Radiofrequency Ablation of Hepatocellular Carcinoma as First-Line Treatment: Long-term Results and Prognostic Factors in 162 Patients with Cirrhosis[1]

Dong Ho Lee, MD
Jeong Min Lee, MD
Jae Young Lee, MD
Se Hyung Kim, MD
Jung Hwan Yoon, MD
Yoon Jun Kim, MD
Joon Koo Han, MD
Byung Ihn Choi, MD

Purpose: To evaluate the long-term outcomes of radiofrequency ablation (RFA) as a first-line therapy for early-stage hepatocellular carcinoma (HCC) and determine the prognostic factors for survival.

Materials and Methods: The institutional review board approved this retrospective study. From January 2006 to December 2007, 162 consecutive patients with cirrhosis (Child-Pugh class A and B, 137 and 25 patients, respectively) who underwent RFA as a first-line treatment for up to three HCCs with a maximum diameter of 5 cm (182 HCCs; mean diameter ± standard deviation, 2.59 cm ± 0.79; 17 multinodular forms) were included. After a mean follow-up of 50.3 months ± 19.9, results were analyzed for tumor recurrence, as well as overall and recurrence-free survival time. The Kaplan-Meier method and Cox proportional hazards regression model were used to evaluate the prognostic factors.

Results: The cumulative incidence of local tumor progression (LTP) was 14.5% at 5 years, with tumor size as the only significant predictive factor (relative risk = 2.13, P = .007). Overall 5-year survival and recurrence-free survival rates were 67.9% and 25.9%, respectively. Significant predictive factors for poor overall survival were Child-Pugh class B (relative risk = 2.43, P = .011), serum α-fetoprotein level (relative risk per 100 units = 1.01; $P < .001$), and presence of portosystemic collaterals (relative risk = 2.15, P = .025). The development of LTP significantly shortened median recurrence-free survival (28.0 months without LTP vs 12.0 months with LTP) and necessitated a higher number of interventional procedures (2.2 sessions without LTP vs 5.1 sessions with LTP).

Conclusion: RFA is a safe and effective first-line treatment for early-stage HCC, with a 5-year survival rate of 67.9%. High serum α-fetoprotein level, advanced Child-Pugh class, and presence of portosystemic collateral vessels had a significant negative effect on overall survival.

[1] From the Department of Radiology (D.H.L., J.M.L., J.Y.L., S.H.K., J.K.H., B.I.C.), Institute of Radiation Medicine (J.M.L., J.Y.L., S.H.K., J.K.H., B.I.C.), and Department of Internal Medicine (J.H.Y., Y.J.K.), Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-744, South Korea. Received April 23, 2013; revision requested June 10; revision received August 8; accepted August 12; final version accepted August 14. **Address correspondence to** J.M.L. (e-mail: *jmsh@snu.ac.kr*).

Hepatocellular carcinoma (HCC) is the fifth most common tumor worldwide and is the third most common cause of cancer-related death (1). Traditionally, hepatic resection and transplantation have been considered the treatments of choice for curative purposes (2). However, radiofrequency ablation (RFA) is emerging as an effective local treatment for curative intent in patients with cirrhosis and HCC smaller than 3 cm in diameter (3,4). Two randomized clinical trials showed that RFA was as safe and effective as hepatic resection for HCC smaller than 3 cm in diameter (4,5). Furthermore, RFA is less invasive and simpler to perform and requires shorter hospitalization compared with hepatic resection (6). For these reasons, RFA has been used in several medical centers as the first-line treatment option for HCC smaller than 3 cm in diameter (7).

Despite the success of the treatment for small tumors, complete ablation rates for HCC larger than 3–5 cm in diameter were reported to range from 61.3% to 82.5% (8,9). Although these results are suboptimal, they may already be outdated. Thanks to recent technical developments, such as the cluster electrode and the use of a generator that can deliver more power to tissues, the outcome of RFA for HCC larger than 3–5 cm in diameter may be more successful and, therefore, may require further investigation. In another study, early-stage HCC was defined as HCC up to 5 cm that included fewer than three nodules (3). Given that there are several treatment options for early-stage HCC, accurate knowledge regarding patient survival after RFA for HCC and the determination of significant prognostic factors that affect survival after RFA are important for optimal treatment planning.

There are several published reports regarding the long-term outcome of RFA when used as the first-line treatment option for HCC for curative purposes (3,7,10–15). These long-term results are often difficult to compare because of the heterogeneity of patient groups (eg, variable causes of cirrhosis), institutional policy regarding the treatment approach used (eg, percutaneous vs intraoperative), and the indications for additional or other treatments (eg, transarterial chemoembolization [TACE]) (7,12,14,16). Furthermore, the influence of tumor parameters, such as size and number of nodules or local recurrence, on long-term survival and recurrence-free survival after RFA in patients with early-stage HCC have been poorly evaluated to date (3,7,12,14,16–18).

The purpose of our retrospective single-institutional study was to evaluate the long-term survival after RFA as a first-line treatment option for early-stage HCC.

Advances in Knowledge

- Radiofrequency ablation (RFA) is a safe and effective first-line treatment modality in patients with early-stage hepatocellular carcinoma (HCC), as it had an estimated 5-year survival rate of 67.9%.
- Patients' overall survival was significantly affected by liver function, defined as the Child-Pugh class, a high baseline serum α-fetoprotein level, and the presence of portosystemic collaterals.
- The cumulative incidence of local tumor progression was 14.5% at 5 years; although the development of local tumor progression did not significantly affect the overall patient survival, it required more frequent interventional procedures to obtain a similar overall survival outcome.

Implications for Patient Care

- RFA can be an effective and safe first-line treatment modality for early-stage HCC, with long-term survival outcomes similar to those of surgical resection.
- As the development of local tumor progression significantly shortened the tumor-free period, more interventional procedures were required to obtain a similar overall survival outcome.

