Clinical Study

Long-Term Survival after Radiofrequency Ablation of Lung Oligometastases from 5 types of Primary Lesions: A Retrospective Evaluation

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Abstract

Purpose: To conduct a retrospective evaluation of long-term survival after radiofrequency (RF) ablation for lung oligometastases from 5 types of primary lesions.

Materials and Methods: The study population consisted of 123 patients with lung oligometastases from colorectal cancer, non-small cell lung cancer, hepatocellular carcinoma, esophageal cancer, and renal cell carcinoma, who were treated with RF ablation. Lung oligometastases were defined as 1–5 metastases confined to the lung, while the primary cancer and other metastases were eradicated. Overall survival (OS) and recurrence-free survival (RFS) were estimated for the overall study population, as well as for the patients with each type of primary lesion. The OS and RFS rates were compared to those of the patients with any of the other four primary lesion types. Finally, various variables were analyzed to determine what factors influenced OS and RFS.

Results: The median follow-up was 45.7 months, and the 5-year OS and RFS rates for all 123 patients were 62% and 25%, respectively. The OS rate for patients with metastases from colorectal cancer was significantly ($P = 0.042$) longer and that from esophageal cancer was significantly ($P = 0.022$) shorter. Longer disease-free interval was significantly ($P = 0.015$) associated with better OS. There was no variable significantly associated with OS and RFS on multivariate analyses.

Conclusions: This single-center study suggests that the long-term survival data after RF ablation of lung oligometastases seems promising.

INTRODUCTION

The lung is the second most frequent site of metastasis from extra-thoracic cancers [1]. For example, approximately 5% of patients who undergo curative resection for colorectal cancer develop lung metastasis; the incidence of lung metastasis is following that of liver metastasis [2]. Curative local therapy can be applied to oligometastases with the aim of long-term survival or even cure. Oligometastases were defined by Hellman and Weichselbaum as metastases that are limited in number and location [3, 4].

Surgical resection is considered the standard curative local therapy for lung metastases. However, many patients are not surgical candidates because of limited organ function, comorbidities, refusal to undergo surgery, etc.

Radiofrequency (RF) ablation is another local therapy for lung metastasis. RF ablation is less invasive, making it an attractive therapy option for nonsurgical candidates. Although some studies [5–8] have shown long-term survival of the patients who underwent RF ablation of lung metastases from various types of primary cancer, population of those studies were not limited to oligometastatic patients. Therefore, long-term survival data following RF ablation of lung oligometastases are still lacking. Thus, the purpose of this study was to undertake a retrospective evaluation of long-term survival after RF ablation of lung oligometastases from 5 types of primary lesions.

MATERIALS AND METHODS

The institutional review board approved this retrospective study (approval number, 2286) and informed consent was obtained from all patients prior to performing the procedure.

Study Population

Between June 2001 and December 2013, 556 patients with lung metastases from various primary lesions underwent RF ablation at our institution. This study focused on lung oligometastases from five types of primary cancer: colorectal cancer (CRC), non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), esophageal cancer (EC), and renal cell carcinoma (RCC). In this study, lung oligometastases were defined as 1–5 metastases confined to the lung while the primary lesion and other metastases, if they existed, were eradicated by any treatment at the time of the initial RF ablation. Patients with lung oligometastases from other primary lesions were excluded because they were limited in number.

The inclusion criteria for this study were as follows: (i) lung oligometastases from any of the above-mentioned primary lesions; (ii) all lung oligometastases were treated with RF ablation; and (iii) follow-up period for surviving patients was longer than 6 months. Thus, the patient (n = 1) who survived but was followed for less than 6 months was excluded, while the patient (n = 2) who died within 6 months after RF ablation were included. The patients who underwent other local therapies (e.g., surgery and stereotactic body radiotherapy) in addition to RF ablation to eradicate lung oligometastases were excluded, but patients who underwent concurrent or adjuvant chemotherapy were included in this study.

