Long-term results of radiofrequency ablation in colorectal lung metastases: Single center experience

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Abstract. This study was undertaken to evaluate long-term results of radiofrequency (RF) ablation in patients with colorectal lung metastases and to stratify patients benefitting from lung RF ablation. Lung RF ablation was performed in 78 patients with 198 colorectal lung metastases. Safety, local tumor progression, and survival were evaluated retrospectively. The mean follow-up period after the 140 lung RF ablation sessions was 24.6±7.6 months. Pneumothorax and pleural effusion requiring chest tube placement occurred respectively in 18 (12.9%, 18/140) and 2 (1.4%, 2/140) sessions. The respective 1-, 3- and 5-year local tumor progression rates were 10.1% (95% CI, 2.9-17.3%), 20.6% (95% CI, 8.9-22.2%) and 20.6% (95% CI, 8.9-22.2%). The 1-, 3- and 5-year survival rates were 83.9% (95% CI, 75.2-92.7%), 56.1% (95% CI, 41.7-70.5%) and 34.9% (95% CI, 18.0-51.9%), with median survival time of 38.0 months. Univariate analysis revealed maximum tumor diameter of 3 cm or less, single-lung metastasis, lack of extrapulmonary metastasis and normal carcinoembryonic antigen (CEA) level as better prognostic factors. The latter two were significant independent prognostic factors. The 1-, 3- and 5-year survival rates were 97.7% (95% CI, 93.3-100%), 82.5% (95% CI, 68.2-96.8%) and 57.0% (95% CI, 34.7-79.2%) in 54 patients with no extrapulmonary metastases and 96.9% (95% CI, 90.8-100%), 86.1% (95% CI, 71.1-100%) and 62.5% (95% CI, 36.3-88.6%) in 33 patients with negative CEA levels. Lung RF ablation is a safe and useful therapeutic option. These identified prognostic factors will help to stratify patients who benefit from lung RF ablation.

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Introduction

Colorectal cancer is a common malignancy throughout the world. Reportedly, 40-50% of all patients who undergo curative surgery for colorectal cancer will ultimately develop recurrence and die (1,2). Following the liver, the lung is the second most common site of distant metastasis (1-3): lung metastases occur in 10-20% of patients (3). Pulmonary metastasectomy has been considered the only therapeutic option providing long survival to patients (4-6). However, lung metastasectomy is applicable in only 2-4% of patients because of the multiplicity of lung metastases and presence of extrapulmonary disease (2,3). In most cases, patients with stage IV colorectal cancer receive palliative care. Despite recent development of new regimens using fluorouracil and leucovorin with irinotecan or oxaliplatin, survival following chemotherapy falls short of that following pulmonary resection (7,8). The median survival after systemic chemotherapy is reportedly 14.8-27.5 months; the 5-year survival rate is still less than 10% (7,8).

It is therefore important to explore other more effective therapeutic options for the treatment of unresectable lung metastases from colorectal cancer. Several studies have already shown the safety, feasibility, and good anticancer effects of radiofrequency (RF) ablation for treatment of colorectal lung metastases (9-16). The 3-year survival rates are reported as 46-48%, with median survival time of 31-33 months (12-14). However, long-term results of lung RF ablation are not clear.

For this study, long-term results after lung RF ablation were studied retrospectively to evaluate whether lung RF ablation is an effective therapeutic option for the treatment of lung metastases in patients with colorectal cancer.

Materials and methods

Study design. This retrospective study was approved by the authors' institutional review board with a waiver of informed consent. Informed consent to perform lung RF ablation had been obtained from all patients before lung RF ablation was performed.