Materials and Methods

Patients

We conducted a retrospective analysis of a patient cohort entered into a prospectively collected database at a single medical institution. Our institutional review board approved this study, and written informed consent was obtained from all patients before undergoing RFA treatment. The inclusion criteria for the study patient selection were as follows: *(a)* fewer than three HCC nodules without extrahepatic metastasis or macrovascular invasion, *(b)* largest tumor size of 5 cm in diameter, *(c)* visualization of the HCC nodule at the planning ultrasonography (US) examination for RFA, *(d)* well-compensated Child-Pugh class A or B liver cirrhosis, and *(e)* prothrombin activity above 40% and a platelet count of more than 5×10^9/L. Close proximity to the colon or the hepatic hilum and abundant ascites were considered to be relative contraindications, as in this patient

Published online before print
10.1148/radiol.13130940 **Content codes:** GI IR VA

Radiology 2014; 270:900–909

Abbreviations:
AFP = α-fetoprotein
BCLC = Barcelona Clinic Liver Cancer
CI = confidence interval
HCC = hepatocellular carcinoma
IDR = intrahepatic distant recurrence
LTP = local tumor progression
RFA = radiofrequency ablation
SD = standard deviation
TACE = transarterial chemoembolization

Author contributions:
Guarantors of integrity of entire study, D.H.L., J.M.L.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, J.M.L.; clinical studies, J.M.L., J.Y.L., S.H.K., J.H.Y., Y.J.K., J.K.H., B.I.C.; statistical analysis, D.H.L.; and manuscript editing, D.H.L., J.M.L., J.Y.L., S.H.K., J.H.Y., Y.J.K., B.I.C.

Conflicts of interest are listed at the end of this article.

group, RFA could not be performed safely (3).

Between January 2006 and December 2007, 169 consecutive patients with HCC and liver cirrhosis were referred to our department for RFA as a first-line treatment. On the basis of a multidisciplinary panel discussion that included liver surgeons, abdominal radiologists, and hepatologists, seven patients were excluded for the following reasons: *(a)* largest tumor size more than 5 cm in diameter (n = 3), *(b)* more than three HCC nodules (n = 2), and *(c)* poor visualization of the HCC nodules at the planning US examination (n = 2). Therefore, the remaining 162 patients with 182 HCCs (mean size ± standard deviation [SD]; 25.9 mm ± 7.9; range; 9–50 mm) were included in our study (Fig 1). The baseline characteristics of all of the study patients are summarized in Table 1. The distribution of the number of HCC nodules was as follows: one nodule in 145 patients, two nodules in 14 patients, and three nodules in three patients. There was no significant difference in baseline patient characteristics among the patient groups according to the origin of liver cirrhosis. We also searched any visible portosystemic collateral vessels at contrast material–enhanced multiphase computed tomography (CT) performed before RFA treatment, as we hypothesized that the presence of portosystemic collaterals seen at CT could be a surrogate marker for the presence of portal hypertension. We recorded the presence or absence of portosystemic collateral vessels, and, if present, we recorded the location.

Diagnosis and Staging of HCC

Before RFA treatment, all patients underwent imaging studies, including contrast-enhanced multiphase CT and/or magnetic resonance (MR) imaging, including dynamic MR imaging. For planning of RFA treatment, US was performed before the RFA session in all patients. A physical examination and laboratory tests were performed before RFA treatment to detect any possible contraindications for RFA. The diagnosis of HCC was assigned by using the noninvasive criteria defined by the American Association for the Study of Liver Disease

Figure 1

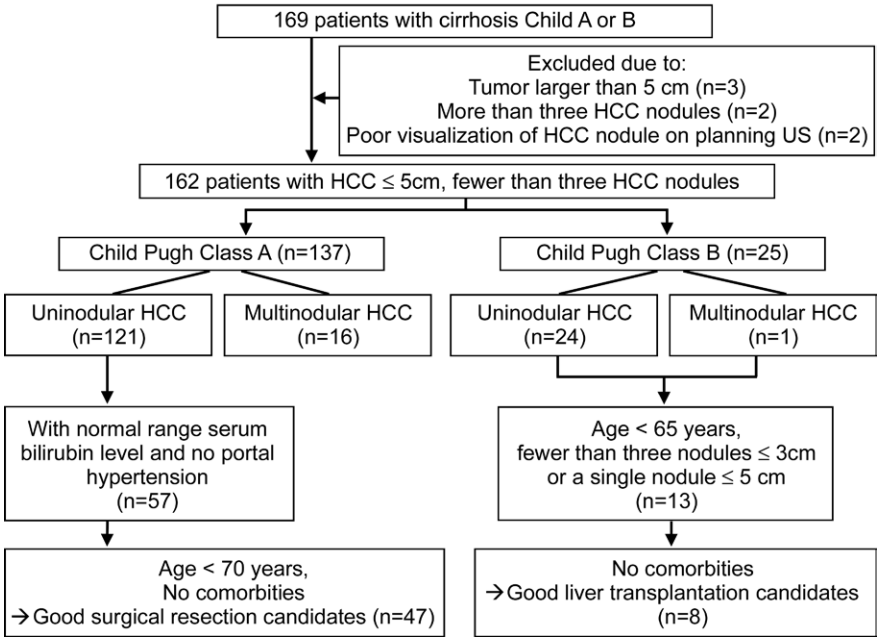

Figure 1: Flowchart summarizes the patient enrollment process in this study.

Table 1

Characteristics of 162 Patients with 182 HCCs

Characteristic	Value
Age	
Mean (y) ± SD	63.8 ± 9.8
Range (y)	35–87
No. of patients older than 70	48 (29.6)
No. of patients	
Men	115 (71.0)
Women	47 (29.0)
Origin of liver cirrhosis	
Hepatitis B virus related	118 (72.9)
Hepatitis C virus related	35 (21.6)
Alcoholism	6 (3.7)
Primary biliary cirrhosis	2 (1.2)
Coinfection of hepatitis B and C viruses	1 (0.6)
Prothrombin activity (internal normalized ratio)	
Mean ± SD	1.18 ± 0.15
Range	0.94–1.88
Serum albumin level (g/L)	
Mean ± SD	37.1 ± 4.7
Range	24–47
Total bilirubin level	
<1.5 mg/dL	132 (81.5)
>1.5 mg/dL	30 (18.5)
Serum AFP level	
<20 ng/mL	92 (56.8)
20–200 ng/mL	40 (24.7)
>200 ng/mL	30 (18.5)
Child-Pugh class	
Class A	137 (84.6)
Class B	25 (15.4)
No. of tumors	
1	145 (89.5)
>1	17 (10.5)
Tumor size	
Mean ± SD (mm)	25.9 ± 7.9
Range (mm)	9–50
No. of tumors > 30 mm	48 (29.6)
Portosystemic collaterals at CT	
No portosystemic collaterals at CT	68 (42.0)
Esophageal and periesophageal region	65 (40.1)
Gastric and perigastric region	13 (8.0)
Splenic and splenorenal shunt	9 (5.6)
Paraumbilical region	7 (4.3)

