

Review

## Radiofrequency Ablation of Lung Cancer at Okayama University Hospital: A Review of 10 Years of Experience

Takao Hiraki<sup>a\*</sup>, Hideo Gobara<sup>a</sup>, Hidefumi Mimura<sup>a</sup>, Shinichi Toyooka<sup>b</sup>,  
Hiroyasu Fujiwara<sup>c</sup>, Kotaro Yasui<sup>d</sup>, Yoshifumi Sano<sup>e</sup>, Toshihiro Iguchi<sup>f</sup>,  
Jun Sakurai<sup>g</sup>, Nobuhisa Tajiri<sup>h</sup>, Takashi Mukai<sup>i</sup>, Yusuke Matsui<sup>a</sup>, and Susumu Kanazawa<sup>a</sup>

Departments of <sup>a</sup>Radiology and <sup>b</sup>Cancer and Thoracic Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan, <sup>c</sup>Department of Diagnostic Radiology, National Cancer Center Hospital, Chuo-ku, Tokyo 104-0045, Japan, <sup>d</sup>Department of Radiology, Okayama Saiseikai General Hospital, Okayama 700-8511, Japan, <sup>e</sup>Department of Thoracic Surgery, Ehime University Hospital, Toon, Ehime 791-0295, Japan, <sup>f</sup>Department of Diagnostic Radiology and Interventional Radiology, Fukuyama City Hospital, Fukuyama, Hiroshima 721-8511, Japan, <sup>g</sup>Department of Radiology, Kagawa Prefectural Central Hospital, Takamatsu 760-8557, Japan, <sup>h</sup>Department of Radiology, Mitoyo General Hospital, Kanonji, Kagawa 769-1695, Japan, and <sup>i</sup>Department of Radiology, Okayama Medical Center, Okayama 701-1192, Japan

The application of radiofrequency ablation for the treatment of lung cancer by our group at Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences began in June 2001, and in the present report, we review our 10-year experience with this treatment modality at Okayama University Hospital. The local efficacy of radiofrequency ablation for the treatment of lung cancer depends on tumor size and the type of electrode used, but not on tumor type. An important factor for the prevention of local failure may be the acquisition of an adequate ablative margin. The combination of embolization and radiation therapy enhances the local efficacy. Local failure may be salvaged by repeating the radiofrequency ablation, particularly in small tumors. Survival rates after radiofrequency ablation are quite promising for patients with clinical stage I non-small cell lung cancer and pulmonary metastasis from colorectal cancer, hepatocellular carcinoma, and renal cell carcinoma. The complications caused by radiofrequency ablation can be treated conservatively in the majority of cases. However, attention should be paid to rare but serious complications. This review shows that radiofrequency ablation is a promising treatment for patients with lung cancer.

**Key words:** radiofrequency ablation, lung cancer, local efficacy, survival, complication

**P** rimary lung cancer is currently the most common cause of cancer-related death in the world. Furthermore, the lung is one of the most common sites of metastases from various primary sites. Surgical resection is currently the most curative

therapy for lung cancer, whether primary or metastatic. However, surgery is not a feasible option for many patients with lung cancer. Research aimed at finding an alternative therapy for lung cancer has therefore been extensive in the past decades.

Radiofrequency ablation (RFA) has received considerable attention as a local therapy for hepatocellular carcinoma. The favorable outcomes of RFA for hepatocellular carcinoma have encouraged the applica-

tion of this technique to neoplasms in other organs, including the lungs. The application of RFA for the treatment of lung cancer by our group at Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences began in June 2001, and during these past 10 years, several ablation sessions for lung neoplasms have been carried out. In the present report, we review our 10-year experience with RFA of lung cancer at Okayama University Hospital.

### Our Standard Protocol

Approval from the institutional review board and informed consent from the patients were obtained to perform RFA of lung cancer. Our institutional review board also provided approval to report retrospective studies using the outcomes of RFA.

**Preprocedural examination.** A complete blood count, blood biochemistry values, and blood coagulation profile are obtained before each RFA treatment session. Chest computed tomography (CT) scanning is performed to assess the tumors and to guide the procedure. The scan includes the abdomen to evaluate extrapulmonary metastasis. Positron emission tomography is also performed whenever possible. Pulmonary function tests are carried out in most cases, in particular for patients at risk for developing pulmonary dysfunction, including patients with a history of pulmonary surgery and radiation and those with underlying lung disease such as chronic obstructive lung disease.

RFA is indicated in those patients for whom the treatment of lung cancer is expected to contribute to prolonged survival and/or improved quality of life. The procedure is not indicated in patients with leukopenia, thrombopenia, coagulation disturbances, or substantial organ dysfunction. For example, patients with a leucocyte count of  $< 3,000$  cells/ $\mu$ l, a platelet count of  $< 50,000$ /ul, a prothrombin time-international ratio of  $> 1.5$ , poor pulmonary function (predicted forced respiratory volume in 1 sec  $\leq 1,000$  ml), and/or poor cardiac function (New York Heart Association Class  $\geq$  III) are not candidates for RFA.

**Procedure techniques.** The RFA procedure is performed as in-patient treatment. All procedures are performed percutaneously using CT-fluoroscopic guidance by an experienced interventional radiologist or a radiology trainee (resident or fellow) under the super-



**Fig. 1** A picture during radiofrequency ablation under CT fluoroscopic guidance. CT fluoroscopic images are displayed on the screen (arrow) immediately after a physician steps on a foot switch. The CT gantry is moved in the cephalocaudal direction for a patient by handling the controller (arrowhead). Thereby, a physician is able to adjust the scanning level of the image.

vision of an experienced interventional radiologist (Fig. 1). The patients are usually placed in a supine or prone position, depending on the tumor location. Standard steel mesh grounding pads are placed on the patient's thighs. Blood pressure, pulse, blood saturation, and electrocardiogram are monitored throughout the procedure.

