazuhiko Koike, MD, PhD[1]

OBJECTIVES: **Radiofrequency ablation (RFA) is widely performed for hepatocellular carcinoma (HCC). However, there has been no report on 10-year outcome of RFA. The objective of this study was to report a 10-year consecutive case series at a tertiary referral center.**

METHODS: **We performed 2,982 RFA treatments on 1,170 primary HCC patients and analyzed a collected database.**

RESULTS: **Final computed tomography images showed complete tumor ablation in 2,964 (99.4%) of 2,982 treatments performed for the 1,170 primary HCC patients. With a median follow-up of 38.2 months, 5- and 10-year survival rates were 60.2% (95% confidence interval (CI): 56.7–63.9%) and 27.3% (95% CI: 21.5–34.7%), respectively. Multivariate analysis demonstrated that age, antibody to hepatitis C virus (anti-HCV), Child-Pugh class, tumor size, tumor number, serum des-γ-carboxy-prothrombin (DCP) level, and serum lectin-reactive α-fetoprotein level (AFP-L3) were significantly related to survival. Five- and 10-year local tumor progression rates were both 3.2% (95% CI: 2.1–4.3%). Serum DCP level alone was significantly related to local tumor progression. Five- and 10-year distant recurrence rates were 74.8% (95% CI: 71.8–77.8%) and 80.8% (95% CI: 77.4–84.3%), respectively. Anti-HCV, Child-Pugh class, platelet count, tumor size, tumor number, serum AFP level, and serum DCP level were significantly related to distant recurrence. There were 67 complications (2.2%) and 1 death (0.03%).**

CONCLUSIONS: **RFA could be locally curative for HCC, resulting in survival for as long as 10 years, and was a safe procedure. RFA might be a first-line treatment for selected patients with early-stage HCC.**

**SUPPLEMENTARY MATERIAL** is linked to the online version of the paper at http://www.nature.com/ajg

*Am J Gastroenterol* 2012; 107:569–577; doi:10.1038/ajg.2011.425; published online 13 December 2011

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignant neoplasm in the world (1). Only 20% of HCC patients are candidates for resection (2). Furthermore, recurrence is frequent even after apparently curative resection. Liver transplantation is restricted by organ donor shortage. Thus, various nonsurgical therapies have been introduced (3–5). Among these, image-guided percutaneous ablation is considered best for early-stage HCC.

Ethanol injection was formerly the standard procedure among the various percutaneous ablation techniques. Randomized controlled trials, however, have demonstrated that radiofrequency ablation (RFA) has a more reliable local antitumor effect, leading to a lower local tumor progression risk and higher survival rates (6–9). RFA has largely replaced ethanol injection (10).

Several reports on 5-year outcome of RFA exist (11–17); however, no study has covered 10-year outcome. We report on a 10-year consecutive case series at a tertiary referral center. We analyzed antitumor effect, patient survival, local tumor progression, and distant recurrence rates, variables relevant to these outcomes, and complications. To our knowledge, this study documents the largest number of RFA treatments performed at a single institution.

## METHODS

### RFA indications

RFA was the treatment of choice in HCC patients satisfying the following criteria: (i) ineligible for surgical resection/liver transplantation or patient refusal for surgery; (ii) no extrahepatic metastasis/vascular invasion; and (iii) no other malignancies that

[1]Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan. **Correspondence:** Shuichiro Shiina, MD, PhD, Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. E-mail: sshiina-tky@umin.ac.jp
**Received 8 May 2011; accepted 5 November 2011**

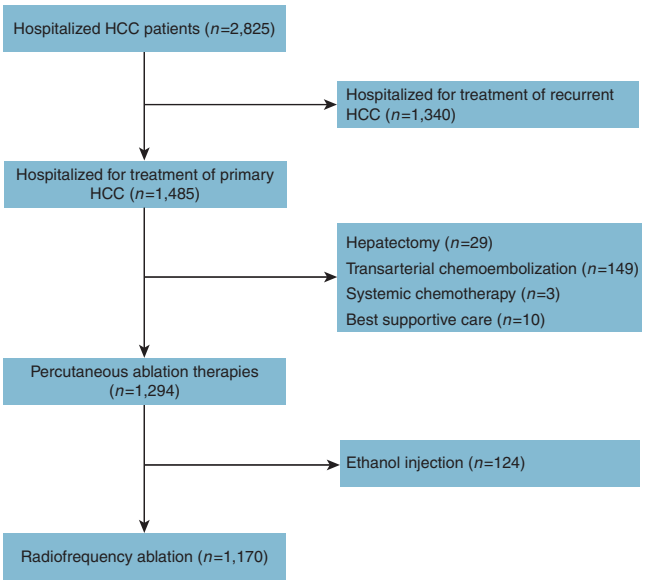


**Figure 1.** Flow of patients in this study. HCC, hepatocellular carcinoma.

may determine the patient's prognosis. Exclusion criteria were as follows: (i) tumor not visualized by ultrasonography/not accessible percutaneously; (ii) total bilirubin level ≥3.0 mg/dl; (iii) platelet count $< 50\times10^9$/l or prothrombin activity < 50%; (iv) refractory ascites; (v) enterobiliary reflux; and (vi) adhesion between the tumor and the gastrointestinal tract. In general, we performed RFA on Child-Pugh class A or B patients, a single tumor ≤5 cm in diameter, or three or fewer tumors ≤3 cm in diameter. In cases beyond these conditions, we performed RFA on patients who were likely to benefit from this procedure for possible cure or prolongation of life. No patients were excluded solely on account of tumor location (18). Informed consent was obtained from each patient. This study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki and approved by the institutional review board (Registration ID: P98C05-11Y).

## Patients

In this cohort study, we analyzed a prospectively collected computerized database. Between February 1999 and December 2009, 2,825 HCC patients were admitted once or more to the Department of Gastroenterology, the University of Tokyo (**Figure 1**). At initial hospitalization, 1,485 had primary HCC and the remaining 1,340 had recurrent HCC. In the recurrent HCC patients, primary HCC had previously been treated by therapies other than RFA.