Patients. From February 2002 to July 2008, 81 consecutive patients with colorectal cancer underwent lung RF ablation for the treatment of lung metastases. Three patients were lost to follow-up. Consequently, 78 patients (96%, 78/81) with 198 lung tumors were enrolled in this study (Table I). Of them, 53 patients were men (67.9%, 53/78) and 25 were women (32.1%, 25/78) with a mean age of 66.1±9.8 years (range, 40-87 years). Primary tumors were colon cancer in 41 patients (52.6%, 41/78) and rectal cancer in 37 patients (47.4%, 37/78). Lung metastasis appeared at 33.4±26.6 months (range, 0-145 months), on average, after resection of primary lesions. The diagnosis of lung metastasis was based on results of imaging findings obtained through serial lung CT studies. New lung masses that had increased in size were considered as lung metastases. Lung biopsy was done in eight patients (8/78, 10.3%) for whom imaging findings were not typical for lung metastases.

Before lung RF ablation, 19 patients (24.4%, 19/78) had received complete resection of lung metastases. Liver metastases had been resected completely (n=10) or ablated by RF ablation (n=16) in 26 patients (33.3%, 26/78). Chemotherapy had been performed in 68 patients (87.2%, 68/78). Extrapulmonary metastases were found in 24 patients (30.1%, 24/78) at the time of lung RF ablation. They were in the lymph node in 12 patients, in the liver in 9 patients, in the pelvic cavity (local recurrence) in 7 patients, in the bone in 2 patients, in the spleen in 1 patient, and in the brain in 1 patient. Of the 24 patients, 10 patients had extrapulmonary metastases in two or more organs. It is our policy to perform systemic chemotherapy after lung RF ablation. Following lung RF ablation, 74 patients (94.9%, 74/78) received systemic chemotherapy. The other four patients received no chemotherapy because of refusal by two patients, and advanced age and renal dysfunction in each of the other two patients.

The mean maximum tumor diameter was 2.0±1.0 cm (range, 0.6-6.0 cm). Of 78 patients, 70 (89.7%, 70/78) had small tumors measuring ≤3 cm; the other 8 patients (10.3%, 8/78) had large tumors >3 cm maximum diameter. Lung tumors were singular in 34 patients (43.6%, 34/78) and multiple in the other 44 patients (56.4%, 44/78); they were found in the lung unilaterally in 49 patients (62.8%, 49/78) and in the lungs bilaterally in the other 29 patients (37.2%, 29/78). Carcinoembryonic antigen (CEA) was negative in 33 patients (42.3%, 33/78) and positive in the other 45 patients (57.7%, 45/78) at the time of lung RF ablation. Safety, local tumor progression, intrapulmonary recurrence, and overall survival were evaluated.

Table I. Patient backgrounds.

Demography	
Age (years)	66.1±9.8
≤65	29 (37.2%)
>65	49 (62.8%)
Sex	
Male	53 (67.9%)
Female	25 (32.1%)
Primary tumor	
Colon	41 (52.6%)
Rectum	37 (47.4%)
Disease-free interval (months)	33.4±26.6
≤3 years	56 (71.8%)
>3 years	22 (28.2%)
Previous lung metastasectomy	
No	59 (75.6%)
Yes	19 (24.4%)
Previous hepatectomy or liver RF ablation	
No	52 (66.7%)
Yes	26 (33.3%)
Previous chemotherapy	
No	10 (12.8%)
Yes	68 (87.2%)
Extrapulmonary metastasis	
No	54 (69.2%)
Yes	24 (30.8%)
Tumor characteristics	
Maximum tumor diameter (cm)	2.0±1.0
≤3 cm	70 (89.7%)
3.1-6.0 cm	8 (10.3%)
No. of tumors	2.6±1.8
Single	34 (43.6%)
Multiple (2-9)	44 (56.4%)
Distribution	
Unilateral lung	49 (62.8%)
Bilateral lungs	29 (37.2%)
Carcinoembryonic antigen	
Negative (≤6.0 ng/ml)	33 (42.3%)
Positive (>6.0 ng/ml)	45 (57.7%)

RF, radiofrequency.

Pretreatment work-up. Routine physical examination, laboratory tests, and imaging studies including a chest radiograph, chest, abdomen, and pelvic computed tomography (CT), and brain magnetic resonance (MR) imaging studies were performed before lung RF ablation in all patients.

