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Does tumor type affect local control by radiofrequency ablation in the lungs?

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ABSTRACT

Objective: : To retrospectively evaluate the effect of tumor type on local control by radiofrequency ablation in the lungs.
Materials and methods: : This study included 252 lung tumors (mean size, 13.5 mm) in 105 patients (73 men and 32 women; mean age, 66.6 years) who underwent radiofrequency ablation with a multitined expandable electrode. Those tumors comprised five tumor types: primary lung cancer ($n=35$) and pulmonary metastases from colorectal cancer ($n=117$), lung cancer ($n=23$), renal cell carcinoma ($n=49$), and hepatocellular carcinoma ($n=28$). Local control was evaluated with contrast-enhanced computed tomography. The overall local control rates were estimated as well as those for each tumor type using the Kaplan-Meier analysis. Local control rates for a given tumor type were compared with those for the four other types. Then, multivariate multilevel analysis was performed using the variables of tumor type, tumor size, contact with a vessel or bronchus, and procedure period.
Results: : The overall local control rates were 97%, 86%, 81%, and 76% at 6, 12, 18, and 24 months, respectively. Local control rates varied among the tumor types, and metastatic colorectal cancer showed significantly ($P=.023$) higher local control rates than those of the four other types. However, multivariate analysis indicated that the relative risk of local progression for a given tumor type was comparable to the risks for the four other types.
Conclusion: : Tumor type per se did not significantly influence local control.

1. Introduction

Primary lung cancer is currently the most common cause of cancer-related death. The lung is one of the most common organs in which metastatic deposits may adhere from various primary sites. Surgical resection is considered to provide the best opportunity for cure of lung cancer, whether primary or metastatic. However, surgery is not a feasible option in a number of patients with lung cancer. Thus, many studies have focused on an alternative therapy for lung cancer. Radiofrequency (RF) ablation has been rapidly gaining popularity as a local therapy to treat both primary and metastatic lung cancer mainly in inoperable patients [1–12].

Various studies have shown that tumor size is a key factor for local control after RF ablation of lung tumors [1–4]. In addition to size, a number of tumor characteristics related to cytology, pathophysiology, and biology possibly affect local control outcomes. Considering that these characteristics may vary with the tumor type, the tumor type may be assumed to affect local control outcomes. However, the effect of tumor type on local control is poorly understood. Therefore, the purpose of the present study is to retrospectively evaluate the effect of tumor type on local control by RF ablation in the lungs.

2. Materials and methods

Approval from the institutional review board and informed consent from the patients were obtained before performing RF ablation of lung tumors. Our institutional review board also gave us an approval and a waiver of informed consent for our retrospective study.

2.1. Study population

The characteristics of patients and tumors are summarized in Table 1. This study included a total of 252 tumors (mean long-axis diameter, 13.5 ± 7.1 mm) in 105 patients (73 men and 32 women; mean age, 66.6 ± 11.4 years), including primary lung cancer ($n=35$ in 32 patients) and pulmonary metastases from colorectal cancer (CRC, $n=117$ in 40 patients), primary lung cancer ($n=23$ in 13

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Table 1
Patient, tumor, and ablation characteristics in each tumor type.

Variables		Primary lung cancer	Pulmonary metastases from				Overall
			Colorectal cancer	Lung cancer	Renal cell carcinoma	Hepatocellular carcinoma	
Patient characteristics							
No. of patients		32	40	13	13	7	105
Age, y	Mean ± SD	73.5* ± 10.5	62.5* ± 9.9	68.6 ± 11.6	63.4 ± 9.7	60.3 ± 10.8	66.6 ± 11.4
Sex	Men/Women	19/13	28/12	9/4	11/2	6/1	73/32
Chemotherapy or immunotherapy after RF ablation	Yes/No	1/31*	19/21*	0/13*	8/5*	4/3	32/73
Tumor characteristics							
No. of tumors		35	117	23	49	28	252
Tumor size (mm)	Mean ± SD	20.0* ± 8.4	11.6* ± 6.2	14.2 ± 5.5	13.7 ± 6.5	12.5 ± 6.6	13.5 ± 7.1
Tumor location	Central/peripheral	6/29	23/94	5/18	11/38	6/22	51/201
Contact with vessel or bronchus	Yes/No	16/19	30/87*	8/15	23/26	13/15	90/162
Procedure period	First 2 years/later years	8/27	41/76	4/19*	28/21*	14/14	95/157
Follow-up period, mo	Mean ± SD	16.4 ± 7.7	16.4 ± 9.2	16.2 ± 10.0	18.0 ± 7.5	9.6* ± 3.1	15.9 ± 8.5
Ablation characteristics							
Maximum power (W)	Mean ± SD	79.9* ± 46.0	48.1* ± 33.6	62.4 ± 41.7	49.4 ± 38.3	40.4 ± 25.9	53.2 ± 38.1
Ablation time (min)	Mean ± SD	28.3* ± 11.3	18.6* ± 10.8	20.4 ± 8.3	20.0 ± 10.3	20.8 ± 29.4	20.5 ± 14.2
Array diameter of electrode	2 cm/3 cm/3.5 or 4 cm	19/9/7*	96/17/4	18/2/3	43/5/1	22/6/0	198/39/15
No. of overlapping ablations	Mean ± SD	2.5* ± 1.1	2.0* ± 0.9	2.0 ± 0.9	2.3 ± 1.0	2.1 ± 1.6	2.1 ± 1.1

Note: SD = standard deviation.
* The difference is statistically significant compared with other four types.

patients), renal cell carcinoma (RCC, $n = 49$ in 13 patients), and hepatocellular carcinoma (HCC, $n = 28$ in 7 patients). All the cases of primary lung cancer were diagnosed on the basis of histological evidence. The histological type of the primary lung cancer was adenocarcinoma ($n = 31$ in 28 patients), squamous cell carcinoma ($n = 3$ in 3 patients), or small cell cancer ($n = 1$ in 1 patient). In the cases of pulmonary metastases from lung cancer, the histological type of the primary lung cancer was adenocarcinoma ($n = 20$ in 10 patients) or squamous cell carcinoma ($n = 3$ in 3 patients). Pulmonary metastases were diagnosed without histological proof; the diagnoses were based on radiological images possibly accompanied with elevation of the tumor marker, except for 3 patients with metastatic CRC (4 tumors) and 5 patients with metastasis from lung cancer (7 tumors) who underwent CT-guided lung biopsy before RF ablation.