Of the 1,485 primary HCC patients, 1,294 (87.1%) underwent percutaneous ablation as the initial treatment, including RFA. The remaining 191 patients underwent other therapies: hepatic resection, 29 patients with good liver function and who consented to an operation; transarterial chemoembolization, 149 with multinodular or large tumors that could not be treated by ablation therapies; systemic chemotherapy, three with extrahepatic metastasis; and only supportive care, 10 with decompensated cirrhosis or poor general condition.

Of the 1,294 patients treated by percutaneous ablation, 1,170 underwent RFA and the other 124 underwent ethanol injection. The choice of therapy was made as follows: between April 1999 and January 2001, 232 patients with three or fewer tumors, each ≤3 cm in diameter, and Child-Pugh class A or B liver function were entered into a randomized controlled trial to compare RFA with ethanol injection (6). Patients outside these inclusion criteria were mostly treated by RFA. After this trial, RFA was generally the treatment of choice, and ethanol injection was administered only to those considered unsuitable for RFA; ethanol injection was administered to those with either enterobiliary reflux or adhesion of the tumor to the gastrointestinal tract.

HCC was diagnosed based on typical imaging findings; that is, early-phase enhancement and late-phase contrast washout on dynamic computed tomography (CT) (19). HCC diagnosis was also confirmed by biopsy in 1,078 (92.1%) of the 1,170 patients with RFA-treated primary HCC. A total of 998 (85.3%) were diagnosed as having liver cirrhosis.

In general, transarterial chemoembolization was combined with RFA in patients with either ≥4 tumors or those with even one tumor >3.0 cm in diameter, although indication criteria of this combination had changed over time. The combination of transarterial chemoembolization with RFA was performed in 324 primary HCC patients.

## Treatment methods

RFA was performed on an inpatient basis. Preoperative planning including evaluation of all imaging studies, and careful ultrasound examination was performed to identify the tumors and determine the access routes.

The procedure was performed according to an institutional protocol and in the presence of three physicians. One physician inserted the electrode under ultrasound guidance while another assisted the procedure; at least one had 8-year or longer experience of percutaneous ablation therapies. The remaining physician was responsible for the ultrasound machine and data recording. Video recording was performed occasionally to improve and standardize the procedure.

The precise techniques of RFA are described elsewhere (6). Briefly, all RFA procedures were performed percutaneously under ultrasound guidance (Power Vision 8000, Aplio XV or Aplio XG; Toshiba, Tokyo, Japan). We used artificial pleural effusion (20) or artificial ascites (21) for tumors, which were in the hepatic dome or adjacent to the gastrointestinal tract. After administration of sedatives and local anesthesia, a 17-gauge cooled-tip electrode (Cool-Tip; RF Ablation System, Covidien, Boulder, Colombia, CO) was inserted. Radiofrequency energy was delivered for 6–12 min for each application. For large tumors, the electrode was repeatedly inserted into different sites, such that the entire tumor could be enveloped by assumed necrotic volumes. Following the procedure, the patient remained in bed until the next morning.

A CT scan with a 5-mm section thickness was performed 1–3 days after RFA to evaluate technique effectiveness (22). Complete ablation was defined as hypoattenuation of the entire tumor. We intended to ablate not only the tumor but also some of the liver

parenchyma surrounding it. When we suspected that unablated tumor portions remained, the procedure was repeated. We did not predefine the procedure number in a treatment: treatment was generally continued until CT imaging demonstrated necrosis of the entire tumor.

### Follow-up

To detect recurrence at an early stage, serum α-fetoprotein (AFP), lectin-reactive AFP (AFP-L3), and des-γ-carboxy-prothrombin (DCP) levels were measured monthly, and CT and ultrasonography were performed every 4 months. Local tumor progression was defined as the appearance of viable cancer tissue touching the initially treated tumor (22) and distant recurrence as the emergence of one or several tumor(s) separate from the primary site. Chest CT or bone scintigraphy was performed if extrahepatic recurrence was suspected. RFA was used for recurrence if the patient still met the indication criteria. If multiple recurrences were not treatable with RFA, transarterial chemoembolization was generally performed.

### Statistical analysis

This is a report of a consecutive case series: all RFA treatments performed on primary HCC patients at the Department of Gastroenterology, University of Tokyo between February 1999 and December 2009 were included and none was excluded. Data are presented as mean±s.d. for quantitative variables, and as absolute frequencies for qualitative variables.

A "procedure" was defined as a single intervention episode comprising one or more ablation performed on one or more tumors and a "treatment" as the completed effort to ablate one or more tumors. A treatment comprised one or more procedures (22).

"Technique effectiveness" rate was defined as the percentage of successfully eradicated macroscopic tumors, as evidenced by CT scan 1–3 days after the last procedure (22).

Overall survival was calculated in the 1,170 primary HCC patients. Survival curves were generated by the Kaplan–Meier method. In addition to overall survival, some subgroup analyses were performed with clinical characteristics including tumor size, tumor number, and liver function. Recurrence was evaluated in 1,138 of the 1,170 primary HCC patients; the remaining 32 patients were excluded from the recurrence analysis because some small tumors had been left untreated by RFA on account of detection failure by ultrasonography. Recurrence rates were calculated by the Gaynor's method (23). All time estimates were made from the date of the first RFA. The follow-up was finalized at either death or the last visit to the outpatient clinic before 31 December 2009. Transplanted patients were censored from this study at the date of transplantation.

The prognostic relevance of 19 baseline variables (**Table 1**), the combination of transcatheter arterial chemoembolization (TACE) with RFA, HCC recurrence, and the number of RFA sessions to survival was analyzed by univariate and multivariate Cox proportional hazards regression models. The prognostic relevance of 19 baseline variables (**Table 1**), the combination of TACE with RFA, and the number of RFA sessions to local tumor progression and distant recurrence was also analyzed by univariate and multivariate models. All variables with a $P$ value $<0.05$ by univariate comparison were subjected to multivariate analysis. Some continuous variables in which log-linearity could not be assumed were transformed into categorical variables. In multivariate analysis, we evaluated two models that contained either Child-Pugh class or its components to avoid multicollinearity. A stepwise variable selection was performed with Akaike Information Criteria in multivariate analysis. The results of multivariate analyses were presented as a hazard ratio with corresponding 95% confidence interval (CI), with $P$ values from the Wald test. All significance tests were two-tailed, and differences with a $P$ value $<0.05$ were considered statistically significant.

