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Bronchoscopy-Guided Cooled Radiofrequency Ablation as a Novel Intervention Therapy for Peripheral Lung Cancer

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Key Words
Radiofrequency ablation · Chest computed tomography imaging guidance · Stereotactic body radiation therapy · Early stage lung cancer

Abstract
Background: Our previous animal and preliminary human studies indicated that bronchoscopy-guided cooled radiofrequency ablation (RFA) for the lung is a safe and feasible procedure without major complications. ***Objectives:*** The present study was performed to evaluate the safety, effectiveness and feasibility of computed tomography (CT)-guided bronchoscopy cooled RFA in patients with medically inoperable non-small-cell lung cancer (NSCLC). ***Methods:*** Patients with pathologically diagnosed NSCLC, who had no lymph node involvement or distant metastases (T1–2aN0M0) but were not surgical candidates because of comorbidities (e.g. synchronous multiple nodules, advanced age, cardiovascular disease, poor pulmonary function, etc.) were enrolled in the present study. The diagnosis and location between the nearest bronchus and target tumor were made by CT-guided bronchoscopy before the treatment. A total of 28 bronchoscopy-guided cooled RFA procedures were performed in 20 patients. After treatment, serial CT imaging was performed as follow-up. ***Results:*** Eleven lesions showed significant reductions in tumor size and 8 lesions showed stability, resulting in a local control rate of 82.6%. The median progression-free survival was 35 months (95% confidence interval: 22–45 months), and the 5-year overall survival was 61.5% (95% confidence interval: 36–87%). Three patients developed an acute ablation-related reaction (fever, chest pain) and required hospitalization but improved with conservative treatment. There were no other adverse events in the present study. ***Conclusions:*** CT-guided bronchoscopy cooled RFA is applicable for only highly selected subjects; however, our trial may be an alternative strategy, especially for disease local control in medically inoperable patients with stage I NSCLC.

Introduction

Lung cancer is the leading cause of cancer-related deaths in Japan [1] and throughout the Western world [2]. Surgery is recognized as the standard treatment for patients with early stage non-small-cell lung cancer (NSCLC) [3]. However, surgery is not indicated in patients with cardiovascular, pulmonary and other medical comorbidities

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Table 1. Clinical characteristics of patients enrolled in the study

Case	Age, years	Sex	Location	Histology	Synchronous lesions	Tumor size, mm	Comorbid diseases or history
1	80	F	rt B2	AD	+	24	cerebral infarction, after lt lobectomy
2	84	F	rt B2	AD	+	24	*Mycobacterium avium* infection, low pulmonary function
3	77	F	rt B3	AD	+	36	low pulmonary function
4	79	F	lt B8	AD	+	18	prior pleuritis, low pulmonary function
5	66	M	lt B9	SCC	–	27	after rt lobectomy, IHD
6	80	M	lt B1 + 2	SCC	–	21	IHD, COPD (GOLD II)
7	83	F	rt B3	undiff.	–	28	IHD, chronic renal failure
8	64	M	rt B1	AD	–	35	dilated cardiomyopathy, atrial fibrillation
9	78	F	lt B3	AD	+	21	low pulmonary function
10	83	M	lt B1 + 2	SCC	–	25	IHD, ASO
11	70	F	lt B3	AD	+	22	after operation for cervical carcinoma
12	84	M	rt B1	AD	–	32	follicular lymphoma
13	87	M	lt B3	AD	–	31	COPD (GOLD III)
14	80	F	rt B4	AD	+	14	liver cirrhosis, after operation for colon cancer
15	71	M	lt B1 + 2	SCC	+	15	COPD (GOLD III)
16	58	F	rt B2	AD	–	12	primary biliary cirrhosis
17	77	F	rt B9	AD	+	24	IHD
18	76	F	lt B4	AD	–	26	after operation for breast and ovarian cancer
19	78	M	rt B2	SCC	+	19	COPD (GOLD III)
			rt B1			19	
20	62	M	lt B8	SCC	+	45	after operation for gastric cancer
			rt B6			20	
			lt B6			24	

F = Female; M = male; rt = right; lt = left; AD = adenocarcinoma; SCC = squamous cell carcinoma; IHD = ischemic heart disease; ASO = arteriosclerosis obliterans; COPD = chronic obstructive pulmonary disease.