One hundred twenty-three patients (84 men and 39 women; mean age, 65.6 years; range, 34–94 years) with a total of 222 lung oligometastases (mean long-axis tumor diameter, 12.5 mm; range, 2–50 mm) met the inclusion criteria. The characteristics of study population are summarized in **Table 1**. This study cohort included 70 patients (CRC, n = 43; HCC, n = 8; EC, n = 14; RCC, n = 5) who had been previously described elsewhere [9–12], and their follow-up data were updated for this study. This study was newly conducted because it enabled comparison of survival after RF ablation of lung oligometastases among the 5 primary lesions. Further, this study was different from the previous studies in that the cohort was confined to the patients with lung oligometastases.

Lung oligometastases were primarily from CRC in 52 patients, NSCLC in 33 patients, HCC in 16 patients, EC in 14 patients, and RCC in 8 patients. One hundred ninety lung metastases were clinically diagnosed based on the results of serial chest computed tomography (CT) scans, while 32 metastases were pathologically confirmed by biopsy. There was a single lung metastasis and multiple lung metastases in 62 and 61 patients, respectively. Ninety-two and 31 patients underwent single and multiple RF ablation sessions, respectively. Fifty-six patients had a previous history of pulmonary metastasis, extrapulmonary metastasis, or both, all of which were eradicated by any therapy at the time of RF ablation.

RF Ablation Techniques

RF ablation techniques used at our institution were similar to those that have previously been described in the literature [13]. RF ablation was always performed in an inpatient setting. Intraprocedural pain was treated using a combination of local or epidural anesthesia and conscious sedation using fentanyl. The procedure was percutaneously carried out under CT-fluoroscopy (Asteion or Aquilion; Toshiba medical, Tochigi, Japan).

The electrode used for RF ablation was a multitined expandable electrode (LeVeen; Boston Scientific, Natick, MA) or a single internally cooled electrode (Cool-tip; Covidien, Mansfield, MA). A multitined expandable electrode was preferred. However, a single internally cooled electrode was used in cases where there was a concern that expendable tines might result in injury to critical structures, such as large vessels. RF ablation was performed with the aim of ablating the tumors with at least 5 mm of marginal parenchyma. Each session targeted only one lung; thus, bilateral metastases were treated with multiple sessions.

Follow-up

Follow-up sessions were conducted at 1 (range, 4–6 weeks), 3 (2–4), 6 (5–7), 9 (8–10), and 12 (11–13) months and at 6 (5–7)-month intervals thereafter. At every follow-up session, chest and abdominal CT was performed before and, whenever possible, after intravenous administration of a contrast agent with 5-mm collimation. The diagnostic criteria for local tumor progression at our institution were similar to those that have previously been described in the literature [13]. In short, local tumor progression was indicated by the appearance of an irregular, scattered, nodular, or eccentric focus in the ablation zone or by circumferential enlargement of the ablation zone.

Study Endpoint

The endpoint of this study was patient survival after RF ablation of lung oligometastases. Survival time was calculated from the time of the initial RF ablation. The terminal event was death from any cause for the estimation of overall survival (OS) and death from any cause or any cancer recurrence for the estimation of recurrence-free survival (RFS). First, OS and RFS were estimated for all 123 patients as well as for the patients with each type of primary lesion. The OS and RFS rates for the patients with each type of primary lesion were compared to those of the patients with any of the other four primary lesion types.

Second, to determine prognostic factors, various variables were collected, and the cohort was divided into two or three groups per variable. Subsequently, OS and RFS were compared between the groups. The variables analyzed included age (≤65 y or >65 y), sex (male or female), number of metastases (1, 2 or 3–5), size of largest metastasis (≤10 mm, 11–20 mm or >20 mm), previous history of any metastasis (yes or no), concurrent or adjuvant systemic chemotherapy (yes or no), and disease-free interval (≤2 y or >2 y). Disease-free interval was the time from therapy for the primary lesion and manifestation of the first metastasis. In this study, survival was calculated from the time of the initial RF ablation, not from the time of therapy for the first metastasis. Thus, the follow-up period began later for patients with a previous history of metastases. Considering this time lag, the comparison of survival in terms of disease-free interval was confined to the patients for whom lung RF ablation was the first therapy for the metastases. Subsequently, multivariate analyses were performed to determine independent prognostic factors for OS and RFS. The variable of disease-free interval was excluded from the analyses, because data were collected from limited patients as described above. All other variables were included in the analyses.

