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Hepatic and Pancreatic Tumors

Combined Hepatectomy and Radiofrequency Ablation for Multifocal Hepatocellular Carcinomas: Long-term Follow-up Results and Prognostic Factors

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Background: For multifocal hepatocellular carcinomas (HCCs) that are untreatable with resection only, locoregional therapies added to hepatectomy have been introduced. However, some preliminary reports have documented average survival results and relatively high complication rates. We evaluated the long-term survival results and safety of combined hepatectomy and radiofrequency ablation (RFA) in patients with HCCs and assessed the prognostic factors affecting their survival.

Methods: A total of 53 patients who had 148 HCCs in their livers underwent hepatectomy combined with ultrasound-guided intraoperative RFA. The mean diameter of the 82 resected tumors was 4.8 cm (range 1.3–21.0 cm) and that of 66 ablated tumors was 1.5 cm (range 0.8–3.5 cm). We evaluated the primary effectiveness rates, survival rates, and complications. In addition, we assessed the prognostic factors associated with the survival rates using Cox proportional hazard models.

Results: The primary effectiveness rate of RFA was 98% (65 of 66). Local tumor progression was observed in two (3%) ablation zones of 65 tumors with complete primary effectiveness. The cumulative survival rates at 1, 2, 3, 4, and 5 years were 87, 83, 80, 68, and 55%, respectively. Patients with smaller resected tumors (≤5 cm) demonstrated better survival results ($P = 0.004$). No procedure-related deaths occurred. We observed hepatectomy-related complications in 4 patients (8%, 4 of 53) and an RFA-related complication in 1 patient (2%, 1 of 53).

Conclusions: Combined hepatectomy and RFA is an effective and safe treatment modality for multifocal HCCs. Resected tumor size was a significant prognostic predictor of long-term survival.

Key Words: Hepatocellular Carcinoma—Hepatectomy—Radiofrequency Ablation—Combined treatment—Survival—Prognostic Factors.

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Although hepatectomy has long been the best treatment option for patients with hepatocellular carcinomas (HCCs), the majority of such patients are

not candidates for curative resection because of inadequate functional hepatic reserve, multifocality, or both.[1–3] In an attempt to provide treatment for the overwhelming number who are not candidates for hepatic resection only, some possible treatment approaches to potentially curing HCCs have been explored.[4–6] Hepatectomy in combination with radiofrequency ablation (RFA) for multifocal hepatic tumors has recently been introduced.[7–10] Combining hepatectomy with RFA permits the surgeon to remove larger tumors while simultaneously ablating any smaller residual tumors. Using the combination treatment, more patients might become candidates for hepatic resection, and all sonographically detectable small tumors can be completely eradicated while preserving hepatic reserve. The purpose of this study was to evaluate the long-term survival results and complications of this combined treatment in patients with multifocal HCCs because this had not yet been established; in addition we assessed the prognostic factors affecting their survival.

SUBJECTS AND METHODS

Patients

Between April 1999 and November 2006, 1,428 patients with nodular HCCs underwent ultrasound (US)-guided percutaneous RFA in our institution, and 211 patients with HCCs received intraoperative RFA. Of these, a total of 67 patients who underwent concurrent intraoperative RFA and hepatectomy for multifocal HCCs were included in the study. Of the 67, we excluded 14 patients with a previous history of treatment with transcatheter arterial chemoembolization (TACE) ($n = 10$), RFA ($n = 1$), or both ($n = 3$). The remaining 53, who had 148 HCCs treated with combined hepatectomy and RFA as the first-line treatment for curative purposes, comprised the final retrospective study population. There were 42 men and 11 women (age range, 28–71 years; median, 53 years; mean, 53.7 years). This study was approved by our institutional review board, which waived the requirement for patient informed consent.