[4–7]. An increasing proportion of elderly patients with NSCLC could be associated with such medical comorbidities [6]. In patients with medically inoperable stage I NSCLC, stereotactic body radiation therapy (SBRT) has been considered a standard care option. SBRT has been shown to be particularly effective in eradicating the primary or metastatic tumor [7–13]. However, radiation pneumonitis is a potentially life-threatening problem, particularly for patients with impaired pulmonary function or synchronous multiple tumors in the lungs [12–14]. Thus, other alternative therapies for patients with medically inoperable early stage NSCLC are required.

We have developed a new cooled-electrode catheter (Japan Application No. 2006-88228) suitable for forceps channel bronchoscopy [15, 16]. Initially, we showed that the bronchoscopy-guided cooled radiofrequency ablation (RFA) could achieve local coagulation necrosis without major complications in the lungs of animal models [15]. Subsequently, we performed computed tomography (CT)-guided bronchoscopy cooled RFA in patients with stage I NSCLC and histologically examined the ablated areas after standard thoracic surgery. The ablated area was enlarged with improvement of the length of catheter tips and ablation time [16]. Thus, CT-guided bronchoscopy cooled RFA, using 10-mm catheter tips and an ablation time of 50 s, appeared to be a safe and feasible procedure without major complications in patients with lung cancer.

We have adopted this procedure in patients with medically inoperable NSCLC and serially evaluated the radiological findings and clinical outcomes. Here, we report the results and discuss the clinical utility and feasibility of bronchoscopy-guided cooled RFA for medically inoperable early stage NSCLC.

Methods

Ethical Considerations

This study was conducted according to the principles of the Declaration of Helsinki. The protocol of this study was approved by our Institutional Review Boards (Shinshu University No. 847), and written informed consent was obtained from all of the patients before enrollment.

Table 2. Responses to initial bronchoscopy-guided cooled RFA and clinical outcomes

Case	Response	Relapse to initial RFA	Time of retry, months	PFI, months	OS, months	Outcome	Other therapies after RFA
1	PR	+	64	60	87	alive	retry
2	SD	+	40	35	93	alive	retry
3	SD	+	21	17	73	alive	retry, SBRT
4	PR	+	26	20	65	alive	retry
5	PD	+	13, 19	6	40.5	dead (lung cancer)	retry
6	PR			34	34	dead (pneumonia)	
7	SD	+		35	50	dead (lung cancer)	
8	PR	+		55	79.5	alive	RT
9	PR	+		60	71	alive	
10	PD	+		4	27.5	dead (lung cancer)	SBRT
11	PR			65.5	65.5	alive	
12	SD			23	23	dead (other malignancy)	
13	PR	+		19.5	30.5	alive	RT
14	SD			30	30	alive	
15	SD			25.5	25.5	alive	BRT for another lesion
16	SD			24	24	alive	
17	PR			23.5	23.5	alive	
18	PR			23	23	alive	
19	PD			3	5	dead (pneumonia)	
	PD			3			
20	SD	+		24	71	alive	chemotherapy
	PR			71			
	PR	+		24			

PR = Partial response; SD = stable disease; PD = progressive disease; retry = repeat therapy; BRT = body radiation therapy; RT = standard radiation therapy.

Patients

Patients who were pathologically diagnosed with NSCLC (clinical stage: T1–2aN0M0) and were medically inoperable or refused thoracic surgery were enrolled in this study. NSCLC patients were stratified according to the sixth edition of the TNM staging classification. The primary tumor size and evaluation of the tumor-bronchus relationship were obtained in all patients by thin-slice CT. The absence of lymph node involvement was confirmed by contrast-enhanced chest CT. To evaluate extrathoracic distant metastasis, abdominal and brain CT, bone scans or ^{18}F-fluorodeoxyglucose positron emission tomography were performed. During the period from July 2006 to April 2012, 20 patients were enrolled in the study.