Statistical Analysis

Survival was estimated with the Kaplan-Meier method and univariate analyses were performed by the log-rank test to compare the survival rates. Multivariate analyses to determine the independent prognostic factors were performed using the Cox proportional-hazards model. For all analyses, a P value of <0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences software (version 22.0; IBM Corp, Armonk, New York).

RESULTS

Concurrent or adjuvant chemotherapy was utilized in 41 patients. There was no mortality related to RF ablation. The median (mean) follow-up period for all 123 patients was 45.7 (52.5) months. After RF ablation, 30% (37/123) of the patients were free from cancer recurrence until the last follow-up, and the remaining 70% (86/123) of the patients had developed recurrence. Seventy-one of the 86 patients with recurrence underwent the treatment for the recurrence. Data on the site of recurrence, the therapy for recurrence, and survival after RF ablation are shown in **Table 2**.

The 5-year OS and RFS rates for all 123 patients were 62% and 25%, respectively (**Figure 1 and Table 3**). The 5-year OS and RFS rates were 70% and 30%, 61% and 16%, 66% and 32%, 33% and 19%, and 47% and 25% for the patients with lung oligometastases from CRC, NSCLC, HCC, EC, and RCC, respectively (**Figure 2, 3** and **Table 3**). The OS rate for patients with lung oligometastases from CRC were significantly (P = 0.042) longer and the OS rate for patients with lung oligometastases from EC were significantly (P = 0.022) shorter than the OS rates for patients with the other four primary lesion types (**Table 3**). In contrast, RFS rate was not significantly different between the five primary lesion types (**Table 3**).

The results of univariate and multivariate analyses performed to determine the factors that influenced OS and RFS in patients with lung oligometastases treated with RF ablation are shown in **Table 4 and Table 5**. In the univariate analyses, a disease-free interval >2 years and female patients were associated with longer OS (P = 0.015 and 0.043, respectively) but were not significantly associated with RFS. A smaller number of lung metastases was significantly associated with longer RFS (P = 0.033). The other variables analyzed, including size of metastases and previous history of metastases, and concurrent or adjuvant chemotherapy were not significantly associated with OS or RFS. In the multivariate analyses, although female patients tended to associate with better OS and smaller number of lung metastases tended to associate with better RFS, there was no independent prognostic factors for OS and RFS.

DISCUSSION

Surgical resection is considered the most radical therapy for lung metastasis. Recent studies have shown that the 5-year survival rates after resection of lung metastases from various primary lesions range from 36% to 46% [14, 15]. The 5-year survival rate after resection of metastases from CRC, HCC, EC, and RCC are 54%–57% [16, 17], 37%–41% [18, 19], 34% [20] and 45% [21], respectively. In this study, the follow-up period started later for the 56 (46%) patients with a previous history of pulmonary metastases than is typical for studies of surgical resection of metastases. Nevertheless, the survival data of our study seem quite promising.