The electrode used for the procedure is a single internally cooled electrode with a 1-, 2-, or 3-cm noninsulated tip (Cool-tip; Covidien, Mansfield, MA, USA) or a multitined expandable electrode with a 2-, 3-, 3.5-, or 4-cm array diameter (LeVeen; Boston Scientific, Natick, MA, USA). A cluster internally cooled electrode (Covidien) was used for the treatment of large tumors during our early experience. However, the use of the cluster electrode was currently suspended because of the high likelihood of complications (see the "Complications" section). Until October 2003, an internally cooled electrode was the only type of electrode available at our institution, and thus it was used for all procedures. After that, multitined expandable electrodes became available, and they are currently the preferred electrode for the RFA procedure based on data showing a significant improvement in the local efficacy compared to the internally cooled electrode (see the "Local tumor control" section). A single internally cooled electrode is alternatively used

when the use of the multitined expandable electrode is deemed unsuitable.

Intraprocedural pain is treated by using local anesthesia or local plus epidural anesthesia, along with conscious sedation with an intravenous drip infusion of fentanyl and an intramuscular injection of hydroxyzine. In the case of expected severe procedural pain, *e.g.*, when the tumor is close to the pleura, or if the patient asks for it, epidural anesthesia is administered. After the administration of anesthesia, the electrode is introduced into the tumor and connected to the generator (CC-1, Covidien, for internally cooled electrodes or RF3000, Boston Scientific, for multitined expandable electrodes). The ablation algorithm according to electrode type is shown in Table 1. For the Covidien devices, an impedance-control algorithm is selected, and the initial radiofrequency power is set at 20 W or 30 W according to the electrodes with noninsulated tip lengths (Table 1). The power is increased by 10 W/min (Table 1). Radiofrequency energy is applied for 12 min during infusion of ice saline into the cooling lumen of the electrode. Immediately after radiofrequency application, the temperature of the tumor at the electrode tip is measured. Whenever the temperature fails to reach 60°C, additional radiofrequency applications are attempted at the same site.

For the Boston Scientific device, the radiofrequency power is set at 10–40 W according to the array diameter; the power is then increased at the rate of 5 W/min or 10 W/min (Table 1). Radiofrequency energy is applied until a dramatic increase in impedance occurs or automatic shut-off occurs at 15 min. After a 30-sec interval, the second radiofrequency energy application is performed at the same site, with the initial power set at half of the maximum power used in the first application. The second radiofre-

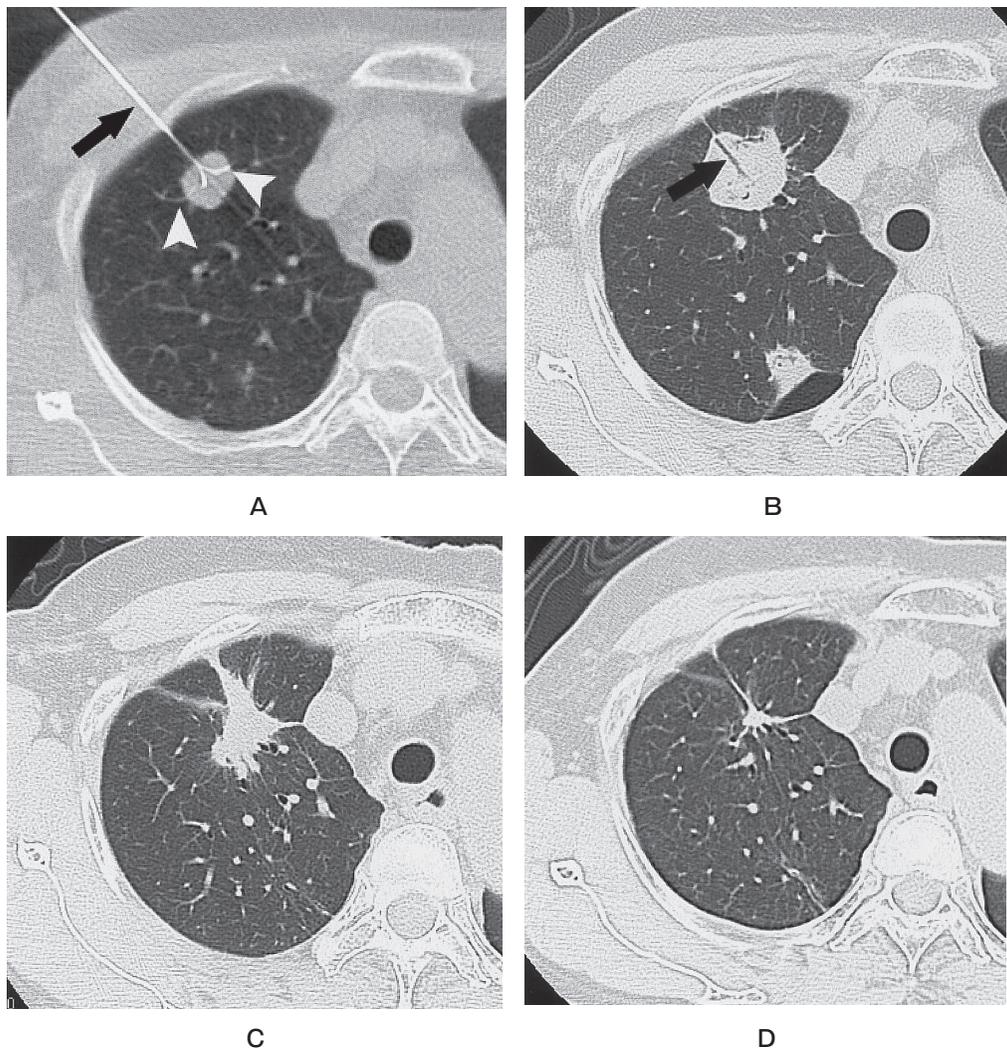
quency energy application is also ended when there is a dramatic increase in impedance or automatic shut-off at 15 min. The procedure is aimed at achieving ablation of the entire tumor, including a parenchymal margin of at least 5 mm, and multiple overlapping ablations are performed whenever deemed necessary to cover the entire area.