Note.—Data are numbers of patients, unless indicated otherwise. Numbers in parentheses are percentages. To convert from milligrams per deciliter (for total bilirubin levels) to millimoles per liter, multiply by 17.104. To convert from nanograms per milliliter (for serum AFP levels) to micrograms per liter, multiply by 1.0.

recommendations, which consisted of arterial hyperenhancement with washout seen on portal or delayed-phase images (n = 135) (19). Liver biopsies with pathologic confirmation were performed in the remaining 27 patients who did not meet the noninvasive diagnostic criteria.

RFA Procedures

Written informed consent was obtained from all patients prior to undergoing treatment. At the beginning of the inclusion period, all RFA procedures were performed percutaneously by using local anesthesia with moderate sedation (fentanyl citrate [Hana Pharm, Seoul, South Korea], midazolam [Hana Pharm], and ketamine [Huons; Hwaseong, Kyunggi, South Korea]) by three physicians (J.M.L., J.Y.L., and S.H.K., who had 10, 6, and 4 years of clinical experience in performing percutaneous ablation, respectively). Real-time US with a 3.5-MHz probe (IU22; Philips, Cleveland, Ohio) was chosen as the first-line guidance modality in all patients.

Assessment of Treatment Response

Immediate follow-up.—Immediately after the RFA procedures, all patients underwent contrast-enhanced, multiphase liver CT. These images were compared with those acquired before the RFA procedures to assess ablation success. Nodular areas of hypoattenuation without contrast enhancement were considered to represent necrotic or treated tissue (20). According to the immediate CT results, response to RFA was classified as complete or incomplete ablation (21,22). In cases of incomplete ablation, another session of RFA was performed immediately after CT to achieve complete ablation on the same day. In the second session of repeated RFA, US was used for first-line guidance. However, CT guidance was also used in three patients for exact tumor localization. One day after the repeat session of RFA, contrast-enhanced multiphase liver CT was performed, and assessment of ablation success was conducted in a manner similar to that of the initial session. Primary technical success was defined as complete ablation of the target tumor, and secondary technical success was defined as achievement of complete ablation of the target tumor after repeat ablation (20). Major and minor complications were assessed in accordance with the Society of Interventional Radiology guidelines (23).

Follow-up.—Follow-up examinations, including contrast-enhanced multiphase liver CT or MR imaging, liver function tests, and measurement of serum α-fetoprotein (AFP) levels, were performed in all patients 1 month after treatment. According to the 1-month follow-up CT or MR imaging results, the technical effectiveness of the RFA procedures was assessed for each patient according to the standardized terminology of the Interventional Working Group on Image-Guided Tumor Ablation (24). When persistent enhancing foci of tissue were observed at the site of the original tumor at 1-month follow-up, it was considered treatment failure (24). For these patients, other possible treatment options were considered, such as hepatic resection, liver transplantation, and TACE. Complete ablation observed on 1-month follow-up images was regarded as treatment success. In cases of treatment success, follow-up US or contrast-enhanced multiphase liver CT or MR imaging and measurement of the serum AFP level were conducted every 3 months.

Local tumor progression (LTP) and intrahepatic distant recurrence (IDR) were evaluated at 3-month intervals (24). The appearance of extrahepatic metastases was also assessed at follow-up imaging. In patients with extrahepatic metastases detected at any time during the follow-up periods, palliative surgery, systemic chemotherapy, radiation therapy, or best conservative management was considered, as needed. We also searched and recorded the total number of interventional procedures, such as RFA, TACE, and percutaneous ethanol injection therapy, in patients who experienced recurrence after performance of RFA to control recurrent tumor.

Statistical Analysis

Categorical variables were compared by using the Fisher exact test, and continuous variables were compared by using the Mann-Whitney U test for univariate analysis. A P value less than .05 was considered to indicate a significant difference. The cumulative incidence for each type of recurrence (ie, LTP, IDR, and extrahepatic metastases) was estimated by using the Kaplan-Meier method. Prognostic factors for LTP were assessed by using the univariate and multivariate Cox proportional hazards model.

Overall survival was defined as the interval between RFA treatment and death or the date of the last follow-up or the date of the most recent follow-up visit before October 31, 2012. Patients who underwent liver transplantation during the follow-up period were censored from this study at the date of their transplantation. The probability of recurrence-free survival was defined as the interval between RFA treatment and the first date of any type of HCC recurrence—that is, local and/or distant recurrence or the last follow-up date without recurrence.

Univariate and multivariate analyses were performed to determine the significant clinical and biologic parameters for prediction of overall patient survival and recurrence-free survival. Survival curves were estimated by using the Kaplan-Meier method. In addition, a univariate Cox proportional hazards model was fitted to each variable. All variables with a P value less than .05 were included in the multivariate analysis by using a stepwise Cox proportional hazards regression model to evaluate their value as independent predictors. All statistical analysis was conducted by using SPSS version 18 software (SPSS, Chicago, Ill).

