

ORIGINAL ARTICLE

Comparative analysis of radiofrequency ablation and surgical resection for colorectal liver metastases

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Purpose: To evaluate the comparative therapeutic efficacy of radiofrequency ablation (RFA) and hepatic resection for the treatment of colorectal liver metastasis (CRLM). **Methods:** Between 1996 and 2008, 177 patients underwent RFA, 278 underwent hepatic resection and 27 underwent combination therapy for CRLM. Comparative analysis of clinical outcomes was performed including number of liver metastases, tumor size, and time of CRLM. **Results:** Based on multivariate analysis, overall survival (OS) correlated with the number of liver metastases and the use of combined chemotherapy ($P < 0.001$, respectively). Disease-free survival (DFS) also correlated with the number of liver metastases ($P < 0.001$). In the 226 patients with solitary CRLM < 3 cm, OS and DFS rates did not differ between the RFA group and the resection group ($P = 0.962$ and $P = 0.980$). In the 70 patients with solitary CRLM ≥ 3 cm, DFS was significantly lower in the RFA group as compared with the resection group ($P = 0.015$). **Conclusion:** The results indicate that RFA may be a safe alternative treatment for solitary CRLM less than 3 cm, with outcomes equivalent to those achieved with hepatic resection. A randomized controlled study comparing RFA and resection for patients with single small metastasis would help to determine the most efficient treatment modalities for CRLM.

Key Words: Radiofrequency ablation, Hepatectomy, Colorectal neoplasms, Liver metastasis

INTRODUCTION

Surgical resection is viewed as the gold standard of treatment for resectable liver metastasis from colorectal cancer (CRLM) [1,2]. Several groups have reported 5-year survival rates in the range of 23 to 71% for surgical resection [3,4]. However, only 10 to 20% of patients with CRLM are candidates for surgical resection; the majority are not suitable for resection because of anatomically ill-located lesions, functional insufficiency of hepatic re-

serves, medical comorbidities and extra-hepatic metastasis [5]. Radiofrequency ablation (RFA) is an alternative therapy for CRLM when hepatic resection cannot be performed. RFA has the advantage of being minimally invasive and is a relatively low-risk procedure for the treatment of focal liver tumors, especially in comparison with open surgical resection [6]. On the other hand, RFA carries its own associated morbidity and mortality rates in both immediate post-procedure and over the long term [7]. Furthermore, there are unresolved technical limitations

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associated with RFA, such as heat sink effects on nearby blood vessels and local tissue destruction [8]. Local recurrence remains one of the greatest disadvantages of RFA for the treatment of hepatic tumors [9]. There are conflicting reports in the literature on the comparative efficacy of RFA and hepatic resection. Some results support a prospective clinical trial comparing RFA and resection, while other reports indicate that RFA is inferior to surgical resection [4,10,11]. Although surgery is still the recommended treatment modality for patients with CRLM, the majority of these patients are not surgical candidates [12]. There are few reports in the literature of randomized controlled trials comparing RFA and resection for CRLM, and analysis of comparative outcomes between RFA and resection has yielded somewhat inconsistent results. Thus, the exact role and long-term outcomes associated with RFA for CRLM are unclear. The purpose of the current study was to evaluate the comparative therapeutic efficacy of RFA and hepatic resection for CRLM.

METHODS

Eligibility and enrollment

Between January 1996 and August 2008, 505 patients with CRLM underwent RFA, hepatic resection or a combination of RFA and resection at Asan Medical Center. All patients had liver metastasis with diagnoses by computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), ultrasonography or biopsy. Patients with extrahepatic metastasis were excluded when treatment of CRLM was performed. Of the 301 patients who underwent hepatic resection, 23 patients with positive resection margin were also excluded. Of the 482 patients included in the study, 177 were treated by RFA, 278 by curative surgical resection, and 27 by combination therapy. Synchronous colorectal cancer and liver metastases were identified in 258 (53.5%) patients and metachronous liver metastases were detected in 224 (46.5%) of the 482 patients. RFA was performed in cases of surgery-prohibitive comorbidities such as severe cardiovascular or pulmonary disease, difficult anatomical site for surgical resection, and more than four hepatic meta-