Lung RF ablation. Lung RF ablation was performed on an inpatient basis. Three radiologists (K.Y., A.N. and H.T.) performed lung RF ablation. Lung RF ablation was performed under moderate sedation and local anesthesia. Fentanyl citrate (Phentanest; Daiichi Sankyo Co., Ltd., Tokyo) at a dose of 0.1-0.2 mg was used for analgesia; lidocaine (Xylocaine; Astellas Pharma Inc., Tokyo) was used for local anesthesia. Antibiotics (Cefazolin, Cefamezin; Astellas Pharma Inc., Tokyo) were administered prophylactically before and for 1-2 days after RF ablation. Real-time CT fluoroscopy (X-Vigor or Aquilion; Toshiba Corp., Tokyo) was used to place the RF electrode in the tumors. An internally cooled electrode (Cool-Tip RF Ablation System; Valleylab, Boulder, CO) was used. The electrode was placed in the center of the tumor in cases where the tumor size was ≤2 cm. The electrode was placed

sequentially at 2-4 different sites in the tumor based on the tumor size and shape when the tumor size was >2 cm. After the electrode was connected with a generator (Series CC-1; Valleylab, Boulder, CO), RF energy was applied for 12 min at each tumor site using an impedance-control algorithm.

At most, three lung tumors were treated in a single day. The remaining tumors were treated using RF ablation the following week.

Technical success was defined as correct placement of RF electrode into all tumor targets with completion of the planned ablation protocol.

Follow-up. Patients were followed-up by two radiologists (K.Y. and H.T.), two gastrointestinal surgeons (Y.I. and M.K.), and two thoracic surgeons (M.T. and H.S.). Routine physical examination, laboratory tests, and measurement of CEA levels were performed every month, as well as chest, abdomen, and pelvic CT studies every 3-4 months.

Local tumor progression was defined as tumor growth from the zone of ablation on CT images (11,17,18). Control of ablated tumors was defined as involution of the ablation zone over time.

Complications. Major complications were assessed based on previously described guidelines of image-guided tumor ablation (17). Complications were assessed based on the number of ablation sessions. The definition of a major complication is an event that engenders substantial morbidity and disability, increases the level of care, or results in hospital admission or a substantially lengthened hospital stay. All other complications were considered minor.

Statistical analysis. Local tumor progression rates were calculated using the Kaplan-Meier method. They were compared between patients with small (≤3 cm) tumors and those with intermediate or large tumors (3.1-6.0 cm) using the log-rank test.

The cumulative survival curves were generated based on patient and tumor characteristics (Table I) using the Kaplan-Meier method. They were compared using the log-rank test (univariate analysis). For overall survival, the time from lung RF ablation to the last follow-up visit or death from any cause was used. The stepwise regression model was also used to assess the baseline predictors for overall survival rates (multivariate analysis). Data are expressed as a mean ± standard deviation. A p-value of <0.05 was inferred as statistically significant. Statistical analyses were performed using commercially available software (SPSS ver. 15; SPSS Inc., Japan, Tokyo).

Results

RF ablation. In all, 140 lung RF sessions were performed; RF electrodes were placed into all tumor targets with completion of the planned ablation protocol completed. Therefore, the technical success rate was 100%.

Complications. No death was related to the RF procedure. Pneumothorax developed in 31 of 140 RF sessions (22.1%). Chest tube placement was necessary in 18 sessions (12.9%). Chest tube placement was also necessary in two other sessions because of aseptic pleuritis (1.4%). No other complication was noted. Consequently, the minor and major complication rates were, respectively, 9.3% (13/140) and 14.3% (20/140).