Immediately after completion of the procedure, CT images of the lung are obtained to assess the ablation zone and procedural complications. An upright chest posteroanterior radiograph is obtained 3 h later and again the following morning, mainly to evaluate the occurrence and the severity of pneumothorax. A symptomatic pneumothorax or a pneumothorax that exceeds 30–40% of the hemothorax is usually treated with chest tube placement.

**Follow-up.** CT images in cases of complete ablation and local progression are shown in Fig. 2 and 3, respectively. Patients are followed up at 1, 3, 6, 9, and 12 months and thereafter at 6-month intervals with chest and abdominal CT images with a contrast medium, whenever possible. The local efficacy is evaluated mainly based on sequential follow-up CT images. During the first 3 months of follow-up, the size of the ablated lesion may exceed the tumor size before ablation, due to the detection of the entire ablated lesion including the marginal parenchyma (Fig. 2, 3). Thus, CT images obtained 1 month after RFA are taken as a term of reference. Thereafter, the local efficacy may be evaluated by comparing the size and geometry of the ablation zone with the observations of the previous CT images. Local tumor progression is considered to have occurred when the ablation zone is circumferentially enlarged or when an irregular, scattered, nodular, or eccentric focus appears in the ablation zone (Fig. 3). This focus generally exhibits some degree of contrast enhance-

**Table 1** Ablation algorithm according to electrode type

	Noninsulated tip length or arrays diameter (cm)	Initial power (W)	Increased rate of power (W/min)
Internally cooled electrode	2	20	10
	3	30	10
Multitined expandable electrode	2	10	5
	3	20	5
	3.5	30	10
	4	40	10



**Fig. 2** CT images in a case of complete ablation. **A**, CT fluoroscopic image during RFA shows that a multitined expandable electrode is introduced into pulmonary metastasis from colon cancer measuring 1.5 cm in diameter in the right upper lobe. The arrow indicates the electrode shaft, and the arrowheads indicate the expanded tines; **B**, CT image 1 month after RFA shows that the size of the ablated lesion exceeds the tumor size before RFA due to the detection of the entire ablated lesion including the marginal parenchyma. The arrow indicates an electrode tract; **C**, CT image 4 month after RFA shows shrinkage of the ablated lesion; **D**, CT image 16 months after RFA shows the ablated lesion as scar-like tissue, suggesting complete ablation.

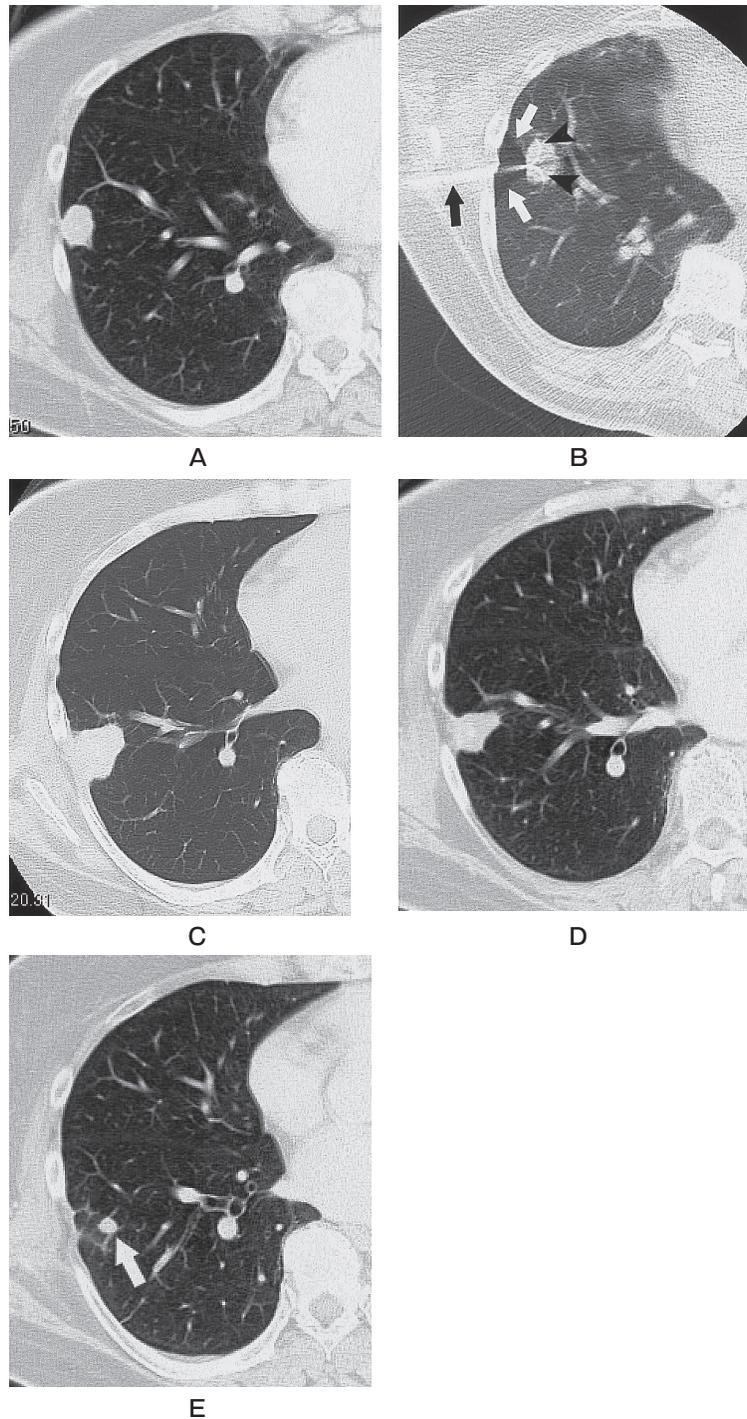
ment and is thus distinguished from the unenhanced necrotic tumor tissue.

Although positron emission tomography is not included in our routine follow-up imaging protocol, it is performed, when deemed necessary, to evaluate local progression and regional and distant metastases.