Results

Technical Success

For the treatment of HCC, 169 RFA sessions were performed: one session in 155 patients and two sessions in seven patients. Primary technical success was

Figure 2

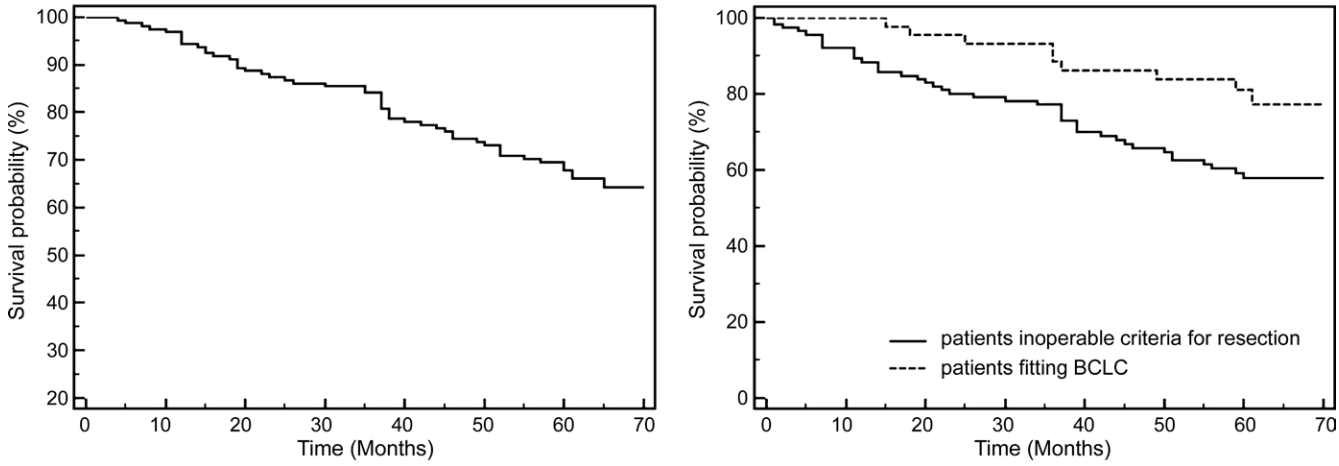

Figure 2: **(a)** Graph shows Kaplan-Meier overall survival estimation for 162 patients who underwent RFA as the first-line treatment for HCC. **(b)** Graph shows Kaplan-Meier estimation of overall survival for 47 patients who met BCLC criteria for resection, compared with 115 patients who did not ($P = .021$). The criteria were patients with a single HCC and a normal serum bilirubin level (<1.5 mg/dL [<25.6 μmol/L]), Child-Pugh class A cirrhosis, and no significant portal hypertension.

obtained in 96.2% (175 of 182) of the HCCs. Seven nodules required a repeat RFA session owing to incomplete ablation seen at contrast-enhanced multiphase liver CT performed immediately after the first RFA session. Secondary technical success was achieved for all seven HCCs. Treatment success at 1-month follow-up imaging after RFA treatment was achieved in 156 of 162 patients (96.3%). Treatment failure was observed in six of 182 nodules (3.3%), including three nodules larger than 3 cm in diameter, two nodules associated with a serum AFP level higher than 200 ng/mL, and one nodule located in an area difficult to ablate (ie, closely abutting the right hepatic vein). Among the six patients who had treatment failure after RFA, one underwent liver transplantation, and one underwent hepatic resection. The remaining four patients were treated with TACE.

Survival and Recurrence

Overall survival.—The mean follow-up period ± SD was 50.3 months ± 19.9; the median follow-up was 49.0 months. Two patients were lost to follow-up after 6 and 7 months, respectively, and were censored at that point. During the follow-up period, 53 of 162 patients (32.7%) died. Among those 53 patients, 41 deaths (77%) were related to HCC progression; eight (15%) to cirrhosis-related complications, such as variceal bleeding; and four (8%) to causes unrelated to liver disease (eg, two to pneumonia, one to stroke, and one to septic shock after another surgery [low anterior resection for sigmoid colon cancer, which was identified 27 months after RFA for HCC]). Eleven of 162 patients (6.8%) underwent liver transplantation after a mean follow-up of 28.3 months ± 17.2 and a median follow-up of 24.0 months, respectively. The reasons for liver transplantation were HCC recurrence in nine patients and liver failure in two patients.

The estimated overall 1-, 3-, and 5-year survival rates after RFA were 94.4%, 84.1%, and 67.9%, respectively (Fig 2a). The factors used to predict overall survival are summarized in Table 2. At univariate analysis, the serum albumin level ($P = .022$), Child-Pugh class ($P = .015$), serum AFP level ($P < .001$), and presence of portosystemic collaterals seen on CT images ($P = .003$) were significantly associated with overall patient survival. When comparing the 47 patients who met the criteria for hepatic resection according to Barcelona Clinic Liver Cancer (BCLC) staging with those considered unsuitable for resection at the outset, the estimated 1-, 3-, and 5-year overall survival rates were 100% versus 95.6%, 93.5% versus 80.2%, and 81.8% versus 61.8%, respectively, and were thus significantly different ($P = .021$) (Fig 2b). LTP was not significantly associated with overall survival ($P = .141$). Tumor size and the number of tumor nodules also did not significantly affect the overall survival rate ($P = .339$ and $P = .119$, respectively). At multivariate analysis by using the Cox proportional hazards model, the serum AFP level ($P < .001$), Child-Pugh class ($P = .011$), and presence of portosystemic collaterals seen at CT ($P = .025$) were found to be independent significant predictors of overall patient survival.

Recurrence of HCC and recurrence-free survival.—Of the 156 patients with successful treatment, LTP was found at follow-up imaging in 21 patients (13.5%) after 2 to 29 months (mean, 13.0 months; median, 14.0 months). The cumulative incidence of LTP was estimated as 5.9%, 14.5%, and 14.5% at 1, 3, and 5 years, respectively. The mean estimate of LTP-free survival was 66.9 months (95% confidence interval [CI]: 63.3, 70.5). At univariate analysis,

tumor size (P = .011) and prothrombin activity (P = .047) were significant predictive factors for developing LTP (Table 3). However, tumor size (P = .007) was the only significant predictive factor for developing LTP seen at multivariate analysis. Among the 21 patients with LTP, eight were treated successfully with repeat RFA, two underwent liver transplantation, and one underwent hepatic resection. The remaining 10 patients were treated with TACE.

One hundred seven of 162 patients (66.0%) had IDR, which was identified 1 month to 64 months after RFA (mean, 20.5 months; median, 16.0 months), and the treatment modalities used for the initial IDR in these patients were as follows: liver transplantation in six patients, repeat RFA in 33 patients, percutaneous ethanol injection therapy in 21 patients, TACE in 46 patients, and best conservative management in one patient. The cumulative incidence of IDR was estimated as 26.3%, 57.6%, and 68.6% at 1, 3, and 5 years, respectively. The mean and median estimates of the IDR-free survival were 37.5 months (95% CI: 33.1, 41.9) and 27.0 months (95% CI: 20.3, 33.8).