Complications were defined according to the guidelines of the Society of Interventional Radiology (24).

## RESULTS

### Antitumor effect

We performed a total of 2,982 RFA treatments for the 1,170 primary HCC patients, comprising 4,514 procedures. Thus, procedure number per treatment was 1.52±0.78. Many patients undergoing RFA for treatment of primary HCC received iterative RFA treatments for recurrence. A total of 485 patients underwent RFA treatment once, 247 twice, 177 thrice, 94 four times, 70 five times, 35 six times, 23 seven times, 14 eight times, 7 nine times, 7 ten times, 6 eleven times, 2 twelve times, 2 thirteen times, and 1 fourteen times.

Technique effectiveness rate was 99.4% (2,964/2,982 treatments). It was similar between the initial RFA treatments and the other RFA treatments for recurrence ($P=0.98$). Complete ablation of the tumor was achieved in 1,163 (99.4%) of the 1,170 initial treatments and in 1,801 (99.4%) of the 1,812 other RFA treatments. However, technique effectiveness rate significantly differed with tumor size ($P=0.023$). No apparent viable portions remained in the treated tumor in 1,642 (99.6%) of 1,648 treatments for tumors ≤2.0 cm in diameter, in 923 (99.2%) of 930 treatments for tumors 2.1–3.0 cm, in 356 (98.9%) of 360 treatments for tumors 3.1–5.0 cm, and in 43 (97.7%) of 44 treatments for tumors >5.0 cm. Final CT imaging demonstrated residual cancer tissue in the remaining 18 treatments. We decided against performing additional procedures, because liver failure rather than HCC seemed to determine the prognosis in 10 treatments, and because additional RFA would have caused complications on account of poor visualization or inaccessibility in the other eight treatments.

### Survival

The 19 baseline clinical characteristics of the 1,170 patients who underwent RFA for treatment of primary HCC are shown in **Table 1**. A total of 269 patients (23.0%) were >75 years old. In all, 422 patients had tumors ≤2.0 cm in diameter, 467 had tumors 2.1–3.0 cm, 246 had tumors 3.1–5.0 cm, and 35 had tumors >5.0 cm; 685 patients had 1 tumor, 395 had 2 or 3 tumors, and 90 had ≥4 tumors.

As of December 2009 (with a median follow-up of 38.2 months), 692 patients (59.1%) remained alive, 39 (3.3%) were lost to

**Table 1. Baseline characteristics of the 1,170 patients undergoing radiofrequency ablation for primary hepatocellular carcinoma**

| Variable | |
|---|---|
| Age (years) | 68.3±8.6 |
| Males, *n* (%) | 751 (64.1) |
| *Viral infection* | |
| HBs-Ag-positive, *n* (%) | 127 (10.9) |
| Anti-HCV-positive, *n* (%) | 870 (74.4) |
| Both positive, *n* (%) | 13 (1.1) |
| Both negative, *n* (%) | 159 (13.6) |
| Alcohol consumption >80 g/d | 170 (14.5) |
| Ascites, *n* (%) | 117 (10.0) |
| Encephalopathy, *n* (%) | 24 (2.1) |
| Albumin (g/dl) | 3.65±0.47 |
| Total bilirubin (mg/dl) | 0.95±0.49 |
| Prothrombin time (%) | 79.6±14.1 |
| Platelet count ($\times 10^4$/mm$^3$) | 11.9±5.6 |
| AST (IU/l) | 61.5±35.9 |
| ALT (IU/l) | 57.3±40.8 |
| *Child-Pugh class,* n *(%)* | |
| A | 868 (74.2) |
| B | 291 (24.9) |
| C | 11 (0.9) |
| Tumor size (cm) | 2.54±1.04 |
| Tumor number | 1.8±1.2 |
| *Serum AFP (ng/dl),* n *(%)* | |
| ≤100 | 928 (793) |
| 101–400 | 146 (12.5) |
| >400 | 96 (8.2) |
| *Serum DCP (mAU/ml),* n *(%)*[a] | |
| ≤100 | 964 (83.1) |
| 101–400 | 126 (10.9) |
| >400 | 70 (6.0) |
| *Serum AFP-L3 (%),* n *(%)* | |
| ≤15 | 1,015 (86.8) |
| 15.1–40 | 74 (6.3) |
| >40 | 81 (6.9) |

AFP, α-fetoprotein; AFP-L3, lectin-reactive α-fetoprotein; ALT, alanine aminotransferase; AST, asparatate aminotransferase; DCP, des-γ-carboxy-prothrombin; HCV, hepatitis C virus.

Data are expressed as mean±s.d.

[a]Serum DCP level could not be measured in 10 patients because they were being administered warfarin.

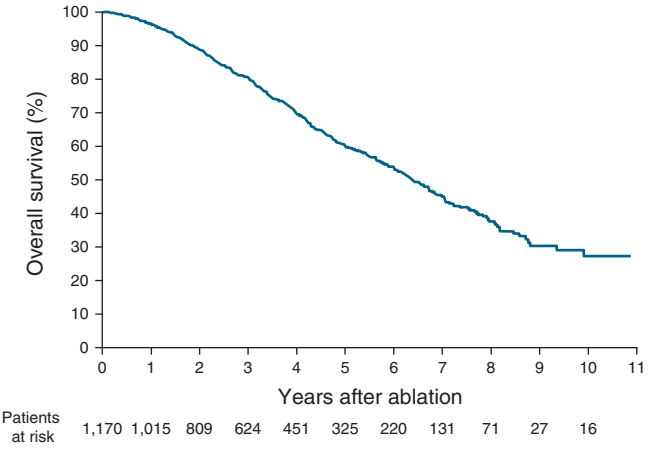


**Figure 2.** Overall survival in 1,170 primary hepatocellular carcinoma patients who underwent radiofrequency ablation.

follow-up, and 439 (37.5%) had died. Of the 1,170 patients, two were transplanted. The number of 5-, 7-, and 10-year survivors was 325, 131, and 16, respectively. The cause of death was HCC in 245 patients (55.8%), liver failure in 89 (20.3%), upper gastrointestinal bleeding in 11 (2.5%), complications related to the procedure in 3 (0.7%), liver-unrelated diseases in 81 (18.5%), and undetermined in 10 (2.3%).