### Ten-year Outcomes

**Feasibility.** We first described the preliminary

results of RFA for the treatment of lung cancer in 2004 [1]. At the time of that report, we had performed RFA in 99 primary or metastatic lung cancers. The reported technical success rate was 100%. Complications were reported after 76% of the sessions. The local control rate was 91% during the mean follow-up period of 7 months. Thereafter, we reported the feasibility of RFA based on our first 3.5-year experience [2]. This study reported the results of 211 RFA sessions for the treatment of 366



**Fig. 3** CT images in a case of local progression. **A**, CT image before RFA shows pulmonary metastasis from colon cancer measuring 1.8 cm in diameter in the right lower lobe; **B**, CT fluoroscopic image during RFA shows that a multitined expandable electrode is introduced into the tumor. The black arrow indicates the electrode shaft, and the arrowheads indicate the expanded tines. The white arrows indicate pneumothorax; **C**, CT image 1 month after RFA shows that the size of the ablated lesion exceeds the tumor size before RFA, due to the detection of the entire ablated lesion, including the marginal parenchyma; **D**, CT image 7 month after RFA shows shrinkage of the ablated lesion; **E**, CT image 7 month after RFA at the upper level of image D shows nodular focus (arrow) at the upper margin of the ablated lesion, suggesting local progression.

tumors in 137 patients. After 211 ablation sessions, there was no procedural mortality, but there were 2 procedure-related deaths (0.9%) that were attributed to intractable pneumothorax and massive hemorrhage.

### **Local tumor control.**

**1. Risk factors for local progression.** A study by us analyzed preliminary local control outcomes and the factors affecting local control [3]. The local control rates of 342 tumors were 72% at 1 year, 60% at 2 years, and 58% at 3 years. The local progression rate after RFA of lung cancer appeared higher than that observed after RFA of hepatocellular carcinoma and renal cell carcinoma. Unlike solid organs, the lungs possess intrinsically unique tissue characteristics that affect the outcome of RFA. The limited electrical and thermal conductivity of the air-containing lung tissues can interfere with the achievement of an adequate ablative margin. Furthermore, ventilation promotes a heat sink effect and thus may inhibit the increase in tissue temperature. These factors may contribute to inferior local control outcomes in the lung. The significant risk factors for local progression determined by univariate analysis were male gender, tumor diameter of  $\geq 2$  cm, central location, contact with a blood vessel, contact with a bronchus, use of an internally cooled electrode, and an estimated ratio of the ablation volume to the tumor volume of  $< 3.0$ . The independent risk factors for local progression determined by multivariate analysis were larger tumor size and the use of an internally cooled electrode. When considering tumors without the independent risk factors (*i.e.*, tumors  $< 2$  cm in size that were treated with a multitined expandable electrode), the technique effectiveness rates were 89% at 1 year and 66% at 2 years.

**2. Tumor type.** In addition to tumor size and electrode type, the local control outcomes can also be determined by tumor type due to a variety of factors related to the cytology, pathophysiology, and biology of the tumor. The sensitivity of cells to heat may vary with cell type. The presence of intratumoral septa and tumor capsules can affect thermal distribution during RFA. A more infiltrating tumor theoretically has a higher risk of local progression. Considering the perfusion-mediated heat sink effect, RFA treatment of hypervascular tumors can be associated with decreased thermal effects. We examined the effect of tumor type on local control outcomes [4]. First, we evaluated

the local control outcomes of a total of 5 types of cancer: primary lung cancer and pulmonary metastases from colorectal cancer, lung cancer, renal cell carcinoma, and hepatocellular carcinoma. The overall local control rates were 86% and 76% at 1 and 2 years, respectively. Metastatic colorectal cancer showed significantly higher local control rates than those of the other 4 types. However, these results alone were insufficient to prove that tumor type affects local control, because the distribution of other factors affecting local control was heterogeneous among the groups. Univariate analysis showed that tumor size, tumor contact with a vessel or bronchus, and tumor treatment during the first 2 years were significantly associated with inferior local tumor control. Therefore, to evaluate the effect of tumor type on local control, we carried out a multivariate analysis to adjust for the differences in these factors and found that the relative risk of local progression was similar among the 5 tumor types. In other words, this study proved that RFA may provide similar local efficacy, independent of tumor type.

**3. Tumor location.** One area of concern with regard to RFA for the treatment of lung cancer is the safety and effectiveness of the procedure in the case of tumors that are in the proximity of the heart or the aorta. In these cases, possible complications include the accidental insertion of an electrode into the heart or the aorta and thermal injury to cardiac components such as the pericardium, myocardium, and coronary artery, resulting in pericardial effusion, arrhythmia, and cardiac infarction, respectively. In addition, the effectiveness might be reduced by the pulsation of these structures and a considerable heat sink effect caused by high blood flow. In a study designed to evaluate the safety and effectiveness of RFA applied to tumors in the proximity of the heart or the aorta [5], we analyzed the effects of RFA of 42 tumors that were less than 10 mm from the heart or the aorta. These tumors were classified into 2 groups: group A was composed of 27 tumors that were close to but separate from the heart or the aorta; group B included 15 tumors that were contiguous to the heart or the aorta. RFA treatment was feasible for all 42 tumors. There were no complications associated with the specific tumor location, such as the accidental insertion of the electrode into the heart or aorta, pericardial effusion, arrhythmia, or cardiac infarction.

tion. The local control rate in group A was 69% at 2 years, compared to only 9% at 1 year in group B. The results of this study indicated that although RFA could be safely performed in tumors near the heart or aorta, the local control of tumors contiguous to the heart or the aorta was quite limited.