Hepatectomy

All patients were deemed to have unresectable HCCs on the basis of tumor multifocality, tumor proximity to major vascular structures precluding a margin-negative resection, or the presence of cirrhosis with functional hepatic reserve inadequate to tolerate the necessary hepatic resection. In our hospital, the indocyanine green dye (ICG) retention test is considered to be among the important criteria to assess the resectability of hepatic tumors. Generally, when ICG-R15 (ICG retention rate 15 min after injection of a 0.5-mg/kg dose) is 10% or less, lobectomy is permitted. All patients met the following criteria for combination treatment with hepatectomy and RFA: one or more (up to three) small (≤ 4 cm in maximum diameter) HCCs eligible for intraoperative RFA are expected to remain after hepatectomy, the absence of portal venous thrombosis and extrahepatic metastases on either CT or MR imaging, and Child-Pugh class B liver cirrhosis or better hepatic function reserve. No patients underwent portal vein embolization prior to the hepatectomy. The hepatectomy procedures performed on the patients consisted of an extended right lobectomy in 1 patient, right lobectomy in 6, left lobectomy in 2, left lateral segmentectomy in 13, other bisegmentectomy (resection of two adjacent segments by Couinaud's segmentation) in 4, unisegmentectomy in 11, and subsegmentectomy in 16. The procedures were performed by one of three experienced surgeons according to the usual methods. The median operative time including RFA was 4.4 h (range, 2.2–6.8 h), with a median amount of estimated blood loss of 0.5 l (range, 0.2–1.1 l).

The resected HCCs were sectioned, and the sizes of the masses were assessed macroscopically. The mean diameter of the largest tumor was 4.8 cm (range, 1.3–21.0 cm; median, 3.7 cm; standard deviation, 3.62 cm). An experienced pathologist performed a microscopic evaluation and histopathological grading of the HCCs based on the Edmondson-Steiner grading system. There were 6 (11%, 6 of 53) grade-I HCCs, 42 (79%) grade II, 4 (8%) grade III, and 1 (2%) grade IV. Both presence of 90% or greater encapsulation of the HCCs and microvascular invasion of tumor cells were assessed. Multiple (up to six) tumors were found in 13 pathology specimens. Of these, 4 were considered multicentric HCCs, and 9 were categorized as metastatic tumors. According to the TNM classification of the International Union Against Cancer,[11] the T stages of HCCs after surgery were T2 in 8 (15%, 7 of 53) patients, T3 in 20 (38%), and T4 in 25 (47%). In 28 (53%, 28 of 53) patients, liver cirrhosis was present as a result of hepatitis B ($n = 22$), hepatitis C ($n = 3$), or an unknown etiology ($n = 3$); 22 patients had chronic hepatitis B without cirrhosis; and the remaining 3 patients had chronic hepatitis C without cirrhosis. Before combined hepatectomy and RFA, 44 had Child-Pugh class A cirrhosis or chronic hepatitis, and 6 patients had Child-Pugh class B cirrhosis.

Radiofrequency ablation

For one or more (up to three) of 59 small (≤ 4 cm in maximum diameter) unresectable HCCs diagnosed using CT or MR imaging, or both, the intraoperative RFA procedures were performed during one operation together with hepatectomy. In 5 patients, 7 other small tumors newly suspected as HCCs during intraoperative US before RFA were additionally treated with RFA. Consequently, 66 tumors were ablated. In most patients (79%, 42 of 53), a single tumor was ablated, while 2 tumors were treated in 9 (17%) patients, and 3 tumors were ablated in 2 (4%). In 29 (55%, 29 of 53) patients, at least 1 of the ablated tumors was located in the opposite lobe with resection (i.e., bilobar tumors). The largest ablated tumor in each patient measured 0.8–3.5 cm at maximum diameter (mean, 1.5 cm; median, 1.3 cm; standard deviation, 0.65 cm) on intraoperative US. The diagnosis of HCC was confirmed by means of needle biopsy in 7 tumors of 7 patients. Of the remaining 46 patients, 52 tumors were considered to be HCCs on the basis of imaging findings[12–15].

All RFA procedures were performed under real-time US guidance by one of five experienced radiologists. In 9 patients, we used an expandable electrode system (RF 2000 system; RadioTherapeutics Corporation, Mountain View, Cal) containing a 100-watt generator. In the remaining 44 patients, we used an internally cooled electrode system (Cool-tip; Valleylab; Boulder, Col). Our strategy during RFA was to include a peripheral margin of 0.5–1.0 cm of normal hepatic parenchyma surrounding the tumor as well as the entire tumor itself, regardless of the RF device used or the size of the tumor.[16,17]

Follow-up

All patients underwent follow-up, four-phase helical CT scans (both unenhanced and contrast-enhanced three-phase CT) 1 month after operation. These scans were used as a baseline study to evaluate therapeutic efficacy. In cases of complete ablation of the tumor with no appearance of a new tumor in other sites of the liver at 1-month follow-up CT, subsequent contrast-enhanced three-phase helical CT examinations were repeated every 3 months. Follow-up CT examinations were performed using one of five helical scanners (HiSpeed CT/i, LightSpeed QX/i, LightSpeed Ultra, LightSpeed 16, GE healthcare, Milwaukee, Wis; Brilliance 40, Philips Medical Systems, Best, The Netherlands).