The 1-, 3-, 5-, 7-, and 10-year survival rates of all 1,170 primary HCC patients were 96.6% (95% CI: 95.5–97.7%), 80.5% (95% CI: 78.0–83.1%), 60.2% (95% CI: 56.7–63.9%), 45.1% (95% CI: 40.9–49.6%), and 27.3% (95% CI: 21.5–34.7%), respectively (**Figure 2**; **Table 2**). Survival rates differed significantly with tumor size ($P<0.0001$), tumor number ($P=0.0003$), and Child-Pugh class ($P<0.0001$). In the Child-Pugh class A or B patients with a single tumor ≤5 cm in diameter, or three or fewer tumors ≤3 cm in diameter, the 5-year survival rate was 63.8% (95% CI: 59.9–67.9%), while in those outside these criteria, it was 46.4% (95% CI: 39.4–54.8%).

Univariate analysis showed 19 of the 22 variables relevant to survival. In multivariate analysis that contained Child-Pugh class but not its components, a model that contained age, antibody to hepatitis C virus (anti-HCV), Child-Pugh class, tumor size, tumor number, serum DCP level, and serum AFP-L3 level was selected (**Table 3**). The other model that contained the components of Child-Pugh class is shown in **Supplementary Table** online.

## Recurrence

Recurrence developed in 741 patients. Local tumor progression alone was found in 25, local tumor progression with distant recurrence was found in 9, and distant recurrence alone was found in the other 707 patients. Of these 707 patients, 13 had the first recurrence in extrahepatic sites: 7 had lymph node metastasis, 3 had peritoneal seeding, 1 had lung metastasis, 1 had bone metastasis, and the remainder had both peritoneal seeding and lung metastasis. No recurrence developed in the remaining 397 patients.

Of the 741 patients, the first recurrence was treated by iterative RFA in 659 (88.9%), transarterial chemoembolization in 69 (9.3%), systemic chemotherapy in 4 (0.5%), surgical resection in 3 (0.4%), radiation therapy in 2 (0.3%), and supportive care in 4 (0.5%).

**Table 2. Survival of patients undergoing radiofrequency ablation, based on tumor number, tumor size, and Child-Pugh class**

| Grading | *n* | Survival (%) | | | | | Median (years) | *P* value |
|---|---|---|---|---|---|---|---|---|
| | | 1-Year | 3-Year | 5-Year | 7-Year | 10-Year | | |
| Overall survival | 1,170 | 96.6 | 80.5 | 60.2 | 45.1 | 27.3 | 6.4 | — |
| *Tumor number* | | | | | | | | |
| Solitary | 685 | 97.2 | 82.6 | 64.6 | 50.5 | 32.0 | 7.0 | 0.0003 |
| 2–3 | 395 | 95.7 | 77.9 | 54.4 | 39.4 | 19.9 | 5.6 | |
| ≥4 | 90 | 96.5 | 76.4 | 53.6 | 30.1 | 17.6 | 5.3 | |
| *Tumor size* | | | | | | | | |
| ≤3 cm | 889 | 97.2 | 83.8 | 65.1 | 47.3 | 30.7 | 6.7 | <0.0001 |
| >3 cm | 281 | 94.8 | 71.0 | 46.5 | 38.0 | 18.6 | 4.6 | |
| *Child-Pugh class* | | | | | | | | |
| A | 868 | 98.0 | 86.0 | 65.9 | 50.2 | 30.1 | 7.0 | <0.0001 |
| B | 291 | 93.2 | 66.4 | 46.5 | 32.4 | 20.6 | 4.6 | |
| C | 11 | 81.8 | 58.4 | 23.4 | 23.4 | — | 3.1 | |
| *Combination of tumor number, tumor size, and Child-Pugh class* | | | | | | | | |
| Solitary, ≤3 cm | 534 | 97.6 | 84.7 | 68.0 | 51.4 | 34.3 | 7.1 | — |
| Solitary, ≤3 cm, Child-Pugh A | 401 | 98.7 | 90.1 | 74.0 | 57.4 | 41.3 | 8.2 | — |
| 1–3 Tumors, ≤3 cm | 822 | 97.1 | 83.7 | 65.2 | 48.8 | 32.5 | 6.9 | — |
| Solitary, ≤5 cm, or 1–3 tumors, ≤3 cm | 947 | 97.2 | 82.8 | 63.8 | 48.8 | 30.6 | 6.9 | — |
| *Child-Pugh A/B* | | | | | | | | |
| Satisfied the indication criteria of surgical resection proposed in the BCLC protocol[a] | 237 | 98.6 | 90.5 | 75.9 | 61.1 | 38.1 | 8.7 | — |

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma.
[a]Child-Pugh class A with a normal level of bilirubin, no significant portal hypertension, and a single HCC.

The 1-, 3-, 5-, 7-, and 10-year rates of local tumor progression with or without distant recurrence were 1.4% (95% CI: 0.7–2.1%), 3.2% (95% CI: 2.1–4.3%), 3.2% (95% CI: 2.1–4.3%), 3.2% (95% CI: 2.1–4.3%), and 3.2% (95% CI: 2.1–4.3%), respectively (**Figure 3**). Univariate analysis demonstrated that prothrombin time and serum AFP, DCP, and AFP-L3 levels were correlated to local tumor progression, whereas multivariate analysis showed that serum DCP level alone was significantly correlated. Tumor size was not correlated to local tumor progression.

The 1-, 3-, 5-, 7-, and 10-year rates of distant recurrence without local tumor progression were 25.6% (95% CI: 23.0–28.2%), 63.3% (95% CI: 60.2–66.4%), 74.8% (95% CI: 71.8–77.8%), 78.1% (95% CI: 75.1–81.2%), and 80.8% (95% CI: 77.4–84.3%), respectively. Univariate analysis demonstrated 14 variables relevant to distant recurrence, whereas multivariate analysis showed that anti-HCV, Child-Pugh class, platelet count, tumor size, tumor number, serum AFP level, and serum DCP level were significantly related to distant recurrence (**Table 3**).

### Complications

A total of 67 complications were encountered (**Table 4**). The incidence rates of complications per treatment and per procedure were 2.2% (67/2,982) and 1.5% (67/4,514), respectively. One patient died of hepatic failure on account of massive hepatic infarction 7 days after the last RFA procedure. He had undergone 12 RFA treatments in 8 years. The treatment mortality rate was 0.03%.

