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Percutaneous Radiofrequency Ablation for Pulmonary Metastases from Colorectal Cancer: Midterm Results in 27 Patients

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PURPOSE: To retrospectively evaluate the midterm outcomes (eg, safety, local efficacy, and survival) after radiofrequency (RF) ablation for pulmonary metastases from colorectal cancer.

MATERIALS AND METHODS: Twenty-seven patients (19 men and eight women; mean age, 61.6 years) with 49 pulmonary metastases (mean long axis diameter, 1.5 cm) from colorectal cancer underwent 41 percutaneous computed tomography (CT)–guided RF ablation sessions. Follow-up examinations were performed with CT by using contrast medium administration in all patients; positron emission tomography was performed in five patients. The safety of the procedure, local tumor control, and patient survival were evaluated. Multiple variables were analyzed to determine prognostic factors.

RESULTS: Pneumothorax occurred after 20 of the 41 sessions (49%), three of which necessitated chest tube placement. A small pleural effusion was found after six of the 41 sessions (15%). No major hemorrhagic event was observed. None of the patients died due to the procedure. The median follow-up period was 20.1 months (range, 11.2–47.7 months). The primary and secondary technique effectiveness rates were 72% and 85%, respectively, at 1 year, 56% and 62% at 2 years, and 56% and 62% at 3 years. The overall survival rates after RF ablation were 96% at 1 year, 54% at 2 years, and 48% at 3 years. The presence of extrapulmonary metastasis was determined to be a prognostic factor ($P = .001$).

CONCLUSIONS: The midterm outcomes of percutaneous RF ablation for colorectal pulmonary metastases appear promising. The presence of extrapulmonary metastasis had an adverse effect on survival after RF ablation.

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Abbreviations: CI = confidence interval, RF ablation = radiofrequency ablation

MOST cases of recurrence after surgical resection of colorectal cancer are locoregional. The most common site of distant metastases is the liver, followed by the lung. Approximately 10% of patients who undergo curative resection for colorectal cancer develop pulmonary metastases (1). Standard treatment options for pulmonary metastases include surgery and chemotherapy. Many surgeons believe that surgical resection is the best treatment that offers the potential for long-term survival in patients with a relatively small number of metastases. Several large studies (>100 patients) have demonstrated a survival rate of approximately 40% 5 years after pulmonary metastasectomy (2–5). Most patients with pulmonary metastases, however, are not candidates for surgery because they have other coexistent metastases, have poor cardiopulmonary function, and refuse to undergo surgery. A recent chemotherapy regimen using fluorouracil and leucovorin with irinotecan or oxaliplatin has been shown to prolong survival, but the long-term results are still less than satisfactory: The median survival was 14.8–21.5 months for patients with metastatic colorectal cancer (6). Therefore, various other treatment modalities may be attractive and have been the focus of research, including stereotactic radiation therapy, cryoablation, laser ablation, and radiofrequency (RF) ablation.

RF ablation is a thermal therapy that results in coagulation necrosis. The procedure involves the placement of an electrode into the target followed by the application of radiofrequency energy. Initially, RF ablation was

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mainly used for treating hepatocellular carcinoma. The favorable outcomes in the treatment of hepatocellular carcinoma have encouraged the application of this technique to neoplasms in other organs, including the lungs. Preliminary studies about the use of RF ablation in treating lung tumors have shown promising initial local control (7–9). The purpose of the present study was to retrospectively evaluate the midterm outcomes of RF ablation for pulmonary metastases from colorectal cancer.

MATERIALS AND METHODS

Approval from the institutional review board and informed consent from the patients were obtained to perform RF ablation of lung tumors.

Study Population

From June 2001 to February 2006, 209 patients with primary or metastatic lung neoplasms underwent 329 percutaneous RF ablation sessions at our institution. Of these 209 patients, 27 with 49 tumors were diagnosed with pulmonary metastases from previously resected colorectal cancer and underwent RF ablation for all of the pulmonary metastases that were demonstrated on preprocedural computed tomographic (CT) scans (ie, RF ablation was performed with curative intent for pulmonary metastases). Thus, these patients formed the basis of our study. We excluded the patients who had pulmonary metastases and underwent RF ablation, but in whom the treatment was aimed at palliation of the patient's symptoms or tumor cytoreduction. The diagnosis was made on the basis of the results of serial CT scans. In five patients, the diagnosis was confirmed with histologic examination. Positron emission tomography (PET) was performed in 11 patients. None of the patients were considered to be candidates for surgery because of their advanced ages, poor cardiopulmonary function, poor performance status, and/or refusal to undergo surgery. All patients met our inclusion criteria with regard to bleeding parameters, as follows: platelet count of more than 50×10^9/L and prothrombin time–international normalized ratio of less than 1.5.

Our study population included 19 men and eight women (mean age, 61.6 years; age range, 43–80 years). The site of the primary cancer was the colon in 14 patients and the rectum in 13. At the time of the first RF ablation session, 11 patients had one tumor, 12 had two tumors, and two each had three and four tumors, respectively. The pulmonary metastases were unilateral in 22 patients and bilateral in five. The mean long axis diameter of the 49 tumors was 1.5 cm (range, 0.3–3.5 cm). The long axis diameter of the largest metastasis in each patient was less than 2 cm in 16 patients (mean, 1.5 cm) and at least 2 cm in 11 patients (mean, 2.5 cm); specifically, the long axis diameter was less than 1 cm in one patient, 1–1.9 cm in 15 patients, 2–2.9 cm in nine patients, and at least 3 cm in two patients. Eleven patients had extrapulmonary metastasis, including metastasis to the liver (n = 8), the pulmonary hilar lymph node (n = 1), the pelvic lymph node (n = 1), and the ovary (n = 1). All eight patients with hepatic metastasis had undergone surgical resection for the metastasis before RF ablation; however, hepatic metastasis recurred at the time of RF ablation in three patients. Three patients with lymph node metastasis or ovarian metastasis had undergone systemic chemotherapy for the metastasis, but it was not completely treated. The pulmonary metastases were identified 0–60.8 months (median, 24.0 months) after surgery for the primary cancer. The first therapy for the pulmonary metastases was surgical resection in 12 patients, systemic chemotherapy in six, and RF ablation in nine. In the 18 patients who underwent surgical resection or chemotherapy as the first therapy, RF ablation was performed for residual or recurrent intrapulmonary tumor 1.2–38.5 months (median, 23.6 months) after the first therapy. The 27 patients underwent a total of 41 RF ablation sessions, including six repeat sessions to treat local progression after a previous session and/or intrapulmonary de novo recurrence. None of the patients underwent concomitant systemic chemotherapy.

RF Ablation Techniques

The electrodes used in the 41 sessions included a multitined expandable electrode with a 2-cm (n = 21) or 3-cm (n = 1) diameter array (LeVeen; Boston Scientific, Natick, Mass) and a single internally cooled electrode with a 1-cm (n =1), 2-cm (n = 17), or 3-cm (n = 1) noninsulated tip (Cool-tip; Valleylab, Boulder, Colo). Each procedure was performed percutaneously by using CT fluoroscopy. Intraprocedural pain was treated by using local anesthesia alone (n = 29) or a combination of local and epidural anesthesia (n = 12). Conscious sedation was obtained with intramuscular administration of hydroxyzine and intravenous drip infusion of fentanyl in all patients. Prophylactic antibiotics were not used in any patient.

The patients were placed in the supine (n = 13) or prone (n = 28) position depending on the tumor location, and grounding pads were placed on their thighs. After the administration of anesthesia, the electrode was introduced into the tumor and connected to a generator (CC-1, Valleylab; RF 2000 or RF 3000, Boston Scientific). In the case of the Valleylab device, radiofrequency energy was applied with an impedance control algorithm for 12 minutes during internal cooling of the electrode. Thereafter, the temperature was measured at the electrode tip; if it had not reached 60°C, another energy application was performed at the same site. When using the Boston Scientific device, the energy was applied until the impedance showed a rapid increase or an automatic shut-off at 15 minutes; this was repeated once at each site. Multiple overlapping ablation zones were created when an ablation zone per application was expected to be smaller than the tumor along with an ablative margin. Immediately after the procedure, CT scans of the entire lung were obtained to assess the procedure. A posteroanterior upright chest radiograph was obtained 4 hours later and again the following morning.

Follow-up

The patients were followed up, whenever possible, 1, 3, 6, 9, and 12 months after the procedure and thereafter at 6-month intervals. At every follow-up, chest CT was performed to assess the RF ablation outcomes. The images were obtained before and 30 and 90 seconds after the initiation of

intravenous contrast medium administration at a rate of 3 mL/sec. For the assessment of hematogeneous metastasis, abdominal and pelvic CT scans were usually obtained at 6-month intervals. PET was also performed in five patients.

Local tumor progression was determined by means of radiologic detection of the residual or recurrent focus in the ablation zone. The tumor was considered to be completely treated when the entire ablation zone was not enhanced with contrast medium or when the ablation zone exhibited contrast enhancement that was peripheral, concentric, symmetric, and uniform, which was considered to correspond to the ablated marginal parenchyma (10). Conversely, local progression of the tumor was indicated by the appearance of an irregular, scattered, nodular, or eccentric enhancement focus in the ablation zone or when the ablation zone was circumferentially enlarged with contrast enhancement. A new pulmonary tumor outside the ablated zone was considered to be an intrapulmonary de novo recurrence.