**4. Repeat RFA for local progression.** One notable advantage of RFA may be the ability to repeat the procedure in cases of local failure. We analyzed the significance of repetition of the procedure for local tumor control [6]. Out of 797 tumors treated from June 2001 to February 2007, 117 tumors were diagnosed as showing local progression. The primary local control rate was 74% at 1 year, 64% at 2 years, 63% at 3 years, and 63% at 4 years. Among the 117 locally progressing tumors, 56 tumors were treated by repeat RFA. Of these 56 tumors, 17 tumors showed local progression for the second time. The secondary local control rate, namely, the local control rate of both the first and the second RFA, was 88% at 1 year, 79% at 2 years, 74% at 3 years, and 74% at 4 years. The secondary local control rates were significantly higher than the primary rates, which suggested that repetition of the procedure contributed to better local tumor control. However, the results also revealed the limitations of the repeat RFA treatment. Tumor size  $\geq 2$  cm at the first RFA and contact with bronchi or vessels were significant risk factors for local control by the repeat RFA. The local control rate was limited to 40% at 2 years for tumors with one or more risk factors, even if the procedure was repeated in cases of local failure.

**5. Single RF application with multitined expandable electrodes.** The area of radiofrequency-induced coagulation is largely dependent on the

noninsulated tip length of internally cooled electrodes or the diameter of the arrays of multitined expandable electrodes. In addition, as described above, the electrode type (internally cooled electrode vs. multitined expandable electrode) may affect the local control outcomes. The ideal tumor candidates for RFA should therefore be determined based on the characteristics of the specific electrode, including its type and noninsulated tip length or the diameter of the arrays. However, the determination of ideal tumor candidates for RFA based on electrode type is not well understood. We aimed at determining which tumors are most likely to respond favorably to RFA involving a single RF application with a single type of electrode (multitined expandable electrode with arrays measuring 2 cm in diameter) [7]. A retrospective evaluation of 88 lung metastases (mean long-axis diameter, 0.9 cm) treated with a single RF application with such an electrode showed overall local control rates of 92% at 1 year and 90% at 2 years. Tumor size  $> 1.0$  cm and contact with the bronchus were the significant risk factors for local progression. The local control rates for the 59 tumors  $\leq 1.0$  cm that were not in contact with the bronchus were 96% each at 1 year and at 2 years. These results suggested that lung metastases  $\leq 1.0$  cm that were not in contact with the bronchus were favorable responders for a single RF application with a multitined expandable electrode with arrays 2 cm in diameter.

**Patient survival.** Survival outcomes of patients with various lung cancers treated with RFA are summarized in Table 2.

**1. Clinical stage I non-small cell lung cancer.** In 2007, we analyzed patient survival after RFA in 20 nonsurgical candidates with clinical stage I non-

**Table 2** Summary of survival outcomes of patients with various lung cancers treated by radiofrequency ablation

Reference number	Cancer type	No. of patients	Follow-up period (months)	Survival rate (%)					Survival time (months)	
				1 year	2 years	3 years	4 years	5 years	Median	Mean
8	Stage I NSCLC	20	22 (median)	90	84	74				42
9	Stage I NSCLC	50	37 (median)	94	86	74	67	61	67	59
10	Metastases from CRC	27	20 (median)	96	54	48				33
11	Metastases from CRC	71	19 (mean)	84	62	46			31	
13	Metastases from HCC	32	21 (median)	87	57	57			38	43
14	Metastases from RCC	15*	25* (mean)	100*	100*	100*	100*	100*		

NSCLC, non-small cell lung cancer; CRC, colorectal cancer; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma.

\*Data are derived from curative group.

small cell lung cancer [8]. During the median follow-up period of 21.8 months, the overall survival rates were 90% at 1 year, 84% at 2 years, and 74% at 3 years; the cancer-specific survival rates were 100% at 1 year, 93% at 2 years, and 83% at 3 years. The mean survival time was 42 months. In an additional study in 2011, we analyzed survival outcomes after RFA in patients with clinical stage I non-small cell lung cancer, using a larger population and longer follow-up periods [9]. The study included 50 patients with a median follow-up period of 37 months. The overall survival rates were 94% at 1 year, 86% at 2 years, 74% at 3 years, 67% at 4 years, and 61% at 5 years. The median and mean survival times were 67 months and 59 months, respectively. The cancer-specific survival rates were 100% at 1 year, 93% at 2 years, 80% at 3 years, 80% at 4 years, and 74% at 5 years; the disease-free survival rates were 82% at 1 year, 64% at 2 years, 53% at 3 years, 46% at 4 years, and 46% at 5 years. Considering that the population included nonsurgical candidates, the reported midterm survival data seem quite promising. At the same time, however, it should be noted that such promising survival data depends, in part, on selection bias; the population had relatively small cancers (mean tumor size, 2.1cm) and included a high proportion (20%, 10/50) of patients with cancer showing pure ground-glass opacity.

Considering unsatisfactory survival of the patients with stage IB or II disease by standard surgery alone, we feel that RFA combined with concurrent chemotherapy and RFA supported by adjuvant chemotherapy for stage IB or II disease would be interesting and should be considered in a future trial.

**2. Pulmonary metastasis from colorectal cancer.** We also assessed survival rates in patients with pulmonary metastases from colorectal cancer [10]. This study included 27 patients having a total of 49 pulmonary metastases (mean long-axis diameter, 1.5cm) from colorectal cancer. During the median follow-up period of 20.1 months after RFA, the overall survival rates were 96% at 1 year, 54% at 2 years, and 48% at 3 years. The most significant prognostic factor was the presence of extrapulmonary metastasis at the time of RFA. Similar favorable survival (46% at 3 years) was reported by a multicenter study in Japan involving Okayama University Hospital [11].

**3. Pulmonary metastases from hepatocellular carcinoma.** With regard to pulmonary metastases from hepatocellular carcinoma, we reported on 2 promising cases of patients who survived for 86 months and 75 months, respectively, after RFA of pulmonary metastases with no evidence of cancer recurrence [12]. We conducted a multicenter study involving 6 institutions in Japan to investigate survival after pulmonary metastases from hepatocellular carcinoma [13]. This study included 32 patients who had no intrahepatic recurrence or had treatable intrahepatic recurrence, who had no other metastases, and for whom RFA was performed with curative intent (*i.e.*, not palliatively). The overall survival rates were 87% at 1 year and 57% at 2 and 3 years during a median follow-up period of 20.5 months. Significantly better survival rates were obtained for patients with an absence of viable intrahepatic recurrence, Child-Pugh grade A, absence of liver cirrhosis, absence of hepatic C virus infection, and  $\alpha$ -fetoprotein levels  $\leq$  10ng/ml at the time of RFA.