stases over the entire liver [13,14]. A total of 44 (24.9%) of the 177 patients presented with comorbid diseases (13 cases of chronic obstructive pulmonary disease, 4 cases of chronic renal failure, 10 cases of liver cirrhosis, 2 transplantations and 15 cases of heart failure), and the position of the hepatic lesion was located in an anatomic site difficult for resection, such as the center of the liver, in 38 (21.5%) of the 177 patients. Otherwise, all patients with CRLM were initially considered for resection. All patients were recruited prospectively. The endpoints were recurrence, disease-free survival (DFS) and overall survival (OS). The study was conducted with the approval of the Institutional Review Board for Human Research (Asan Clinical Research Center, Seoul, Korea) in accordance with the Helsinki Declaration.

Treatments and follow-up

RFA was performed intraoperatively under general anesthesia or percutaneously under local anesthesia using ultrasonographic guidance to ensure that at least a 1-cm ablation margin was achieved around the tumor. Single or triple-cluster, 17 gauge (4.5 Fr), internally cooled electrodes (Valleylab, Boulder, CO, USA) were used. A single electrode with a 3-cm exposed tip was used for small tumors; a triple-cluster electrode with a 2.5-cm exposed tip for large tumors was used at the discretion of the radiologist. Radiofrequency current was emitted for 10 to 15 minutes with the generator set to deliver the maximum power in impedance control mode. Destruction of the liver metastasis was confirmed by follow-up CT and ultrasonography the next day.

Synchronous hepatic resection by primary operation was performed on 214 patients (77.0%) and metachronous resection was done on 64 (23.0%) of the 278 patients in the resection group. Fourteen patients underwent lobectomy, 42 patients segmentectomy, and 222 patients subsegmentectomy. The surgical resection margin was 0.7 ± 0.8 cm (range, 0.1 to 7.0 cm). During laparotomy, intraoperative ultrasonography of the liver was routinely performed to detect metastatic tumors and to evaluate their anatomical location and resectability. In the RFA group, 164 (92.7%) of the 177 patients underwent post-treatment chemotherapy; 247 (88.8%) of the 278 patients in the re-

section group and all 27 patients (100%) in the combination therapy group underwent post-treatment chemotherapy.

Follow-up was carried out postoperatively every 3 to 6 months. The evaluation included clinical examination, common blood chemistry, serum CEA, abdomen/chest CT, and specific procedures such as MRI, PET and bone scan when indicated.

Statistical analysis

Clinicopathologic continuous variables among the groups were compared using Student's t-test, Kruskal Wallis test or one-way analysis of variance with least significant difference multiple comparison. Categorical variables were compared by cross table analysis using the χ^2

test or Fisher exact test and potential variables were verified by multivariate analysis using binary logistic regression. OS and DFS were compared using the Kaplan-Meier method with log-rank test, and survival factors were verified using a Cox proportional hazard regression model. The significance level was set at 5% for each analysis, and all calculations were performed using SPSS ver. 18 (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical characteristics of the patients

The clinical characteristics of the 482 patients included in the analysis are summarized in Table 1 (RFA, 177 pa-

Table 1. Patient clinicopathological characteristics

Variable	RFA (n = 177)	Resection (n = 278)	P-value ^{a)}	Resection + RFA (n = 27)	P-value ^{b)}
Age (yr)	60.4 ± 10.7	57.1 ± 10.9	0.001	55.7 ± 11.1	0.013
Sex					
Male	121 (68.4)	168 (60.4)	0.091	15 (55.6)	0.178
Female	56 (31.6)	110 (39.6)		12 (44.4)	
Synchronicity					
Synchronous metastasis	17 (9.6)	214 (77.0)	<0.001	27 (100)	<0.001
Metachronous metastasis	160 (90.4)	64 (23.0)		0 (0)	
No. of liver metastasis					
Mean	1.6 ± 0.9	1.5 ± 0.8	0.162	3.1 ± 1.6	<0.001
Single	113 (63.8)	183 (65.8)	0.546	0 (0)	<0.001
Multiple	64 (36.2)	95 (34.2)		27 (100)	
Maximum tumor size					
Mean (cm)	2.1 ± 1.0	2.6 ± 2.0	0.004	2.1 ± 1.4	0.010
<3 cm	145 (81.9)	182 (65.5)	<0.001	21 (77.8)	0.001
≥3 cm	32 (18.1)	96 (34.5)		6 (22.2)	
Location of liver metastasis					
Unilobar	148 (83.6)	224 (80.6)	0.456	12 (44.4)	<0.001
Bilobar	29 (16.4)	54 (19.4)		15 (55.6)	
Chemotherapy after treatment					
No	13 (7.2)	31 (11.2)	0.197	0 (0)	0.092
Yes	164 (92.7)	247 (88.8)		27 (100)	
Hospital admission (day)	4.2 ± 2.8	13.4 ± 4.5	<0.001	15.0 ± 14.7	<0.001
Morbidity	11 (6.2)	59 (21.2)	<0.001	10 (37.0)	<0.001
Bleeding (transfusion)	2	13		3	
Abscess	8	17		3	
Wound infection	0	10		3	
Transient respiratory failure	1	8		1	
Ileus	0	11		0	