## DISCUSSION

This study describes our 10-year clinical experience with RFA at a high-volume center. We performed the 2,982 RFA treatments on a total of the 1,170 primary HCC patients, showing that RFA has a high antitumor effect. Tumors were judged to have been completely ablated by final CT imaging in 99.4% of the treatments. Complete response was achieved not only in the first RFA but also in iterative RFA for recurrence. Although complete response rate differed with tumor size, there was not a sharp drop-off in effectiveness. The complete response rate may be higher in this study than others probably because we generally repeated the procedure until CT imaging demonstrated complete tumor necrosis, whereas many other studies limited the procedure number of RFA to 2–3 (11,13,15). Complete ablation of tumors has been reported to be related to improved survival (25). There were the 18 treatments in which we did not perform additional RFA for residual cancer tissue. In those treatments, usefulness of RFA had been unclear at the initial session because of liver dysfunction or tumor burden.

**Table 3. Multivariate analysis of variables relevant to survival, local tumor progression, and distant recurrence**

| Variable | Multivariate analysis Hazard ratio (95% CI) | *P* value |
|---|---|---|
| *Survival* | | |
| Age (per year) | 1.03 (1.02–1.04) | <0.0001 |
| Anti-HCV-positive | 1.34 (1.03–1.76) | 0.03 |
| Child-Pugh class | | |
| A | 1 | |
| B or C | 2.08 (1.69–2.56) | <0.0001 |
| Tumor size (cm) | | |
| ≤2.0 | 1 | |
| 2.1–3.0 | 1.40 (1.10–1.80) | 0.007 |
| 3.1–5.0 | 1.80 (1.37–2.38) | <0.0001 |
| >5.0 | 1.50 (0.90–2.49) | 0.12 |
| Tumor number | | |
| Solitary | 1 | |
| 2–3 | 1.28 (1.04–1.59) | 0.02 |
| ≥4 | 1.58 (1.13–2.21) | 0.008 |
| Serum DCP (mAU/ml) | | |
| ≤100 | 1 | |
| 101–400 | 1.22 (0.88–1.69) | 0.24 |
| >400 | 1.66 (1.14–2.42) | 0.008 |
| Serum AFP-L3 (%) | | |
| ≤15 | 1 | |
| >15 | 1.45 (1.11–1.91) | 0.008 |
| *Local tumor progression* | | |
| Serum DCP (mAU/ml) | | |
| ≤100 | 1 | |
| 101–400 | 2.51 (1.02–6.20) | 0.05 |
| >400 | 6.52 (2.63–16.1) | <0.0001 |
| *Distant recurrence* | | |
| Anti-HCV-positive | 1.44 (1.19–1.75) | 0.0002 |
| Child-Pugh class | | |
| A | 1 | |
| B or C | 1.23 (1.03–1.45) | 0.02 |
| Platelet count (/l) | | |
| $>10^{11}$ | 1 | |
| $\leq 10^{11}$ | 1.36 (1.12–1.64) | 0.002 |
| Tumor size (cm) | | |
| ≤2.0 | 1 | |
| 2.1–3.0 | 1.30 (1.10–1.55) | 0.003 |
| 3.1–5.0 | 1.29 (1.05–1.60) | 0.02 |
| >5.0 | 1.25 (0.75–2.08) | 0.4 |
| Tumor number | | |
| Solitary | 1 | |
| 2–3 | 1.36 (1.16–1.59) | 0.0002 |
| ≥4 | 2.02 (1.53–2.66) | <0.0001 |
| Serum AFP (ng/dl) | | |
| ≤100 | 1 | |
| 101–400 | 1.15 (0.92–1.44) | 0.22 |
| >400 | 1.36 (1.03–1.81) | 0.03 |
| Serum DCP (mAU/ml) | | |
| ≤100 | 1 | |
| 101–400 | 1.19 (0.92–1.54) | 0.19 |
| >400 | 1.72 (1.22–2.42) | 0.002 |

AFP, α-fetoprotein; CI, confidence interval; DCP, des-γ-carboxy-prothrombin; HCV, hepatitis C virus.

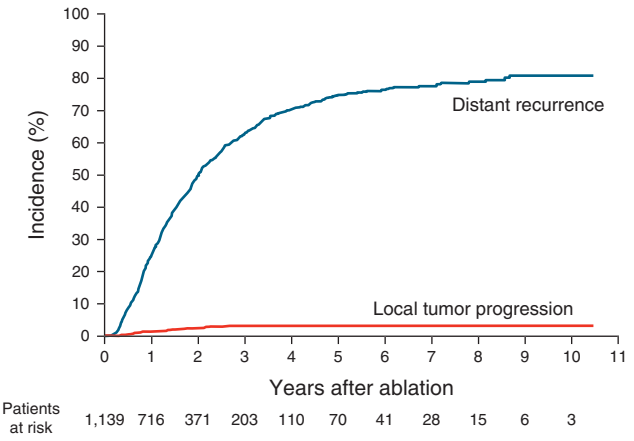


**Figure 3.** Local tumor progression and distant recurrence in patients who underwent radiofrequency ablation.

This study shows that RFA could achieve long-term survival for as long as 10 years. Sixteen patients treated by RFA survived for >10 years. The variables relevant to survival were similar to those found in previous studies on ethanol injection (26,27), RFA, hepatic resection (28), and transarterial chemoembolization (29). Both liver function and tumor-related factors were associated with survival. In addition, age and anti-HCV were relevant to survival in this study. Age was among the prognostic factors, probably because 23.0% of the patients were >75 years old, which resulted in a higher percentage (18.5%) of liver-unrelated deaths in this study compared with others. Anti-HCV was among the prognostic factors, probably because anti-HCV-positive patients developed distant recurrence more frequently.