de Baère et al. [5] recently reported the survival outcomes of 566 patients after RF ablation of lung metastases in a multicenter prospective study. The primary tumor type was variable, but it was CRC in 52% of the patients. The median follow-up period was 36 months, and the 5-year OS was 51.5%. Type of primary tumor, disease-free interval, and number of lung metastases were associated with OS. Chua et al. [6] reported prospective survival outcomes of 140 patients with lung metastases treated by RF ablation. The primary tumor type was CRC in 77% of the patients. The median follow-up period was 29 months, and the 3-year and 5-year OS rates were 60% and 45%, respectively. The 3-year and 5-year survival rates after RF ablation of colorectal metastases were 57%–72% [7, 8, 10] and 50%–52% [7, 10], respectively. Our retrospective study revealed a 5-year OS rate of 62% and a median survival time of 90 months for patients with lung oligometastases from 5 types of primary lesion types over a median follow-up period of 46 months. Of note, 30% of the patients survived without cancer recurrence, which indicates that RF ablation is a potentially curative treatment for patients with lung oligometastases. Stereotactic body radiation therapy (SBRT), another local therapy for lung metastases, may be competitive with RF ablation in terms of survival. Recent studies have shown that the 2-year and 5-year OS rates of patients with lung metastases treated with SBRT are 60%–84% and 49%–56%, respectively [14, 22]. Survival outcomes after therapy for lung metastases, regardless of the type of therapy (metastasectomy, RF ablation, or SBRT), are similar.

In this study, the OS rate for patients with metastases from CRC seems longer and the OS rate for patients with metastases from EC seems shorter than the OS rates for patients with the other four primary lesion types. In contrast, RFS does not seem different between the five primary lesion types. This discrepancy between the differences in OS and RFS when comparing the patients with different primary lesion types may mainly be due to differences in the aggressiveness of recurrence among the different primary lesion types.

However, as the number of patients with each primary lesion type was too small, our results cannot be conclusive. Therefore, a larger study is necessary to draw final conclusions on the relationship between survival and primary lesion type.

In our study, longer disease-free interval was significantly associated with better OS in the univariate analysis. However, none of the variables were significantly associated with OS and RFS in the multivariate analyses. Based upon the results, we suggest that RF ablation be considered regardless of the size or number (up to 5) of metastases because neither of these two factors significantly affected OS. Similarly, we suggest that patients with a history of metastasis should also be treated with RF ablation if the previous metastasis completely resolved because survival was not significantly different between patients with a previous history of metastasis and those without it. The patients with a shorter disease-free interval had a significantly shorter OS. This may be due to the more aggressive nature of tumors that progress in a shorter interval. Similar results have been reported in surgical literatures [15, 17, 22, 23].

Our study has various limitations. This was a retrospective, single-center study with a limited population size. The therapies implemented for recurrence after lung RF ablation depended on cancer state and patient condition. In other words, the treatment strategy for recurrence was individualized and was not uniform among patients. The survival outcomes shown in this study resulted not only from lung RF ablation but also from multidisciplinary treatments for previous metastases and recurrence after RF ablation.

Although our survival outcomes seem encouraging, this study did not show any survival advantage of RF ablation over other therapies, such as metastasectomy and SBRT. One may indicate the issue of competing risk when estimating RFS by the Kaplan-Meier method. However, we considered that competing risk was too small to affect the outcomes considerably, because this study included only two patients who were dead without recurrence. Finally, there are residual survival factors to be evaluated. For example, mutations such as KRAS for CRC and epidermal growth factor receptor for NSCLC have prognosis implications. However, data on such mutations were missing in many patients and thus those were not evaluated.

In conclusion, the observed survival outcomes after RF ablation of lung oligometastases from the 5 types of primary lesions seem promising. A longer disease-free interval was significantly associated with better OS.

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Table 1. Characteristics of All 123 Patients Treated by RF Ablation.

Variable		Primary cancer (No. of patients)					
		CRC (52)	NSCLC (33)	HCC (16)	EC (14)	RCC (8)	All (123)
Age (y)	Mean	66	68	62	65	63	66
	Range	37–94	48–84	35–82	44–75	34–77	34–94
Sex	Male	30	23	11	14	6	84
	Female	22	10	5	0	2	39
Follow up period (mo)	Median (mean)	50 (55)	54 (59)	26 (45)	35 (42)	43 (49)	46 (53)
	Range	9–128	5–129	2–121	12–94	28–87	2–129
No. of tumors	1/2/3/4/5	25/15/9/1/2	20/8/3/1/1	4/7/2/2/1	9/4/1/0/0	4/3/0/0/1	62/37/15/4/5
	Median	2	1	2	1	1.5	1
No. of sessions	Single	38	30	7	11	6	92
	Multiple	14	3	9	3	2	31
Tumor size (mm)	Mean	12.0	12.9	12.2	15.0	11.6	12.5
	Range	3–33	2–30	3–50	6–28	3–37	2–50
Electrode type (No. of tumors)	Multitined expandable electrode	84	42	31	12	14	183
	Internally cooled	12	12	6	8	1	39
Previous metastases	Pulmonary only	20	4	7	2	5	38
	Extra pulmonary only	7	3	0	2	1	13
	Both	3	1	1	0	0	5
	None	22	25	8	10	2	67
Concurrent or adjuvant systemic chemotherapy		21	6	3	8	3	41