RFA Preparation

We prepared an original electrode catheter for RFA, a cooled-electrode catheter with a 10-mm active tip with 5 beads (diameter: 1.67 mm; Japan Application No. 2006-88228; Shinshu University, Nagano, Japan). The electrode catheters were attached to a monopolar radiofrequency generator (Shinshu University). Tissue impedance was monitored continuously by the generator, and an impedance-controlled radiofrequency algorithm was used. During the RFA procedure, a thermometer embedded within the electrode catheter tip continuously measured the temperature. The output power of the monopolar radiofrequency generator and the upper limit of temperature were set at 20 W and 60°C until September 2009, and then at 30 W and 70°C, respectively. Grounding was achieved by attaching standard steel mesh dispersive electrodes to the patient's abdomen. A peristaltic pump (Shinshu University) was used to infuse cold water (4°C) into the internal lumen of the electrode catheter at 50 ml/min to avoid the pop phenomenon in which coagulated necrotic tissue is formed around the electrode tip and tissue impedance increases rapidly. The cooled RFA enables a greater power output for a longer time compared with standard noncooled RFA, resulting in a larger area of coagulation necrosis due to the ablation effect reaching deeper and wider areas. RFA was continued for 50 s under spontaneous breathing. When the desired power output could not be applied as a result of the increase in impedance due to tissue boiling, the generator automatically switched off the electrode. Current pulsing was also performed manually to avoid charring of local tissue caused by the rapid increase in impedance, which limited further heat diffusion.

Bronchoscopy Procedure and RFA Procedure

Conventional standard premedication before bronchoscopy was performed. Briefly, administration of 1 mg of atropine sulfate, 100 μg of pethidine hydrochloride and airway anesthesia with 4% lidocaine hydrochloride were applied orally. Then, patients lay on the table of the CT scanner. Percutaneous oxygen saturation and heart rate were monitored continuously during bronchoscopy by pulse oximetry and electrocardiogram monitoring. A variety of

flexible bronchoscope (Olympus, Tokyo, Japan), model BF 260 (outer diameter: 4.9 mm, forceps channel: 2.0 mm), were used in the present study. All procedures were performed via the transnasal or transoral route under local anesthesia. The bronchoscope was inversed and advanced to the lobe and segment known to be the location of the target lesion. First, the electrode tip was advanced into the bronchus under bronchoscope guidance. Next, low-dose CT guidance, with dose parameters of 120 kV and 10 mA/s, was performed to correlate the location of the electrode catheter tip in the lung tumor. The appropriate peripheral location of the electrode catheter tip was confirmed on both CT images and by checking for impedance less than 300 Ω. RFA were performed 2–3 times in each patient. In general, low-dose CT was used 4–5 times within the limited area focused on the targeted tumor. The technical procedures described above were similar with our previous reports [16, 17], and the duration was approximately within 20 min in almost all cases.

Response Evaluation and Data Analysis

An initial follow-up CT scan was performed 1 month after RFA, followed by further scans at 3, 6 and 12 months. Chest CT was repeated at least every 6 months thereafter. When enlargement of the target lesion was observed, a CT scan follow-up was performed as necessary. The median follow-up interval was 46 months, ranging from 23 to 93 months. The response to CT-guided bronchoscopy cooled RFA was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST). In the present study, determination of stable disease required disease stabilization on CT findings for at least 6 months after RFA. The overall survival time (OS) in 20 subjects was measured from the first day of treatment with CT-guided bronchoscopy cooled RFA to the date of death or last follow-up. The progression-free interval (PFI) in all lesions was measured from the first day of treatment to the date of disease progression on chest CT findings. OS and PFI were calculated using the Kaplan-Meier method. All statistical analyses were performed using MedCalc version 11.4.4 (MedCalc Software, Mariakerke, Belgium).