All 252 tumors were subjected to RF ablation with a multitined expandable electrode between October 2003 and December 2007, and the patients were followed up for ≥6 months. None of the patients underwent RF ablation in combination with radiation therapy or concurrent chemotherapy. After RF ablation, 24 patients (90 tumors) underwent systemic chemotherapy; 8 patients with RCC (42 tumors) underwent systemic immunotherapy.

2.2. RF ablation techniques

RF ablation was performed percutaneously under CT fluoroscopic guidance (Asteion; Toshiba, Tokyo, Japan). The patient was placed in the prone or supine position, and standard steel mesh grounding pads were placed on the patient's thighs. A multitined expandable electrode (LeVeen; Boston Scientific, Natick, MA) equipped with a 2 cm ($n = 198$), 3 cm ($n = 39$), 3.5 cm ($n = 12$), or 4 cm ($n = 3$) diameter array was used. Intraprocedural pain was minimized using local anesthesia along with intravenous administration of fentanyl or epidural anesthesia. Epidural anesthesia was used when the tumor was near the pleura or the patient asked for it.

The electrode was introduced into the tumor and connected to an RF generator (RF 2000 or RF 3000; Boston Scientific). Ablation algorithm did not vary depending on tumor type, but on array diameter of the electrode. Electrodes with array diameters of 2, 3, 3.5, and 4 cm were initially supplied with RF ablation power of strengths 10, 20, 30, and 40 W, respectively; the power was then increased at the rates of 5, 5, 10, and 10 W/min, respectively. RF energy was applied until a rapid increase in the impedance occurred or automatic shut-off at 15 min. After a 30 s interval, RF energy was reapplied at the same site. In the second application, the initial RF power was half of the maximum RF power in the previous RF energy application, and it was subsequently increased at the same rate as in the previous application until a rapid increase in the impedance occurred or automatic shut-off at 15 min. The procedure aimed to treat the tumors and achieve an ablative margin of at least 0.5 cm all around the tumor. Multiple overlapping ablations were carried out as needed to obtain such ablative margins. The characteristics of ablation procedures are summarized in Table 1. The maximum power was the highest RF power throughout the RF energy application for each tumor. The ablation time was the total RF energy application time for each tumor. The number of overlapping ablations was defined as the number of sites where RF energy was applied to each tumor.

2.3. Assessment of local tumor control

The patients were followed up at 1, 3, 6, 9, and 12 months and thereafter at 6 month intervals with chest CT images with 5 mm collimation before, and 30 and 90 s after the intravenous administration of a contrast medium at a rate of 3 ml/s. The size of the ablated lesion for the first 3 months usually exceeds the tumor size before ablation because the ablated lesion is detected together with the ablated marginal parenchyma [13]. Thus, CT images 1 month after RF ablation were taken as a term of reference. Local efficacy was evaluated by comparing the size and geometry of the ablation zone with the observations in the previous CT images. Local tumor progression was considered to have occurred when the ablation zone was circumferentially enlarged. The appearance of an irregular, scattered, nodular, or eccentric focus in the ablation zone was also considered to indicate local progression. The focus generally exhibited some degree of contrast enhancement, and thus contrasted against the unenhanced necrotic tumor tissue. Local control was considered to have been achieved when no evidence suggestive of local progression was observed on follow-up CT images.

2.4. Statistical analysis

The characteristics of patients (age, sex, and application of systemic chemotherapy or immunotherapy after RF ablation), tumors (size, location, contact with a vessel or bronchus, procedure period,

and follow-up period) and ablations (maximum power, ablation time, array diameter of the electrode, and the number of overlapping ablations) in each group were compared with those of the four other groups (i.e. primary lung cancer group vs. others, metastatic CRC group vs. others, metastasis from lung cancer group vs. others, metastatic RCC group vs. others, and metastatic HCC group vs. others). Numerical values were compared using the Student's *t*-test; categorical values were compared using the X^2-test or the Fisher exact test. Furthermore, the relationship between the tumor size and ablation factors including the maximum power, the ablation time, and the number of overlapping ablations was investigated by Pearson's correlation coefficient test.

The overall local control rates for all 252 tumors were estimated as well as those for each tumor type. The local control rates for each tumor type were compared with those for the 4 other tumor types. Kaplan-Meier analysis was used to estimate the local control rates, while the log-rank test was used to compare these rates.

To determine the factors affecting local control by using univariate analysis, various variables for each tumor were classified into 2 or 3 groups. These variables included age (≤60 or > 60 years), sex, tumor size (1–9, 10–19, or ≥20 mm), tumor location (central or peripheral), tumor contact with a blood vessel or bronchus (yes or no), procedure period (first 2 years or later years), and application of systemic chemotherapy or immunotherapy after RF ablation (yes or no). The tumor location was considered as central or peripheral, if the center of the tumor was located in the inner or outer half of the lungs, respectively, as observed on CT images. Tumors were considered to be contact with a blood vessel or bronchus if those were contiguous with a vessel of diameter ≥ 3 mm or a bronchus with inner diameter ≥ 2 mm. The procedures during the first 2 years were performed between October 2003 and September 2005, while those during the later years were performed between October 2005 and December 2007. The local control rates were compared between the groups for each of the above-mentioned variables. The variables showing a significant difference were used for the subsequent multivariate analysis.