RF = radiofrequency, CRC = colorectal cancer, NSCLC = non-small cell lung cancer, HCC = hepatocellular carcinoma, EC = esophageal cancer, RCC = renal cell carcinoma.

Table 2. Information on Cancer State and Patient Survival after RF Ablation of Lung Metastases

Variable	Primary cancer (No. of patients)					
	CRC (52)	NSCLC (33)	HCC (16)	EC (14)	RCC (8)	All (123)
Site of recurrence after RF ablation						
None	18	9	4	4	2	37
Lung only	17	14	6	5	3	45
Extra-lung only	13	8	3	3	1	28
Lymph node	3	3		2		8
Liver	5		1			6
Lymph node and liver			1			1
Pleura		4				4
Peritoneum	1	1				2
Bone	1			1		2
Bone and liver			1			1
Brain	2				1	3
Pancreas	1					1
Both (with lung)	4	2	3	2	2	13
Lymph node	4		2	1	1	8
Bone		2				2
Liver			1	1		2
Adrenal					1	1
Recurrence-free interval (mo)						
Median (Mean)	15 (47)	15 (25)	11 (31)	6.2 (41)	29 (41)	15 (29)
Range	1.2–127	1.1–110	1.0–116	1.3–94	8.5–87	1.1–127
Therapy for recurrence after RF ablation						
Local therapy only	23	15	6	5	4	53
RF ablation	13	12	2	2	2	31
Surgery	9	1	1	1	2	14
RT	1	1	1			3
TACE			2			2
RF ablation and RT		1		1		2
RF ablation and surgery				1		1
Systemic chemotherapy only	6	2	2	0	2	12
Both (with systemic chemotherapy)	1	1	0	4	0	6
RT		1		3		4
RF ablation				1		1
Surgery	1					1
None	3	5	4	1	0	13
NA	1	1	0	0	0	2
Cause of death						
Alive	37	16	10	5	4	72
Died of cancer	11	10	4	6	3	34
Died of other disease	4	7	2	3	1	17

RF = radiofrequency, CRC = colorectal cancer, NSCLC = non-small cell lung cancer, HCC = hepatocellular carcinoma, EC = esophageal cancer, RCC = renal cell carcinoma, NA = data not available, RT = radiation therapy, TACE = transcatheter arterial chemoembolization.

Table 3. Results of Survival of the Patients with Lung Oligometastasis from Each Type of Primary Lesion Treated with RF Ablation

Primary cancer	No. of patients	Follow-up period (mo)	Overall survival							Recurrence-free survival						
			Rate (%)						Time (mo)	Rate (%)						Time (mo)
		Median (Mean)	1 y	2y	3y	4y	5y	*P* value*	Median (Mean)	1 y	2y	3y	4y	5y	*P* value*	Median (Mean)
CRC	52	50 (55)	98	89	84	76	70	0.042**	NR (93)	56	43	35	30	30	0.46	15 (47)
NSCLC	33	54 (59)	97	84	76	68	61	0.71	90 (80)	63	32	28	25	16	0.59	15 (33)
HCC	16	26 (45)	94	66	66	66	66	0.85	121 (85)	47	40	40	32	32	0.67	11 (32)
EC	14	35 (42)	93	77	62	44	33	0.022**	42 (50)	50	36	29	29	19	0.47	6 (29)
RCC	8	43 (49)	100	100	70	70	47	0.58	58 (60)	88	75	38	25	25	0.43	29 (41)
All	123	46 (53)	95	83	76	68	62		90 (82)	58	41	33	28	25		17 (41)

RF = radiofrequency, CRC = colorectal cancer, NSCLC = non-small cell lung cancer, HCC = hepatocellular carcinoma, EC = esophageal cancer, RCC = renal cell carcinoma, NR = not reached, *Survival rates were compared between corresponding cancer and other four types with the log-rank test, **statistically significant.