HCC frequently recurred after RFA; most recurrences were, however, not local tumor progression but distant recurrence. Frequent recurrence is not specific to RFA. After hepatic resection, the

**Table 4. Complications in 2,982 treatments of radiofrequency ablation for hepatocellular carcinoma**

| Complication | No. of complications |
|---|---|
| Neoplastic seeding | 24 |
| Liver abscess | 6 |
| Hemoperitoneum | 12 |
| Hemothorax | 5 |
| Symptomatic pleural effusion | 1 |
| Massive hepatic infarction | 6 |
| Gastrointestinal perforation or penetration | 5 |
| Hemobilia | 2 |
| Skin burn | 1 |
| Pneumothorax | 3 |
| Gallbladder injury | 1 |
| Cerebral infarction | 1 |

tumor recurrence rate exceeds 70% at 5 years (30,31). In this study, periodic follow-up detected most recurrences at limited stage. RFA was performed again for first recurrence in almost 90% of cases, although multimodal treatments were used in a long-term follow-up. On the other hand, repeat resection rate for first recurrence has been reported to range from 10.4 to 30.6% (31,32). Because RFA is less invasive than hepatic resection, iterative RFA can be performed for recurrence more easily.

Local tumor progression was found less frequently in this study than in other studies, having been reported to be around 10% at 3 years following RFA (13,14). Furthermore, different from the findings in previous reports (33,34), tumor size was not related to local tumor progression in this study. These differences are probably because we repeated RFA until we considered we had ablated not only the tumor itself but also some of the liver tissue surrounding it. Furthermore, to avoid local tumor progression, we were more cautious in the treatment of larger tumors when deciding whether sufficient ablation had been performed. Only serum DCP level was significantly related to local tumor progression in this study. Elevated serum DCP level may be related to the malignant potential of HCC such as the development of portal venous invasion (35).

The frequency of distant recurrence in this study was similar to that reported in other studies (13). Among the variables significantly related to distant recurrence, tumor size, tumor number, serum AFP level, and serum DCP level were probably related to micrometastasis, which had not been detected by imaging modalities before the treatment, while anti-HCV, Child-Pugh class, and platelet count were related to metachronous multicentric carcinogenesis, which developed based on underlying chronic liver disease.

From the viewpoint of survival and distant recurrence, patients with 2.1–5.0 cm tumors had significantly worse outcomes than those with ≤2.0 cm tumors while those with tumors >5.0 cm did not have worse rates than those with tumors ≤2 cm. This is probably because the number of patients with tumors >5.0 cm ($n=35$) were not large enough for the difference to be statistically significant. Another possibility is selection bias. It is possible that patient with tumors >5.0 cm who underwent RFA had more favorable conditions for survival and distant recurrence except tumor size than those with 2.1–5.0 cm tumors.

In this study, 324 of the 1,170 patients were treated with combination of TACE and RFA at the initial treatment. Thus, we evaluated the combination as a possible variable that influences survival or recurrence. Univariate analysis demonstrated that the combined therapy was significantly correlated to overall survival, whereas multivariate analysis did not show the relationship. TACE was generally combined with RFA in patients with either ≥4 tumors or those with even one tumor >3.0 cm in diameter. This is why the correlation was significant in univariate analysis, while it was not in multivariable model in which the effect of other risk factors, such as tumor number and tumor size were adjusted. The combination of TACE and RFA was not significantly related to either local tumor progression or distant recurrence.

RFA was a safe procedure. Although many patients treated by RFA in this study were at high risk for surgical treatment because of advanced cirrhosis or other comorbidities, complications occurred in only 2.2% of the treatments. Other investigators have also reported low complication rates of 0–6.1% (11,13–16). For hepatic resection, morbidity rates of 38–47% have been reported even in recent studies (36–38).

To date, percutaneous ethanol injection has been considered the standard in ablation (5). However, randomized controlled trials have demonstrated the superiority of RFA (6–9), with RFA now largely replacing ethanol injection. We have also shifted from ethanol injection to RFA (10). At our department, RFA is currently the first option and ethanol injection is performed only on patients on whom RFA cannot be performed safely because of either enterobiliary reflux, adhesion between the tumor and the gastrointestinal tract, or other reasons.

Surgical resection has been considered the treatment of choice for HCC. Our first option for resectable HCC was also surgery. However, most patients who came to our department visited us because they did not want surgical resection. Thus, many patients in this study underwent RFA not because of unresectable tumor but because of refusal of surgery. Those who preferred surgery would have directly gone to the surgical department that has extensive experience in hepatic resection (38).

It is not easy to compare outcomes between RFA and surgical resection; the indications are different between the two treatments. Furthermore, indications for each treatment are different from institution to institution. Thus, a case adjudged to be treatable by RFA or surgical resection at an institution may not be given the same treatment at another. The best known indication criteria for surgical resection may be those proposed in the Barcelona Clinic Liver Cancer (BCLC) protocol (5), which states that surgical resection should be restricted to patients with performance status 0, Child-Pugh class A, single HCC, normal portal pressure, and normal serum bilirubin level. In patients satisfying those criteria, the 5-year survival rate is expected to be >70% (30). In this study, 237

(20.3%) of 1,170 patients satisfied those criteria and were thus considered good candidates for surgical resection; their 5-year survival rate was 75.9%, which appears satisfactory when compared with outcomes following surgical resection. Furthermore, in all 1,170 primary HCC patients treated by RFA, 5- and 10-year survival rates were 60.2% and 27.3%, respectively. In patients treated by surgical resection, 5- and 10-year survival rates were 34.4–70.0% and 10.5–52.0%, respectively (32,39–45). Although this is an observational study with no control, survivals following RFA appear comparable to those reported following surgical resection.

Two recent randomized controlled trials showed no significant difference in survival between RFA and surgical resection (46,47). Several nonrandomized controlled trials reported that RFA had similar overall survival rates to resection (48–50), while others found resection to be associated with higher survival rates (51–53). Further studies are necessary to resolve comparison of RFA with resection.

We have made strenuous efforts to standardize the RFA procedure. Although many physicians have participated in RFA at our institution, the procedure was invariably performed according to the institutional protocol and in the presence of experienced physicians. Video recording was also used to monitor the procedure. Additionally, preoperative planning and postoperative evaluation of technique effectiveness were also carried out by at least three physicians. We also believe that not only proficient practice of RFA but also detailed preoperative planning, cautious postoperative evaluation of therapeutic effect, and careful follow-up are vital to achieve satisfactory outcomes.

Source population in this study may represent selection bias, as we performed RFA on most patients who were hospitalized at our department; however, many patients with unfavorable tumor conditions for RFA might not have been referred to us. Therefore, caution is required when extrapolating our findings to the general population of HCC patients.