Finally, in order to evaluate the effect of tumor type on local control, multivariate analyses were performed using tumor type and the significant variables by the above univariate analysis. Multivariate analysis was performed using multilevel analysis for each tumor type vs. the remaining types (i.e. primary lung cancer vs. others, metastatic CRC vs. others, metastasis from lung cancer vs. others, metastatic RCC vs. others, and metastatic HCC vs. others). Multilevel analysis was used to adjust the potential correlation of multiple tumors in a single patient [14]. The hazard ratio (HR) and 95% confidence intervals (CIs) for each variable were estimated, compared to that for the reference. For clarity, the HR was termed 'relative risk of local progression'.

A *P* value <.05 was considered indicative of a statistically significant difference. The Student's *t*-test, the X^2-test, the Fisher exact test, Pearson's correlation coefficient test, Kaplan-Meier analysis, and the log-rank test were performed with commercially available software (version 11.0; SPSS, Chicago, IL). Multivariate multilevel analysis was performed using a free software (R, version 2.7.1; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Patients with primary lung cancer were significantly ($P < .0001$) older, while patients with CRC were significantly ($P < .01$) younger (Table 1). Patients with primary lung cancer and metastasis from lung cancer were significantly ($P < .0001$ and $P < .01$, respectively) less likely to undergo systemic chemotherapy or immunotherapy after RF ablation (Table 1). In contrast, patients with CRC and RCC were significantly ($P < .01$ and $P = .014$, respectively) more likely to undergo it (Table 1).

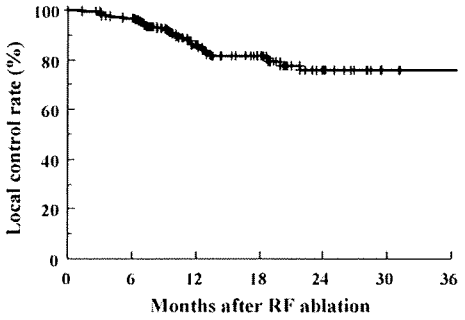

Fig. 1. Graph shows the overall local control rates for all 252 tumors. The overall local control rates were 97% at 6 months, 86% at 12 months, 81% at 18 months, and 76% at 24 months.

With regard to tumor characteristics, primary lung cancer was significantly ($P < .0001$) larger. Metastatic CRC was significantly smaller ($P < .0001$) and less likely to be in contact with a vessel or bronchus ($P < .01$) (Table 1). Metastatic RCC was significantly ($P < .01$) more likely to be treated during the first 2 years, and metastasis from lung cancer was significantly ($P = .035$) more likely to be treated later (Table 1). Follow-up period of metastatic HCC was significantly ($P < .0001$) shorter (Table 1).

With regard to ablation characteristics, primary lung cancer was treated with a significantly larger value of maximum power ($P < .0001$), longer ablation time ($P < .001$), the electrode with larger array ($P < .0001$), and a larger number of overlapping ablations ($P = .016$) (Table 1). Metastatic CRC was treated with significantly a smaller value of maximum power ($P = .044$), shorter ablation time ($P = .032$), and a smaller number of overlapping ablations ($P = .016$) (Table 1). The maximum power, ablation time, and the number of overlapping ablations were significantly ($P < .0001$ for each) correlated with tumor size ($\gamma = 0.732$, 0.672, and 0.582, respectively).

The overall local control rate at the time of this study was 85% (213/252). Kaplan-Meier analysis showed that the overall local control rates were 97% at 6 months, 86% at 12 months, 81% at 18 months, and 76% at 24 months (Fig. 1). The local control rates for each tumor type are shown in Fig. 2 and Table 2. The local control rates varied among the 5 tumor types, with ranges of 89%–100% at 6 months, 82%–89% at 12 months, 65%–86% at 18 months, and 0%–86% at 24 months. Metastatic CRC showed significantly ($P = .023$) higher local control rates.

Univariate analysis showed that variables such as tumor size, contact with a vessel or bronchus, and procedure period significantly affected local control rates ($P < .0001$, $P = .016$, and $P = .047$, respectively) (Table 3). Thus, larger tumors, tumors contact with a vessel or bronchus, and tumors treated in the first

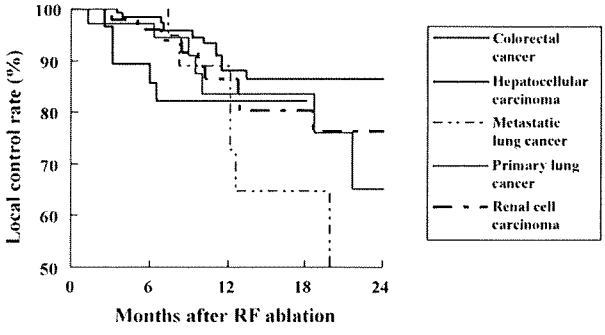

Fig. 2. Graph shows the local control rates for each tumor type.

Table 2
Local control rates in each tumor type.

Tumor type	Local control rate (%)				Comparison analysis[†]
	6 mo	12 mo	18 mo	24 mo	*P*-value
Primary lung cancer ($n=35$)	97	84	84	65	.58
Pulmonary metastases					
From colorectal cancer ($n=117$)	98	88	86	86	.023*
Lung cancer ($n=23$)	100	89	65	0	.086
Renal cell carcinoma ($n=49$)	96	86	80	76	.89
Hepatocellular carcinoma ($n=28$)	89	82	82	–	.076

Note: [†]Local control rates were compared between corresponding cancer and other four types by log-rank test.
* Statistically significant difference.