Study Endpoints

The study endpoints included the safety of the procedure, local tumor control, patient survival, and determination of prognostic factors. To evaluate the safety of the treatment, the side effects and complications of the treatment were evaluated on the basis of the CT scan obtained during and immediately after RF ablation, the follow-up chest radiographs, and the medical records. Complications were categorized as major or minor according to the guidelines for standardization of terminology and reporting criteria regarding tumor ablation established by the International Working Group on Image-Guided Tumor Ablation (11). A major complication was defined as an event that led to substantial morbidity and disability, increasing the level of care, or resulted in hospital admission or substantially lengthened hospital stay; all other complications were considered minor (11). To evaluate local tumor control, the presence of local tumor progression was initially determined on every follow-up CT scan by using the diagnostic criteria specified earlier.

Statistical Analysis

The primary and secondary technique effectiveness rates were calculated by using Kaplan-Meier analysis. The primary technique effectiveness was defined as the local tumor control with the first ablation session; the secondary effectiveness was defined as the local tumor control with all ablation sessions, including the repeat sessions.

Patient survival rates were estimated by using Kaplan-Meier analysis both from the time of RF ablation and from the time of the first therapy for pulmonary metastases. To determine the prognostic factors, multiple variables were analyzed. These variables included sex, age, long axis diameter of the largest tumor, pre-RF ablation carcinoembryonic antigen level, tumor number, previous pulmonary metastasectomy, previous systemic chemotherapy, the type of the first therapy for pulmonary metastases, disease-free interval—which is defined as the time between surgery for primary cancer and radiologic detection of pulmonary metastases, the time between surgery for primary cancer and RF ablation, and the presence of extrapulmonary metastasis. Extrapulmonary metastasis was considered to be present even if it was cured with therapy at the time of RF ablation. The survival rates from the time of RF ablation were compared between the two groups for each variable by using the log-rank test. Variables showing a statistically significant difference were considered to be prognostic factors.

For all the analyses, a P value of less than .05 was considered indicative of a statistically significant difference. The statistical analysis was performed by using software (version 11.0; SPSS, Chicago, Ill).

RESULTS

Side Effects and Complications

Pneumothorax occurred after 20 of the 41 sessions (49%). Three pneumothorax cases (15%) necessitated chest tube placement; the rest resolved spontaneously. Pleural effusion was encountered after six of the 41 sessions (15%), but none required treatment. Consequently, major complications occurred in three of the 41 procedures (7%) and minor complications in 23 (56%). No hemorrhagic event necessitating treatment was observed. None of the patients died due to the procedure.

Local Tumor Control

Local progression was observed in 15 of the 49 tumors (31%) 2.6–19.9 months (median, 7.3 months) after the first session. Of the 15 tumors with local progression, seven (47%) were treated with six repeat sessions. Thereafter, local progression was observed again in two tumors after the repeat session. Thus, the local progression rate after all sessions, including repeat sessions, was 20% (10 of 49 procedures) at the time of the study. The primary and secondary technique effectiveness rates were 72% and 85%, respectively, at 1 year, 56% and 62% at 2 years, and 56% and 62% at 3 years.

Survival and Prognostic Factors

The median follow-up period after RF ablation was 20.1 months (range, 11.2–47.7 months). The median follow-up period after the first therapy for pulmonary metastases was 29.4 months (range, 11.6–80.1 months). Of the 27 patients, 10 (37%) had already died when we collected data for the study. Seven died due to cancer progression; the remaining three died of other causes. Of the 17 surviving patients, 10 were free from any recurrence and seven showed recurrences at one or more sites. Recurrence in the surviving patients included local progression of the treated tumor (n = 2), intrapulmonary de novo recurrence (n = 9), hilar and/or mediastinal lymph node metastasis (n = 6), and recurrences elsewhere (n = 8). The overall survival rates after RF ablation were 96% (95% confidence interval [CI]: 88%, 100%) at 1 year, 54% (95% CI: 31%, 76%) at 2 years, and 48% (95% CI: 25%, 71%) at 3 years (**Fig 1**). The mean survival after RF ablation was 33.0 months. The overall survival rates after the first therapy for pulmonary metastasis (surgery, systemic chemotherapy, and RF ablation in 12, six, and nine patients, respectively) were 96% (95% CI: 89%, 100%) at 1 year, 67% (95% CI: 46%, 88%) at 3 years, and 53% (95% CI: 30%, 77%) at 5 years.

The results of univariate analyses to

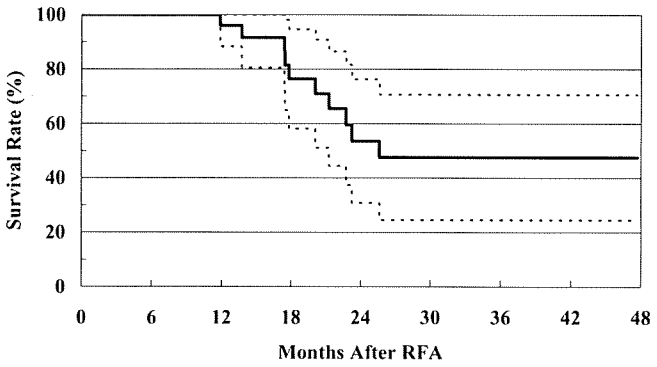

Figure 1. Graph shows the overall survival rates after RF ablation, as follows: 96% (95% CI: 88%, 100%) at 1 year, 54% (95% CI: 31%, 76%) at 2 years, and 48% (95% CI: 25%, 71%) at 3 years. Dotted lines indicate 95% CI curves.

determine prognostic factors are shown in the **Table**. The presence of extrapulmonary metastasis was determined to be a prognostic factor (P = .001). The survival rates in 16 patients without extrapulmonary metastasis were 100% (95% CI: 100%, 100%) at 1 year, 76% (95% CI: 53%, 100%) at 2 years, and 68% (95% CI: 41%, 94%) at 3 years, whereas those in the 11 patients with extrapulmonary metastasis were 89% (95% CI: 68%, 100%) at 1 year, 0% (95% CI: 0%, 0%) at 2 years, and 0% (95% CI: 0%, 0%) at 3 years (**Fig 2**). None of the other variables had a significant effect on survival after RF ablation.

DISCUSSION

Surgical resection is regarded as the best treatment in the selected patients with pulmonary metastases from colorectal cancer. Given that pulmonary metastases have a multifocal nature and thereby pose a high risk of intrapulmonary de novo recurrence after resection, the treatment of pulmonary metastases should aim to save as much parenchyma as possible to preserve pulmonary function. Thus, limited resection is currently the standard surgery if an adequate surgical margin can be obtained around the tumor. Vogelsang et al (12) showed that survival was longer after parenchymal-saving extraanatomic resection than after anatomic resection such as segmentectomy, lobectomy, and pneumonectomy. Mineo et al (13) reported that the methods of resection, including laser, conventional resection, and lobectomy, did not have a significant effect on survival; furthermore, they recommended laser resection because of the shorter periods of air leakage and hospital stay. Similar to laser resection, RF ablation represents a local therapy; thus, it may have the potential to play an important role in the treatment of colorectal pulmonary metastases.

Our results suggested that RF ablation for colorectal pulmonary metastasis was a safe procedure. An international survey proved that RF ablation of lung tumors has an extremely low mortality rate (0.4%) (14). The most common complication is pneumothorax, but most cases are treated conservatively (14,15). Although mid- to long-term local tumor control with RF ablation remains poorly understood, various studies with a mean follow-up of at least 1 year showed that the primary local control rate was approximately 60%–70% (16–19), which is applicable in our study. The primary local control may improve by repeating the procedures for local recurrence (19). The ability to repeat the procedures whenever required may be a great advantage of this method. The studies regarding surgical resection of colorectal pulmonary metastases have demonstrated that the extent of the surgical margin had an effect on local recurrence (20) and patient prognosis (21). If the same scenario is applied to RF ablation, the use of an electrode with an adequately larger active tip length or array diameter than tumor size or otherwise multiple overlapping ablations is important.

There have been few reports regarding patient survival after RF ablation of pulmonary metastases from colorectal cancer. Yan et al (22) reported that the survival rates were 85% at 1 year, 64% at 2 years, and 46% at 3 years in 55 patients with a median follow-up of 24 months. A multicenter study in Japan (23) demonstrated fairly similar survival rates in 71 patients with a mean follow-up of 19 months, as follows: 84% at 1 year, 62% at 2 years, and 46% at 3 years. The survival rates in our study were equivalent to these rates.

The present retrospective study suffered from the nonuniformity among the patients with regard to the use and timing of other therapies such as pulmonary surgery and chemotherapy. It should be noted that two-thirds of the patients had already undergone other therapies for pulmonary metastases, and RF ablation was performed at a median of approximately 2 years after the first therapy. Thus, it is difficult to compare survival after RF ablation with survival after other treatment modalities used as primary therapy. Nevertheless, the survival rate of 53% at 5 years after the first therapy in our study is encouraging when compared to approximately 40% at 5 years after surgical resection of colorectal pulmonary metastases (2–5). Several authors have advocated repeat thoracotomies for recurrent pulmonary metastases; the survival rate of patients who underwent a second thoracotomy was similar to that of patients undergoing a single thoracotomy (24,25). This is likely to indicate that repeated metastasectomy may set the clock back. Our results appear to suggest that RF ablation may be used as an alternative to repeat surgery in the treatment of intrapulmonary recurrence after pulmonary metastasectomy.