Values are presented as mean ± SD or number (%).

RFA, radiofrequency ablation.

^{a)}RFA vs. resection. ^{b)}RFA vs. resection vs. resection + RFA.

tients; resection, 278 patients; combination therapy, 27 patients). Examples of radiologic findings indicating that RFA was recommended in the current study are presented in Fig. 1. The RFA group had more patients with metachronous liver metastasis whereas the resection group had more patients with synchronous liver metastasis. All patients in the combination therapy group had synchronous liver metastasis. Both the RFA and resection groups had more patients with single metastasis; all patients in the combination therapy group had multiple metastases. The mean number of liver metastases was 1.6 (range, 1 to 5) in the RFA group, 1.5 (range, 1 to 6) in the resection group and 3.1 (range, 2 to 8) in the combination

therapy group. The mean maximum tumor diameter was 2.1 cm (range, 0.5 to 6.2 cm) in the RFA group, 2.6 cm (range, 0.5 to 13.0 cm) in the resection group and 2.1 cm (range, 0.5 to 6.0 cm) in the combination therapy group. Unilobar metastases were observed in 148 (83.6%) of 177 patients in the RFA group, 224 (80.6%) of 278 patients in the resection group and 12 (44.4%) of 27 patients in the combination therapy group. There were no significant differences in the frequency of chemotherapy among the groups ($P = 0.092$). The mean hospitalization period was 4.2 days (range, 1 to 32 days) in the RFA group, 13.4 days (range, 7 to 42 days) in the resection group and 15.0 days (range, 8 to 66 days) in the combination group. There was