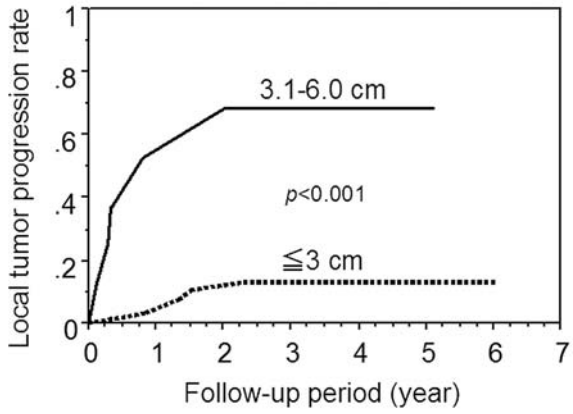


Figure 1. Local tumor progression rates based on the maximum diameter of lung tumors. The maximum diameter of the lung tumor is a significant factor affecting local tumor progression. The 1-, 3- and 5-year local tumor progression rates are 5.1% (95% CI, 0-10.8%), 13.8% (95% CI, 2.9-14.6%) and 13.8% (95% CI, 2.9-14.6%) in patients with small lung tumors (≤3 cm). They were 53.1% (95% CI, 16.6-89.7%), 68.8% (95% CI, 33.8-100%) and 68.8% (95% CI, 33.8-100%) in patients with lung tumors >3 cm (3.1-6.0 cm) (p<0.001).

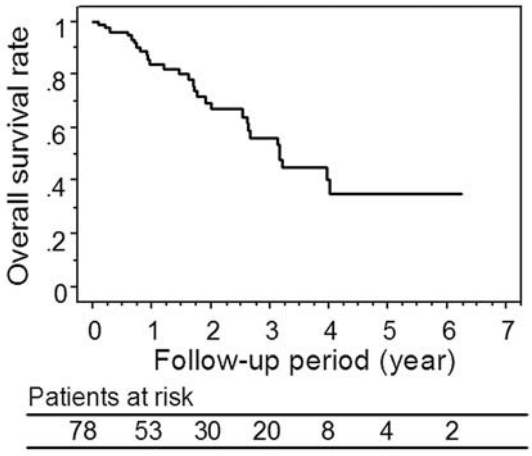
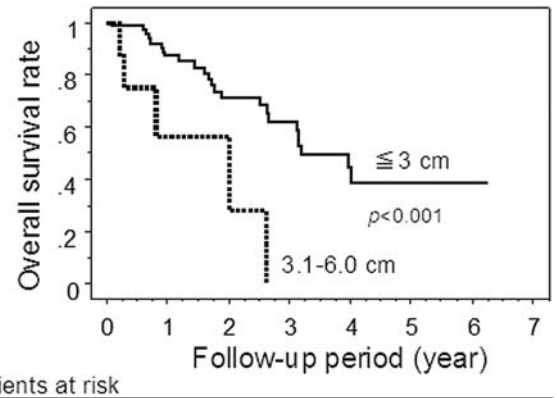


Figure 2. Overall survival in all patients. The 1-, 3- and 5-year survival rates are 83.9% (95% CI, 75.2-92.7%), 56.1% (95% CI, 41.7-70.5%) and 34.9% (95% CI, 18.0-51.9%), respectively, for all 78 patients. The median survival time is 38.0 months.

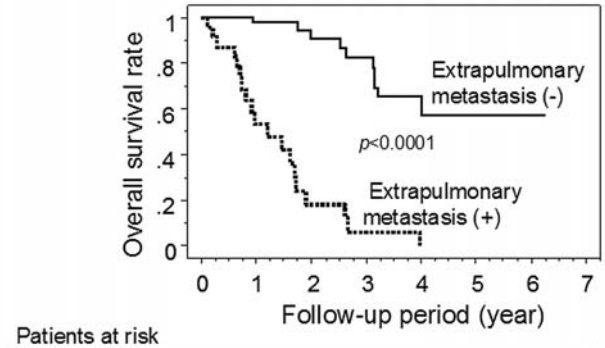
Local tumor progression. The mean follow-up period was 24.6±17.6 months (range, 6.0-84.1 months) for all patients. Local tumor progression was found in 11 patients (14.1%, 11/78). The 1, 3- and 5-year local tumor progression rates were, respectively, 10.1% [95% confidence interval (CI), 2.9-17.3%], 20.6% (95% CI, 8.9-22.2%) and 20.6% (95% CI, 8.9-22.2%). A significant difference was found in the local tumor progression rate in patients with tumors measuring ≤3 cm and those >3 cm (Fig. 1).