The data regarding prognostic factors after RF ablation of pulmonary metastases from colorectal cancer are sparse. Yan et al (22) suggested that the largest size of the pulmonary metastatic tumor, the location of lung metastasis, and repeat RF ablation for local tumor progression were prognostic factors by univariate analysis; the largest size of the pulmonary metastatic tumor was an independent prognostic factor by multivariate analysis. The multicenter study in Japan (23) indicated that the largest size of the pulmonary metastatic tumor, the presence of extrapulmonary metastasis, and carcinoembryonic antigen levels

Results of Univariate Analyses with the Log-Rank Test to Determine Prognostic Factors

Variable	No. of Patents	Survival Rate (%) 1 y	2 y	3 y	*P* Value
Sex					.90
Male	19	100	54	—	
Female	8	86	51	51	
Age (y)					.27
<65	16	100	65	56	
≥65	11	90	34	—	
Long axis diameter of largest tumor (cm)					.85
<2	16	93	54	—	
≥2	11	100	53	40	
Pre-RF ablation carcinoembryonic antigen level (μg/L)					.46
>5	11	100	41	—	
>5	14	92	55	55	
No. of tumors					.57
Single	11	90	53	—	
Multiple	16	100	56	47	
Previous pulmonary metastasectomy					.29
Yes	15	100	64	55	
No	12	91	39	—	
Previous chemotherapy					.21
Yes	13	92	47	—	
No	11	100	69	69	
First therapy for pulmonary metastases					.98
RF ablation	9	88	49	—	
Surgery/chemotherapy	18	100	54	47	
Disease-free interval (y)					.33
0–2	13	92	65	65	
>2	14	100	45	—	
Time between surgery for primary cancer and RF ablation (y)					.98
0–3	10	89	53	—	
>3	17	100	54	45	
Extrapulmonary metastasis					.001
Yes	11	89	0	0	
No	16	100	76	68	

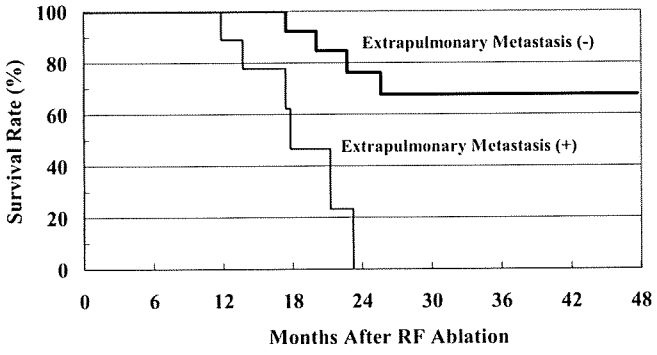

Figure 2. Graph shows the survival rates after RF ablation for patients with and patients without extrapulmonary metastasis. For patients without extrapulmonary metastasis, the survival rates were 100% at 1 year, 76% at 2 years, and 68% at 3 years. For patients with extrapulmonary metastasis, the survival rates were 89% at 1 year, 0% at 2 years, and 0% at 3 years. The survival rates for patients without extrapulmonary metastasis were significantly higher than those in patients with extrapulmonary metastasis (P = .001).

were prognostic factors, as determined with univariate analysis; furthermore, the former two were independent prognostic factors, as determined with multivariate analysis. Our study also indicated that extrapulmonary metastasis is a prognostic factor (determined with univariate analysis). We did not perform multivariate analysis to determine an independent prognostic factor because univariate analysis indicated only one variable to be statistically significant. According to the previous studies about surgical resection for colorectal pulmonary metastases, the coexistence of curable hepatic metastases did not decrease the survival after pulmonary metastasectomy (2,5,25); conversely, hilar and/or mediastinal lymph node metastasis was related to poor prognosis (2,26). Our group with extrapulmonary metastasis involved three cases of recurrent hepatic metastasis after surgical resection and each case of metastasis to the hilar lymph node, the pelvic lymph node, and the ovary that were not cured with chemotherapy. The inferior survival of the group with extrapulmonary metastasis might be attributed to such uncontrollable extrapulmonary metastases. In our study, regrettably, a meaningful comparison analysis of survival between the group with cured extrapulmonary metastasis and that with recurrent or residual metastasis was not possible because of the small population size of each group.

Unlike the two previous studies (22,23), the findings in our study did not show tumor size to be a prognostic factor (P = .85). Although the reason for such discrepancy cannot be determined, it might be somewhat related to the fact that tumor size was not largely different between the two groups compared (mean size, 1.5 cm vs 2.5 cm) and that the statistical power was limited due to a small study population.

Our study has several limitations. This was a retrospective study based on a relatively small population. The treatment strategies for pulmonary metastases were not uniform, which resulted in difficulty in drawing a conclusion with regard to the ultimate role of RF ablation in treatment. The ablation systems and ablation algorithms used were also heterogeneous. Nevertheless, the midterm outcomes of percutaneous RF ablation for colo-

rectal pulmonary metastases in our study appear promising. The presence of extrapulmonary metastasis had an adverse effect on the survival after RF ablation, and we presume that the patients with uncontrollable extrapulmonary metastasis were not suitable candidates for RF ablation.

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ORIGINAL ARTICLE

Preliminary retrospective investigation of FDG-PET/CT timing in follow-up of ablated lung tumor

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Shiro Akaki · Toshihide Tsuda · Susumu Kanazawa**

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Abstract
Objective The aim of this study was to clarify the most appropriate follow-up initiation time point for positron emission tomography (PET)/computed tomography (CT) following radio frequency ablation (RFA) of lung tumors, and the cutoff values of maximum standard uptake value (SUV_{max}) to evaluate local tumor progression.
Methods We enrolled 15 patients (8 men, median age 62 years) with 60 tumors, who were treated with RFA of lung tumors and underwent fluorodeoxyglucose (FDG)-PET/CT following RFA. Local tumor progression was assessed by periodic chest CT images prior to and following intravenous administration of a contrast medium. The SUV_{max} of three periods, namely, 0–3 months, 3–6 months, and 6–9 months after RFA, was evaluated. The appropriate time point for follow-up initiation and the cutoff value of SUV_{max} were determined using receiver-operating characteristic (ROC) analysis.
Results The median follow-up period was 357 days. Of 60 tumors, 10 showed local progression. The area under the ROC curve (Az) for the 6–9 months ($P = 0.044$) was the largest and almost equal to that of the 3–6 months ($P = 0.024$). Az for the 0–3 months was the smallest and statistically insignificant ($P = 0.705$). The cutoff value of 1.5 of SUV_{max} at 3–9 months after RFA showed 77.8% sensitivity and 85.7–90.5% specificity.
Conclusions The appropriate follow-up initiation time point is at least 3 months following RFA. Thus, SUV_{max} is a useful and reliable predictive indicator.

Keywords Radio frequency ablation · PET/CT · Local tumor progression · Lung tumor · SUV

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Introduction

Radio frequency ablation (RFA) has been accepted as an intervention technique mainly for the local control of liver tumors, and favorable results have been reported with this technique [1, 2]. Therefore, RFA has also been applied to the treatment of renal cell carcinomas, breast carcinomas, metastatic mediastinal lymph node [3–5], and lung tumors. In particular, initial studies on RFA of lung tumors showed promising results. A prospective evaluation that included 60 patients with 100 lung tumors also showed a high local efficacy of RFA, and the rate of incomplete local treatment was 7% per tumor at 18 months [6–12]. Thus, RFA of lung tumors has been recognized as a therapy for local tumor control. However, the treated tumor occasionally shows local progression during the follow-up period. Thus, the early detection of local progression is crucial because minimal local progression can be treated with repeat RFA.

Conventional methods for the evaluation of local tumor progression include computed tomography (CT) or CT with contrast administration. Magnetic resonance

imaging (MRI) has also been reported to be a useful modality for the evaluation of ablated tumors [13]. However, a size comparison of the tumor is not helpful in the first 3 months [12] because the peritumoral ablative margin appears fused, and the ablated tumor is demonstrated to have a larger size than the initial size even when the tumor is completely treated. Further, even with the administration of contrast, the resolution of the CT image is not adequately high to detect recurrent foci; this is because the enhancement of lung tumors is often not sufficiently clear to make a judgment. Biopsy might be a reliable proof for the detection of tumors; however, it is an invasive procedure with potential risks. Consequently, no definitive method has been established for the early detection of local tumor progression.

Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT is considered to be suitable for the detection of viable cells, with superior outcomes to CT for the assessment of non-small-cell lung cancer [14] and following radiation therapy and chemotherapy [15–16]. Furthermore, PET/CT is superior to PET for the accurate detection of localization. On the basis of this fact, we performed PET/CT following RFA expecting to detect untreated viable cells. On the other hand, PET/CT in the early follow-up period could possibly result in an increased number of false-positive cases owing to a marked inflammatory change following RFA. The timing of PET/CT following RFA has been discussed. Although there have been some reports of PET following RFA in animal lung models, the appropriate timing of PET/CT after RFA of human lung tumors is yet to be reported. Additionally, quantitative evaluation and visual evaluation of PET/CT are generally accepted for the assessment of viable cells. Ablated tumors with visually marked FDG uptake are treated as local progression. In contrast, it is clinically difficult to evaluate ablated tumors with visually slight FDG uptake; therefore, we focused on quantitative evaluation of ablated tumors. Thus, the objective of this study was to determine the appropriate initiation time point and the cutoff value of the maximum standard uptake value (SUV_{max}) in PET/CT to evaluate the tumor after RFA.

Materials and methods

Patients and tumors

We did not routinely perform PET/CT scan before and after RFA because our institution was not equipped with a PET/CT scanner. However, we encouraged the patients to undergo PET/CT scanning at other institutions. As a result, PET/CT images were obtained in two patients before RFA, in 11 patients both before and after RFA, and in 4 patients after RFA from July 2004 to October 2005 at the same neighboring institution, with these results forming the basis of our study. A total of 15 patients after RFA (8 men, median age 62 years) with 60 lung tumors, which included 11 patients before RFA with 42 lung tumors, were enrolled in this study. The median SUV_{max} value before RFA was 2.2 (0.7–15.5). Our study excluded the patients who underwent PET/CT scanning but whose images were obtained at different institutions to evaluate SUV values under the same condition. Primary lesion, number of tumors, and number of PET/CT scans for each of the 15 patients are shown in Table 1. The mean tumor size before RFA was 1.4 ± 0.7 cm (standard deviation).

Table 1 Details of patients

Patient	Primary lesion	Number of tumors	Number of PET/CT scan
1	Colorectal Ca	1	1
2	Colorectal Ca	10	3
3	Colorectal Ca	1	1
4	Colorectal Ca	1	2
5	Colorectal Ca	1	2
6	Lung Ca (adeno Ca)	1	1
7	Lung Ca (adeno Ca)	1	2
8	Lung Ca (adeno Ca)	1	1
9	Lung Ca (adeno Ca)	1	1
10	Urachal Ca	18	2
11	Urethral Ca	9	1
12	Stomach Ca	7	1
13	Pancreatic Ca	6	1
14	Esophageal Ca	1	1
15	Breast Ca	1	1

PET/CT positron emission tomography/computed tomography, *Ca* carcinoma

RFA technique

The RFA procedure was always performed percutaneously with CT fluoroscopy (Asteion; Toshiba, Tokyo, Japan) by any two of the authors, all of whom had begun performing RFA of lung tumors from 2001. The electrodes that were used included a multitined expandable electrode with a 2-cm- ($n = 46$) and 3-cm- ($n = 5$) diameter array (LeVeen; Boston Scientific, Natick, MA, USA), a single internally cooled electrode with a 1-cm- ($n = 1$) and 2-cm ($n = 7$) noninsulated tip (Cool-tip; Valleylab, Boulder, CO, USA), and a combined use of LeVeen with a 3-cm-diameter array and Cool-tip with a 2-cm noninsulated tip ($n = 1$). The electrode was introduced into the tumor and was connected to an RF generator (CC-1 generator, Valleylab, for internally cooled electrodes; or RF2000 or 3000 generator, Boston Scientific, for multitined expandable electrodes). In the case of the CC-1

generator, an impedance control algorithm was selected, and RF energy was applied for 12 min with the infusion of ice saline into the cooling lumen of the electrode. Immediately following RF application, the temperature of the tumor at the electrode tip was measured. If the temperature had not reached 60°C, an additional application of RF energy was attempted at the same site. In the case of the RF 2000 or 3000 generator, RF energy was applied until a rapid increase in impedance occurred or until automatic shut-off at 15 min; this procedure was repeated twice at each site. Multiple overlapping ablation zones were created when the expected ablation zone per application was smaller than the tumor plus an ablative margin.

Assessment of local tumor progression

According to our follow-up protocol, chest CT images were obtained before and after intravenous administration of the contrast medium (iopamidol, Iopamiron 300; Nihon Schering, Osaka, Japan) at 1 month, 3 months, 6 months, 9 months, and 12 months, and then at 6-month intervals, if possible. The effectiveness of RFA was assessed on the basis of these CT images as follows: when the entire ablation zone was not contrast-enhanced or when the ablation zone had contrast enhancement, but was peripheral, concentric, symmetric, and uniform with smooth inner margins, the tumor was considered to be completely treated; whereas an irregular, scattered, nodular, or eccentric enhancement in the ablation zone or circumferential tumor enlargement with contrast enhancement was considered to indicate local tumor progression. These radiological assessments were carried out by the consensus of two authors who had 12 years and 16 years of experience in chest diagnosis. When evidence of local tumor progression was demonstrated on the follow-up CT images, the tumor was designated as a tumor with local progression. On the other hand, when there was no evidence of local tumor progression on the latest follow-up CT images, the tumor was designated as a tumor without local progression.

PET/CT

The PET/CT scanning was performed one to three times for each patient at various time points after RFA; a total of 21 PET/CT scans were done for those 15 patients (Table 1). Whole-body PET was performed using a combined PET/CT system (Discovery LS; GE Medical Systems, Milwaukee, WI, USA). After at least a 4-h fasting time, the patients received an intravenous injection of 0.15 mCi (44.4 MBq)/kg of FDG. The PET images were obtained 60 min after the FDG injection. Patients were required to rest during the time between injection and imaging. The PET images were reconstructed with an ordered-subset expectation maximization (OSEM) iterative reconstruction algorithm. The technical parameters for a four-detector row helical CT included a section thickness of 5 mm, a pitch of 6 : 1, and a gantry rotation speed of 0.5 s (auto-mA mode). The blood glucose level of all patients was 86–112 mg/dl.

For the measurement of FDG uptake, the region of interest (ROI) was manually placed on the entire tumor using the CT image. The SUV_{max} value was used to evaluate the degree of FDG uptake. SUV was calculated using the following formula:

$$SUV = ROI\text{-}RC/(ID/BW),$$

where ROI-RC is the radioactivity concentration in the ROI (in becquerels per milliliter), ID is the injected dosage of FDG (in becquerels), and BW is the body weight (in grams). SUV_{max} is the maximum SUV.

When PET/CT was performed two or three times for each nodule, each SUV was considered to be independent, and all values were thus included in the statistical evaluation. Among the 60 tumors, PET/CT was performed twice for 28 tumors and thrice for 3 tumors. As a result, a total of 94 SUVs were included in this study. Of these, 43, 33, and 18 values were obtained from PET/CT images at 0–3 months, 3–6 months, and 6–9 months after RFA, respectively (Table 2).

Determination of the appropriate follow-up initiation time point and the cut-off value of SUV_{max}

First, we divided all SUV_{max} values into three periods as follows: period 1 included values obtained at 0–3 months after RFA, period 2 included values obtained at 3–6 months after RFA, and period 3 included values obtained at 6–9 months after RFA. Next, the receiver-operating characteristic (ROC) curves of all the periods were obtained; each curve was obtained using all SUV_{max} values ($n = 43$, 33, and 18) of periods 1, 2, and 3, respec-

Table 2 Number of SUV for each time point

Time points after RFA (months)	Number of SUV obtained
0–1	14
1–2	8
2–3	21
3–4	16
4–5	8
5–6	9
6–7	16
7–8	1
8–9	1

RFA radio frequency ablation, *SUV* standard uptake value

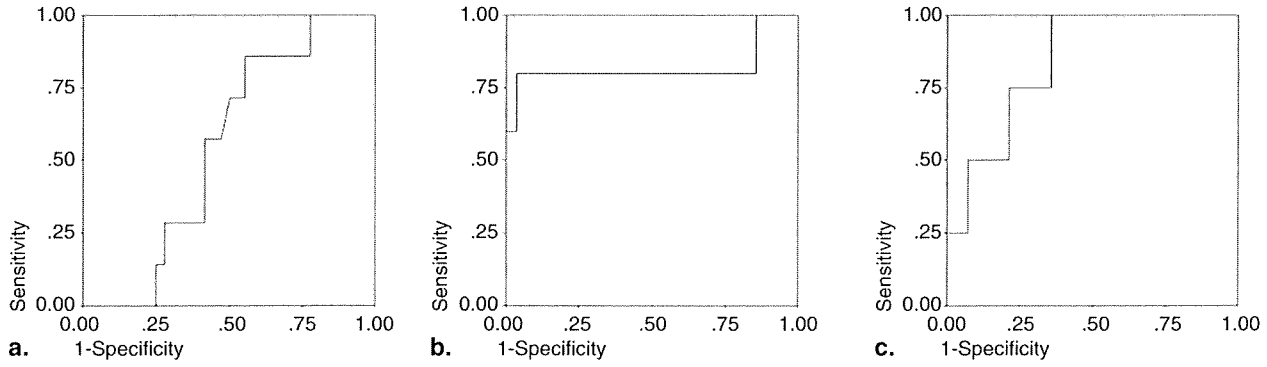

Fig. 1 Receiver-operating characteristic (ROC) curve at three periods. **a** Period 1 [0–3 months after radio frequency ablation (RFA)], $n = 43$. Area under the ROC curve (Az) value was 0.546. Standard error was 0.092, $P = 0.705$. Confidence interval (95%) was 0.364–0.727. **b** Period 2 (3–6 months after RFA), $n = 33$. Az value was 0.821. Standard error was 0.153, $P = 0.024$. Confidence interval (95%) was 0.521–1.122. **c** Period 3 (6–9 months after RFA), $n = 18$. Az value was 0.839. Standard error was 0.100, $P = 0.044$. Confidence interval (95%) was 0.644–1.035. These ROC curves showed that maximum standard uptake value (SUV_{max}) of period 1 was statistically insignificant. On the other hand, SUV_{max} of periods 2 and 3 was statistically significant

tively. The area under the ROC curve (Az) was compared among these three curves.