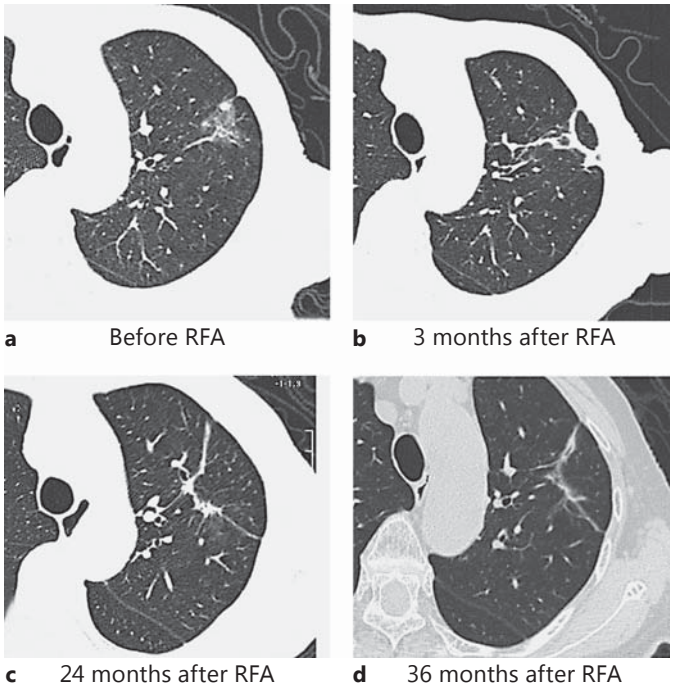

Fig. 1. Serial CT findings before and after CT-guided bronchoscopy cooled RFA in case 9. Tumor shadow, showing ground glass opacity with solid components (adenocarcinoma), was observed in the left S3 area (**a**, before RFA), linear lines and scarring shadow after RFA (**b**, 3 months; **c**, 2 years; **d**, 3 years after RFA).

Results

The clinical characteristics of patients enrolled in the study are summarized in table 1. Twenty patients, 9 men and 11 women, had a mean age of 75.9 years (58–88 years). The histological types included 12 adenocarcinomas, 6 squamous cell carcinomas and 1 undifferentiated type. Several patients had synchronous multiple lesions that were suspected to be malignant lung tumors on thin-slice CT in addition to the target lesion. Among them, 2 tumors in case 19 and 3 tumors in case 20 were treated with CT-guided bronchoscopy cooled RFA on separate days. Thus, a total of 23 lesions were treated by CT-guided bronchoscopy cooled RFA. Two patients (cases 16 and 18) refused thoracic surgery, but the other patients were considered to have medically inoperable NSCLC. The reasons for medically inoperable cases were coexistence of ischemic heart disease,

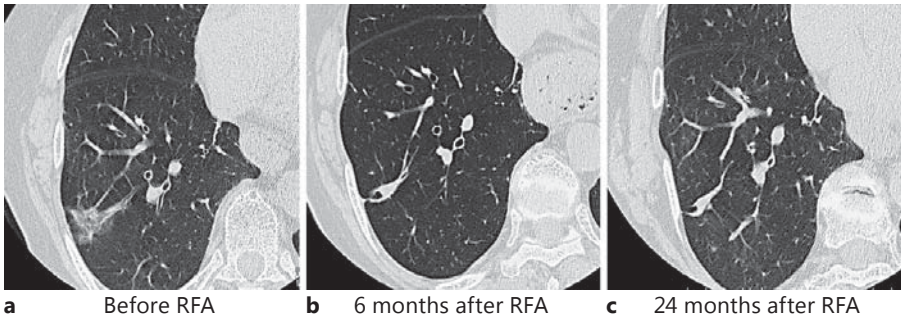

Fig. 2. Serial CT findings before and after CT-guided bronchoscopy cooled RFA in case 17. Tumor shadow in the right B8 area was diagnosed as adenocarcinoma (**a**). The shadow changed to linear lines and scarring shadow 6 months (**b**) and 24 months (**c**) after RFA.

impaired pulmonary functions [chronic obstructive pulmonary disease (COPD), prior pleuritis, postthoracic surgery], multiple lesions and renal dysfunction (table 1). The median tumor size was 24 mm ranging from 12 to 45 mm.

Response

The initial responses to CT-guided bronchoscopy cooled RFA in each case are summarized in table 2. Response was evaluated in 23 lesions. Significant reduction in tumor size (partial response) by CT-guided bronchoscopy cooled RFA was observed in 11 lesions, with a resulting response rate of 47.8%. Stable disease was also observed in 8 lesions, thus resulting in a local tumor control rate of 82.6% (19/23 lesions). The changes in chest CT findings after CT-guided bronchoscopy cooled RFA in patients showing partial response are shown in figures 1 and 2. During CT follow-up after treatment, local progression occurred in 12 lesions and retreatment with bronchoscopy-guided cooled RFA was performed in 5 lesions (cases 1–5). In case 5, who had a history of right lobectomy for lung cancer, a rapidly growing mass in the left lower field was observed and diagnosed as squamous cell carcinoma (fig. 3). Although the initial response to CT-guided bronchoscopy cooled RFA was evaluated as progression, the patient was retreated with RFA, and tumor control was obtained for 20 months after RFA. After progression, radiotherapy including SBRT was added in 3 patients, and chemotherapy was performed in 1 patient (table 2).