Table 4. Results of Univariate and Multivariate Analyses to Determine Prognostic Factors for Overall Survival in Patients with Lung Oligometastasis Treated with RF Ablation

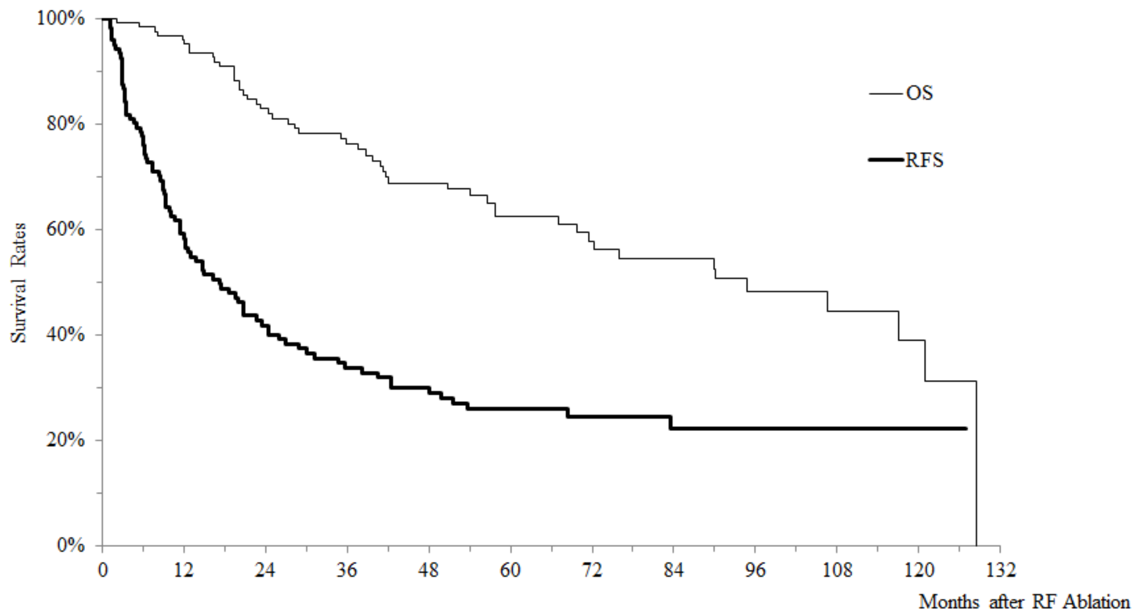
Variable		No. of patients	Univariate analysis				Multivariate analysis	
			Overall survival rate (%)					
			1 y	3y	5y	*P* value	HR (95% CI)	*P* value
Age (y)	≤65	55	95	80	70	0.058	1.00	Ref
	>65	68	96	72	54		1.72 (0.92–3.22)	0.088
Sex	Male	84	94	72	57	0.043*	1.00	Ref
	Female	39	97	85	74		0.50 (0.24–1.04)	0.063
No. of lung metastases	1	62	97	78	60	0.85	1.00	Ref
	2	37	97	77	62		0.67 (0.30–1.50)	0.33
	3–5	24	88	69	69		0.53 (0.21–1.31)	0.17
Largest size of lung metastases (mm)	≤10	34	100	83	78	0.081	1.00	Ref
	11–20	66	97	75	60		0.50 (0.20–1.25)	0.14
	>20	23	83	70	51		0.87 (0.43–1.75)	0.67
Previous history of metastases	No	67	94	74	59	0.55	1.00	Ref
	Yes	56	97	78	66		1.00 (0.55–1.83)	0.99
Concurrent or adjuvant systemic chemotherapy	No	82	95	75	60	0.59	1.00	Ref
	Yes	41	95	78	69		0.86 (0.42–1.79)	0.69
Disease-free interval (y)**	≤2	34	88	63	45	0.015*		
	>2	33	100	87	75			