Statistical analysis

Receiver-operating characteristic (ROC) analysis was used to determine the appropriate follow-up initiation time point. The various cutoff values of SUV_{max} were obtained by the ROC analysis. The ROC curve with the largest Az was considered to be obtained at the most appropriate initiation time point. P values less than 0.05 were considered to be statistically significant. The ROC analysis was carried out using SPSS software (version 11.0; SPSS, Chicago, IL, USA).

Results

Local tumor progression

The median follow-up period for all 60 tumors was 357 days (range 146–730 days). On the basis of the follow-up CT images, 10 tumors (17 values) were designated as tumors with local tumor progression; 50 tumors (78 values) were designated as tumors without local tumor progression. The median follow-up period until local tumor progression was 327 days (range 145–384 days).

Appropriate follow-up initiation time point and cut-off value of SUV_{max}

Three ROC curves were obtained by using the values of periods 1–3 (Fig. 1). The Az value of period 3 was the largest among those of periods 1–3, and it was almost equal to that of period 2. The Az value of period 2 and that of period 3 were both larger than that of period 1. Additionally, the Az value of period 1 was the smallest among those of periods 1–3, and it was statistically insignificant ($P > 0.05$). Thus, it was suggested that 3 months after RFA was the most appropriate follow-up initiation time point.

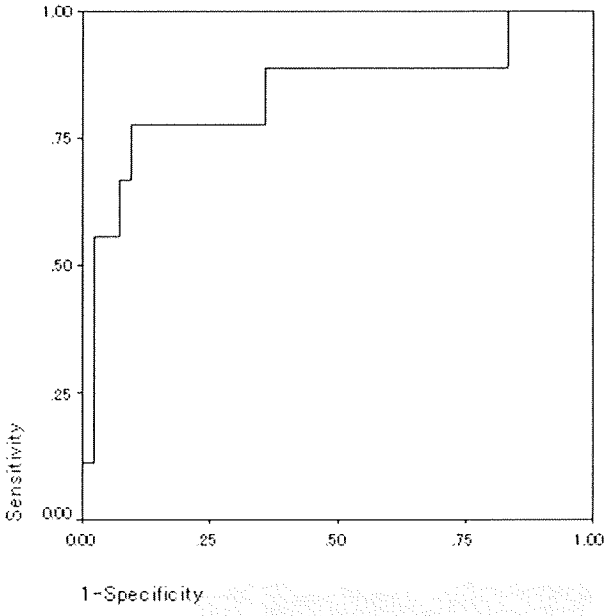

Fig. 2 ROC curve at period 2 + period 3 (3–9 months after RFA), $n = 51$. Az value was 0.839. Standard error was 0.090, $P = 0.002$. Confidence interval (95%) was 0.662–1.015

An ROC curve was obtained by using the values of periods 2 and 3 to determine the cutoff values (Fig. 2)

because the Az values of periods 2 and 3 were almost equal and statistically significant. Various values of SUV_{max} were obtained from the ROC curve. The sensitivity and specificity at various values of SUV_{max} are shown in Table 3. SUV_{max} of 1.5 showed 77.8% sensitivity and 85.7–90.5% specificity.

Discussion

Radio frequency ablation of lung tumors has been recognized as a therapy for local tumor control [6–12], and the evaluation of ablated tumors is also now considered important. The morphologic modality of CT or MRI was not sufficient to evaluate ablated tumors, particularly during the early periods after RFA. Therefore, FDG-PET/CT has been performed to detect untreated cells. However, the timing of PET/CT is crucial for accurate evaluation. A preliminary study suggested the usefulness of FDG-PET during the early periods after RFA [17], and Okuma et al. [18] have reported that FDG-PET at 4 weeks or more after RFA was useful in an animal lung model. However, our study showed that the diagnostic accuracy of PET/CT in the first 3 months after RFA was not sufficient and the appropriate follow-up initiation time point was at least 3 months after RFA.

Histopathological changes after RFA in animal models have been demonstrated [13, 18, 19]. Immediately following RFA, the ablated tumor consists of an inner zone and an outer zone. Coagulation necrosis is observed in the inner zone, and the outer zone shows congestion. In the subacute phase of 1 week after RFA, the necrotic area of the inner zone shows progression, and the outer zone shows inflammatory changes including infiltration of neutrophils, lymphocytes, and macrophages. During the chronic phase 4–8 weeks after RFA, the size of the inner zone decreases and the outer zone of the inflammatory granulation tissue undergoes fibrous transformation. We think that the outer zone of granulation tissue persisted until 3 months after RFA, and this resulted in the accumulation of FDG [20] and false-positive cases (Fig. 3).

For the second result, we indicated the various cutoff values of SUV_{max} and the main cutoff value of SUV_{max} of 1.5 at 3–9 months after RFA. SUV is generally used as a semiquantitative means for estimating the likelihood of benign or malignant lesions. We used SUV_{max} because local progression usually occurred in the localized region of the ablated tumor. In earlier reports, the cutoff value for benign and malignant untreated lung tumors was an SUV average of 2.5, with the sensitivity for malignant tumors of 97% and the specificity for malignant tumors of 82% [21–23]. Lung tumors with an SUV of <2.5 were also significant, and a retrospective analysis showed a cutoff SUV of 1.59 with 81% sensitivity and 85% specificity [24]. Our study showed a cutoff

Table 3 Sensitivities and specificities at various values of SUV_{max} at 3–9 months after RFA

SUV_{max}	Sensitivity (%)	Specificity (%)
0.8	88.9–100	0–21.4
1.2	77.8–88.9	61.9–73.8
1.5	77.8	85.7–90.5
1.6	66.7	90.5
1.7	66.7	92.9
1.8	55.6	92.9
2.1	55.6	97.6
3.6	11.1	97.6

SUV_{max} maximum standard uptake value

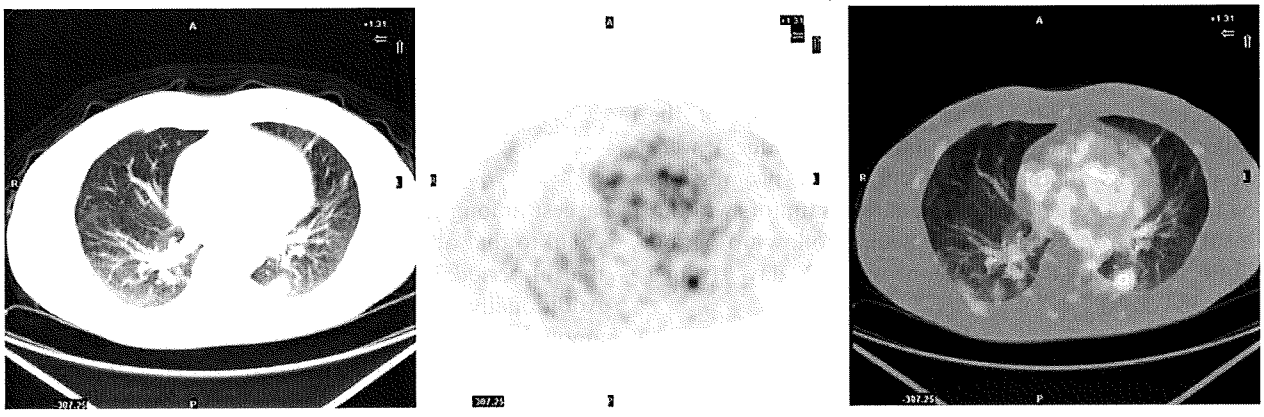

Fig. 3 A false-positive case. A 43-year-old man with lung metastasis (*left* S6) of colon cancer underwent positron emission tomography/computed tomography 90 days after RFA. SUV_{max} was 2.9. He was followed up for 364 days, and local progression was not recognized

value below 2.5. We believe that this value is reasonable because untreated benign lung tumors have viable cells that accumulate FDG; however, ablated lung tumors at 3 months after RFA without local progression consist of an inner zone comprising a necrotic area and an outer zone comprising a fibrovascular rim that have no viable cells.

It is considered that PET has the ability to evaluate viable cells and that it is more sensitive than CT for the detection of solitary primary lung tumors [14, 25]. Previous prospective analysis showed that PET/CT had 96% sensitivity and 82–88% specificity when compared with sensitivity and specificity of 96% and 53%, respectively, of CT [14, 26]. Comparing these previous results, the sensitivity with all cutoff values was not sufficiently high. Tumor size has been considered as an important factor for accurate diagnostic evaluation in PET. A previous study compared the accuracy of PET in nodules that had a diameter of 5–10 mm with that in nodules greater than 10 mm in diameter. This previous study showed 69% sensitivity for detecting a malignancy in 5–10 mm nodules and 95% sensitivity in nodules greater than 10 mm [27]. In our study, the mean tumor size was 14 mm and the extent of local progression was considered to be insufficient; we believe that this is the reason for the increase in the number of false-negative cases.