Assessment of treatment efficacy and complications

We evaluated the primary (technique) effectiveness in terms of residual unablated tumors on 1-month follow-up CT scans.[17] Residual unablated tumors were defined as irregular peripheral-enhancing foci in the ablation zones.[17,18] Local tumor progression was defined when a later follow-up CT demonstrated any growing or enhancing tumor in the ablation zone, where complete primary effectiveness had been accomplished (i.e., no evidence of residual tumor).[17]

The overall survival time was defined as the interval between the first operation and death or the last visit to the outpatient clinic through 15 March 2007. Cancer-free survival was considered to be the survival time from the first operation to the last follow-up, local tumor progression, occurrence of new HCCs in the liver, or distant metastasis.

Complications were assigned to major and minor categories. Major complications were defined as those that required therapy or additional hospitalization, or that involved permanent adverse sequelae.[17] Complications were also separated into hepatectomy-related and RFA-related groups.

Statistical analysis

We calculated the rates of overall survival and cancer-free survival using the Kaplan-Meier method. We considered baseline characteristics such as patient age older than 53 years (median age), gender, hepatitis B surface antigen, hepatitis C virus antibody, Child-Pugh classes (A vs B), ICG-R15 smaller than 10%, and serum (-fetoprotein (AFP) level smaller than 100 μg/l as the possible prognostic factors. Additionally, hepatectomy-related, pathology-related, and RFA-related variables were assessed using the multivariate Cox proportional hazard models. These variables included operation time shorter than 4 h, estimated amount of blood loss less than 0.5 l, extent of the resection smaller than bisegmentectomy, resected tumor size larger than 5 cm in diameter, resected tumor multiplicity (single vs two or more), Edmonson-Steiner grade (grades I or II vs grades III or IV), tumor encapsulation, microvascular invasion, cirrhosis of the liver, ablated tumor size larger than 2 cm in diameter, and ablated tumor multiplicity. A P value < 0.05 was considered significant. Data processing and analysis were performed using commercially available software (SPSS for Windows, version 13.0; SPSS, Chicago, Ill).

RESULTS

Local tumor control

Of a total of 66 ablated tumors, complete primary effectiveness was demonstrated in 65 (98%) on the 1-month follow-up CT scans. The residual tumor in the one remaining HCC (3.1 cm in diameter) was treated with TACE because of very low conspicuity of the tumor on US. Of the 65 tumors in which complete primary effectiveness was observed, we identified local tumor progression in 2 (3%) on follow-up CT scans obtained at 4 and 20 months after RFA procedures. Two patients with locally progressive tumor also underwent TACE, as new HCCs appeared simultaneously in other sites of the liver. Neither residual tumors nor local tumor progression were observed in the resection sites.

Long-term survival and new HCCs

The patients were followed up for 2–75 months (mean, 25.6 months; median, 22 months). All patients, except 2 who died earlier, were followed up for at least 4 months. Among a total of 53 patients, 12 (23%) died as a result of progression of HCCs ($n = 10$) or complications of cirrhosis ($n = 2$) before 15 March 2007, 2 (4%) patients were lost to follow-up, and 39 (74%) are alive.

The cumulative overall survival rates estimated at 1, 2, 3, 4, and 5 years were 87, 83, 80, 68, and 55%, respectively. The median survival time was 67 months. There was a significant difference in survival between the subgroups separated according to resected tumor sizes ($P = 0.004$, multivariate Cox proportional hazard models) (Table 1 and Fig. 1). There were no significant differences among the subgroups that were separated according to the other variables.

The cumulative cancer-free survival rates that were estimated at 1, 2, 3, 4, and 5 years were 41, 31, 28, 28, and 0%, respectively. The median survival time was 11 months. There were significant differences among the subgroups separated according to the presence of microvascular invasion ($P = 0.003$) and resected tumor size ($P = 0.012$) (Table 2 and Fig. 2). There were no significant differences among the subgroups that were separated according to the other variables.