Table 3
Results of univariate analysis using log-rank test to determine factors for local progression.

Variables		No. of tumors	Local control rate (%)				*P*-value
			6 mo	12 mo	18 mo	24 mo	
Sex							.31
	Male	185	97	85	80	72	
	Female	67	97	90	84	84	
Age (y)							.39
	≤60	114	95	85	77	74	
	>60	138	99	87	86	76	
Tumor size (mm)							<.0001*
	1–9	78	97	96	96	96	
	10–19	138	98	85	75	69	
	≥20	36	92	66	66	44	
Tumor location							.34
	Peripheral	201	97	86	82	77	
	Central	51	96	85	77	71	
Contact of tumors with vessel or bronchus							.016*
	Yes	90	96	84	73	64	
	No	162	98	87	86	83	
Procedure period							.047*
	First 2 years	95	96	82	77	65	
	Later years	157	97	89	85	85	
Chemotherapy or immunotherapy after RF ablation							.41
	Yes	132	96	81	79	77	
	No	120	98	91	84	73	

* Statistically significant difference.

2 years were associated with significantly lower local control rates.

The relative risks of local progression (i.e., the HR) for each variable estimated by the multivariate analysis are shown in Table 4. Tumor size consistently exerted a significant effect on local tumor control. Compared with tumors of size 1–9 mm, those of sizes 10–19 mm or ≥20 mm were at 4.88–5.31 times or 13.8–16.9 times higher relative risk of local progression, respectively. Compared to tumors treated during later years, those treated during the first 2 years were at 1.57–1.65 times higher relative risk of local progression, but the differences were not statistically significant. Tumor contact with a vessel or bronchus did not significantly influence local tumor control. With regard to tumor type, metastatic HCC was at 2.92 times higher relative risk of local progression, but the difference was not statistically significant ($P=.086$). The relative risk of local progression for each of the other tumor types compared with the risks for the 4 remaining types were comparable.

4. Discussion

The present study was based on the assumption that tumor type possibly affects local control outcomes because cytological, pathological, physiological, and biological characteristics depend on the tumor type. The sensitivity of cells to heat may vary with the cell type [15]. The presence of intratumoral septa and tumor capsules might affect thermal distribution during RF ablation. The extent of microscopic invasion around a tumor may also affect local control outcomes; that is, a more infiltrating tumor theoretically has a higher risk of local progression. Considering the perfusion-mediated heat sink effect [16], tumor vascularity may also influence thermal effects. In fact, the extent of coagulation was shown to increase markedly by prior transcatheter arterial chemoembolization in the RF ablation of HCC [17]. When the tumor is not completely treated, altered biological behaviour might modify the time during which the residual tumor tissue enlarges until it is recognized as local progression on radiological images.

Kaplan-Meier analysis in the present study showed that local control rates after RF ablation in the lungs differed with the tumor type. Specifically, metastatic CRC showed significantly higher local control rates, as assessed using univariate analysis. However, these results alone are insufficient to prove that tumor type affects local control because the distribution of other factors affecting local control was heterogeneous among the groups. Obviously, tumor size is important for local control by RF ablation [1–4]. Besides, our univariate analysis showed that tumor contact with a vessel or bronchus and tumor treatment with the first 2 years were significantly associated with inferior local tumor control. In order to evaluate the effect of tumor type per se on local tumor control, the

Table 4
Adjusted relative risks of local progression by multivariate multilevel analysis.

Variables			Pulmonary metastases from							
	Primary lung cancer		Colorectal cancer		Lung cancer		Renal cell carcinoma		Hepatocellular carcinoma	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Tumor size (mm)										
1–9	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
10–19	5.31 (1.45–19.5)	.012*	4.88 (1.35–17.6)	.016*	5.01 (1.39–18.1)	.014*	4.92 (1.35–17.9)	.016*	5.26 (1.46–18.9)	.011*
≥20	16.9 (3.99–71.9)	<.001*	13.8 (3.37–56.4)	<.001*	14.3 (3.52–58.0)	<.001*	14.7 (3.57–60.3)	<.001*	16.7 (4.06–68.7)	<.0001*
Contact with vessel or bronchus										
No	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Yes	1.07 (0.51–2.23)	.87	1.03 (0.49–2.17)	.93	1.06 (0.51–2.20)	.88	1.07 (0.51–2.23)	.87	1.02 (0.49–2.12)	.95
Procedure period										
Later years	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
First 2 years	1.59 (0.71–3.55)	.26	1.64 (0.74–3.63)	.22	1.62 (0.74–3.55)	.23	1.65 (0.74–3.69)	.22	1.57 (0.72–3.44)	.26
Tumor type										
Others	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Corresponding cancer	0.63 (0.24–1.69)	.36	0.69 (0.30–1.60)	.38	1.97 (0.66–5.90)	.23	0.94 (0.32–2.72)	.91	2.92 (0.86–9.91)	.086

Note: HR = hazard ratio, CI = confidence intervals, Ref = reference value.
* Statistically significant difference.

differences in these factors need to be adjusted. Thus, we carried out multivariate analysis using these factors and tumor type.

One might critique the fact that ablation factors such as the maximum power, the ablation time, and the number of overlapping ablations were not evaluated for investigation of risk factors for local progression. However, our ablation algorithm did not vary according to the tumor type, but to array diameter of the electrode. Thus, all those ablation factors were significantly correlated with tumor size. In order to avoid multilinearity, they were excluded from the analyses of risk factors for local progression.