RF = radiofrequency, HR = hazard ratio, CI = confidence interval, Ref = reference value. *statistically significant, **Univariate analysis was performed confined to patients in whom RF ablation of lung metastases was the first treatment of metastasis, and this variable was excluded from multivariate analysis.

Table 5. Results of Univariate and Multivariate Analyses to Determine Prognostic Factors for Recurrence-free Survival in Patients with Lung Oligometastasis Treated with RF Ablation

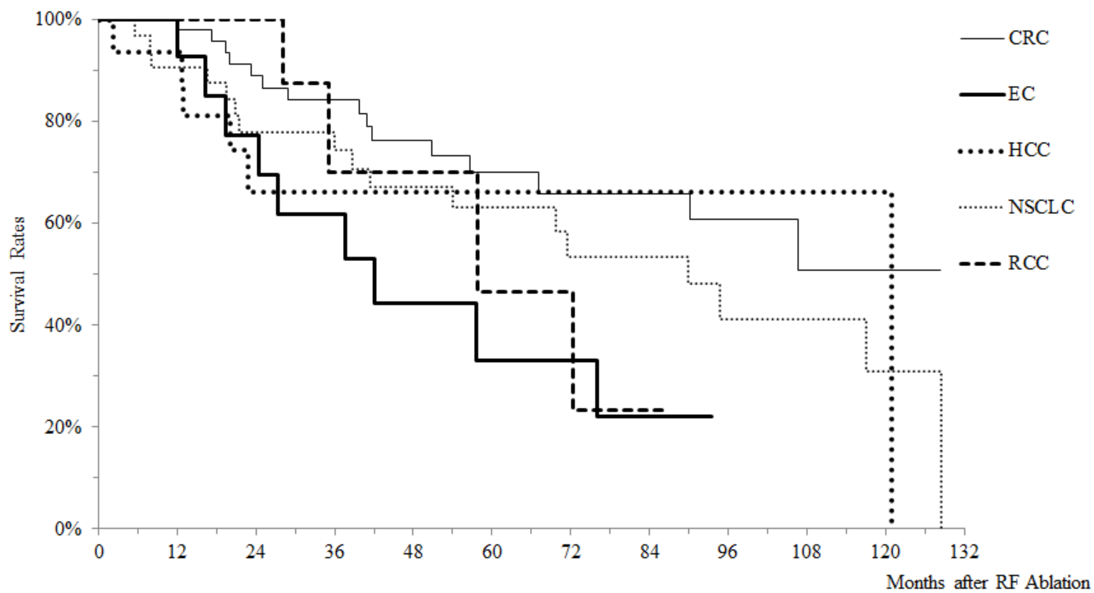
Variable		No. of patients	Univariate analysis				Multivariate analysis	
			Recurrence-free survival rate (%)					
			1 y	3y	5y	*P* value	HR (95% CI)	*P* value
Age (y)	≤65	55	56	35	27	0.97	1.00	Ref
	>65	68	60	31	22		1.06 (0.69–1.63)	0.80
Sex	Male	84	57	29	22	0.17	1.00	Ref
	Female	39	62	41	31		0.73 (0.44–1.21)	0.22
No. of lung metastases	1	62	67	38	30	0.033*	1.00	Ref
	2	37	56	31	22		0.58 (0.33–1.02)	0.059
	3–5	24	38	22	15		0.75 (0.40–1.41)	0.38
Largest size of lung metastases (mm)	≤10	34	62	36	33	0.87	1.00	Ref
	11–20	66	55	30	19		1.16 (0.55–2.44)	0.71
	>20	23	63	37	31		1.44 (0.76–2.75)	0.26
Previous history of metastases	No	67	63	33	24	0.69	1.00	Ref
	Yes	56	53	33	27		1.03 (0.68–1.60)	0.85
Concurrent or adjuvant systemic chemotherapy	No	82	62	46	26	0.34	1.00	Ref
	Yes	41	51	32	22		1.23 (0.78–1.95)	0.37
Disease-free interval (y)**	≤2	34	59	28	24	0.83		
	>2	33	67	37	23			