**4. Pulmonary metastases from renal cell carcinoma.** In cases of pulmonary metastases from renal cell carcinoma, patient survival was evaluated using data from 2 institutions, including Okayama University Hospital [14]. This study included 39 nonsurgical candidates who were divided into 2 groups: a curative ablation group, which was formed by 15 patients with 6 or fewer lung metastases measuring  $\leq$  6cm that were confined to the lung and who had all lung tumors ablated, and the palliative ablation group, which included 24 patients with extrapulmonary lesions, 7 or more lung tumors, or large tumors of  $>$  6cm, and who had mass reduction. The overall survival rates in the curative and palliative ablation groups were 100% and 90% at 1 year, 100% and 52% at 3 years, and 100% and 52% at 5 years, respectively. The maximum lung tumor diameter was a significant prognostic factor.

**Complications.** The incidence of various complications by RFA is summarized in Table 3.

**1. Pneumothorax.** Pneumothorax is the most common complication following RFA. We evaluated the incidence of pneumothorax after RFA of lung cancer [15] and found an incidence rate of 52%. Risk factors for pneumothorax included male gender, no history of pulmonary surgery, a greater number of tumors ablated, involvement of the middle or lower lobes, and increased length of the aerated lung tra-

**Table 3** Summary of incidence of various complications of radiofrequency ablation

Reference number	Complication	Incidence for procedures (%)
15	Pneumothorax	52
15	Pleural effusion	19
17	Bronchopleural fistula	0.6
18	Needle-tract seeding	0.3
19	Brachial nerve injury	0.5
21	Pulmonary artery pseudoaneurysm	0.2

versed by the electrode. Among those affected, 21% of the pneumothoraces required chest tube treatment. The risk factors for chest tube placement for pneumothorax included no history of pulmonary surgery, the use of a cluster electrode, and involvement of the upper lobe.

**2. Pleural effusion.** In the same study [15], we also evaluated the incidence and risk factors associated with the development of pleural effusion. The incidence of pleural effusion reported in this study was 19%, and the majority of these cases were treated conservatively. The significant risk factors associated with the development of pleural effusion were the use of a cluster electrode, decreased distance to the nearest pleura, and a decrease in the length of the aerated lung that was traversed by the electrode. We investigated the relationship between pleural temperature and pleural events (*e.g.*, pneumothorax and pleural effusion) after the RFA of lung tumors [16]. The occurrence of pleural effusion was shown to be associated with higher pleural temperatures during the procedure, whereas pneumothorax was not related to pleural temperature.

**3. Bronchopleural fistula.** Although pneumothorax can usually be treated conservatively or via the placement of a chest tube without the persistence of air leakage, we reported on 2 cases of intractable pneumothorax resulting from the development of a bronchopleural fistula [17]. The incidence of intractable pneumothorax due to bronchopleural fistula in our series was 0.6% (2/334). In both cases, RFA induced necrosis of the lung tissue between the pleural space and the bronchus. The bronchopleural fistula formed after sloughing of the necrotic tissue. Management of the bronchopleural fistula was quite challenging, requiring various treatment modalities that included pleurodesis, endobronchial management, and/or surgical repair. In one case, air leakage per-

sisted despite these efforts, and the patient died of acute pneumonia 52 days after the procedure.

**4. Needle-tract seeding.** Rare but important complications of RFA treatment for lung cancer were reported by us, including 2 cases of needle-tract seeding [18], 4 cases of brachial nerve injury [19], and 1 case of *Aspergillus* infection [20]. The frequency of needle-tract seeding after RFA of lung tumors was 0.5% (2/374) for patients, 0.3% (2/661) for procedures, and 0.2% (2/1,024) for tumors. In both of the needle tract seeding cases, RFA was performed with a single internally cooled electrode; the electrode tip temperature immediately after radiofrequency application was <60°C; the electrode was then removed without cauterizing the electrode tract. The conclusions of the study were that cancer cells attached to the electrode tip may remain viable even after radiofrequency application and become detached along the tract during removal of the electrode.

**5. Brachial nerve injury.** The rate of incidence of brachial nerve injury was 0.5% (4 of 733 procedures), and in all 4 cases, the treated tumor was in the lung apex. When the analysis was confined to the procedures for apical lung cancer, the incidence of brachial nerve injury was 15% (4 of 26). The patients developed symptoms of a low brachial plexus injury, which, despite partially receding over time, remained a grade 2 injury in 3 patients and a grade 3 injury in 1 patient (according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0).

**6. Aspergillus infection.** With regard to the single reported case of aspergilloma, a large cavity was formed after the RFA for lung cancer, which resulted in a scaffold for *Aspergillus* infection. We suggested that the possibility of aspergilloma should be considered in the case of consolidation formed in a cavity after RFA, and it should be differentiated from

local tumor progression.

**7. Pulmonary artery pseudoaneurysm.** We reported another rare (0.2%, 1 of 538 procedures) but serious complication after lung RFA: pulmonary pseudoaneurysm that caused massive hemoptysis and was successfully treated with transcatheter coil embolization [21].

#### *Attempts to enhance the efficacy of RFA.*

**1. Pulmonary artery embolization.** In an attempt to enhance the local efficacy of RFA in the lungs, studies were conducted on animal models [22, 23]. We noted a heat sink effect in the pulmonary artery that may decrease the thermal effect during RFA. We therefore performed RFA after pulmonary artery embolization using degradable starch microspheres in a porcine lung model [22]. As expected, RFA after pulmonary artery embolization resulted in significantly enlarged coagulation compared with RFA alone.