Multivariate analysis indicated that tumor size was an independent factor for local tumor control. Although the difference was not statistically significant, tumors treated during later years were at lower risk of local progression; this result may be explained by our learning curve with the procedure. With regard to tumor type, metastatic CRC was not significantly associated with a lower risk of local progression anymore. This result suggested that the better local control rates for metastatic CRC were mainly due to significantly smaller tumor size and less likelihood of contact with a vessel or bronchus. Metastatic HCC was at a higher risk of local progression. We speculated that this was to some extent related to the hypervascular nature of the tumor, but the difference was not statistically significant. Further, none of the other tumor types had a significant effect on local control. In other words, our study showed that RF ablation may provide similar local efficacy to such types of tumors. This study included mainly small tumors; the mean tumor size was 13.5 mm, and 31% (78/252) of the tumors measured less than 10 mm. We assume that in such a tumor population, the variety of tumor characteristics was not great enough to affect local control by RF ablation.

This retrospective study has limitations. The population per tumor type was not quite large, possibly resulting in insufficient statistical power. The follow-up period was relatively short. The majority of the pulmonary metastases were diagnosed without histological evidence. Further, local progression after RF ablation was not histologically confirmed. The histological type of the primary lung cancers was heterogeneous, although the majority of them were adenocarcinomatous. The grading of the cell differentiation of the primary cancers was not addressed because such data were not available in a number of patients. Multiple statistical testing is necessarily associated with inflated type I error rates.

5. Conclusion

The local control rates varied among the tumor types. However, such variation was accounted for mainly by significant differences in tumor size, tumor contact with a vessel or bronchus, and the procedure period between these groups. The tumor type per se did not influence the local control by RF ablation in the lungs.

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Radiofrequency Ablation of Small Lung Metastases by a Single Application of a 2-cm Expandable Electrode: Determination of Favorable Responders

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PURPOSE: To determine which lung metastases are most likely to be treated effectively with a single radiofrequency (RF) application (defined as two separate applications of RF energy at a single electrode position) with a multitined expandable electrode with arrays 2 cm in diameter.

MATERIALS AND METHODS: The authors retrospectively evaluated 88 lung metastases (mean long-axis diameter, 0.9 cm) in 36 patients (20 men and 16 women; mean age, 57 years) treated with a single RF application with a multitined expandable electrode with arrays 2 cm in diameter. Based on follow-up computed tomographic examinations, the technique effectiveness rates were estimated with Kaplan-Meier analysis. Multiple variables were analyzed with the log-rank test to determine risk factors for local progression. Then, the technique effectiveness rates were again estimated when considering only metastases without risk factors and compared with those of other tumors.

RESULTS: The median follow-up period was 13.2 months (range, 6.0–24.7 months). Tumor size greater than 1.0 cm ($P = .033$) and contact with the bronchus with an inner diameter of at least 2 mm ($P = .047$) were the significant risk factors for local progression. The technique effectiveness rates for metastases 1.0 cm or smaller that were not in contact with the bronchus ($n = 59$) were 96% at 1 year and at 2 years; those rates were significantly ($P = .010$) higher than those in other tumors ($n = 29$).

CONCLUSIONS: A single RF application with a multitined expandable electrode with arrays 2 cm in diameter is most likely to suffice in small (≤1 cm) lung metastases not in contact with a bronchus.

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Abbreviation: RF = radiofrequency

THE use of radiofrequency (RF) ablation for the treatment of lung tumors has increased rapidly in the hope that it might serve as an adjunct or an alternative to the current local therapies used in the treatment of lung cancer (1–8). However, thus far, the control of local tumor offered by this therapy in the intermediate term is not satisfactory. Various studies with a mean follow-up period of 12 months or longer showed that the primary local control rate was approximately 60%–70% (4,6–8). Appropriate tumor selection is necessary to improve the outcomes of the therapies.

The size of coagulation obtained by RF ablation depends largely on the noninsulated tip length of monopolar straight electrodes or the diameter of the arrays of multitined expandable electrodes. In addition, the electrode design (ie, monopolar straight electrode vs multitined expandable electrode) may affect the local control outcomes (8). Considering these facts, the ideal tumor candidates for RF ablation should be determined according to the characteristics of the specific electrode, including its design and noninsulated tip length or diameter of the arrays. Consequently, the objective of the present study was to determine which tumors are most likely to respond favorably to RF ablation involving a single RF application with a single type of electrode (multitined expandable electrode with arrays measuring 2 cm in diameter), and what factors are predictive of when such an ablation did not suffice.

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MATERIALS AND METHODS

Approval from the institutional review board and informed consent from each patient were obtained to perform the percutaneous RF ablation of lung tumors. In addition, our institutional review board gave us approval and a waiver of informed consent to conduct this retrospective study.

Study Population

Between June 2001 and June 2006, we treated 195 patients with 633 lung metastases by performing 352 percutaneous RF ablation sessions at our institution. Until October 2003, only an internally cooled electrode (Cool-tip; Valleylab, Boulder, Colorado) had been available at our institute; therefore, all the procedures were performed with this electrode. However, since then, multitined expandable electrodes (LeVeen; Boston Scientific, Natick, Massachusetts) have become available. As a result, 260 tumors were treated by an internally cooled electrode with a 1-cm (n = 64), 2-cm (n = 158), or 3-cm (n = 34) noninsulated tip or with an internally cooled cluster electrode (n = 4). Additionally, 373 tumors were treated by a multitined expandable electrode with array diameters of 2 cm (n = 333), 3 cm (n = 31), 3.5 cm (n = 6), or 4 cm (n = 3). Among the 333 tumors that were treated by a multitined expandable electrode with arrays that were 2 cm in diameter, 202 tumors were ablated with RF application at multiple sites. The remaining 131 tumors were ablated at a single electrode position, ie, with a single RF application; however, 43 tumors were excluded as a result of inadequate follow-up period (<6 months). The remaining 88 tumors in 36 patients (20 men and 16 women; mean age, 57.0 years; age range, 35–80 y) were included in the present study. All 88 tumors were metastatic lung tumors that primarily originated from colorectal cancer in 11 patients (26 tumors), renal cell carcinoma in four patients (eight tumors), hepatocellular carcinoma in four patients (seven tumors), leiomyosarcoma in four patients (eight tumors), adenoid cystic carcinoma in three patients (eight tumors), and other neoplasms in 10 patients (31 tumors). The mean long-axis diameter of the tumor was 0.9 cm ± 0.3 (median, 0.9 cm; range, 0.4–1.6 cm). Adjuvant systemic chemotherapy was administered in 16 patients (40 tumors), it was not administered in 14 patients (31 tumors), and the relevant data regarding the adjuvant therapy were missing for six patients (17 tumors).