During the follow-up period, 30 patients (57%, 30 of 53) demonstrated new HCCs in other sites of the liver. Of these patients, 20 (67%, 20 of 30) were initially treated with TACE, 6 (20%) with RFA, 1 (3%) with tumorectomy, and 1 (3%) with radiation therapy. The remaining 2 patients (7%) did not receive any specific treatments prior to death. A total of 13 patients (25%, 13 of 53) developed extrahepatic metastases, which were found primarily in the lungs ($n = 9$; 69%, 9 of 13), bones ($n = 2$; 15%), lymph nodes ($n = 1$; 8%), and adrenal gland ($n = 1$; 8%).

Complications

No procedure-related death occurred. We observed hepatectomy-related major complications in 4 patients (8%, 4 of 53), 3 of whom suffered from hepatic insufficiency after surgery, and finally recovered. In the remaining patient, a fever was noted, and a 9-cm hematoma near the resection site was found on US and CT 10 days after surgery. During the follow-up period, only one (2% per RFA treatment, 1 of 53) minor RFA-related complication was identified. A moderate degree of dilatation of upstream bile ducts in the lateral segment of the left hepatic lobe was found initially on the 4-month follow-up CT after RFA for a 1.2-cm HCC in the medial segment. The patient had no symptoms and did not require specific treatment. The dilatation of bile ducts has decreased on subsequent follow-up CT scans.

DISCUSSION

Until now, hepatic resection, not RFA, has been the best treatment modality for patients with HCCs. Recurrence rates after RFA are higher than those after resection; survival rates after RFA may be lower than those after resection.[19] The availability of surgical resection for HCCs might be important for a better long-term survival. Thus, hepatectomy is principally recommended for patients with resectable HCCs. In those patients with multifocal HCCs that are untreatable with hepatectomy only, their dominant tumors should be resected first, and the remaining tumors can be treated simultaneously with RFA when the patients have sufficient hepatic functional reserve. Intraoperative RFA can be performed for some tumors ineligible for percutaneous RFA. Tumors near the hepatic hilum, stomach, colon, or diaphragm can be treated with intraoperative RFA. Moreover, intraoperative US can detect very small HCCs of less than 1 cm that may be missed on liver CT, MR imaging, or both.[20] Although conceptually appealing, there is presently little data to support the usefulness of this combination therapy.

To permit complete treatment of unresectable hepatic tumors, particularly bilobar tumors, RFA or

TABLE 1. *The 3-year and 5-year overall survival results of combined radiofrequency ablation (RFA) and hepatectomy for multifocal hepatocellular carcinomas (HCCs). NS not significant, HBsAg hepatitis B surface antigen, HCVAb hepatitis C virus antibody, ICG-R15 indocyanine green dye retention rate 15 min after injection of a 0.5-mg/kg dose, AFP α-fetoprotein.*

Characteristics	No. of patients	3-Year survival rate (%)	5-Year survival rate (%)	Median survival (months)[b]	*P* value[c]
Overall	53	80	55	67	
Age					
Younger (≤53 years)	26	85	85	NA	NS (0.193)
Older (>53 years)	27	74	37	58	
Gender					
Male	42	78	52	67	NS (0.945)
Female	11	81	81	NA	
HbsAg					
Present	42	82	66	NA	NS (0.587)
Absent	11	67	33	58	
HCVAb					
Present	6	100	50	58	NS (0.192)
Absent	47	77	62	NA	
Child-Pugh class					
Class A	47	79	63	67	NS (0.956)
Class B	6	83	42	58	
ICG-R15					
<10%	24	78	78	NA	NS (0.830)
≥10%	29	81	50	67	
AFP					
<100 μg/l	34	81	61	67	NS (0.531)
≥100 μg/l	19	77	51	NA	
Operation time					
<4 h	20	94	63	NA	NS (0.141)
≥4 h	33	70	52	67	
Estimated blood loss					
<0.5 l	25	87	44	44	NS (0.638)
≥0.5 l	28	73	55	67	
Extent of the resection					
<Bisegmentectomy	29	95	63	NA	NS (0.463)
≥Bisegmentectomy	24	65	43	58	
Resected tumor size [a]					
≤5 cm	37	89	67	NA	0.004
>5 cm	16	57	29	58	
Resected tumor number					
Single	40	84	63	NA	NS (0.776)
2–6	13	66	44	44	
Edmonson-Steiner grade					
Grade I or II	48	82	68	67	NS (0.102)
Grade III or IV	5	6	0	58	
Tumor encapsulation					
Present	42	89	59	NA	NS (0.709)
Absent	11	53	35	58	
Microvascular invasion					
Present	26	79	68	58	NS (0.601)
Absent	27	91	73	67	
Cirrhosis of the liver					
Present	28	84	56	67	NS (0.676)
Absent	25	71	71	NA	
Ablated tumor size [a]					
≤2 cm	42	85	58	67	NS (0.072)
>2 cm and ≤ 4 cm	11	61	61	NA	
Ablated tumor number					
Single	42	74	59	67	NS (0.071)
2–3	11	100	0	58	