Next, we used PET/CT for the quantitative evaluation of SUV. Although PET has been widely used for the quantitative evaluation of tumors, PET/CT is superior to PET for determining the precise localization of sites of increased FDG uptake. In particular, the extent of local progression after RFA is small and the accumulation is not sufficient to accurately define the location.

Our study has several limitations. First, the primary lesions of lung tumors were not the same and the sample size was small. The correlation between FDG uptake and tumor types has been reported [28]. We examined the inflammatory change after RFA and discussed the timing of PET/CT after RFA. However, further studies focused on the tumor type of lung tumor should be explored. Second, the follow-up period was not sufficiently long and thus, tumors designated as tumors without local tumor progression may show local tumor progression in the future. Third, dual-time point images, obtained at 1 h and 2 h following the administration of FDG, have been reported to be useful for the diagnosis of malignant lesions [18, 29]. Our study is a retrospective study, and we did not use dual-time point images. The predictive cutoff value of SUV_{max} should ideally be determined individually depending on the detector type (BGO, LSO, or germanium oxyorthosilicate), the reconstruction method (filtered back-projection or OSEM), or the scanner type (PET or PET/CT).

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Repeat Radiofrequency Ablation for Local Progression of Lung Tumors: Does It Have a Role in Local Tumor Control?

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PURPOSE: To retrospectively evaluate the role of repeat radiofrequency (RF) ablation for local progression of lung tumors in local tumor control.

MATERIALS AND METHODS: From June 2001 to February 2007, the authors treated 797 lung tumors (primary lung cancer, $n = 66$; metastatic lung neoplasm, $n = 731$; mean tumor size, 1.7 cm) in 295 patients with RF ablation. After RF ablation, patients were followed-up with contrast-enhanced chest computed tomography at 1, 3, 6, 9, and 12 months and thereafter at 6-month intervals. Local progression was observed in 117 of the 797 lung tumors. Fifty repeat RF ablation sessions were performed for 56 tumors (primary lung cancer, $n = 9$; metastatic lung neoplasm, $n = 47$; mean tumor size, 2.7 cm) in 46 patients (33 men, 13 women; mean age, 59.6 years). Repeat RF ablation was not performed for the remaining 61 locally progressing tumors because it was not presumed to provide survival benefit. For all 797 tumors, the overall primary and secondary technique effectiveness rates (TERs) after the first RF ablation were compared with each other. To determine the risk factors for local control with repeat RF ablation, multiple variables were analyzed. Next, local control with repeat RF ablation was evaluated for tumors with and tumors without risk factors.

RESULTS: The overall secondary TERs were significantly higher than the overall primary TERs ($P < .00001$). Tumor size of at least 2 cm at the first RF ablation ($P = .045$) and contact with bronchi ($P = .045$) or vessels ($P = .048$) were risk factors for local control with repeat RF ablation. The secondary TERs after the first RF ablation were 94% at 1 year, 68% at 2 years, and 55% at 3 years for tumors without risk factors and 60% at 1 year and 40% at 2 years for tumors with at least one risk factor. Among the 50 repeat RF ablation sessions, pneumothorax occurred in 13 sessions (26%), one of which necessitated chest tube placement; pleural effusion occurred in nine sessions (18%), all of which resolved spontaneously. Thermal injury of the brachial plexus occurred after one session.

CONCLUSIONS: Repeat RF ablation improved the overall local control outcomes. In particular, it offered an opportunity to salvage tumors that had no risk factors but nevertheless progressed locally after the first RF ablation. Conversely, tumors with risk factors were not controlled sufficiently even after repeating the procedure.

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Abbreviations: RF = radiofrequency, TER = technique effectiveness rate

RADIOFREQUENCY (RF) ablation has received considerable attention as a local therapy for hepatic tumors (1–4). The favorable outcomes of RF ablation for hepatic tumors have facilitated the application of this technique to neoplasms in other organs, including the lungs. The local control outcomes of RF ablation for lung tumors, however, appear somewhat inferior to those for hepatic tumors. Several studies with a mean follow-up of at least 1 year showed that the primary local control rate of lung tumors was approximately 60%–70% (5–8). Lung cancer, whether primary or secondary, may show microscopic extension around the tumor (9,10). Thus, ablation of the surrounding parenchyma together with the tumor appears important for complete treatment. How-

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ever, the severely limited electrical and thermal conductivity of the air-containing lung tissue may interfere with acquiring an adequate ablative margin, thereby possibly contributing to the inferior outcome.

The ability to repeat the procedure whenever the treated tumor shows local progression is an advantage of this therapy, but the role of the repeat procedure in local control is poorly understood. Theoretically, repeating the procedure for local progression should improve local tumor control. Nevertheless, some tumors cannot be controlled despite repeating the procedure. Herein, we focused on repeat RF ablation for local progression of lung tumors after the first RF ablation. The purpose of our study was to retrospectively evaluate the outcomes of repeat RF ablation and to help clarify its role in local tumor control.

MATERIALS AND METHODS

Institutional review board approval and patient informed consent were obtained to perform RF ablation of lung tumors. The institutional review board also approved the reporting of this retrospective study.

Study Population

From June 2001 to February 2007, we treated 797 lung tumors in 295 patients (186 men, 109 women; mean age, 63.8 years; age range, 24–94 years) by performing 501 RF ablation sessions at our institution. These tumors comprised our study population. The mean tumor size was 1.7 cm ± 1.2 (range, 0.3–9.6 cm). After the first RF ablation, 117 tumors were diagnosed as showing local progression. Of these, 56 tumors in 46 patients (33 men, 13 women; mean age, 59.6 years; age range, 24–88 years) were treated with 50 repeat RF ablation sessions; these tumors were thus the main focus of our study. The 56 tumors were classified as either primary lung cancers (n = 9) or metastatic lung neoplasms (n = 47). The metastatic neoplasms originated primarily from colorectal cancer (n = 17), lung cancer (n = 8), hepatocellular carcinoma (n = 5), renal cell carcinoma (n = 4), and other sources (n = 13). Repeat RF ablation was not performed for the remaining 61 locally progressing tumors because it was not presumed to provide survival benefit. The data for this study were collected in February 2007.

RF Ablation Techniques

We used two types of electrodes for RF ablation: a multitined expandable electrode (LeVeen; Boston Scientific, Natick, Massachusetts) and an internally cooled electrode (Cool-tip; Valleylab, Boulder, Colorado). Until October 2003, only the internally cooled electrode was available at our institution; therefore, all RF ablation procedures were performed with this electrode. Since then, multitined expandable electrodes have become available. The type of electrode used mainly depended on the location and size of the tumor and the physician's preference. The electrode used for repeat RF ablation of the 56 tumors was a multitined expandable electrode with a 2-cm- (n = 19), 3-cm- (n = 2), 3.5-cm- (n = 2), or 4-cm- (n = 1) diameter array; a single internally cooled electrode with a 2-cm (n = 28) or 3-cm (n = 3) noninsulated tip; or an internally cooled cluster electrode (n = 1).

Conscious sedation was obtained with intramuscular administration of hydroxyzine (Atarax-P; Pfizer, Tokyo, Japan) and intravenous drip infusion of fentanyl (Fentanest; Daiichi-Sankyo, Tokyo, Japan). Prophylactic antibiotics were not used. Intraprocedural pain was treated by using local anesthesia alone or a combination of local and epidural anesthesia. Local anesthesia was given by using 1% lidocaine (Xylocaine; Astrazeneca, Osaka, Japan); epidural anesthesia was given by using fentanyl and 0.2% ropivacaine (Anapeine; Astrazeneca). RF ablation was always performed percutaneously with computed tomographic (CT) fluoroscopy (Asteion; Toshiba, Tokyo, Japan). The electrode was introduced into the tumor and connected to an RF generator. A CC-1 generator (Valleylab) was used for the internally cooled electrodes; the RF 2000 or RF 3000 generator (Boston Scientific) was used for the multitined expandable electrodes. In the case of the Valleylab device, an impedance control algorithm was selected and RF energy applied for 12 minutes while infusing ice saline into the cooling lumen of the electrode. Immediately after the RF application, the temperature of the tumor was measured at the electrode tip. If the temperature had not reached 60°C, an additional application of RF energy was performed at the same site. In the case of the Boston Scientific device, RF energy was applied until a rapid increase in impedance or automatic shut-off at 15 minutes; this was repeated once at each site. In an attempt to obtain an ablative margin, multiple overlapping ablation zones were created when using an electrode with an array diameter or a noninsulated tip length that was equal to or smaller than the tumor diameter.

Assessment of Local Tumor Control

Our institution was not equipped with facilities for positron emission tomography (PET). Therefore, we evaluated the outcomes of the RF ablation treatment with chest CT. CT scans were obtained with 5-mm-thick sections before and 30 and 90 seconds after the intravenous administration of contrast medium (iopamidol [Iopamiron 300; Nihon Schering, Osaka, Japan]) at a rate of 3 mL/sec. Patients were followed-up, whenever possible, at 1, 3, 6, 9, and 12 months after RF ablation and thereafter at 6-month intervals.