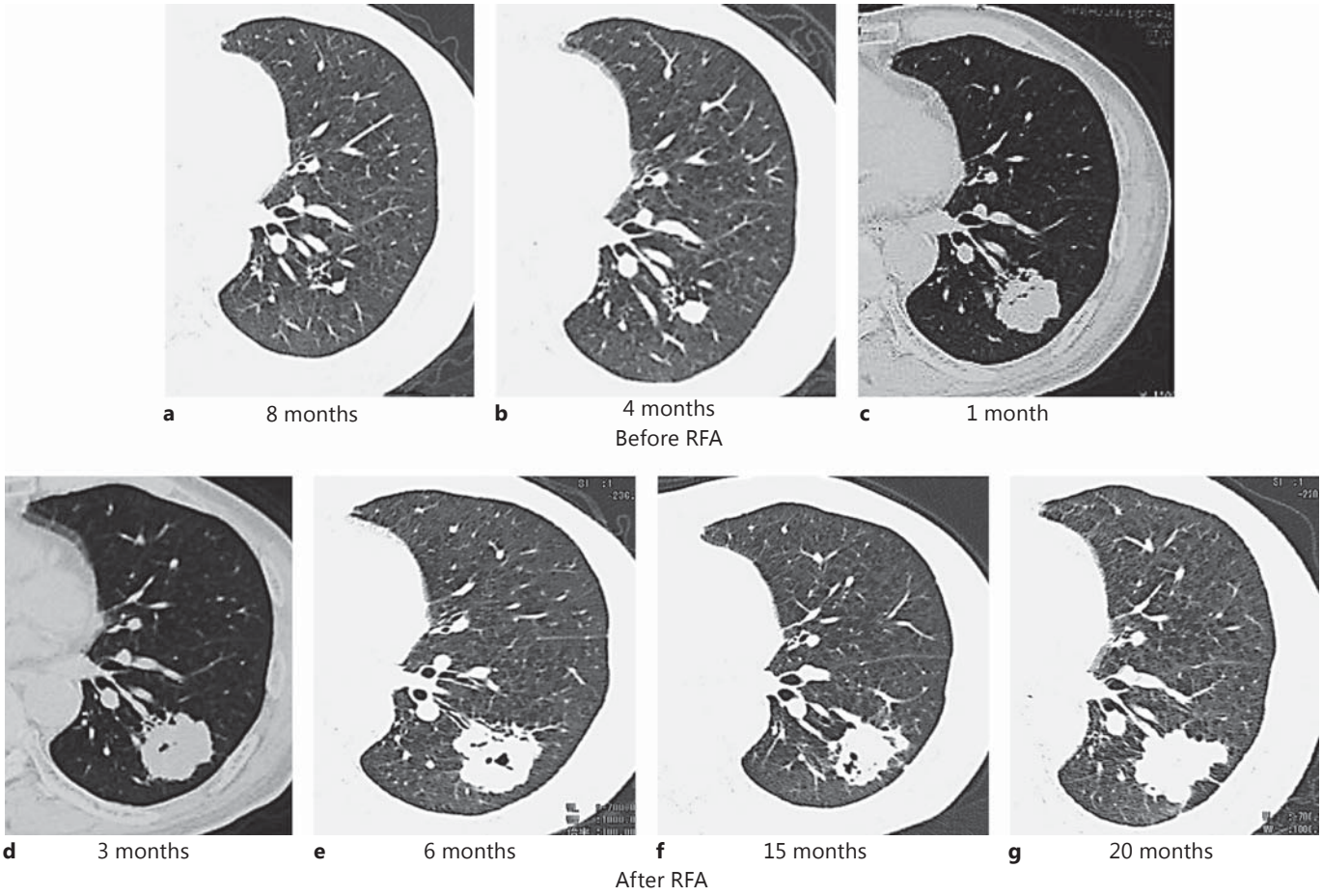

Fig. 3. Serial CT findings before (**a–c**) and after (**d–g**) CT-guided bronchoscopy cooled RFA in case 5. Tumor shadow in the left B8 area was detected during follow-up for right lower lobectomy for lung cancer and found to increase in size for 8 months (**a**, 8 months; **b**, 4 months before RFA; **c**, 1 month before RFA). The patient was diagnosed as having primary squamous cell lung cancer. CT-guided bronchoscopy cooled RFA was repeated 3 times, and the shadow was stable for 20 months after RFA (**d**, 3 months; **e**, 6 months; **f**, 15 months; **g**, 20 months after RFA).