During the follow-up period, extrahepatic metastases developed in 19 of 162 patients (11.7%) 3 to 54 months after RFA treatment (mean, 23.9 months; median, 25.0 months), and the location of the initial extrahepatic metastases was as follows: lung (n = 8), bone (n = 3), lymph nodes (n = 4), adrenal gland (n = 2), brain (n = 1), and chest wall (n = 1). Among these patients, seven were treated with systemic chemotherapy, seven with radiation therapy, and five with best conservative management. The cumulative incidence of extrahepatic metastases was estimated as 4.4%, 9.4%, and 13.6% at 1, 3, and 5 years, respectively. The mean estimate of extrahepatic metastases–free survival was 89.0 months (95% CI: 84.8, 93.3).

The estimated 1-, 3-, and 5-year recurrence-free survival rates were 72.6%, 37.4%, and 25.9%, respectively (Fig 3a). Estimates of the mean and median recurrence-free survival were 34.2 months (95% CI: 29.8, 38.5) and 23.0 months (95% CI: 17.5, 28.5), respectively. Factors associated with recurrence-free survival are summarized in Table 4. In univariate analysis, Child-Pugh class (P = .006), serum AFP level (P = .002), and LTP (P < .001) were significantly associated with recurrence-free survival. In multivariate analysis with the Cox proportional hazards model, serum AFP level (P < .001), Child-Pugh class (P = .009), and LTP (P < .001) were significant predictive factors for recurrence-free survival. In patients without LTP, estimated 1-, 3-, and 5-year recurrence-free survival rates were 74.4%, 44.4%, and 30.4%, respectively, and estimates of the mean and median recurrence-free survival were 37.7 months (95% CI: 33.0, 42.5) and 28.0 months (95% CI: 18.8,

Table 2

Cox Survival Analysis of the Predictors for Overall Survival in 162 Patients with 182 HCCs after RFA

	Univariate Analysis			Multivariate Analysis		
Characteristic	Relative Risk	95% CI	*P* Value	Relative Risk	95% CI	*P* Value
Male sex	0.77	0.43, 1.36	.361			
Age (per 1 year)	1.00	0.97, 1.03	.895			
No. of tumors (>1)	1.77	0.86, 3.64	.119			
Total bilirubin level (mg/dL)	0.99	0.84, 1.18	.946			
Serum albumin level (g/L)	0.52	0.30, 0.91	.022	0.74	0.31, 1.78	.730
Prothrombin activity (INR)	3.37	0.67, 17.0	.141			
Child-Pugh class B	2.26	1.18, 4.34	.015	2.43	1.22, 4.88	.011
Serum AFP level (ng/mL)	1.01	1.01, 1.01	<.001	1.01	1.01, 1.01	<.001
Portosystemic collaterals seen at CT	2.54	1.38, 4.69	.003	2.15	1.10, 4.21	.025
Tumor size (cm)	1.19	0.83, 1.71	.339			
LTP	2.16	0.77, 6.04	.141			
Appropriate for resection*	0.43	0.21, 0.88	.021	0.88	0.30, 2.56	.813

Note.—Relative risk for AFP level is per 100 units. Numbers in parentheses are percentages. To convert from milligrams per deciliter (for total bilirubin level) to millimoles per liter, multiply by 17.104. To convert from nanograms per milliliter (for serum AFP level) to micrograms per liter, multiply by 1.0. INR = international normalized ratio.

* According to BCLC criteria.

Table 3

Cox Analysis of the Predictors for LTP in 156 Patients with 176 HCCs after RFA

	Univariate Analysis			Multivariate Analysis		
Characteristic	Relative Risk	95% CI	*P* Value	Relative Risk	95% CI	*P* Value
Male sex	1.22	0.49, 3.03	.667			
Age (per 1 year)	0.99	0.95, 1.04	.701			
No. of tumors (>1)	0.97	0.23, 4.15	.963			
Total bilirubin level (mg/dL)	1.03	0.82, 1.29	.803			
Serum albumin level (g/L)	1.66	0.62, 4.45	.318			
Prothrombin activity (INR)	12.2	1.03, 142.8	.047	15.0	0.94, 172.0	.078
Child-Pugh class B	1.99	0.75, 5.24	.166			
Serum AFP level (ng/mL)	1.00	0.99, 1.01	.606			
Tumor size (cm)	2.04	1.18, 3.54	.011	2.13	1.23, 3.71	.007

Note.—Relative risk for AFP level is per 100 units. To convert from milligrams per deciliter (for total bilirubin level) to millimoles per liter, multiply by 17.104. To convert from nanograms per milliliter (for serum AFP level) to micrograms per liter, multiply by 1.0. INR = international normalized ratio.