[a]When a patient had multiple HCCs, the largest tumor was selected
[b]Estimation of median survival was limited to the largest survival time when it was censored (NA, not available)
[c]Statistics using multivariate Cox proportional hazard models

other locoregional therapies added to hepatic resection have been proposed. Several studies[8–10,21] reported that RFA (or microwave ablation) in combination with resection was a possible treatment option for patients with hepatic metastases that were unresectable using traditional methods.

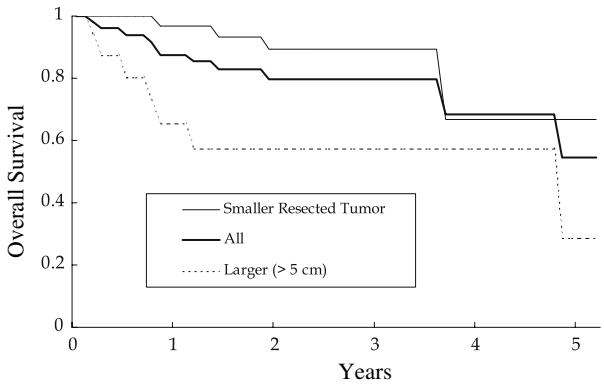

FIG. 1. Cumulative overall survival rates of 53 patients (*thick solid line*) and rates according to resected tumor size. Cumulative overall survival rates were significantly higher in patients with smaller resected tumors (≤5 cm, *thin solid line*) than in patients with larger resected tumors (> 5 cm, *dashed line*; $P = 0.004$, multivariate Cox proportional hazard models).

Wakabayashi et al.[22] suggested that reduction surgery offered a survival benefit for patients with multiple HCCs when combined with intraoperative adjuvant therapy for remaining satellite tumors. The cumulative survival rates (58, 27, and 22, at 1, 3, and 5 years, respectively) of these patients with reductive hepatic resection were significantly better than those of patients treated nonsurgically with TACE or ethanol ablation.

Recently, Raut et al.[7] reported that RFA resulted in better long-term survival for 194 cirrhotic patients with early-stage, unresectable HCCs. Among their study population, 22 patients underwent combined intraoperative RFA with hepatic resection. For these 22 patients, the 1-, 3-, and 5-year overall survival rates were 58, 45, and 45%, respectively. The cancer-free survival rates at 1, 3, and 5 years were 43, 7, and 7%, respectively.

In patients with HCC in a cirrhotic liver, however, preoperative evaluation including Child-Pugh classification, ICG retention test, and volumetric analysis is essential.[1,3,4,23–25] Survival after resection for properly selected candidates can reach 70% at 5 years.[3] Indeed, large series of resections for HCCs reported 3-year and 5-year survival rates between 51 and 73% and 34 and 59%, respectively.[23,26–28] Our results suggested that resection plus RFA provided a long-term survival comparable to that with hepatectomy alone, although the combination treatment was only performed in patients whose disease would be unresectable by classic criteria. Our good survival results might reflect the usefulness of aggressive liver-directed therapy for HCC in patients with chronic hepatocellular diseases, as resection was added with RFA to eradicate all tumors, including those suspected only on intraoperative US.

In three studies [29–31] with large populations, long-term survival of patients with HCCs treated with percutaneous RFA as a first-line treatment depended on the Child-Pugh class, serum AFP level, tumor size, age, and multiplicity of tumors. Additionally, several prior reports[23,25,32–35] suggested various prognostic factors after surgical resection for HCCs. Among them, histopathological grading of resected HCCs, tumor size, Child-Pugh class, fibrosis staging of the liver, hepatitis viral type, serum AFP level, and microvascular invasion were usually considered to be significant prognostic predictors. In our results, however, resected tumor size and microvascular invasion were significant independent predictive factors of long-term overall or cancer-free survival rates in multivariate analyses. Other possible variables could not show statistical significance due to the small numbers of patients in our study.