**2. Infusion of saline into the lung.** We also noted that alveolar air was an obstacle to ablation, because air has limited electrical and thermal conductivity. Therefore, we infused hypertonic saline into the lung parenchyma immediately before and during RFA [23]. RFA with infusion of saline into the lung successfully enlarged coagulation compared with RFA without it.

**3. Combination therapy.** In the clinical setting, we described 2 cases of large (6 cm and 5.5 cm in size) primary lung cancer treated with RFA followed by conventional radiation therapy [24]. Radiation therapy was initiated 2 months or 10 days after RFA. The radiation dose administered was 50 Gy per 25 fractions or 60 Gy per 30 fractions. The tumors were well controlled until patient death 17 months or 6 months after the therapy. We also reported a case of complete treatment of a 4.7-cm hypervascular pulmonary metastasis from a hepatocellular carcinoma close to the pulmonary hilum [25]. Transcatheter embolization, then RFA, and lastly external beam radiation were applied to eradicate the tumor. Transcatheter embolization may enhance the effect of the subsequent RFA by decreasing blood flow. RFA treatment might improve the efficacy of subsequent radiation treatment, because the effect of radiation therapy depends on tumor volume, and RFA can considerably reduce viable tumor volume. The combination of RFA with different therapeutic modalities can therefore be of great benefit not only through an additive effect but

also due to synergistic effects.

**4. Pain control during procedures.** Pain control during RFA for lung cancer is an important concern. Intraprocedural pain is more prominent when treating tumors close to the pleura. The parietal pleura and chest wall are sensitive to pain because abundant sensory nerve branches originate at the intercostal nerve, contrary to the visceral pleura and lung parenchyma. We induced artificial pneumothorax during RFA in 7 cases to reduce procedural pain [26]. Artificial pneumothorax was induced as follows: the multitined expandable electrode was placed in the tumor, and the tines were fully expanded. The electrode was then pushed forward by applying pressure, thereby creating a space in the pleural cavity. If pain relief was not satisfactory, an 18-gauge intravenous catheter was introduced into the pleural cavity, and CO<sub>2</sub> was administered through the catheter to enlarge the pleural cavity. All 7 cases experienced considerable pain relief after the induction of artificial pneumothorax.

## Conclusions

The local efficacy of RFA for the treatment of lung cancer depends on tumor size and the type of electrode used, but not on tumor type. An important factor for the prevention of local failure may be the acquisition of an adequate ablative margin. The combination of embolization and radiation therapy enhances the local efficacy. Local failure may be salvaged by repeating the RFA, particularly in small tumors. Survival rates after RFA are quite promising for patients with clinical stage I non-small cell lung cancer and pulmonary metastasis from colorectal cancer, hepatocellular carcinoma, and renal cell carcinoma. The complications caused by RFA can be treated conservatively in the majority of cases. However, attention should be paid to rare but serious complications.

*Acknowledgments.* We are very grateful to emeritus professor Yoshio Hiraki and a number of colleagues in the Department of Radiology for their considerable contributions to RFA of lung cancer at Okayama University Hospital.

## References

1. Yasui K, Kanazawa S, Sano Y, Fujiwara T, Kagawa S, Mimura H, Dendo S, Mukai T, Fujiwara H, Iguchi T, Hyodo T, Shimizu N,