RF = radiofrequency, HR = hazard ratio, CI = confidence interval, Ref = reference value. *statistically significant, **Univariate analysis was performed confined to patients in whom RF ablation of lung metastases was the first treatment of metastasis, and this variable was excluded from multivariate analysis.



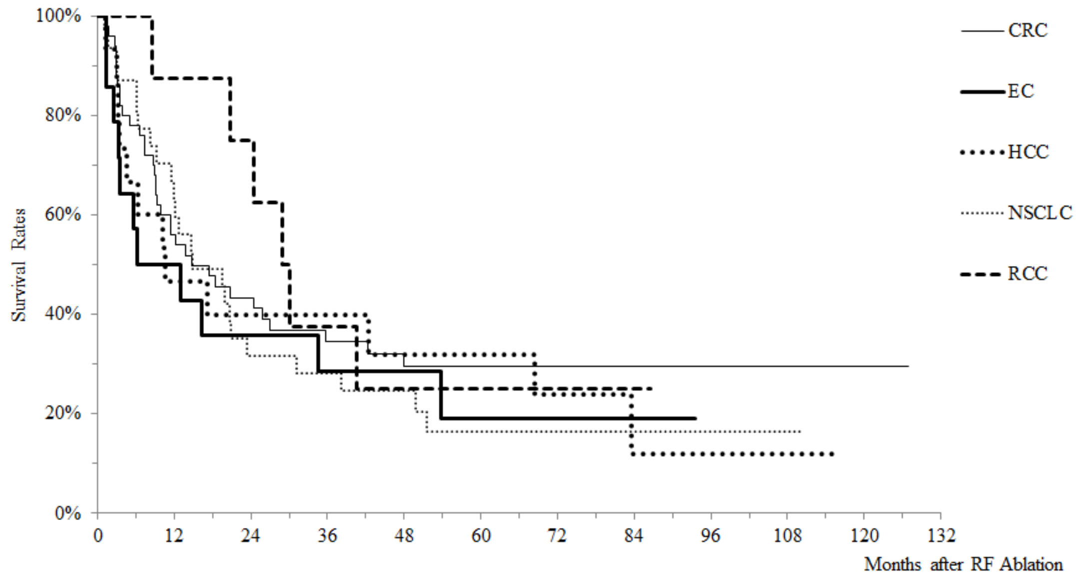
OS	123	113	88	71	59	44	35	28	19	11	5 No. of Patients at Risk
RFS	123	66	45	35	27	17	14	10	7	4	1

Figure 1. Overall survival rates and recurrence-free survival rates of 123 patients after radiofrequency ablation estimated by the Kaplan-Meier method.



CRC	52	48	38	32	27	19	15	13	11	4	3 No. of Patients at Risk
NSCLC	33	29	24	21	17	16	11	10	6	5	1
HCC	16	15	8	7	7	4	4	3	2	2	1
EC	14	13	10	7	4	3	3	1	0	0	0
RCC	8	8	8	4	4	2	2	1	0	0	0

Figure 2. Overall survival rates of patients with each type of primary cancer.



CRC	52	27	20	15	12	8	6	5	4	2	1	No. of Patients at Risk
NSCLC	33	18	9	8	6	2	2	2	2	1	0	
HCC	16	7	5	5	4	4	3	1	1	1	0	
EC	14	7	5	4	3	2	2	1	0	0	0	
RCC	8	7	6	3	2	1	1	1	0	0	0	

Figure 3. Recurrence -free survival rates of patients with each type of primary cancer.