Despite the theoretical appeal of this combination therapy, safety can be a concern because both resection and intraoperative RFA are procedures that may cause potential morbidity. In fact, in a report by Raut et al.[7], the complication rate after RFA combined with resection for HCCs was 32% (7 of 22). Of the patients in that study, 4 (18%) died of post-operative complications—hepatic insufficiency ($n = 2$), hepatorenal syndrome ($n = 1$), and pneumonia followed by multiorgan failure ($n = 1$). In another prior report,[36] a complication rate of 13% (4 of 31) was documented after intraoperative RFA for HCCs. Ascites ($n = 2$), hepatic insufficiency ($n = 1$), and hemorrhage from incision site ($n = 1$) were cited in these cases. These results appear to be higher than those of our study and could show that combined RFA and resection was not safe. However, based on our results, hepatic resection combined with RFA appears to be safe and well tolerated. Our study revealed a relatively short operation time and a small amount of blood loss. In most cases, hepatic resection plus RFA added minimal complexity to the operation.

There were, however, several limitations to our study. First, it was performed retrospectively; hence, we did not show the accurate number of patients who indeed could be treated only with RFA for HCCs. We presumed that 29 patients (55%, 29 of 53) with a relatively smaller (up to 4 cm) dominant tumor could be treated with RFA, at least intraoperatively. In our series, three different surgeons performing hepatic resections might make slightly different decisions regarding the unplanned addition of RFA for

TABLE 2. *The 3-year and 5-year cancer-free survival results of combined radiofrequency ablation (RFA) and hepatectomy for multifocal hepatocellular carcinomas (HCCs). NS not significant, HBsAg hepatitis B surface antigen, HCVAb hepatitis C virus antibody, ICG-R15 indocyanine green dye retention rate 15 min after injection of a 0.5-mg/kg dose, AFP α-fetoprotein.*

Characteristics	No. of patients	3-Year survival rate (%)	5-Year survival rate (%)	Median survival (months)	*P* value [b]
Cancer-free	53	28	0	11	
Age					
Younger (≤53 years)	26	27	27	9	NS (0.906)
Older (> 53 years)	27	30	0	12	
Gender					
Male	42	25	0	11	NS (0.126)
Female	11	41	41	26	
HbsAg					
Present	42	30	30	11	NS (0.920)
Absent	11	23	0	7	
HCVAb					
Present	6	20	0	17	NS (0.558)
Absent	47	30	30	11	
Child-Pugh class					
Class A	47	30	0	12	NS (0.450)
Class B	6	17	17	7	
ICG-R15					
< 10%	24	33	33	10	NS (0.915)
≥10%	29	26	0	12	
AFP					
< 100 μg/l	34	28	0	11	NS (0.207)
≥100 μg/l	19	28	0	12	
Operation time					
< 4 h	20	37	37	17	NS (0.958)
≥4 h	33	22	0	10	
Estimated blood loss					
< 0.5 l	25	31	31	17	NS (0.863)
≥0.5 l	28	26	0	10	
Extent of the resection					
< Bisegmentectomy	29	32	32	12	NS (0.307)
≥Bisegmentectomy	24	24	0	8	
Resected tumor size [a]					
≤5 cm	37	36	36	17	0.012
> 5 cm	16	8	0	6	
Resected tumor number					
Single	40	30	0	12	NS (0.503)
2–6	13	20	20	8	
Edmonson-Steiner grade					
Grade I or II	48	33	33	12	NS (0.273)
Grade III or IV	5	0	0	7	
Tumor encapsulation					
Present	42	30	30	12	NS (0.493)
Absent	11	9	0	7	
Microvascular invasion					
Present	26	12	12	7	0.003
Absent	27	44	0	24	
Cirrhosis of the liver					
Present	28	33	0	12	NS (0.883)
Absent	25	21	21	11	
Ablated tumor size [a]					
≤2 cm	42	28	0	12	NS (0.882)
> 2 cm and ≤ 4 cm	11	31	31	11	
Ablated tumor number					
Single	42	27	0	12	NS (0.286)
2–3	11	30	30	11	

[a]When a patient had multiple HCCs, the largest tumor was selected
[b]Statistics using multivariate Cox proportional hazard models

patients in whom treatment with resection only had initially been planned. In fact, RFA was abruptly added to resection in 11 patients (21%, 11 of 53) after a surgeon performed a laparotomy and investigated the gross morphology of their livers. The surgeon decided to add RFA because he was concerned about the potential hepatic insufficiency of the patient after extensive resection or the complexity of resection only.