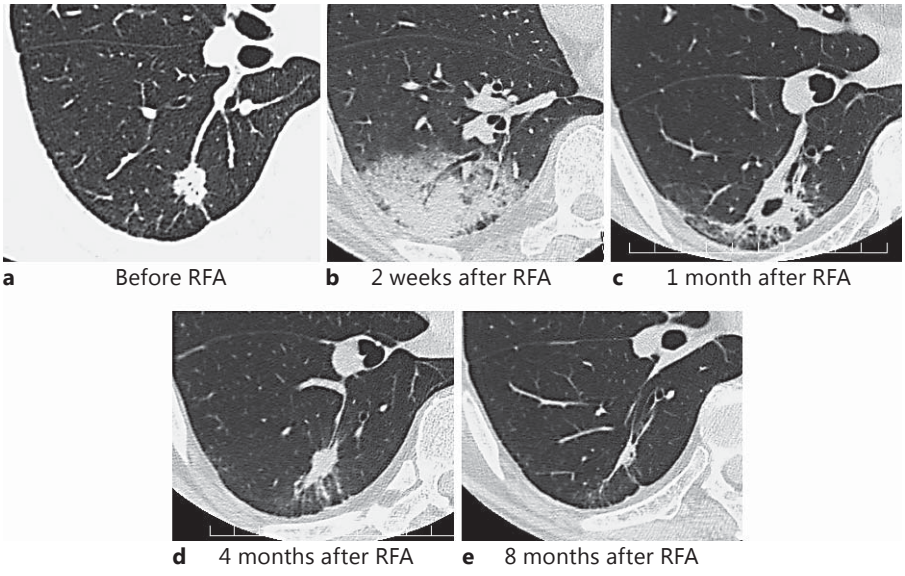

Fig. 4. Serial CT findings before and after CT-guided bronchoscopy cooled RFA in case 20. RFA was performed for a mass in the right B6 area (adenocarcinoma, **a**). The patient presented with right chest pain and fever after the treatment, and chest CT findings revealed consolidation in the right lower lung field (**b**). Then, the shadow decreased and changed to a scarring shadow without any specific treatments (**c–e**).