Figure 3

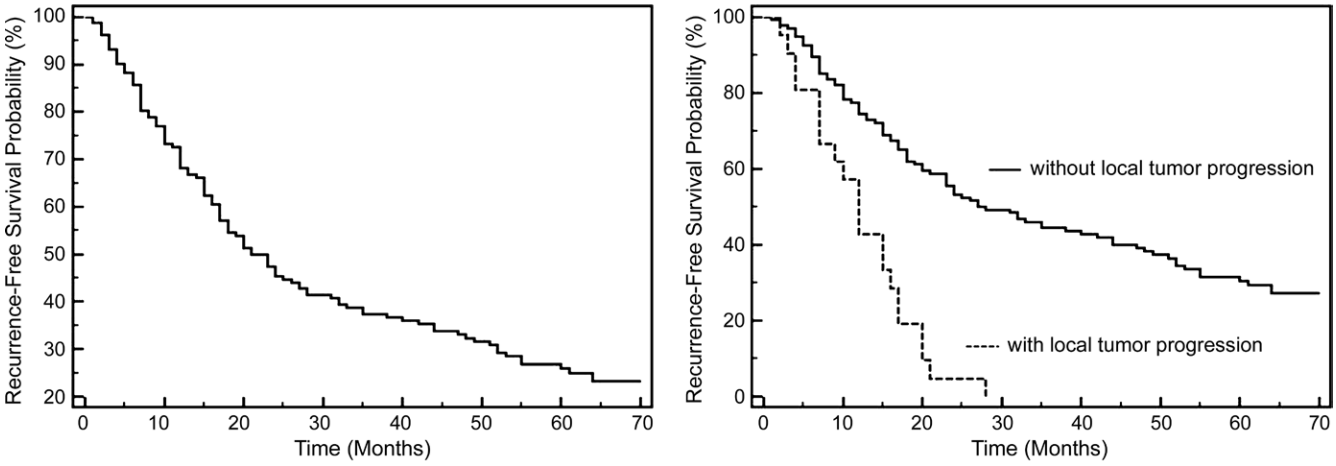

Figure 3: **(a)** Graph shows Kaplan-Meier estimation of recurrence-free survival for 156 patients for whom complete HCC ablation (ie, treatment success) was achieved with RFA. **(b)** Graph shows Kaplan-Meier estimation of recurrence-free survival for 135 patients without LTP compared with 21 patients with LTP ($P < .001$).

Table 4

Cox Survival Analysis of the Predictors for Recurrence-free Survival in 156 Patients with 176 HCCs after Successful RFA Treatment

	Univariate Analysis			Multivariate Analysis		
Characteristic	Relative Risk	95% CI	*P* Value	Relative Risk	95% CI	*P* Value
Male sex	0.82	0.54, 1.23	.332			
Age (per 1 year)	1.01	0.99, 1.03	.594			
No. of tumors (>1)	1.50	0.86, 2.63	.155			
Total bilirubin level (mg/dL)	1.02	0.93, 1.11	.716			
Serum albumin level (g/L)	0.84	0.56, 1.26	.394			
Prothrombin activity (INR)	2.72	0.80, 9.27	.110			
Child-Pugh class B	1.93	1.21, 3.10	.006	1.89	1.17, 3.04	.009
Serum AFP level (ng/mL)	1.01	1.01, 1.01	.002	1.01	1.01, 1.01	<.001
Portosystemic collaterals seen at CT	1.33	0.92, 1.93	.135			
Tumor size (cm)	1.09	0.86, 1.39	.470			
LTP	3.57	2.15, 5.91	<.001	3.61	2.16, 6.03	<.001

Note.—Relative risk for AFP level is per 100 units. To convert from milligrams per deciliter (for total bilirubin level) to millimoles per liter, multiply by 17.104. To convert from nanograms per milliliter (for serum AFP level) to micrograms per liter, multiply by 1.0. INR = international normalized ratio.

37.2), respectively. In patients with LTP, however, the estimated 1-, 3-, and 5-year recurrence-free survival rates were 57.1%, 0%, and 0%, respectively, and estimates of the mean and median recurrence-free survival were 12.3 months (95% CI: 9.3, 15.3) and 12.0 months (95% CI: 9.0, 15.0), respectively. This difference was significant ($P < .001$) (Fig 3b).

During the follow-up period, 417 interventional procedures (one hepatic resection, 47 sessions of RFA, 65 sessions of percutaneous ethanol injection therapy, and 304 sessions of TACE), were conducted in 115 patients with any type of recurrence to control the recurrent tumor. For the 21 patients with LTP, the mean number of required interventional procedures was 5.1 sessions ± 3.7 (range, 1–15). For the 141 patients without LTP, however, the mean number of necessary interventional procedures was 2.2 sessions ± 2.9 (range, 0–13), and this difference was significant ($P < .001$).

RFA Complications

Overall, 169 RFA sessions were performed in the 162 study patients, including seven sessions for treatment of incomplete ablation. There was no procedure-related death. Major complications were observed in five patients (3.1%) (bile duct injuries [$n = 2$], needle-tract seeding [$n = 1$], colon perforation [$n = 1$], and patient confusion [$n = 1$]). One patient experienced bile duct injury from RFA treatment. Fistula formation to the gallbladder, combined with gallbladder injury, was also suspected in this patient, who was treated with surgical correction (laparoscopic cholecystectomy and drainage of fluid). Another patient developed cholangitis associated with a treatment-related bile duct injury. The patient fully recovered after a course of broad-spectrum antibiotics. One patient developed a seeding nodule in the needle tract 14 months after RFA treatment for a large (35-mm) subdiaphragmatic HCC. This patient also had extrahepatic metastases

in the lung, which were treated with systemic chemotherapy, although the patient died because of HCC progression 21 months after RFA treatment. One patient had colon injury adjacent to the ablation zone, as well as abscess formation, both of which were treated with colon resection. After surgery, the patient recovered completely. One patient experienced confusion of unknown cause after RFA treatment and fully recovered with conservative management.

Discussion

In our study, the estimated overall 1-, 3-, and 5-year survival rates after RFA were 94.4%, 84.1%, and 67.9%, respectively, and our results are comparable to those seen in the literature (4,10,11,25,26). In addition, our results regarding the estimated 5-year survival rate were similar to those in previous surgical studies in which the reported 5-year survival rates were between 34.4% and 70.0% (27–33). Furthermore, if we analyze the results of RFA in 47 patients who met the BCLC criteria for resection, the 5-year overall survival rate reached 81.8%, which is even better than that reported in other studies that included patients who were treated with either RFA or hepatic resection (3,4,11,26,34).

Despite the positive survival results, when RFA was compared with hepatic resection as the initial treatment of HCC, RFA had some intrinsic drawbacks. First, tumors located near the major hepatic vessels are not easy to ablate completely, owing to a heat-sink effect. In our study, one of the six treatment failures developed in a tumor with close proximity to the right hepatic vein. Second, the risk of LTP of HCC was higher for RFA than for hepatic resection (35). In our study, however, the major complication rate was 3.1% (five of 162 patients), and this result coincides with the findings of other studies in which low complication rates of 0%–6.1% were reported (3,11,14,15). Indeed, all patients with major complications recovered fully, without any serious adverse sequelae, except for one case of a seeding nodule in the needle tract. For hepatic resection, the reported morbidity rates ranged from 38% to 47% (36–38). Considering these results, we believe that the merits of RFA compared with those of hepatic resection can compensate for its drawbacks and could explain our results, in which we showed an overall survival rate similar to that of hepatic resection.