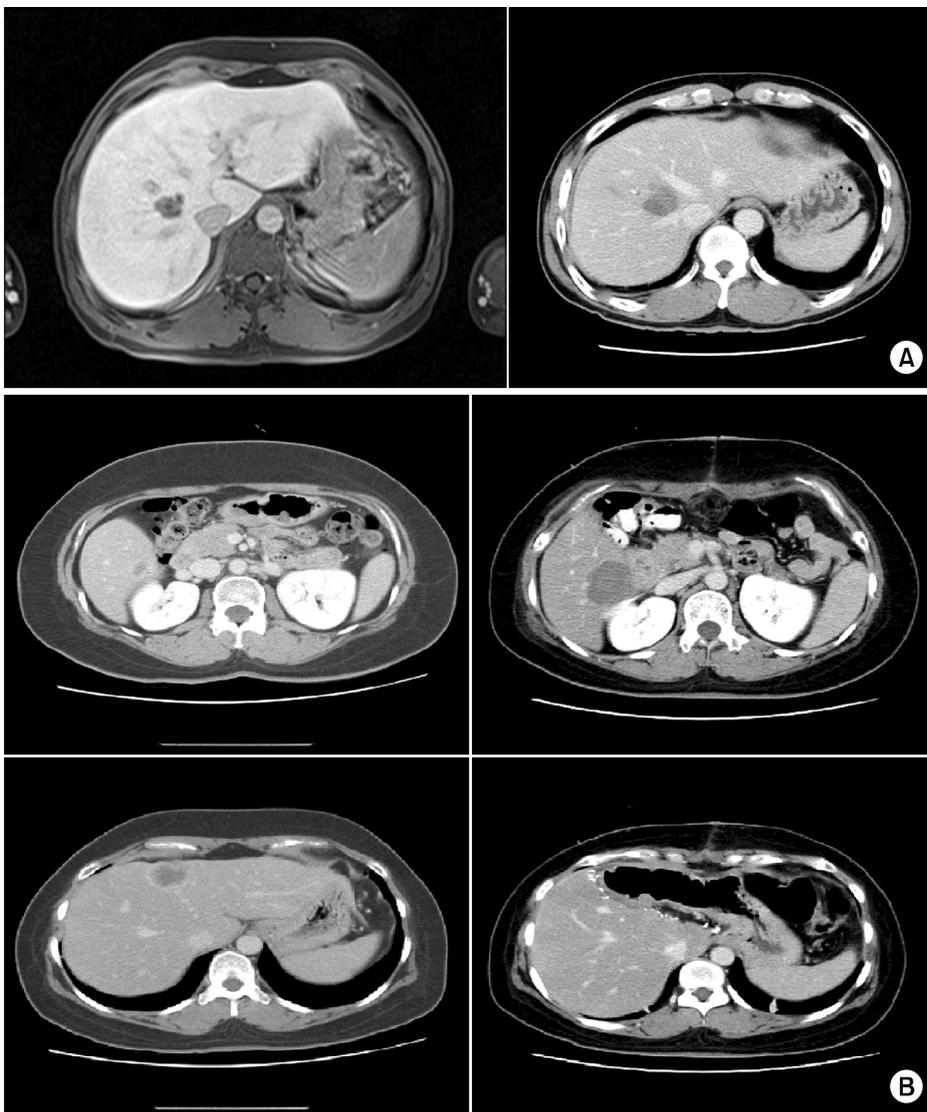


Fig. 1. Examples of radiologic images indicating that radiofrequency ablation (RFA) was recommended in the current study. (A) Anatomic sites difficult for resection (left image, pre-RFA; right image, post-RFA). (B) Multiple lesions treated with combination therapy (left images, pre-treatment; right images, post-treatment).

no treatment-related mortality in each group. The morbidity rates were significantly lower in the RFA group (RFA group vs. resection group, 6.2% vs. 21.2%; $P <$

0.001). The clinical features of patients with solitary CRLM < 3 cm are in Table 2 and solitary CRLM ≥ 3 cm in Table 3.

Table 2. Clinicopathological features of patient with solitary CRLM less than 3 cm

Variable	RFA (n = 99)	Resection (n = 127)	P-value
Age	59.8 ± 11.4	56.8 ± 11.7	0.054
Sex			
Male	65 (65.7)	81 (63.8)	0.781
Female	34 (34.3)	46 (36.2)	
Synchronicity			
Synchronous metastasis	9 (9.1)	104 (81.9)	< 0.001
Metachronous metastasis	90 (90.9)	23 (18.1)	
Tumor size	1.7 ± 0.6	1.4 ± 0.7	0.003
Chemotherapy after treatment			
No	9 (9.1)	13 (10.2)	0.825
Yes	90 (90.9)	114 (89.8)	

Values are presented as mean ± SD or number (%).
CRLM, colorectal liver metastasis; RFA, radiofrequency ablation.

Table 3. Clinicopathological features of patient with solitary CRLM equal to or greater than 3 cm

Variable	RFA (n = 14)	Resection (n = 56)	P-value
Age	65.1 ± 8.9	58.9 ± 9.7	0.031
Sex			
Male	12 (85.7)	32 (57.1)	0.043
Female	2 (14.3)	24 (42.9)	
Synchronicity			
Synchronous metastasis	1 (7.1)	34 (60.7)	< 0.001
Metachronous metastasis	13 (92.9)	22 (39.3)	
Tumor size	3.6 ± 0.5	4.8 ± 2.2	0.058
Chemotherapy after treatment			
No	0 (0)	6 (10.7)	0.248
Yes	14 (100)	50 (89.3)	

Values are presented as mean ± SD or number (%).
CRLM, colorectal liver metastasis; RFA, radiofrequency ablation.