RF Ablation

The RF ablation procedure was always performed percutaneously under the guidance of computed tomographic (CT) fluoroscopy (Asteon; Toshiba, Tokyo, Japan). Procedural positioning was determined depending on the tumor location; it was supine for 37 tumors and prone for 51 tumors. Steel mesh grounding pads were placed on the patients' thighs. Cardiac and respiratory parameters were monitored throughout the procedure. Intraprocedural pain was treated by a combination of local anesthesia and intravenous administration of fentanyl for 39 sessions or local plus epidural anesthesia for 16 sessions.

Our RF ablation system comprised a 17-gauge multitined expandable electrode with arrays that were 2 cm in diameter and an RF generator (RF 2000 or RF 3000; Boston Scientific). After administering the anesthetic agent, the tip of the electrode was introduced into the center of the tumor and the electrode tines were then fully expanded. The electrode was connected to the RF generator. According to the manufacturer's recommendations, the RF energy was applied by increasing the RF power in incremental steps until a noticeable increase was observed in the impedance (n = 80) or automatic shutoff occurred at 15 minutes (n = 8). In general, the initial RF power was set at 10–20 W, which was increased by 2–5 W per minute. In addition, application of RF energy was repeated once at the same electrode position. Repositioning of the electrode was not performed, so all the tumors were considered to be treated with a single RF application.

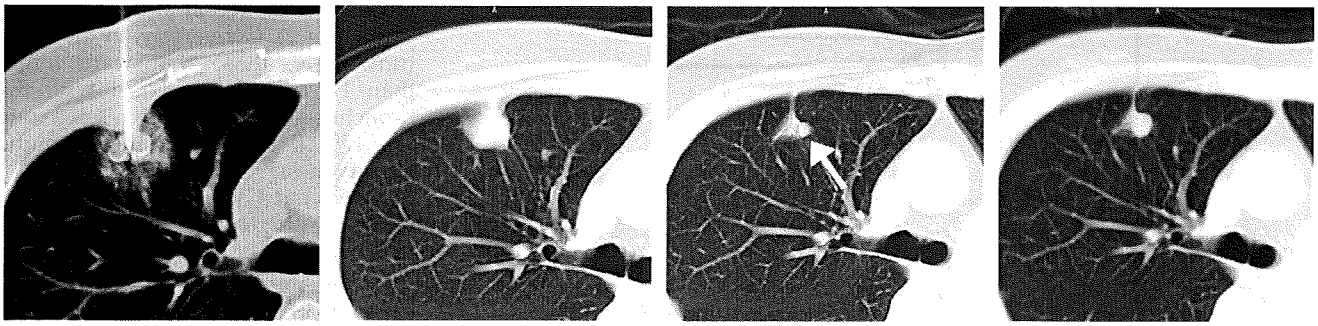
Immediately after the procedure, CT of the entire thorax was performed to evaluate the presence of any procedural complications and ground-glass attenuation surrounding the treated tumor. In addition, upright posteroanterior chest radiographs were obtained 4 hours after the procedure and again the following morning.

Follow-up and Assessment of Local Progression

We investigated the procedural complications. A major complication was defined as an event that led to substantial morbidity and disability, thereby warranting an increase in the level of care or resulting in hospital admission or prolonged hospital stay; all other complications were considered minor (9).

We evaluated the local effectiveness of RF ablation with chest CT. The patients underwent periodic follow-up CT imaging at 1, 3, 6, 9, and 12 months; thereafter, they underwent scanning at 6-month intervals. The CT images were obtained with 5-mm section thickness before and 30 and 90 seconds after intravenous administration of contrast medium (iopamidol, Iopamiron 300; Nihon Schering, Osaka, Japan) that was injected at a rate of 3 mL/sec.

As described in a previous study (10), in the first 3 months, the size of the ablated lesion usually exceeds that of the tumor before ablation despite complete ablation of the tumor; this is because the zone of ablation includes the tumor and the ablated marginal of parenchyma to a certain extent. Hence, during this period, the effectiveness of RF ablation cannot be determined by comparing the tumor size but it can be determined by assessing the contrast enhancement. The tumor was considered to be completely treated when there was no contrast enhancement in the entire ablation zone or when the ablation zone exhibited a peripheral rim of contrast enhancement that was concentric, symmetric, and uniform with smooth inner margins. Such an enhancement zone is considered to correspond to reactive hyperemia, inflammation, or granulation tissue formation at the marginal parenchyma (10). After the first 3 months, the ablation zone exhibits gradual involution if the tumor has been ablated completely (10). The appearance of irregular, scattered, nodular, or eccentric foci in the ablation zones was considered as an indicator of local tumor progression. In addition, local progression was indicated when the ablation zone demonstrated circumferential enlarge-



a. b. c. d.