A second limitation is that study population cannot be clearly defined. This study was based on daily clinical practice over a 10-year period. Indication criteria of RFA have changed over time, mainly because another percutaneous ablation, that is, ethanol injection has also been performed. Furthermore, various treatments besides percutaneous ablation were available for HCC, such as surgical resection and transarterial chemoembolization, with frequently overlapping indications.

One further limitation is the fact that this was a single-center study; these results might not be reproducible consistently in other settings. To extrapolate the findings in this study to patients at other institutions, careful consideration should be given to differences in the indications, methods, expertise, performance of available ultrasound and CT equipment, and others. Treatment outcome may be influenced by the physicians' expertise and the institution's volume of care. We started ethanol injection in 1985 and microwave ablation in 1995, that is, before the introduction of RFA. Recently, we have performed over 900 RFA treatments per year, which may represent a far greater number of treatments than those in most other institutions. We would not recommend any change in daily clinical practice solely on the strength of our study findings.

In conclusion, our 10-year clinical experience shows that RFA could be locally curative, resulting in survival for as long as 10 years, and was a safe procedure. RFA might be a first-line treatment for selected patients with early-stage HCC.

## CONFLICT OF INTEREST

**Guarantor of the article:** Shuichiro Shiina, MD, PhD.

**Specific author contributions:** Study concept and design, analysis and interpretation of data, and drafting of the manuscript: Shuichiro Shiina; analysis and interpretation of data and statistical analysis: Ryosuke Tateishi; study execution and data acquisition: Toru Arano, Koji Uchino, Kenichiro Enooku, Hayato Nakagawa, Yoshinari Asaoka, Takahisa Sato, Ryota Masuzaki, Yuji Kondo, and Tadashi Goto; revised the article critically for important intellectual content: Haruhiko Yoshida; Masao Omata, and Kazuhiko Koike. All authors have read and approved the submitted manuscript.

**Financial support:** This study was partly supported by Health Sciences Research Grants of The Ministry of Health, Labor and Welfare of Japan (Research on Hepatitis).

**Potential competing interests:** None.

## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

- ✓ Radiofrequency ablation (RFA) has been widely performed for hepatocellular carcinoma (HCC).
- ✓ RFA has a more reliable local antitumor effect and higher survival than ethanol injection.
- ✓ There has been no report on 10-year outcome of RFA.

### WHAT IS NEW HERE

- ✓ Five- and 10-year survival rates in 1,170 patients with primary hepatocellular carcinoma (HCC) were 60.2 and 27.3%, respectively.
- ✓ Age, antibody to hepatitis C virus, Child-Pugh class, tumor size, tumor number, serum des-γ-carboxy-prothrombin level, and serum lectin-reactive α-fetoprotein level were significantly related to survival.
- ✓ Five- and 10-year local tumor progression rates were both 3.2%. Five- and 10-year distant recurrence rates were 74.8 and 80.8%, respectively.

## REFERENCES

1. Parkin DM, Bray F, Ferlay J *et al.* Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001;94:153–6.
2. Borie F, Bouvier AM, Herrero A *et al.* Treatment and prognosis of hepatocellular carcinoma: a population based study in France. J Surg Oncol 2008;98:505–9.
3. Ryder SD. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. Gut 2003;52 (Suppl 3): iii1–8.
4. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907–17.
5. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208–36.
6. Shiina S, Teratani T, Obi S *et al.* A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. Gastroenterology 2005;129:122–30.
7. Lin SM, Lin CJ, Lin CC *et al.* Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma ≤4 cm. Gastroenterology 2004;127:1714–23.