Table 4. Cox proportional hazard regression analysis of factors associated with overall survival after treatment of liver metastasis

Variable	Univariate analysis			Multivariate analysis ^{a)}		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Age	1.01	1.00-1.03	0.001	1.02	1.01-1.03	0.002
Sex						
Male	1					
Female	1.25	0.98-1.59	0.075			
Type of treatment						
Resection	1					
RFA	1.20	0.91-1.56	0.191			
Resection + RFA	1.52	0.86-2.68	0.149			
No. of liver metastasis						
Single	1					
Multiple	1.69	1.33-2.14	< 0.001	1.74	1.37-2.21	< 0.001
Maximum tumor size						
< 3 cm	1					
≥ 3 cm	1.22	0.94-1.57	0.128			
Synchronicity						
Synchronous metastasis	1					
Metachronous metastasis	1.05	0.82-1.33	0.714			
Location of liver metastasis						
Unilobar	1					
Bilobar	1.21	0.91-1.61	0.196			
Chemotherapy after treatment						
Yes	1					
No	1.75	1.22-2.51	0.002	1.77	1.23-2.54	0.002

Mean follow-up period: 41.2 months (range, 2.5 to 151.6 months).

CI, confidence interval; RFA, radiofrequency ablation.

^{a)}Variable selection: backward elimination.

Factors associated with OS and DFS

Univariate and multivariate analysis using Cox proportional hazard analysis revealed several factors associated with OS after treatment of liver metastasis (Table 4). OS correlated with age ($P = 0.002$), number of liver metastases ($P < 0.001$) and use of chemotherapy ($P = 0.002$). Factors associated with DFS after treatment of liver metastasis were also analyzed (Table 5). DFS was significantly related to type of treatment (RFA, $P = 0.004$) and number of liver metastases ($P < 0.001$).

Outcome for patients according to patterns of liver metastases

Of the 482 patients, 296 (61.4%) had solitary liver metastasis. In the 226 patients with a single metastatic tumor < 3 cm (99 patients in the RFA group, 127 patients in the resection group), OS and DFS rates did not differ between patients who underwent RFA and resection ($P = 0.96$

and 0.98, respectively). Specifically, 5-year OS and DFS rates were 51.1% and 33.6%, respectively, in the RFA group and 51.2% and 31.6%, respectively, in the resection group (Fig. 2). Among the 70 patients with solitary metastatic tumor ≥ 3 cm (14 patients in the RFA group and 56 patients in the resection group), DFS rates were significantly lower in the RFA group (RFA group, 23.1%; resection group, 36.6%; $P = 0.01$) (Fig. 3).

OS and DFS rates of the 186 patients with multiple liver metastases are shown in Fig. 4 (RFA, 64 patients; resection, 95 patients; combination therapy, 27 patients). There were no statistically significant differences in OS rates among the groups ($P = 0.330$). Five-year OS was 14.3% in the RFA group, 34.6% in the resection group, and 22.9% in the combination therapy group. However, DFS in the RFA group was significantly lower than the other groups ($P = 0.037$). The 5-year DFS rate was 6.4% in the RFA group, 16.2% in the resection group, and 18.4% in the combination therapy

Table 5. Cox proportional hazard regression analysis of factors associated with disease-free survival after treatment of liver metastasis

Variable	Univariate analysis			Multivariate analysis ^{a)}		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Age	1.01	1.00-1.02	0.042			
Sex						
Male	1					
Female	1.20	0.97-1.48	0.100			
Type of treatment						
Resection	1					
RFA	1.37	1.10-1.72	0.005	1.40	1.12-1.75	0.004
Resection + RFA	1.30	0.81-2.08	0.280	0.87	0.54-1.42	0.586
No. of liver metastasis						
Single	1					
Multiple	1.77	1.44-2.19	< 0.001	1.85	1.48-2.30	< 0.001
Maximum tumor size						
< 3 cm	1					
≥ 3 cm	1.02	0.81-1.29	0.856			
Synchronicity						
Synchronous metastasis	1					
Metachronous metastasis	1.21	0.98-1.49	0.071			
Location of liver metastasis						
Unilobar	1					
Bilobar	1.46	1.15-1.86	0.002			
Chemotherapy after treatment						
Yes	1					
No	1.39	0.98-1.99	0.067			

Mean follow-up period: 21.6 months (range, 0.1 to 151.6 months).

CI, confidence interval; RFA, radiofrequency ablation.

^{a)}Variable selection: backward elimination.