Figure 1. Images from a 55-year-old woman with metastatic lung cancer from uterine leiomyosarcoma. **(a)** Chest CT image during RF ablation for a metastatic tumor 1.3 cm in long-axis diameter in the right upper lobe shows that ground-glass attenuation surrounds the tumor entirely. **(b)** Chest CT image 2 months after RF ablation shows that the ablated lesion enlarges compared with the tumor before RF ablation. **(c)** Chest CT image 5 months after RF ablation shows that the ablated lesion remarkably decreases in size, but a small nodular focus (arrow) appears at its periphery, indicating local progression. **(d)** Chest CT image 6 months after RF ablation shows that the nodular focus enlarges substantially.

ment. The local progression usually exhibited contrast enhancement (defined as an increase of >15 HU after contrast medium administration), thereby contrasting against the non–contrast-enhanced necrotic tumor tissue.

Investigation of Factors Affecting Local Tumor Control

The tumors were classified into two groups according to the following variables that presumably affect local tumor control: long-axis tumor diameter (≤1.0 cm or >1.0 cm); contact of tumors with the pleura, vessel, and bronchus (yes or no); maximum RF power (≤30 W or >30 W); and total duration of application (≤10 min or >10 min).

Maximum RF power was defined as the peak power during a single application. The tumor was considered to be in contact with a blood vessel if it was contiguous to a vessel that was 3 mm or greater in diameter. Similarly, the tumor was considered to be in contact with the bronchus when it was contiguous to a bronchus that had an inner diameter of at least 2 mm.

Statistical Analyses

The overall technique effectiveness rates were estimated with the Kaplan-Meier method. The technique effectiveness rates were compared between the two groups for each variable. The technique effectiveness rates were then recalculated when considering only tumors without the variables that were shown to adversely affect local control significantly; subsequently, these rates were compared with those of the other tumors. Comparison of the technique effectiveness rates was performed by the log-rank test. For all the comparison analyses, a P value less than .05 was considered to indicate a statistically significant difference. Statistical analyses were performed with SPSS software (version 11.0; SPSS, Chicago, Illinois).

RESULTS

In the present study, 88 tumors in 36 patients were treated in 55 sessions. During the 55 sessions, an additional 55 tumors were simultaneously treated by multiple RF applications. Combined, a total of 143 tumors were treated in 55 sessions (ie, an average of 2.6 tumors were treated per session). However, the latter 55 tumors were not included in the analysis of local tumor control because those were not treated with a single application.

Procedural complications were observed after 43 of the 55 total sessions (78%). Among them, six (14%) were major complications, all of which were pneumothoraces and required insertion of chest tubes; the remaining 37 (86%) were minor complications including small pneumothorax in 35 sessions and small hemothorax in two sessions.

CT images that were obtained immediately after RF ablation demonstrated that 85 of the 88 tumors (97%) were entirely surrounded by ground-glass attenuation that was at least 5 mm in thickness (**Fig 1**). Three tumors (3%) were almost but not entirely surrounded by ground-glass attenuation. The mean and median follow-up periods for all 88 tumors were 13.2 months (range, 6.0–24.7 months). Seven tumors (8%) exhibited local progression at 3.9–12.2 months after RF ablation (median, 10.1 months). Of the seven tumors that showed local progression, six had been completely covered by ground-glass attenuation (**Fig 1**); the remaining tumor had been almost but not entirely surrounded by ground-glass attenuation. The overall technique effectiveness rates were 92% (95% CI, 85%–98%) and 90% (95% CI, 82%–97%) at 1 and 2 years, respectively (**Fig 2**).

A comparison analysis with multiple variables showed that factors including tumor size (P = .033) and tumor contact with the bronchus (P = .047) significantly affected local tumor control (**Table**). Tumor contact with the vessel (P = .052) had a tendency to be associated with higher local progression rate; however, the results did not attain the desired levels of significance. When considering the tumors without significant risk factors, ie, those that were no larger than 1.0 cm in diameter and were not in contact with the bronchus, the local progression rate was 3% (two of 59) and the technique effectiveness rates were 96%

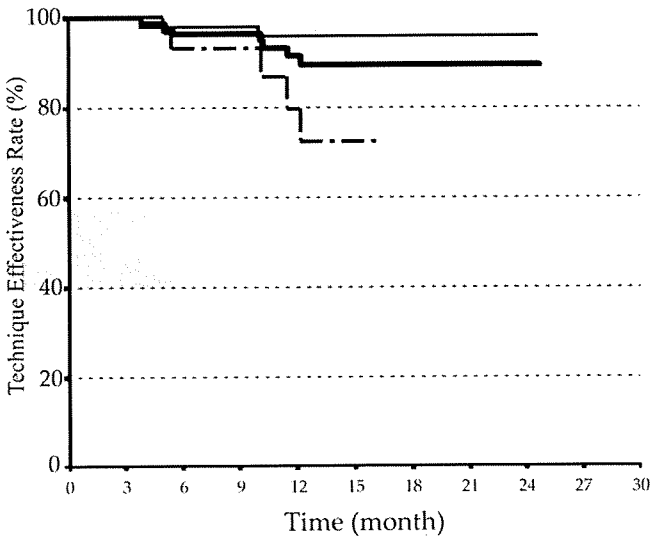


Figure 2. Overall and recalculated technique effectiveness rates by a single RF application with arrays 2 cm in diameter. The overall technique effectiveness rates were 92% at 1 year and 90% at 2 years (bold line). The recalculated rates of tumors that were no larger than 1.0 cm in diameter and are not in contact with the bronchus are 96% each at 1 year and at 2 years (solid line); that of tumors that were larger than 1.0 cm or were in contact with the bronchus was 80% at 1 year (dotted line). The former is significantly (P = .010) higher than the latter.