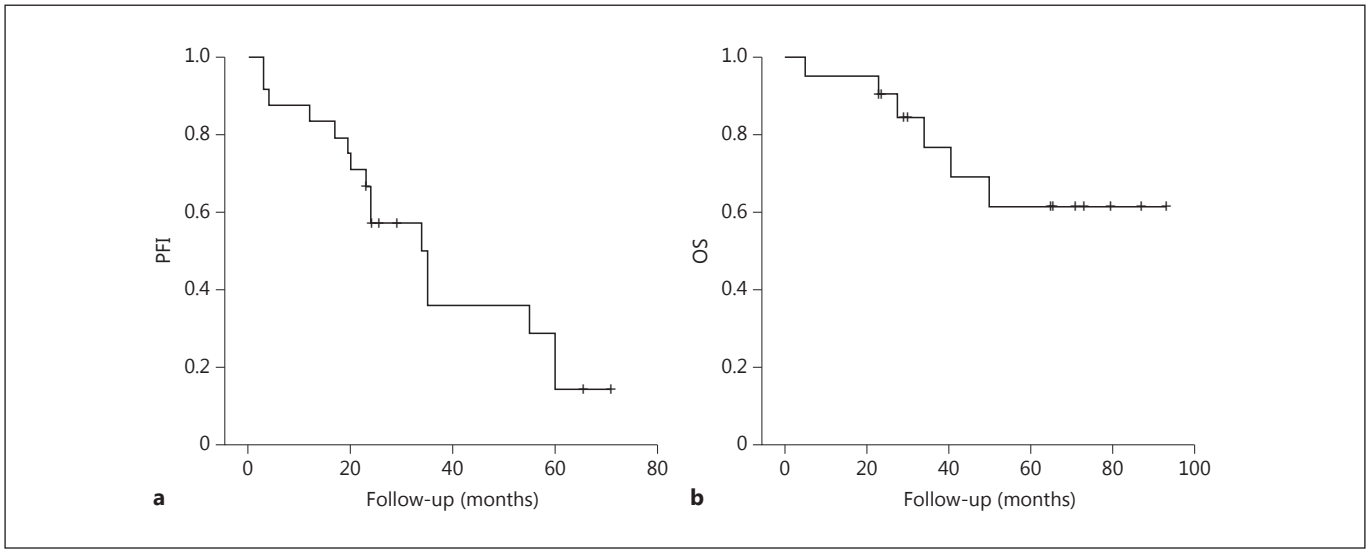

Fig. 5. PFI (**a**) in all lesions and OS (**b**) in 20 subjects. Follow-up was performed by months.

Complication

No serious adverse event was noted. Two patients complained of weak chest pain during the treatment. In these cases, RFA was stopped immediately. We slightly drew the catheter, and RFA was continued. There were no specific toxicities, such as hypoxemia or arrhythmia, during CT-guided bronchoscopy cooled RFA. In addition, neither bleeding nor pneumothorax occurred. However, radiographic consolidation, probably induced by an acute ablation-related reaction, was observed in 3 cases. They presented fever 2–3 days after treatment and required hospitalization, but improved with conservative treatment. The typical radiographic changes are shown in figure 4.

Survival

PFI and OS are shown in figure 5. PFI were evaluated in 23 lesions. The median PFI was 35 months (95% con-

fidence interval: 22–45 months). The 5-year survival rate was 61.5% (95% confidence interval: 36–87 months; fig. 5). Six patients enrolled in the present study died. The cause of death was progression of the original lung cancer in 3 cases (OS after initial RFA of 27.5 months in case 10, 40.5 months in case 5 and 50 months in case 7), pneumonia unrelated to lung cancer in 2 cases (OS after initial RFA of 5 months in case 19 and 34 months in case 6) and another malignancy in 1 case (OS after initial RFA of 23 months in case 12).

Discussion

We report our clinical experience of CT-guided bronchoscopy cooled RFA for medically inoperable stage I NSCLC (T1–2aN0M0). The local control rate after the RFA was 82.6%, and the 5-year survival was 61.5%. Based on the review by Bilal et al. [11], the 5-year survival rate in early stage medically inoperable NSCLC was 47% with SBRT and 20.1–27% with percutaneous RFA therapy, respectively. Palma et al. [8] also described 28% of the 5-year survival rate in stage I NSCLC with GOLD III–IV COPD when treated with SBRT. Clinical outcomes in the present study do not appear to be inferior to those reports [7–12]. Although CT-guided bronchoscopy cooled RFA is indicated only in highly selected subjects, our trial indicated that this is a safe and useful therapeutic approach for medically inoperable patients with stage I NSCLC. This is the first report showing clinical efficacy of bronchoscopy-guided cooled RFA.

RFA is suitable for use on lung tumor because the radiofrequency energy to a tumor relies on the insulation effect by the existence of normal surrounding lungs [18]. It is well known that percutaneous RFA has found clinical applications for medically inoperable patients with lung tumors with good reported results [19, 20]. Since the electrode is placed percutaneously directly into the tumor under cross-sectional imaging guidance such as chest CT, pneumothorax requiring a placement of a chest catheter occurs with frequency [19, 20]. As an alternative therapy to percutaneously guided RFA, SBRT has been applied for medically inoperable lung tumors. Even in SBRT, half of the patients received SBRT reported to have grade 1–2 radiation pneumonitis [13]. SBRT pulmonary complications include radiation pneumonitis, bacterial pneumonia, or atelectasis over grade 3 [8, 10]. The pneumothorax in percutaneous RFA and pulmonary complications in SBRT are certainly undesirable adverse events for patients with respiratory impairment. In the present study, there were several patients with impaired pulmonary function including COPD, postthoracic surgery or prior pleuritis, etc. However, no major complications, such as bronchial bleeding or pneumothorax, were observed. Thus, CT-guided bronchoscopy cooled RFA could avoid or minimize injury to lung tissues and is suitable for use in patients with medical comorbidities, especially impaired pulmonary function.