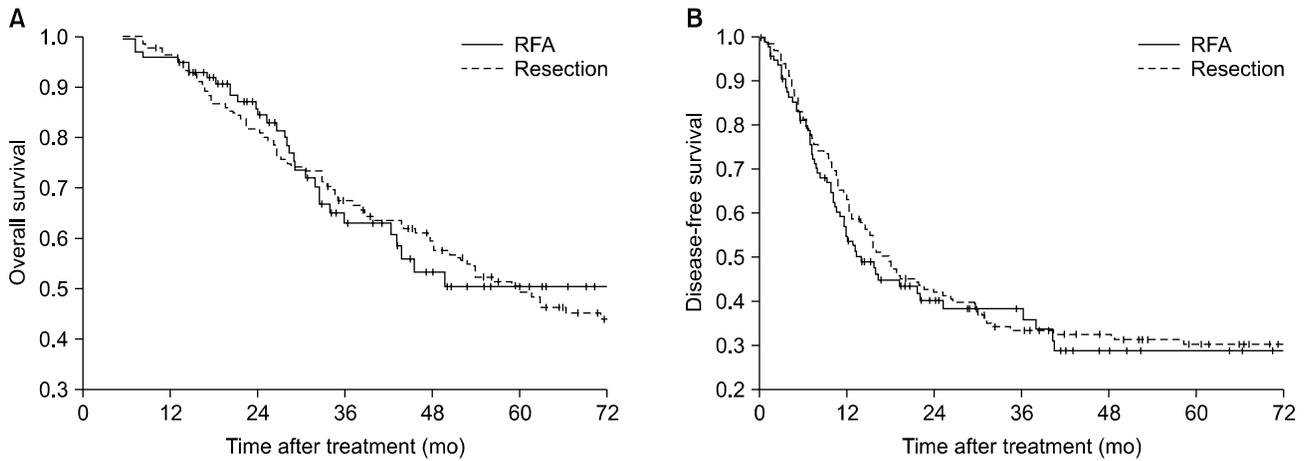


Fig. 2. Survival of patients with solitary colorectal liver metastasis less than 3 cm treated by radiofrequency ablation (RFA) and resection. (A) Overall survival ($P = 0.962$). (B) Disease-free survival ($P = 0.980$).

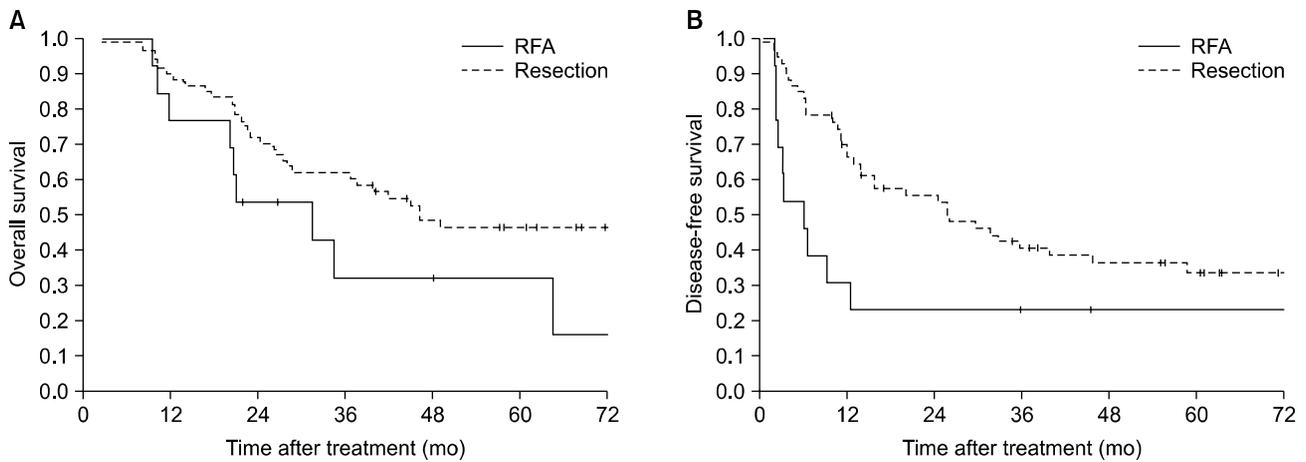


Fig. 3. Survival of patients with solitary colorectal liver metastasis equal to or greater than 3 cm treated by radiofrequency ablation (RFA) and resection. (A) Overall survival ($P = 0.152$). (B) Disease-free survival ($P = 0.015$).