Comparison Analysis (Log-rank Test) to Determine Factors Affecting Local Tumor Control by a Single Multitined Expandable Electrode Application

Variables	No. of Tumors	Technique Effectiveness (%) 1 y	2 y	*P* Value*
Tumor factors				
Tumor size				.033
≤1.0 cm	63	95	95	
>1.0 cm	25	83	NA	
Contact of tumor with pleura				.819
Yes	26	92	NA	
No	62	91	88	
Contact of tumor with vessel				.052
Yes	24	83	NA	
No	64	94	94	
Contact of tumor with bronchus				.047
Yes	7	80	NA	
No	81	93	93	
Ablation factors				
Maximum RF power				.533
≤30 W	68	91	91	
>30 W	20	95	NA	
Total application time				.627
≤10 min	43	89	89	
>10 min	45	95	91	

Note.—NA = not available.
* P values <.05 were considered to indicate a significant difference.

(95% CI; 91%–100%) at 1 year and 2 years (**Fig 2**). Conversely, in the other tumors—ie, those that were larger than 1.0 cm or in contact with the bronchus—the local progression rate was 17% (five of 29) and the technique effectiveness rate was 80% (95% CI, 61%–99%) at 1 year (**Fig 2**). The technique effectiveness rates of tumors that were no larger than 1.0 cm in diameter and were not in contact with the bronchus were significantly higher than those of other tumors (P = .010; **Fig 2**).

DISCUSSION

RF ablation has been investigated as a therapy for local control of lung tumors (1–8). One of the most important limitations of this therapy is the difficulty of accurately demarcating the treatment zone during the procedure. This may contribute to the relatively high local progression rate after this therapy.

At the time of the procedure, the presence of ground-glass attenuation surrounding the treated tumors might facilitate in determining the extent of ablation zone. However, there is a possibility that ground-glass attenuation does not provide the exact extent of coagulation necrosis because parenchymal hemorrhage, congestion, and sublethal thermal damage—which results in an ablation zone that is accompanied by alveolar exudates—may appear as ground-glass attenuation. In fact, an animal experiment (11) showed that residual viable cells remained in 32%–43% of the treated tumors, all of which were completely surrounded by ground-glass attenuation on CT images. Another animal experiment (12) also suggested that the ground-glass attenuation overestimated the coagulation zone. Additionally, in the present clinical study, among the 85 tumors that had been completely covered by ground-glass attenuation, six tumors (7%) exhibited local progression subsequently. Therefore, coverage of the tumor by ground-glass attenuation does not always ensure complete tumor ablation. Therefore, it is important to realize beforehand which lung tumors can be effectively treated with the use of a given electrode.

The present study showed that local tumor control significantly de-

pends on the tumor size and contact of tumors with the bronchus. The restricted ablation volume is an important limitation of RF ablation; it results in worse outcomes for larger tumors (5,8,13,14). The bronchi may interfere with local tumor control because of limited electrical and thermal conduction of the air present in the bronchus and perfusion-mediated heat-sink effect resulting from the constant airflow occurring during respiration (15). Blood vessels are considered to affect the outcome of RF ablation because they exhibit the perfusion-mediated heat-sink effect. In bovine lungs in vivo, vessels with diameters larger than 3 mm remain unaffected by thermal injury (16). However, in this study, tumor contact with the vessel was not a significant risk factor, although there seemed to be a tendency toward an association with poor local tumor control.

Local control of tumors no larger than 1.0 cm that were not in contact with the bronchus is considerably favorable (97%, 57 of 59) and therefore such tumors are suggested as favorable responders for single RF application with a 2-cm-diameter array electrode. This result is most likely indicative of the fact that single RF application with a multitined expandable electrode with arrays that were 2 cm in diameter consistently offers coagulation with a short-axis diameter larger than 1.0 cm when the tumor is not in contact with the bronchus. The exact cause of local progression in two tumors cannot be determined; however, some mechanical error, tumor seeding, or de novo tumor focus might have resulted in the progression. Conversely, considering that other tumors (those >1.0 cm in diameter or in contact with the bronchus) showed a greater likelihood of local progression (local progression rate of 17%), such tumors were deemed as inappropriate candidates for single application with a 2-cm-diameter array electrode.

This study does not aim at suggesting minimal ablation to treat lung tumors. Local progression would probably be less likely as a tumor was treated with larger ablation zone. Although we suggest that a local control rate as high as the 97% reported here is an acceptable level, we do not dismiss the idea of using a larger-diameter array electrode for such tumors in an attempt to minimize risk of local progression. The important suggestion in this study is that, for the treatment of tumors larger than 1.0 cm or in contact with the bronchus, single application with a 2-cm-diameter array electrode is not advisable; a larger-diameter array electrode should be used or multiple applications should be attempted.

In the present study, the complication rate was high; however, the majority of the complications were minor. Most of the complications (41 of 43, 95%) were pneumothoraces. Hiraki et al (17) suggested that the incidence of pneumothorax was associated with the number of tumors ablated per session. Therefore, we assume that the high complication rate in this study is most likely the result of a larger number of tumors ablated per session (mean, 2.6 tumors). We simultaneously treated 55 tumors with multiple RF applications during the 55 sessions. Multiple RF applications require repositioning of the electrode, which probably contributed to the high rate of pneumothorax.

The present study has limitations, including its retrospective design and a follow-up period that was not sufficiently long. We excluded tumors that had been planned to be treated by a single application but required additional application at another site, eg, when the electrode failed to be positioned in the center of the tumor. This may be a selection bias. Local tumor control was determined only by radiologic assessments and was not confirmed through histologic findings. The CT resolution is not adequately high to detect microscopic recurrent foci, even with contrast agent administration. Combined, these factors may have underestimated the local progression rate. The study included various different histologic tumor types that might show different histologic characteristics, biological behavior, and therapeutic response to RF ablation. Our results were based on the population that comprised only metastatic lung tumors and therefore may not be applicable to primary lung cancer. Although adjuvant chemotherapy might affect the outcomes of RF ablation, its effect was not evaluated because a substantial amount of data regarding adjuvant therapy were missing.

In conclusion, a single RF application is most likely to suffice in small (≤1 cm) tumors not in contact with a bronchus.

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