As described in a previous study (11), in the first 3 months, the size of the ablated lesion usually exceeds that of the tumor before ablation even if the tumor is completely ablated; this is because the zone of ablation includes the tumor and the ablated margin of the parenchyma to a certain extent. Hence, during this period, the effectiveness of RF ablation can be determined not by comparing the tumor size but by assessing the contrast enhancement. Tumor treatment was considered complete when contrast enhancement was not observed 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 at the marginal parenchyma (11). After the first 3 months, the ablation zone exhibits gradual involution over time when the tumor is completely ablated (11). The appearance of an irregular, scattered, nodular, or eccentric focus in the ablation

zone is indicative of local progression (11). Local progression was also indicated when the ablation zone demonstrated circumferential enlargement. Local progression generally exhibits contrast enhancement to some extent, thereby contrasting against the nonenhancing necrotic tumor tissue.

We assessed the presence of local progression on each follow-up CT scan and estimated the technique effectiveness rates (TERs). Primary technique effectiveness was defined as local tumor control achieved with the first RF ablation alone; secondary technique effectiveness was defined as local tumor control achieved with two RF ablations, including the repeat RF ablation (12). By using the outcomes of all 797 tumors, the overall primary and secondary TERs were estimated from the time of the first RF ablation. TERs were also estimated from the time of the repeat RF ablation by using the outcomes of the 56 tumors treated with repeat RF ablation.

We measured the size of the 56 tumors at the first RF ablation and at the repeat RF ablation. Tumor size was determined by using the long-axis diameter on axial CT scans. Subsequently, we classified the 56 tumors into three groups according to changes in tumor size over time after the first RF ablation. In group A, the ablation zone did not decrease in size after the first RF ablation and enlarged over time. In group B, the ablation zone initially decreased in size but enlarged subsequently. In group C, the ablation zone decreased in size considerably and formed a linear opacity suggestive of scar tissue; however, this was followed by the appearance of a nodular focus at the periphery of the scar. In each group, the tumor size at the first RF ablation and the frequency of contact of tumors with vessels and bronchi were determined. If a tumor was contiguous with a vessel at least 3 mm in diameter, it was considered to be in contact with the vessel; similarly, if a tumor was contiguous with a bronchus with an inner diameter of at least 2 mm, it was considered to be in contact with the bronchus.

Study Endpoints

The first study endpoint was to clarify whether the repeat RF ablation improved local tumor control in the entire study population. Therefore, the overall secondary TERs after the first RF ablation were compared with the overall primary TERs after the first RF ablation. The second endpoint was to clarify whether the local control offered with repeat RF ablation was equivalent to that offered with the first RF ablation. Therefore, the TERs after repeat RF ablation for the 56 tumors were compared with the overall primary TERs after the first RF ablation.

The third endpoint was to clarify the type of tumors that were favorably controlled with repeat RF ablation. For this assessment, we analyzed multiple variables that may affect local control; these included tumor size at the first RF ablation, contact of tumors with bronchi with an internal diameter of at least 2 mm or vessels with a diameter of at least 3 mm, type of electrode used at the repeat RF ablation, and tumor type (primary vs metastatic). First, the 56 tumors were classified into two groups: Group 1 included tumors that showed no local progression for at least 12 months after the repeat RF ablation, and group 2 included those that showed local progression again after the repeat RF ablation. We excluded the tumors that did not show local progression but in which the follow-up period was shorter than 12 months. This is because our previous study (8) showed that local control of lung tumors with RF ablation decreased considerably with time, especially within 1 year, and, therefore, we assumed that absence of local progression could not be secured with a follow-up shorter than 1 year. Then, the above variables were compared between the two groups. The variables that were significantly associated with group 2 were determined to be risk factors.

The fourth endpoint was to evaluate the role of repeat RF ablation in the local control of tumors with and tumors without risk factors. Therefore, TERs after the repeat RF ablation for tumors without risk factors treated with repeat RF ablation were compared with the primary TERs after the first RF ablation for all tumors without risk factors among the 797 tumors. Furthermore, the primary and secondary TERs after the first RF ablation for tumors without risk factors treated with repeat RF ablation were estimated; the secondary TERs for these tumors were compared with the primary TERs after the first RF ablation for all tumors without risk factors among the 797 tumors. For tumors with at least one risk factor that were treated with repeat RF ablation, the TERs after the repeat RF ablation and the secondary TERs after the first RF ablation were estimated.

Statistical Analyses

TERs were estimated with Kaplan-Meier analysis and compared by using the log-rank test. Comparison of the variables was performed by using the Fisher exact test. A P value of less than .05 was considered indicative of a statistically significant difference. These statistical analyses were performed by using software (SPSS version 11.0; SPSS, Chicago, Ill).

RESULTS

Although all 56 tumors should have undergone every scheduled follow-up CT examination after the repeat RF ablation, 15, seven, five, and three tumors did not undergo CT at 1, 3, 6, and 9 months, respectively. The mean follow-up period for the 56 tumors was 8.5 months after the repeat RF ablation (median, 6.4 months; range, 0.0−32.5 months). After the repeat RF ablation, local progression was again observed in 17 of the 56 tumors (30%). In seven of the 17 tumors, local progression was diagnosed within 3 months after the repeat RF ablation because the tumors possessed a contrast-enhancing nodular part. In another seven tumors, local progression was diagnosed at 6−9 months because the tumors enlarged circumferentially with contrast enhancement (n = 5) or a nodular focus appeared at the margin of the ablation zone (n = 2). In the remaining three tumors, local progression was diagnosed at 12−18 months because the tumors enlarged circumferentially with contrast enhancement (n = 2) or a nodular focus appeared at the margin of the ablation zone (n = 1). For all 797 tumors, the overall primary and secondary TERs after the first RF ablation were 74% and 88%, respectively, at 1 year, 64% and 79% at 2 years, 63% and 74% at 3 years, and 63% and 74% at 4 years; the secondary TERs were significantly higher than the primary TERs (P <

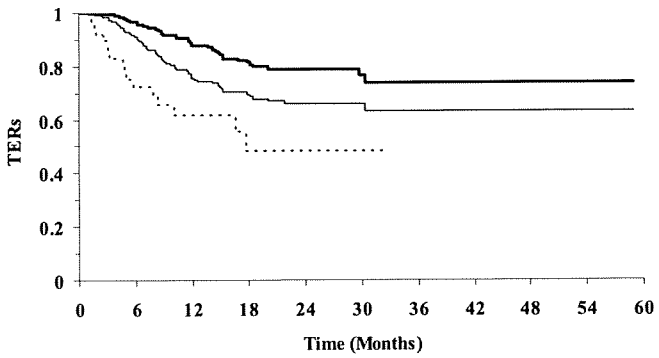

Figure 1. Graphs show the overall primary (solid line) and secondary (bold line) TERs after the first RF ablation for all 797 tumors and the TERs after the repeat RF ablation for the 56 tumors treated with repeat RF ablation (dotted line).

Table 1
Results of Comparative Analyses of Multiple Variables between Groups Classified according to Local Tumor Control with Repeat RF Ablation

Variable	Group 1 (n = 9)	Group 2 (n = 17)	P Value
Tumor size at first RF ablation (cm)			.045*
<2	8	8	
≥2	1	9	
Tumor in contact with bronchus			.045*
Yes	1	9	
No	8	8	
Tumors in contact with vessel			.048*
Yes	2	11	
No	7	6	
Type of electrode used for repeat RF ablation			.20
Internally cooled	8	11	
Multitined expandable	1	6	
Tumor type			.16
Primary	0	4	
Metastatic	9	13	

Note.—Group 1 includes the tumors that showed no local progression for a minimum of 12 months after the repeat RF ablation. Group 2 includes the tumors that showed local progression after the repeat RF ablation.
* Statistically significant difference at $P < .05$.

.00001) (**Fig 1**). The TERs after the repeat RF ablation were 61% at 1 year and 48% at 2 years; these rates were significantly lower than the overall primary TERs after the first RF ablation (P = .002) (**Fig 1**).

After the repeat RF ablation, 39 of the 56 tumors (70%) did not show local progression. Of these 39 tumors, nine showed no local progression for at least 12 months after the repeat RF ablation, and the remaining 30 showed no local progression during less than 12 months. Thus, with regard to the groups classified according to local control with repeat RF ablation, groups 1 and 2 were composed of nine and 17 tumors, respectively. The frequency of tumor size of at least 2 cm at the first RF ablation (P = .045) and contact with both bronchi (P = .045) and vessels (P = .048) was significantly higher in group 2 than in group 1; thus, these were determined to be risk factors (**Table 1**).