Survival and prognostic factors. During the follow-up period, 29 of 78 patients (37.2%) died. Death occurred in 28 patients (96.6%, 28/29) because of cancer progression and in 1 (3.4%,



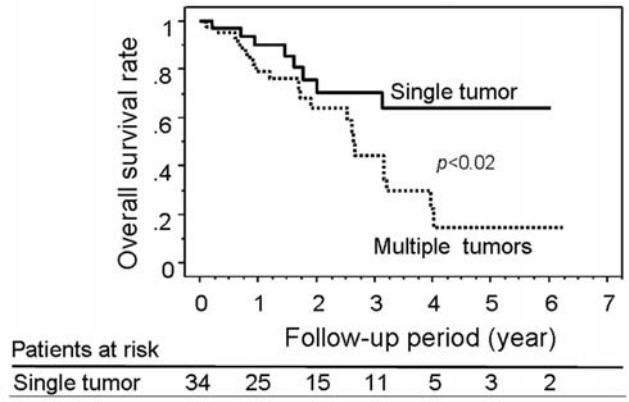
Patients at risk							
≦3cm	70	51	28	20	8	4	2
3.1-6.0cm	8	2	2	0			

Figure 3. Overall survival based on the maximum diameter of lung tumors. The small tumor diameter (≤3 cm) is a significantly better prognostic factor. The 1-, 3- and 5-year survival rates are 86.9% (95% CI, 78.5-95.4%), 61.9% (95% CI, 47.2-76.6%) and 38.5% (95% CI, 20.2-56.8%) in patients with small (≤3 cm) lung tumors. They are 56.3% (95% CI, 17.3-95.2%), 0% and 0% in patients with intermediate or large tumors (3.1-6.0 cm) (p<0.001).



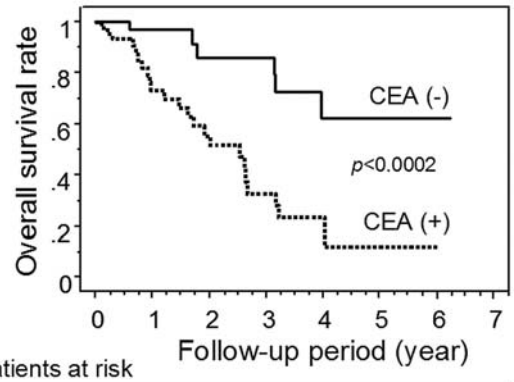
Patients at risk							
Extrapulmonary metastasis (-)	54	43	27	19	8	4	2
Extrapulmonary metastasis (+)	24	10	3	1	0		

Figure 5. Overall survival based on extrapulmonary metastasis. Absence of extrapulmonary metastasis is a significantly better prognostic factor. The 1-, 3- and 5-year survival rates are 97.7% (95% CI, 93.3-100%), 82.5% (95% CI, 68.2-96.8%) and 57.0% (95% CI, 34.7-79.2%) in patients without extrapulmonary metastasis. They are 53.3% (95% CI, 31.7-74.9%), 6.0% (95% CI, 0-17.3%) and 0% in patients with extrapulmonary metastasis (p<0.0001).



Patients at risk							
Single tumor	34	25	15	11	5	3	2
Multiple tumors	44	28	15	9	3	1	

Figure 4. Overall survival based on the number of lung tumors. Single-lung metastasis is a significantly better prognostic factor. The 1-, 3- and 5-year survival rates are 90.1% (95% CI, 79.3-100%), 70.5% (95% CI, 51.6-89.5%) and 64.1% (95% CI, 43.1-85.1%) in patients with single-lung tumor. They are 79.1% (95% CI, 66.2-92.1%), 44.1% (95% CI, 24.2-64.1%) and 14.7% (95% CI, 0-32.0%) in patients with multiple lung tumors (p<0.02).