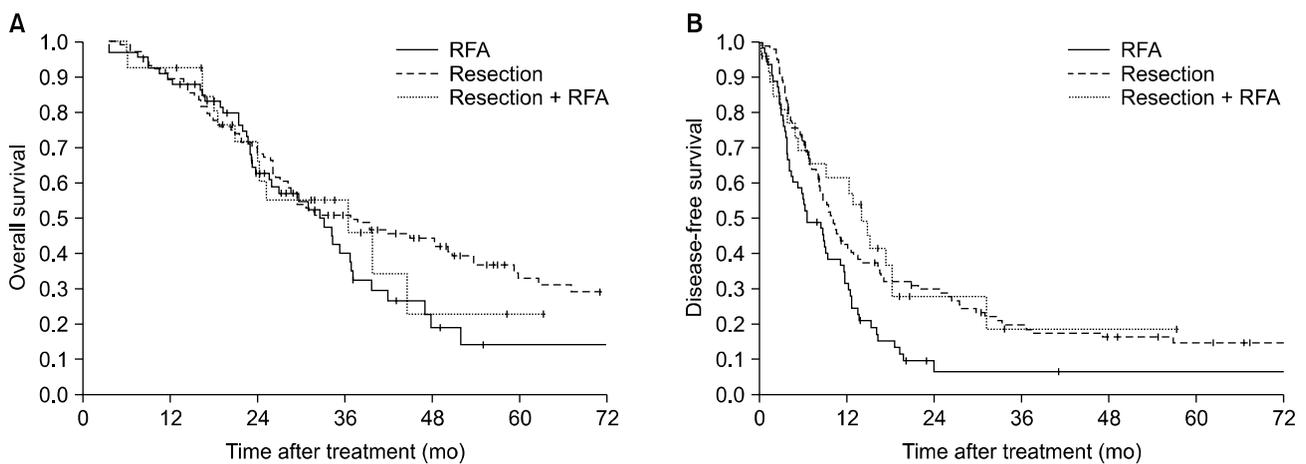


Fig. 4. Survival of patients with multiple colorectal liver metastasis treated by radiofrequency ablation (RFA), resection and combination therapy. (A) Overall survival ($P = 0.330$). (B) Disease-free survival ($P = 0.037$).

group.

Of the 224 patients with metachronous liver metastases, 148 had solitary liver metastasis (RFA group, 103 patients; resection group, 45 patients). The 5-year OS rate was 47.6% in the RFA group and 56.0% in the resection group ($P = 0.308$). There was no statistical difference in 5-year DFS between the RFA and the resection groups (32.2% vs. 34.0%, $P = 0.164$). A trend in OS and DFS rates was observed, but the difference was not statistically significant.

DISCUSSION

RFA produces coagulation necrosis using a high-frequency alternating current delivered through an electrode placed in the center of the tumor [8]. RFA treatment often results in local tissue temperatures that approach or exceed 100°C , inducing parenchyma and tumor cell death. Ultimately, the local microvasculature is destroyed as a result of thrombosis. The use of RFA is generally not recommended for tumors larger than 5 to 6 cm because of technical limitations and the inability to achieve complete necrosis [15]. The purpose of the current study was to compare RFA with hepatic resection for the treatment of CRLM. Mulier et al. [4] recently advocated a randomized clinical trial comparing RFA and resection for resectable CRLM. At present, the use of RFA as an alternative treatment for patients with solitary CRLM smaller than 3 cm is controversial. Here, we showed that outcomes associated with RFA were not inferior to hepatic resection in the treatment of single CRLM of less than 3 cm. However, DFS rates after RFA were lower than surgical resection for single CRLM ≥ 3 cm. These findings suggest that RFA may have a valuable place in the treatment of solitary CRLM of less than 3 cm.