Among all 797 tumors, 256 tumors did not have risk factors; that is, these tumors were smaller than 2 cm at the first RF ablation and were not in contact with either vessels or bronchi. Of these 256 tumors, 20 showed local progression after the first RF ablation and were then treated with repeat RF ablation. The TERs after repeat RF ablation for the 20 tumors (80% at 1 year and 58% at 2 years) were not significantly different from the primary TERs after the first RF ablation for the 256 tumors (83% at 1 year, 70% at 2 years, and 65% at 3 years) (P = .34). For the 20 tumors, the primary and secondary TERs after the first RF ablation were 22% and 94%, respectively, at 1 year, 0% and 68% at 2 years, and 0% and 55% at 3 years; the secondary TERs after the repeat RF ablation for the 20 tumors were not significantly different from the primary TERs after the first RF ablation for the 256 tumors (P = .81) (**Fig 2**). Of the 56 tumors treated with repeat RF ablation, 36 had at least one risk factor. For these 36 tumors, the TERs after repeat RF ablation were 45% at 1 year and 22% at 2 years (**Fig 3**); the secondary TERs after the first RF ablation were 60% at 1 year and 40% at 2 years (**Fig 3**).

With regard to size change of the 56 tumors after the first RF ablation, groups A, B, and C consisted of 16, 29, and 11 tumors, respectively. The tumor size at the first RF ablation and the frequency of contact with vessels and bronchi were in the following order: group A > group B > group C (**Table 2**). Tumor size at repeat RF ablation was smaller than that at the first RF ablation in 10 tumors and equal or larger in 46 tumors. The mean size of the 56 tumors was 2.2 cm (range, 0.4–7.3 cm) at the first RF ablation and 2.7 cm (range, 0.8–7.8 cm) at the repeat RF ablation.

Among the 50 repeat RF ablation sessions, pneumothorax occurred in 13 (26%), one of which necessitated chest tube placement; pleural effusion occurred in nine sessions (18%), all of which resolved spontaneously. After one session for ablation of a tumor in the left lung apex, sensory and motor abnormality of the left arm occurred; this was suggested as a result of thermal injury of the left brachial plexus. Thus, the rate of major complications, defined as an event that led to substantial morbidity and disability, increasing the level of care or resulting in hospital admission or substantially lengthened hospital stay (12), was 4% (two of 50 sessions). No patients died of the procedure.

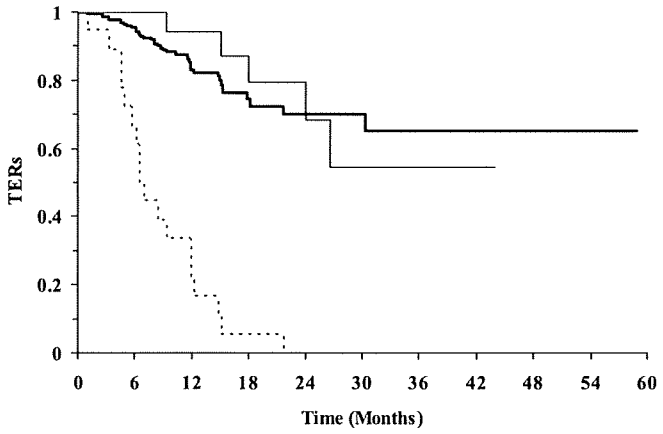

Figure 2. Graphs show the primary (dotted line) and secondary (solid line) TERs after the first RF ablation for the 20 tumors without risk factors treated with repeat RF ablation and the primary TERs after the first RF ablation for all 256 tumors without risk factors treated with the first RF ablation (bold line).

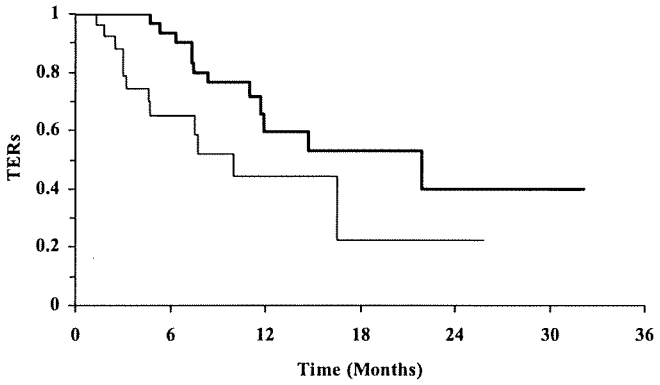

Figure 3. Graphs show the TERs after the repeat RF ablation (solid line) and the secondary TERs after the first RF ablation (bold line) for the 36 tumors with at least one risk factor treated with repeat RF ablation.

Table 2
Tumor Characteristics of Each Group according to Tumor Size Change after the First RF Ablation

Group	Mean Tumor Size at First RF Ablation (cm)	Contact with Vessels	Contact with Bronchi
A (n = 16)	2.8	14 (88)	10 (63)
B (n = 29)	2.1	13 (45)	11 (38)
C (n = 11)	1.3	4 (36)	2 (18)

Note.—In group A, the ablation zone did not decrease in size and enlarged over time. In group B, the ablation zone initially decreased in size but enlarged subsequently. In group C, the ablation zone decreased in size considerably, resulting in a scarlike tissue; however, a nodular focus subsequently appeared. Numbers in parentheses are percentages.

DISCUSSION

In our study, the overall secondary TERs for all 797 tumors were significantly higher than the overall primary TERs; that is, repeat RF ablation offered a significant benefit in local control for the entire population. However, the TERs after repeat RF ablation were significantly lower than the overall primary TERs after the first RF ablation. This indicates that tumors that showed local progression after the first RF ablation were associated with a higher risk of local progression even after repeat RF ablation. This is not surprising because local control with RF ablation is largely dependent on tumor-specific factors such as tumor size and contact with vessels and bronchi (8), and such factors affect the local control outcomes after repeat RF ablation as well as those after the first RF ablation.

The restricted ablation volume is an important limitation of RF ablation, and several studies have shown that tumor size has a significant effect on local control (8,13,14). Blood vessels exhibit the perfusion-mediated heat sink effect, thereby compromising local tumor control. Experiments on bovine lungs demonstrated that vessels larger than 3 mm in diameter remain unaffected by thermal injury (15). Therefore, complete ablation of tumors located near such vessels is considered difficult because the neoplastic tissue adjacent to the vessels fails to achieve the optimal temperature necessary for ablation due to the heat sink effect. The bronchi may also interfere with the outcome because of the limited electrical and thermal conductivity of the air present in the bronchi and the perfusion-mediated heat sink effect mediated by the constant air flow that accompanies respiration (16).

Tumor size may change with time after RF ablation. During the first 3 months, the size of the ablated lesion usually exceeds the size of the tumor before RF ablation. Thereafter, it shows gradual involution if the tumor is well-treated (11). Theoretically, there should be a better chance of gaining local control with repeat RF ablation if the tumor decreased in size considerably after the first RF ablation and local progression was treated before it enlarged considerably. In our study, however, 16 of the 56 tumors (28%) did not decrease in size at all after the first RF ablation; tumor size at repeat RF ablation was equal to or greater than the original tumor size in most cases (46/56, 72%); thus, the mean tumor size at repeat RF ablation (2.7 cm) was greater than the original mean tumor size (2.2 cm). This is very likely to have decreased the effect of repeat RF ablation on local control.

We assume that the change in tumor size after RF ablation is largely related to the proportion of treated tumor volume to untreated tumor volume; that is, tumors change in size based on a balance between shrinkage of the treated tumor and enlargement of the untreated tumor. Our results of classifying the tumors into groups

A–C showed that smaller tumors with less likelihood of being in contact with vessels and bronchi were more likely to decrease in size after RF ablation. In other words, a large portion of such tumors can be treated with RF ablation, resulting in subsequent tumor shrinkage. Therefore, such tumors have greater chances of not only cure with the first RF ablation but also salvage with repeat RF ablation in the event of local progression. In fact, when considering only tumors without risk factors (ie, tumors <2 cm in size originally and not in contact with vessels or bronchi), the TERs after repeat RF ablation were not different from the primary TERs. This suggests that, in such tumors, the effect on local control offered with repeat RF ablation was similar to that with the first RF ablation. Moreover, for such tumors, repeat RF ablation considerably improved the local control rates, and the secondary TERs were equivalent to the primary TERs for the 256 tumors without risk factors after the first RF ablation. Therefore, we suggest that repeat RF ablation may offer a chance to compensate for local progression of such tumors after the first RF ablation. Conversely, with regard to tumors with at least one risk factor, the effect of repeat RF ablation on local control was insufficient, and local control was far from satisfactory even after repeating the procedure (secondary TERs after the first RF ablation = 40% at 2 years).

This study had some limitations. The retrospective design of the study could introduce selection biases. The tumor population treated with repeat RF ablation was relatively small, and the follow-up period after the repeat RF ablation was not sufficiently long. Diagnosis of local progression was made on the basis of CT alone. The use of PET might be more preferable, but its role in the assessment of local control after RF ablation of lung tumors has not yet been determined. Several different tumor types with different biological characteristics and therapeutic responses to RF ablation were included in the study. In addition, the ablation systems and ablation algorithms used were heterogeneous.

In conclusion, repeat RF ablation for local progression of lung tumors after previous RF ablation significantly improved the overall local control outcomes. In particular, repeat RF ablation offered an opportunity to salvage tumors that were suitable for local control with RF ablation (ie, tumors that were <2 cm in size originally and were not in contact with vessels or bronchi) but nevertheless showed local progression after the first RF ablation. Conversely, tumors that were unsuitable for RF ablation could not be controlled sufficiently even after repeating the procedure.

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