Patients at risk							
CEA (-)	33	28	16	13	6	3	1
CEA (+)	45	25	14	7	2	1	1

Figure 6. Overall survival based on carcinoembryonic antigen (CEA). Negative CEA is a significantly better prognostic factor. The 1-, 3- and 5-year survival rates are 96.9% (95% CI, 90.8-100%), 86.1% (95% CI, 71.1-100%) and 62.5% (95% CI, 36.3-88.6%) in negative CEA patients. They are 73.3% (95% CI, 58.9-87.7%), 32.8% (95% CI, 14.3-51.3%) and 11.7% (95% CI, 0-30.1%) in positive CEA patients (p<0.0002).

1/29) because of cerebral infarction. The 1-, 3- and 5-year survival rates were 83.9% (95% CI, 75.2-92.7%), 56.1% (95% CI, 41.7-70.5%) and 34.9% (95% CI, 18.0-51.9%), respectively, for all patients (Fig. 2). The median survival time was 38.0 months.

Maximum tumor diameter of ≤3 cm (Fig. 3), single-lung metastasis (Fig. 4), lack of extrapulmonary metastasis (Fig. 5), and normal carcinoembryonic antigen (CEA) level (Fig. 6) were identified using univariate analysis as better prognostic factors (Table II). In the multivariate analysis, absence of extrapulmonary metastasis (hazard ratio, 0.098; 95% CI, 0.040-0.241; p<0.0001) and the normal CEA level (hazard ratio, 0.288; 95% CI, 0.107-0.774; p<0.02) were found to be significant independent factors affecting the prognosis.

Discussion

The results of this retrospective study indicate that lung RF ablation is a safe and effective therapeutic option for treatment of unresectable colorectal lung metastases. Pneumothorax was the most frequent complication in the present study, as results of previous studies have already suggested (9-16,19). Chest tube placement was required in 14.3% of the RF sessions in patients with pneumothorax and aseptic pleuritis. The complication rates recorded in this study closely resembled those reported previously (9-16,19).

Information on the 5-year survival rate following lung RF ablation remains scarce. Simon *et al* reported a good 5-year survival rate of 58% in 18 patients with colorectal lung

Table II. Survival based on pretreatment baseline.

	n	Survival rate (%)			MST (month)	P-value
		1-year	3-year	5-year		
Age (years)						
≤65	29	79.6	60.6	30.3	37.9	0.59
>65	49	86.5	53.4	38.2	47.5	
Sex						
Male	53	82.6	66.3	38.0	46.5	0.30
Female	25	86.6	31.0	31.0	30.5	
Primary tumor						
Colon	41	80.6	60.7	40.9	47.5	0.34
Rectum	37	87.8	50.2	NA	37.5	
Disease-free interval						
≤3 years	56	80.8	54.0	36.0	37.9	0.42
>3 years	22	93.3	62.2	33.2	38.4	
Previous lung metastasectomy						
No	59	83.1	62.8	34.9	37.5	0.44
Yes	19	86.7	66.9	35.7	47.5	
Previous hepatectomy or liver RF ablation						
No	52	79.9	55.1	42.4	37.9	0.83
Yes	26	90.0	64.6	32.3	38.0	
Previous chemotherapy						
No	10	100	53.3	53.3	NA	0.23
Yes	68	81.4	55.4	30.8	37.9	
Extrapulmonary metastasis						
No	54	97.7	82.5	57	NA	<0.0001
Yes	24	53.3	6	0	14.4	
Maximum tumor diameter (cm)						
≤3 cm	70	86.9	61.9	38.5	38.4	<0.001
3.1-5 cm		8	56.3	0	24.0	
No. of tumors						
Single	34	90.1	70.5	64.1	NA	<0.02
Multiple (2-9)	44	79.1	44.1	14.7	31.7	
Distribution						
Unilateral lung	49	86.2	58.8	44.9	48.3	0.30
Bilateral lungs	29	80.6	52.1	21.7	37.9	
Carcinoembryonic antigen						
Negative (≤6.0 ng/ml)	33	96.9	86.1	62.5	NA	<0.001
Positive (>6.0 ng/ml)	45	73.3	32.8	11.7	30.5	
Total	78	83.9	56.1	34.9	38.0	

RF, radiofrequency; MST, median survival time; NA, not applicable.

metastasis following lung RF ablation (10), but no details are described in their study.