Our results also show that the significant predictive factors for poor overall survival were Child-Pugh class B (relative risk = 2.43; 95% CI: 1.21, 4.88; $P = .011$), serum AFP level (relative risk per 100 units = 1.01; 95% CI: 1.01, 1.01; $P < .001$), and the presence of portosystemic collaterals (relative risk = 2.15; 95% CI: 1.10, 4.21; $P = .025$). Not surprisingly, a high serum AFP level was a significant predictor for poor overall survival and a high rate of recurrence after RFA, and this result is well correlated with those seen in previous studies (3,7,10,39).

In our study, Child-Pugh class B was another significant predictor for poor overall survival and a high rate of recurrence and corroborates the findings of previous studies (7,10,12–14,16,40,41). The severity of the underlying liver disease may also be a risk factor for the development and recurrence of HCC and thus reinforces the importance and the role of liver function in hepatocarcinogenesis (3). Furthermore, the presence of portosystemic collateral vessels seen on pretreatment CT images, such as esophageal varices, was also a significant predictor for poor overall survival, even after adjusting the Child-Pugh class in the multivariate Cox model. The presence of these portosystemic collaterals is an obvious sign of portal hypertension (19), and multidetector CT can be used to evaluate the presence of portosystemic collaterals in patients with liver cirrhosis (42–44). With regard to hepatic resection, the presence of portal hypertension is a well-known predictive factor for poor survival, regardless of the Child-Pugh class (19,34,45). Our study showed the significance of the effect of portal hypertension on the overall survival in patients with HCC who were treated with RFA, and it was similar to the results seen with hepatic resection (19,34,45). In our study, however, the number and size of the HCC nodules treated with RFA did not significantly affect either the overall survival or the recurrence-free survival, and this also correlated well with the results seen in previous studies (3,7,25).

In our study, the estimated 1-, 3-, and 5-year recurrence-free survival rates were 72.6%, 37.4%, and 25.9%, respectively. LTP was identified in 21 of 156 patients (13.5%). This rate is similar to that seen in other studies, which has been reported to be approximately 10% 3 years after RFA treatment (7,14). Furthermore, tumor size was the only significant predictor for developing LTP, which corroborates reports by others (25), and it also did not significantly affect the overall survival, as reported it by Lam et al (16). However, the recurrence-free survival rate was significantly lower in patients with LTP. The estimated median of recurrence-free survival was 28.0 months in patients without LTP and 12.0 months in patients with LTP. Therefore, the development of LTP significantly shortened the tumor-free periods. Because of the early tumor recurrence in patients with LTP, the required number of interventional procedures for controlling recurrent tumor and maintaining the survival status was significantly higher in patients with LTP. Patients with LTP therefore required approximately three more interventional procedures than those in patients who did not have LTP to obtain a similar overall survival outcome. For this purpose, a carefully performed ablation procedure with a sufficient safety margin might be required. In addition, a larger tumor had the tendency to develop more LTP. Therefore, more meticulous RFA procedures may be needed for the treatment of large tumors.

Our study has some limitations. First, as it was a retrospective study, there might be the potential risk for selection bias. Second, as there were 11 of 162 patients (6.8%) who

underwent liver transplantation during the follow-up period, this might have favorably affected the survival outcome in this study. To avoid this potential bias, however, all patients who underwent liver transplantation were censored at the date of transplantation. Moreover, the substantially long waiting times after RFA for transplantation (mean, 28.3 months ± 17.2; median, 24.0 months) support the appropriateness of RFA as a bridging treatment for liver transplantation (3,46).

In conclusion, RFA is a safe and effective first-line treatment modality for patients with early-stage HCC, and the 5-year survival rate in our study (67.9%) was comparable to that of hepatic resection. Therefore, the use of RFA for early-stage HCC as a first-line treatment modality can be justified even for patients who were usually considered good candidates for hepatic resection, especially regarding its markedly lower rate of procedure-related mortality and morbidity and its higher repeatability in case of tumor recurrence. The overall survival rates were significantly affected by liver function, defined as Child-Pugh class, high baseline serum AFP level, and presence of portosystemic collaterals. Although the development of LTP did not significantly affect overall patient survival, it significantly shortened the tumor-free period and therefore required more interventional procedures to obtain a similar overall survival outcome.