8. Lin SM, Lin CJ, Lin CC *et al.* Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. Gut 2005;54:1151–6.
9. Lencioni RA, Allgaier HP, Cioni D *et al.* Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. Radiology 2003;228:235–40.
10. Shiina S, Teratani T, Obi S *et al.* Nonsurgical treatment of hepatocellular carcinoma: from percutaneous ethanol injection therapy and percutaneous microwave coagulation therapy to radiofrequency ablation. Oncology 2002;62 (Suppl 1): 64–8.
11. N'Kontchou G, Mahamoudi A, Aout M *et al.* Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. Hepatology 2009;50:1475–83.
12. Tateishi R, Shiina S, Teratani T *et al.* Percutaneous radiofrequency ablation for hepatocellular carcinoma. An analysis of 1000 cases. Cancer 2005;103:1201–9.
13. Lencioni R, Cioni D, Crocetti L *et al.* Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. Radiology 2005;234:961–7.
14. Choi D, Lim HK, Rhim H *et al.* Percutaneous radiofrequency ablation for early-stage hepatocellular carcinoma as a first-line treatment: long-term results and prognostic factors in a large single-institution series. Eur Radiol 2007;17:684–92.
15. Livraghi T, Meloni F, Di Stasi M *et al.* Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? Hepatology 2008;47:82–9.
16. Buscarini L, Buscarini E, Di Stasi M *et al.* Percutaneous radiofrequency ablation of small hepatocellular carcinoma: long-term results. Eur Radiol 2001;11:914–21.
17. Raut CP, Izzo F, Marra P *et al.* Significant long-term survival after radiofrequency ablation of unresectable hepatocellular carcinoma in patients with cirrhosis. Ann Surg Oncol 2005;12:616–28.
18. Teratani T, Yoshida H, Shiina S *et al.* Radiofrequency ablation for hepatocellular carcinoma in so-called high-risk locations. Hepatology 2006;43:1101–8.
19. Araki T, Itai Y, Furui S *et al.* Dynamic CT densitometry of hepatic tumors. AJR Am J Roentgenol 1980;135:1037–43.
20. Kondo Y, Yoshida H, Tateishi R *et al.* Percutaneous radiofrequency ablation of liver cancer in the hepatic dome using the intrapleural fluid infusion technique. Br J Surg 2008;95:996–1004.
21. Kondo Y, Yoshida H, Shiina S *et al.* Artificial ascites technique for percutaneous radiofrequency ablation of liver cancer adjacent to the gastrointestinal tract. Br J Surg 2006;93:1277–82.
22. Goldberg SN, Grassi CJ, Cardella JF *et al.* Image-guided tumor ablation: standardization of terminology and reporting criteria. Radiology 2005;235:728–39.
23. Gaynor JJ, Feuer EJ, Tan CC *et al.* On the use of cause-specific failure and conditional failure probabilities: examples from clinical oncology data. J Am Stat Assoc 1993;88:400–9.
24. Sacks D, McClenny TE, Cardella JF *et al.* Society of interventional radiology clinical practice guidelines. J Vasc Interv Radiol 2003;14:S199–202.
25. Sala M, Llovet JM, Vilana R *et al.* Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. Hepatology 2004;40:1352–60.
26. Lencioni R, Bartolozzi C, Caramella D *et al.* Treatment of small hepatocellular carcinoma with percutaneous ethanol injection. Analysis of prognostic factors in 105 Western patients. Cancer 1995;76:1737–46.
27. Castellano L, Calandra M, Del Vecchio Blanco C *et al.* Predictive factors of survival and intrahepatic recurrence of hepatocellular carcinoma in cirrhosis after percutaneous ethanol injection: analysis of 71 patients. J Hepatol 1997;27:862–70.
28. Franco D, Capussotti L, Smadja C *et al.* Resection of hepatocellular carcinomas. Results in 72 European patients with cirrhosis. Gastroenterology 1990;98:733–8.
29. Takayasu K, Arii S, Ikai I *et al.* Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology 2006;131:461–9.
30. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999;30:1434–40.
31. Minagawa M, Makuuchi M, Takayama T *et al.* Selection criteria for repeat hepatectomy in patients with recurrent hepatocellular carcinoma. Ann Surg 2003;238:703–10.
32. Poon RT, Fan ST, Lo CM *et al.* Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg 2002;235:373–82.
33. Ishii H, Okada S, Nose H *et al.* Local recurrence of hepatocellular carcinoma after percutaneous ethanol injection. Cancer 1996;77:1792–6.
34. Mulier S, Ni Y, Jamart J *et al.* Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. Ann Surg 2005;242:158–71.
35. Koike Y, Shiratori Y, Sato S *et al.* Des-gamma-carboxy prothrombin as a useful predisposing factor for the development of portal venous invasion in patients with hepatocellular carcinoma: a prospective analysis of 227 patients. Cancer 2001;91:561–9.
36. Capussotti L, Muratore A, Amisano M *et al.* Liver resection for hepatocellular carcinoma on cirrhosis: analysis of mortality, morbidity and survival--a European single center experience. Eur J Surg Oncol 2005;31:986–93.
37. Taketomi A, Kitagawa D, Itoh S *et al.* Trends in morbidity and mortality after hepatic resection for hepatocellular carcinoma: an institute's experience with 625 patients. J Am Coll Surg 2007;204:580–7.
38. Imamura H, Seyama Y, Kokudo N *et al.* One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg 2003;138:1198–206; discussion 206.
39. Park YK, Kim BW, Wang HJ *et al.* Hepatic resection for hepatocellular carcinoma meeting Milan criteria in Child-Turcotte-Pugh class a patients with cirrhosis. Transplant Proc 2009;41:1691–7.
40. Wang CC, Iyer SG, Low JK *et al.* Perioperative factors affecting long-term outcomes of 473 consecutive patients undergoing hepatectomy for hepatocellular carcinoma. Ann Surg Oncol 2009;16:1832–42.
41. Kamiyama T, Nakanishi K, Yokoo H *et al.* Recurrence patterns after hepatectomy of hepatocellular carcinoma: implication of Milan criteria utilization. Ann Surg Oncol 2009;16:1560–71.
42. Yamamoto J, Kosuge T, Saiura A *et al.* Effectiveness of hepatic resection for early-stage hepatocellular carcinoma in cirrhotic patients: subgroup analysis according to Milan criteria. Jpn J Clin Oncol 2007;37:287–95.
43. Nuzzo G, Giuliante F, Gauzolino R *et al.* Liver resections for hepatocellular carcinoma in chronic liver disease: experience in an Italian centre. Eur J Surg Oncol 2007;33:1014–8.
44. Hanazaki K, Kajikawa S, Shimozawa N *et al.* Survival and recurrence after hepatic resection of 386 consecutive patients with hepatocellular carcinoma. J Am Coll Surg 2000;191:381–8.
45. Shimada K, Sano T, Sakamoto Y *et al.* A long-term follow-up and management study of hepatocellular carcinoma patients surviving for 10 years or longer after curative hepatectomy. Cancer 2005;104:1939–47.
46. Chen MS, Li JQ, Zheng Y *et al.* A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg 2006;243:321–8.
47. Lu MD, Kuang M, Liang LJ *et al.* [Surgical resection versus percutaneous thermal ablation for early-stage hepatocellular carcinoma: a randomized clinical trial]. Zhonghua Yi Xue Za Zhi 2006;86:801–5.
48. Hong SN, Lee SY, Choi MS *et al.* Comparing the outcomes of radiofrequency ablation and surgery in patients with a single small hepatocellular carcinoma and well-preserved hepatic function. J Clin Gastroenterol 2005;39:247–52.
49. Yamagiwa K, Shiraki K, Yamakado K *et al.* Survival rates according to the Cancer of the Liver Italian Program scores of 345 hepatocellular carcinoma patients after multimodality treatments during a 10-year period in a retrospective study. J Gastroenterol Hepatol 2008;23:482–90.
50. Yamakado K, Nakatsuka A, Takaki H *et al.* Early-stage hepatocellular carcinoma: radiofrequency ablation combined with chemoembolization versus hepatectomy. Radiology 2008;247:260–6.
51. Vivarelli M, Guglielmi A, Ruzzenente A *et al.* Surgical resection versus percutaneous radiofrequency ablation in the treatment of hepatocellular carcinoma on cirrhotic liver. Ann Surg 2004;240:102–7.
52. Guglielmi A, Ruzzenente A, Valdegamberi A *et al.* Radiofrequency ablation versus surgical resection for the treatment of hepatocellular carcinoma in cirrhosis. J Gastrointest Surg 2008;12:192–8.
53. Abu-Hilal M, Primrose JN, Casaril A *et al.* Surgical resection versus radiofrequency ablation in the treatment of small unifocal hepatocellular carcinoma. J Gastrointest Surg 2008;12:1521–6.