- Tanaka N and Hiraki Y: Thoracic tumors treated with CT-guided radiofrequency ablation: initial experience. *Radiology* (2004) 231: 850–857.
2. Sano Y, Kanazawa S, Gobara H, Mukai T, Hiraki T, Hase S, Toyooka S, Aoe M and Date H: Feasibility of percutaneous radiofrequency ablation for intrathoracic malignancies: a large single-center experience. *Cancer* (2007) 109: 1397–1405.
  3. Hiraki T, Sakurai J, Tsuda T, Gobara H, Sano Y, Mukai T, Hase S, Iguchi T, Fujiwara H, Date H and Kanazawa S: Risk factors for local progression after percutaneous radiofrequency ablation of lung tumors: evaluation based on a preliminary review of 342 tumors. *Cancer* (2006) 107: 2873–2880.
  4. Hiraki T, Gobara H, Mimura H, Sano Y, Tsuda T, Iguchi T, Fujiwara H, Kishi R, Matsui Y and Kanazawa S: Does tumor type affect local control by radiofrequency ablation in the lungs? *Eur J Radiol* (2010) 74: 136–141.
  5. Iguchi T, Hiraki T, Gobara H, Mimura H, Fujiwara H, Tajiri N, Sakurai J, Yasui K, Date H and Kanazawa S: Percutaneous radiofrequency ablation of lung tumors close to the heart or aorta: evaluation of safety and effectiveness. *J Vasc Interv Radiol* (2007) 18: 733–740.
  6. Hiraki T, Mimura H, Gobara H, Sano Y, Fujiwara H, Date H and Kanazawa S: Repeat radiofrequency ablation for local progression of lung tumors: does it have a role in local tumor control? *J Vasc Interv Radiol* (2008) 19: 706–711.
  7. Sakurai J, Hiraki T, Mimura H, Gobara H, Fujiwara H, Tajiri N, Sano Y and Kanazawa S: Radiofrequency ablation of small lung metastases by a single application of a 2-cm expandable electrode: determination of favorable responders. *J Vasc Interv Radiol* (2010) 21: 231–236.
  8. Hiraki T, Gobara H, Iishi T, Sano Y, Iguchi T, Fujiwara H, Tajiri N, Sakurai J, Date H, Mimura H and Kanazawa S: Percutaneous radiofrequency ablation for clinical stage I non-small cell lung cancer: results in 20 nonsurgical candidates. *J Thorac Cardiovasc Surg* (2007) 134: 1306–1312.
  9. Hiraki T, Gobara H, Mimura H, Matsui Y, Toyooka S and Kanazawa S: Percutaneous radiofrequency ablation of clinical stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg* (2011) 142: 24–30.
  10. Hiraki T, Gobara H, Iishi T, Sano Y, Iguchi T, Fujiwara H, Tajiri N, Sakurai J, Date H, Mimura H and Kanazawa S: Percutaneous radiofrequency ablation for pulmonary metastases from colorectal cancer: midterm results in 27 patients. *J Vasc Interv Radiol* (2007) 18: 1264–1269.
  11. Yamakado K, Hase S, Matsuoka T, Tanigawa N, Nakatsuka A, Takaki H, Takao M, Inoue Y, Kanazawa S, Inoue Y, Sawada S, Kusunoki M and Takeda K: Radiofrequency ablation for the treatment of unresectable lung metastases in patients with colorectal cancer: A multicenter study in Japan. *J Vasc Interv Radiol* (2007) 18: 393–398.
  12. Hiraki T, Gobara H, Mimura H, Yagi T, Sano Y, Tanaka N and Kanazawa S: Long-term survival after radiofrequency ablation for pulmonary metastasis from hepatocellular carcinoma: report of two cases. *J Vasc Interv Radiol* (2009) 20: 1106–1107.
  13. Hiraki T, Yamakado K, Ikeda O, Matsuoka T, Kaminou T, Yamagami T, Gobara H, Mimura H, Kawanaka K, Takeda K, Yamashita Y, Inoue Y, Ogawa T, Nishimura T and Kanazawa S: Percutaneous radiofrequency ablation for pulmonary metastases from hepatocellular carcinoma: results of a multicenter study in Japan. *J Vasc Interv Radiol* (2011) 22: 741–748.
  14. Soga N, Yamakado K, Gohara H, Takaki H, Hiraki T, Yamada T, Arima K, Takeda K, Kanazawa S and Sugimura Y: Percutaneous radiofrequency ablation for unresectable pulmonary metastases from renal cell carcinoma. *BJU Int* (2009) 104: 790–794.
  15. Hiraki T, Tajiri N, Mimura H, Yasui K, Gobara H, Mukai T, Hase S, Fujiwara H, Iguchi T, Sano Y, Shimizu N and Kanazawa S: Pneumothorax, pleural effusion and chest tube placement after radiofrequency ablation of lung tumors: incidence and risk factors. *Radiology* (2006) 241: 275–283.
  16. Tajiri N, Hiraki T, Mimura H, Gobara H, Mukai T, Hase S, Fujiwara H, Iguchi T, Sakurai J, Aoe M, Sano Y, Date H and Kanazawa S: Measurement of pleural temperature during radiofrequency ablation of lung tumors to investigate its relationship to occurrence of pneumothorax or pleural effusion. *Cardiovasc Intervent Radiol* (2008) 31: 581–586.
  17. Sakurai J, Hiraki T, Mukai T, Mimura H, Yasui K, Gobara H, Hase S, Fujiwara H, Iguchi T, Tajiri N, Aoe M, Sano Y, Date H and Kanazawa S: Intractable pneumothorax due to bronchopleural fistula after radiofrequency ablation of lung tumors. *J Vasc Interv Radiol* (2007) 18: 141–145.
  18. Hiraki T, Mimura H, Gobara H, Sano Y, Fujiwara H, Iguchi T, Sakurai J, Kishi R and Kanazawa S: Two cases of needle-tract seeding after percutaneous radiofrequency ablation for lung cancer. *J Vasc Interv Radiol* (2009) 20: 415–418.
  19. Hiraki T, Gobara H, Mimura H, Sano Y, Toyooka S, Shibamoto K, Kishi R, Uka M and Kanazawa S: Brachial nerve injury caused by percutaneous radiofrequency ablation of apical lung cancer: a report of four cases. *J Vasc Interv Radiol* (2010) 21: 1129–1133.
  20. Hiraki T, Gobara H, Mimura H, Sano Y, Takigawa N, Tanaka T and Kanazawa S: Aspergilloma in a cavity formed after percutaneous radiofrequency ablation for lung cancer. *J Vasc Interv Radiol* (2009) 20: 1499–1500.
  21. Sakurai J, Mimura H, Gobara H, Hiraki T and Kanazawa S: Pulmonary artery pseudoaneurysm related to radiofrequency ablation of lung tumor. *Cardiovasc Intervent Radiol* (2010) 33: 413–416.
  22. Hiraki T, Gobara H, Sakurai J, Mimura H, Mukai T, Hase S, Iguchi T, Fujiwara H, Tajiri N, Yanai H, Yoshino T and Kanazawa S: Radiofrequency ablation of normal lungs after pulmonary artery embolization with use of degradable starch microspheres: results in a porcine model. *J Vasc Interv Radiol* (2006) 17: 1991–1998.
  23. Iishi T, Hiraki T, Mimura H, Gobara H, Kurose T, Fujiwara H, Sakurai J, Yanai H, Yoshino T and Kanazawa S: Infusion of hypertonic saline into the lung parenchyma during radiofrequency ablation of the lungs with multitined expandable electrodes: results using a porcine model. *Acta Med Okayama* (2009) 63: 137–144.
  24. Mukai T, Mimura H, Gobara H, Takemoto M, Himei K, Hiraki T, Hase S, Fujiwara H, Iguchi T, Tajiri N, Sakurai J, Yasui K, Sano Y, Date H and Kanazawa S: Radiofrequency ablation followed by radiation therapy for large primary lung tumors. *Acta Med Okayama* (2007) 61: 177–180.
  25. Hiraki T, Gobara H, Takemoto M, Mimura H, Mukai T, Himei K, Hase S, Iguchi T, Fujiwara H, Yagi T, Tanaka N and Kanazawa S: Percutaneous radiofrequency ablation combined with previous bronchial arterial chemoembolization and followed by radiation therapy for pulmonary metastasis from hepatocellular carcinoma. *J Vasc Interv Radiol* (2006) 17: 1189–1193.
  26. Hiraki T, Gobara H, Shibamoto K, Mimura H, Soda Y, Uka M, Masaoka Y, Toyooka S and Kanazawa S: Technique for creation of artificial pneumothorax for pain relief during radiofrequency ablation of peripheral lung tumors: report of seven cases. *J Vasc Interv Radiol* (2011) 22: 503–506.