Disclosures of Conflicts of Interest: D.H.L. No relevant conflicts of interest to disclose. **J.M.L.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: author received money for a board membership from Bayer Healthcare; grants from Bayer Healthcare, GE Healthcare, and Star-Med; and payment for lectures from Bayer Healthcare. Other relationships: author received payment for travel/accommodations/meeting expenses from Bayer Healthcare. **J.Y.L.** No relevant conflicts of interest to disclose. **S.H.K.** No relevant conflicts of interest to disclose. **J.H.Y.** No relevant conflicts of interest to disclose. **Y.J.K.** No relevant conflicts of interest to disclose. **J.K.H.** No relevant conflicts of interest to disclose. **B.I.C.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: institution received a grant from Samsung Electronics. Other relationships: none to disclose.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001;94(2):153–156.
2. Mazzaferro V. Results of liver transplantation: with or without Milan criteria? Liver Transpl 2007;13(11 Suppl 2):S44–S47.
3. 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(5):1475–1483.
4. 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(3):321–328.
5. Lü MD, Kuang M, Liang LJ, et al. Surgical resection versus percutaneous thermal ablation for early-stage hepatocellular carcinoma: a randomized clinical trial [in Chinese]. Zhonghua Yi Xue Za Zhi 2006;86(12):801–805.
6. Kuang M, Xie XY, Huang C, et al. Long-term outcome of percutaneous ablation in very early-stage hepatocellular carcinoma. J Gastrointest Surg 2011;15(12):2165–2171.
7. 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(3):684–692.
8. Lupo L, Panzera P, Giannelli G, Memeo M, Gentile A, Memeo V. Single hepatocellular carcinoma ranging from 3 to 5 cm: radiofrequency ablation or resection? HPB (Oxford) 2007;9(6):429–434.
9. Harrison LE, Koneru B, Baramipour P, et al. Locoregional recurrences are frequent after radiofrequency ablation for hepatocellular carcinoma. J Am Coll Surg 2003;197(5):759–764.
10. Shiina S, Tateishi R, Arano T, et al. Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. Am J Gastroenterol 2012;107(4):569–577; quiz 578.
11. 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(1):82–89.
12. Tateishi R, Shiina S, Teratani T, et al. Percutaneous radiofrequency ablation for hepatocellular carcinoma: an analysis of 1000 cases. Cancer 2005;103(6):1201–1209.
13. 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(8):616–628.
14. 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(3):961–967.
15. Buscarini L, Buscarini E, Di Stasi M, Vallisa D, Quaretti P, Rocca A. Percutaneous radiofrequency ablation of small hepatocellular carcinoma: long-term results. Eur Radiol 2001;11(6):914–921.
16. Lam VW, Ng KK, Chok KS, et al. Risk factors and prognostic factors of local recurrence after radiofrequency ablation of hepatocellular carcinoma. J Am Coll Surg 2008;207(1):20–29.
17. Ng KK, Poon RT, Lo CM, Yuen J, Tso WK, Fan ST. Analysis of recurrence pattern and its influence on survival outcome after radiofrequency ablation of hepatocellular carcinoma. J Gastrointest Surg 2008;12(1):183–191.
18. Guglielmi A, Ruzzenente A, Sandri M, et al. Radio frequency ablation for hepatocellular carcinoma in cirrhotic patients: prognostic factors for survival. J Gastrointest Surg 2007;11(2):143–149.
19. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005;42(5):1208–1236.
20. Goldberg SN, Grassi CJ, Cardella JF, et al. Image-guided tumor ablation: standardization of terminology and reporting criteria. J Vasc Interv Radiol 2009;20(7 Suppl):S377–S390.
21. Lee J, Lee JM, Yoon JH, et al. Percutaneous radiofrequency ablation with multiple electrodes for medium-sized hepatocellular carcinomas. Korean J Radiol 2012;13(1):34–43.
22. Nakazawa T, Kokubu S, Shibuya A, et al. Radiofrequency ablation of hepatocellular carcinoma: correlation between local tumor progression after ablation and ablative margin. AJR Am J Roentgenol 2007;188(2):480–488.
23. Cardella JF, Kundu S, Miller DL, Millward SF, Sacks D, Society of Interventional Radiology. Society of Interventional Radiology clinical practice guidelines. J Vasc Interv Radiol 2009;20(7 Suppl):S189–S191.
24. Goldberg SN, Grassi CJ, Cardella JF, et al. Image-guided tumor ablation: standardization of terminology and reporting criteria. Radiology 2005;235(3):728–739.

25. Kim YS, Lim HK, Rhim H, et al. Ten-year outcomes of percutaneous radiofrequency ablation as first-line therapy of early hepatocellular carcinoma: analysis of prognostic factors. J Hepatol 2013;58(1):89–97.

26. Takahashi S, Kudo M, Chung H, et al. Outcomes of nontransplant potentially curative therapy for early-stage hepatocellular carcinoma in Child-Pugh stage A cirrhosis is comparable with liver transplantation. Dig Dis 2007;25(4):303–309.

27. 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(7):1832–1842.

28. Park YK, Kim BW, Wang HJ, Kim MW. Hepatic resection for hepatocellular carcinoma meeting Milan criteria in Child-Turcotte-Pugh class a patients with cirrhosis. Transplant Proc 2009;41(5):1691–1697.

29. 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(6):1560–1571.

30. 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(4): 287–295.

31. Nuzzo G, Giuliante F, Gauzolino R, Vellone M, Ardito F, Giovannini I. Liver resections for hepatocellular carcinoma in chronic liver disease: experience in an Italian centre. Eur J Surg Oncol 2007;33(8):1014–1018.

32. Shimada K, Sano T, Sakamoto Y, Kosuge T. A long-term follow-up and management study of hepatocellular carcinoma patients surviving for 10 years or longer after curative hepatectomy. Cancer 2005;104(9):1939–1947.

33. 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(4):381–388.

34. Bruix J, Castells A, Bosch J, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology 1996;111(4):1018–1022.

35. Choi D, Lim HK, Kim MJ, et al. Recurrent hepatocellular carcinoma: percutaneous radiofrequency ablation after hepatectomy. Radiology 2004;230(1):135–141.

36. 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(4):580–587.

37. Capussotti L, Muratore A, Amisano M, Polastri R, Bouzari H, Massucco P. Liver resection for hepatocellular carcinoma on cirrhosis: analysis of mortality, morbidity and survival—a European single center experience. Eur J Surg Oncol 2005;31(9):986–993.

38. Imamura H, Seyama Y, Kokudo N, et al. One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg 2003;138(11): 1198–1206; discussion 1206.

39. Miyaaki H, Nakashima O, Kurogi M, Eguchi K, Kojiro M. Lens culinaris agglutinin-reactive alpha-fetoprotein and protein induced by vitamin K absence II are potential indicators of a poor prognosis: a histopathological study of surgically resected hepatocellular carcinoma. J Gastroenterol 2007; 42(12):962–968.

40. Xu HX, Lu MD, Xie XY, et al. Prognostic factors for long-term outcome after percutaneous thermal ablation for hepatocellular carcinoma: a survival analysis of 137 consecutive patients. Clin Radiol 2005;60(9):1018–1025.

41. Guglielmi A, Ruzzenente A, Battocchia A, Tonon A, Fracastoro G, Cordiano C. Radiofrequency ablation of hepatocellular carcinoma in cirrhotic patients. Hepatogastroenterology 2003;50(50):480–484.

42. Kim SH, Lee JM, Choi JY, et al. Changes of portosystemic collaterals and splenic volume on CT after liver transplantation and factors influencing those changes. AJR Am J Roentgenol 2008;191(1):W8–W16.

43. Kang HK, Jeong YY, Choi JH, et al. Three-dimensional multi-detector row CT portal venography in the evaluation of portosystemic collateral vessels in liver cirrhosis. RadioGraphics 2002;22(5):1053–1061.

44. Cho KC, Patel YD, Wachsberg RH, Seeff J. Varices in portal hypertension: evaluation with CT. RadioGraphics 1995;15(3):609–622.

45. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999;30(6): 1434–1440.

46. Mazzaferro V, Battiston C, Perrone S, et al. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. Ann Surg 2004;240(5):900–909.