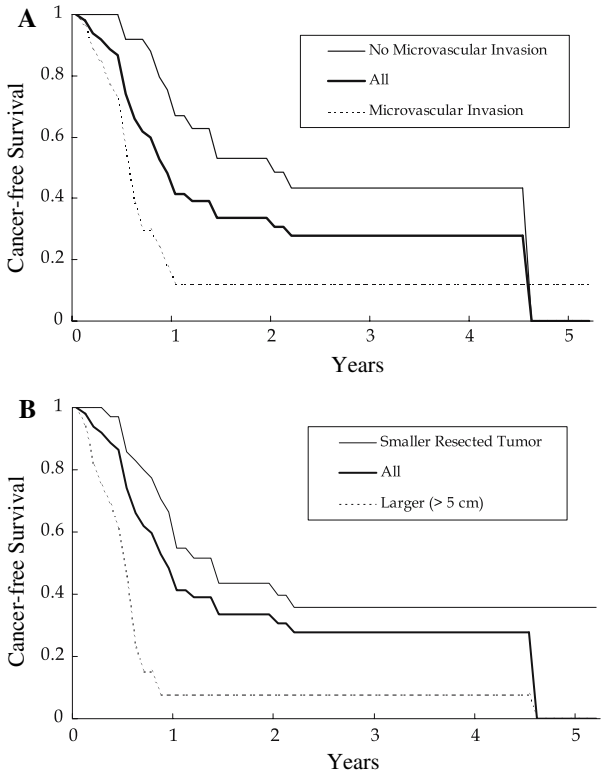

FIG. 2. Cumulative cancer-free survival rates of 53 patients (*thick solid line*) and rates according to the presence of microvascular invasion and resected tumor size. (**A**) Cumulative cancer-free survival rates were significantly higher in patients without microvascular invasion (*thin solid line*) than in patients with microvascular invasion (*dashed line*; $P = 0.003$, multivariate Cox proportional hazard models). (**B**) Cumulative cancer-free survival rates were significantly higher in patients with smaller resected tumors (≤5 cm, *thin solid line*) than in patients with larger resected tumors (> 5 cm, *dashed line*; $P = 0.012$, multivariate Cox proportional hazard models).

Second, the patients were treated using various RFA devices due to the temporal refinement and availability during the study period. We believe that this was not a significant factor affecting the therapeutic outcomes, because the same treatment strategy was applied to all of the tumors, no matter what devices were used. A recent comparative study[37] between internally cooled electrodes and expandable electrodes demonstrated that both allowed equally effective treatment of small HCCs.

Finally, many tumors were not pathologically proven, but were considered to be HCCs on the basis of characteristic imaging features. We tried to obtain pathological evidence in almost all patients during the initial study period. However, we realized it was difficult and impractical to perform invasive biopsies for the confirmation of all small tumors that were found on multiphasic CT and MR imaging of patients with chronic hepatocellular disease who showed characteristic radiological findings.[13–15] We believed that biopsy procedures could result in an increased chance of a tumor seeding in the needle tract.

Most patients with HCCs received multi-modality treatments that included hepatectomy, TACE, RFA, ethanol ablation, microwave ablation, radiation therapy, or systemic chemotherapy, either in sequence or combination. For patients with multifocal HCCs, we treated them with concurrent hepatic resection and RFA. Our study results confirmed that combined hepatectomy and RFA could be a safe and effective technique for the treatment of multifocal HCCs. We observed good long-term survival results that were comparable to those after either RFA only or resection only, very low complication rates, and no procedure-related mortality in patients who had multiple HCCs that were untreatable with hepatectomy only. Therefore, aggressive combination treatment of hepatectomy plus RFA may allow more patients to become candidates for resection to multifocal HCCs, particularly bilobar HCCs, and may improve chances of long-term survival in patients with advanced-stage HCCs. However, further investigation of a greater number of patients is needed to confirm our encouraging results.

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