RFA has been shown to be much less invasive than hepatic resection, with a lower complication rate and shorter hospital stays [3,16-18]. Our results were consistent with these studies. Results from a large multicenter study demonstrated that RFA is a relatively safe procedure for treating focal liver tumors, with a very low mortality rate of 0.2% and a major complication rate of 2.2% [6]. Although RFA has been investigated as an alternative to surgery in

terms of safety and feasibility, the comparative effectiveness of RFA and other treatment modalities has yet to be clearly demonstrated. RFA technology continues to improve, as does the skill and experience of physicians, both of which improve the potential of RFA as a treatment option for patients with CRLM. Results reported by Oshowo et al. [16] demonstrated that survival after RFA and resection of solitary CRLM is comparable, suggesting that RFA is an effective alternative treatment to conventional surgery. A separate but related study reported that excellent local control can be achieved with RFA for small liver metastasis of less than 3 cm. Local recurrence rates reached 8.8% overall and 1.6% for CRLM smaller than 3 cm in diameter [19]. In patients with solitary CRLM of less than 3 cm, reported 5-year survival rates, including overall and local recurrence free survival rates, were similar between RFA and surgical resection, providing further support for RFA as an alternative treatment in patients with solitary CRLM smaller than 3 cm who are not suitable candidates for hepatic resection [20]. The results of the present study are consistent with these earlier studies as well as previous work by our group showing that RFA is a viable alternative treatment for solitary CRLM smaller than 3 cm [11]. On the other hand, several studies have shown that RFA is associated with higher local recurrence and shorter time to progression, and that there is no difference in OS compared to hepatic resection for CRLM [10,21]. These results are in line with the current finding that there was no statistically significant difference in OS between RFA and resection.

RFA and resection were equivalent in terms of survival outcome in patients with solitary liver metastasis of less than 3 cm. Several studies support hepatic resection as the preferred treatment for CRLM, even in patients with solitary tumors of less than 3 cm [3,11,22,23]. It has also been reported that survival following RFA for patients with unresectable tumors is only slightly superior to nonsurgical treatment [24]. In the current study, the survival rate of the hepatic resection group was higher than the RFA group in patients with solitary CRLM ≥ 3 cm. For patients with solitary CRLM smaller than 3 cm, our results suggest that RFA is equivalent to hepatic resection. These findings appear to contradict the results of earlier studies, including

previous work by our group looking at a smaller number of patients [11]. However, these discrepancies may be due to improvements in the technical accuracy and performance of RFA in accordance with learning curve.

The results of a prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma (HCC) were recently reported. Percutaneous local ablative therapy was as effective as surgical resection for the treatment of solitary and small HCC [25]. CRLM is metastatic, whereas HCC is a primary malignancy. However, treatment modalities are identical in small solitary tumors. The results of the present study indicate that RFA is a viable treatment alternative in patients with small solitary CRLM with poor medical conditions or for whom surgical resection would be difficult, and support moving forward with a prospective randomized clinical trial comparing RFA and hepatic resection for solitary CRLM of less than 3 cm. In patients with multiple lesions, there were no significant differences in survival rates among the RFA, resection, and combination therapy groups. A trend towards slightly superior outcomes in the resection group was observed, but this was not statistically significant. These results are in agreement with previous reports that using RFA in addition to resection is beneficial in patients with multiple liver metastases because of the ability to extend the limits of resection [26,27].

Multivariate analysis identified the number of liver metastases and treatment with chemotherapy as risk factors for OS and the number of liver metastases and type of treatment as risk factors for DFS. These results suggest that systemic treatment may be more important for OS [28], and that local controls might be more important for DFS. The synchronicity of liver metastasis may also be an important factor in deciding whether to perform RFA or resection. In patients with metachronous CRLM, there is a tendency to avoid operation if possible because of invasiveness. Likewise, risk of damage to the diaphragm, adjacent stomach or colon would be factors against the use of RFA. For patients with solitary metachronous CRLM who want to avoid hepatic resection, RFA appears to be an attractive alternative. RFA technology continues to improve, and it may soon be possible to achieve precise tar-

geting of tumors and larger ablation zones with a single electrode position [29]. Thus, RFA has the potential to improve survival rates and reduce complications in selected patients with CRLM who are not suitable for or refuse hepatic resection because of comorbidities. The limitation of the present study was that this report was based on not a randomized controlled study, but a retrospective study.

In conclusion, the present study suggests that RFA may be a safe alternative tool for the treatment of solitary CRLM less than 3 cm, with outcomes equivalent to those achieved with hepatic resection. A prospectively controlled study of RFA and resection for patients with single small metastasis would help to determine the most efficient treatment modalities for CRLM.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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