In our series, retreatment by CT-guided bronchoscopy cooled RFA was performed in 5 progressive lesions. The repeat attempts could be applied in certain cases. We emphasize that safety and repeatability are the greatest advantage of our cooled electrode-using bronchoscopy. When pretreatment is necessary, it is important to evaluate regional lymph node involvement or distant metastasis, since the goal of this approach was only focused on local control of the primary lesion in patients without distant and/or regional lymph node metastasis.

COPD may be an important comorbidity in patients with medically inoperable early NSCLC. Severe COPD increases the risk of postoperative complications and reduces the extent of the lung that can be safely resected [21–23]. In studies focusing on resected patients with early NSCLC, coexisting COPD was associated with poorer survival outcome in comparison to those without COPD [23, 24]. In addition, it is well known that the prevalence rates of lung cancer and COPD increase with age [21, 25]. Furthermore, COPD is an independent risk factor for lung cancer, and an inverse correlation between the degree of airflow obstruction and lung cancer risk was clearly demonstrated [26]. Thus, aging of the population will likely be accompanied by an increase in the number of patients with a high risk of postoperative complications and/or unsuitable for surgical treatment in the field of lung cancer. In these clinical situations, our approach using bronchoscopy-guided cooled RFA provides clinical benefits in certain selected patients among medically inoperable patients with early stage NSCLC.

We encountered 2 patients who developed chest pain during the RFA procedure. We speculated that these symptoms were related to the location of the catheter in the peripheral target tumor near the pleura. In addition, as shown in figure 4, 3 patients showed enlarged consolidation in the ablated lesion just after bronchoscopy-guided cooled RFA. We believe that the response is reflected as acute ablation-induced inflammation. Three patients were treated with a generator power of 30 W and a temperature of 70°C. We have previously shown that the size of the ablated area could be affected by the ablation time [16], but the relationship between the response and tem-

perature or power remains unclear. Further trials are needed to achieve more suitable and appropriate RFA conditions.

The efficacy of CT-guided bronchoscopy cooled RFA is dependent on the location of the nearest bronchus to the target tumor on CT findings, especially thin-slice CT. Indeed, CT-guided bronchoscopy for diagnosis was performed in each patient, and all patients enrolled in the present study were histologically diagnosed with NSCLC. The location of the probe within the tumor on CT images was carefully evaluated at diagnosis. Several investigators indicated that the bronchus sign identified on CT scan was important for the endobronchial approach [27, 28]. The bronchus sign is related to the rate of navigation success and the diagnosis of peripheral nodules. We believe that this sign on thin-slice CT is a key variable as an indication for our CT-guided bronchoscopy cooled RFA therapy. Conversely, we speculate that peripheral tumors without an endobronchial route, such as metastatic tumors, are unsuitable for bronchoscopy-guided cooled RFA.

The difficulty in the accurate response evaluation after bronchoscopy-guided cooled RFA may be a clinical concern. We used RECIST criteria for evaluation in the present study, because scant changes on CT images after RFA could correspond to partial response in RESIST criteria. However, the remaining opacity on chest CT after RFA may include viable malignant cells and RFA-induced inflammation, necrosis or fibrosis. Thus, it is difficult to distinguish remaining viable tissue from the ablated area after RFA therapy, which was similar to the problems in percutaneous RFA or SBRT [29]. Thus, serial CT findings during follow-up may only be available to provide information regarding the response or local progression after RFA.

In conclusion, CT-guided bronchoscopy cooled RFA is a safe and effective procedure that could become a useful therapeutic tool for local control in medically inoperable patients with stage I NSCLC. This technique could be an alternative strategy, especially in patients with the bronchus sign on CT findings.

Financial Disclosure and Conflicts of Interest

T.K had received a grand from the Japanese Foundation for Research and Promotion of Endoscopy in 2012. For the remaining authors no conflicts of interest were declared.

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