The 5-year survival rate achieved in this study was 34.9% with median survival time of 38.0 months. These results seem to be better than those following chemotherapy (7,8). This finding suggests that the combination of lung RF ablation with systemic chemotherapy improves prognosis because most patients received systemic chemotherapy before and after lung RF ablation. Inoue *et al* reported a significant superiority in combination therapy to achieve a 3-year survival rate that is better than that obtained using systemic chemotherapy alone (87.5 vs. 33.3%) (20).

Four variables were identified as prognostic factors in this study. There is apparently some similarity of prognostic factors in lung RF ablation to those in metastasectomy. Given that both lung metastasectomy and lung RF ablations are locoregional treatments and that the local tumor progression rate following lung RF ablation becomes close to 0%, it is reasonable that similar prognostic factors be identified. Extrapulmonary metastasis and the CEA level were significantly independent prognostic factors that were identified through multivariate analyses. The 5-year survival (57%) in patients with no extrapulmonary metastasis is comparable to that following lung metastasectomy. The 5-year survival rates following lung metastasectomy have been reported as 39.6-61.4% (4-6). Given that the presence of extrapulmonary metastasis is an exclusion criterion for lung metastasectomy, this finding is noteworthy (2,3).

The results suggest that previous lung and/or liver metastases are not negative prognostic factors when the metastases were treated completely by lung and liver resection and liver RF ablation before lung RF ablation. Yan *et al* reported that lung RF ablation is a useful therapeutic option for treatment of patients who had previously undergone hepatectomy for colorectal metastasis (15).

The CEA level is also known to be a significant prognostic factor in patients with lung metastases from colorectal cancer who underwent metastasectomy and RF ablation (4,5,14,21). In fact, CEA is a complex of glycoprotein produced by 90% of colorectal cancers; it contributes to the malignant charac-teristics of a tumor (22). This antigen promotes mutual adhesion of tumor cells or host cells (23). Tumor cells in aggregates have an increased capacity to arrest in a capillary bed and therefore have increased potential for metastasis (23).

In addition to extrapulmonary metastasis and the CEA level, the maximum tumor diameter and number were found, using univariate analysis, to be significant prognostic factors. Results of some studies have also shown that tumor size is a significant prognostic factor in patients who receive lung RF ablation, irrespective of the primary cancer (9-11,14). That result might be related to local tumor control. Although the 5-year local progression rate was 13.8% for patients with small tumors, it was as high as 68.8% for those with intermediate or large tumors in this study. Results of previous studies underscore the difficulty in controlling tumors of size greater than 3 cm using lung RF ablation (9,10,12). Given that control of treated lesions is an important prognostic factor in patients with metastatic lung tumors (24), it is reasonable that the tumor size is a prognostic factor following lung RF ablation. Moreover, these findings suggest a limited capability of RF ablation to treat large tumors.

Some reports have described that tumor number is a prognostic factors in patients who receive metastasectomy, as shown also by results of the present study (4,21). However, results of other studies show that the tumor number is not a prognostic factor following lung metastasectomy or lung RF ablation (5,14). This controversy can be resolved through examination of a larger patient series.

On the other hand, patients with bilateral lung metastases are poor candidates for surgical intervention (5). In the present study, tumor distribution was not a prognostic factor, as Yan *et al* reported (14). These findings suggest an advantage of lung RF ablation over surgical intervention. The lesser invasiveness of the former appears to support the indication of lung RF ablation.

The retrospective character of this study is a study limitation. Despite this limitation, these encouraging results suggest a useful framework for future prospective studies and randomized trials examining systemic chemotherapy and pulmonary metastasectomy.

In conclusion, lung RF ablation is a safe and effective treatment in selected patients with unresectable lung metastases from colorectal cancer. Prognostic factors identified in this study will help to stratify patients who would benefit from lung RF ablation.

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