Percutaneous radiofrequency ablation of clinical stage I non-small cell lung cancer

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Objective: This study aimed at retrospectively evaluating the outcomes of radiofrequency ablation of clinical stage I non-small cell lung cancer.

Methods: This study was carried out on 50 nonsurgical candidates (29 men and 21 women; mean age, 74.7 years) with clinical stage I (IA, n = 38; IB, n = 12) histologically proven non-small cell lung cancer. A total of 52 tumors were treated with 52 ablation sessions. Radiofrequency ablation was performed percutaneously under computed tomography fluoroscopic guidance. The outcomes of radiofrequency ablation were evaluated, including toxicity, local efficacy, and patient survival. Toxicity was evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0. Local efficacy was evaluated by using computed tomography scan with a contrast medium. The overall, cancer-specific, and disease-free survivals were estimated with Kaplan–Meier analysis.

Results: Grade 2 and 3 adverse events occurred after 6 (12%) and 3 (6%) of the 52 sessions, respectively. The median follow-up period was 37 months. Local progression was observed in 16 (31%) of the 52 tumors. The median survival time was 67 months. The overall, cancer-specific, and disease-free survivals were 94%, 100%, and 82% at 1 year, 86%, 93%, and 64% at 2 years, and 74%, 80%, and 53% at 3 years, respectively.

Conclusions: Radiofrequency ablation of clinical stage I non-small cell lung cancer was minimally invasive and provided promising patient survival, although the local efficacy needs to be improved. (*J Thorac Cardiovasc Surg* 2011;142:24-30)

Primary lung cancer is the most common malignancy and the leading cause of death from cancer worldwide. Surgical resection with a lobectomy is suggested as the first-line treatment for treating early-stage non-small cell lung cancer (NSCLC). Unfortunately, certain patients are considered medically inoperable, and conventional external beam radiation therapy (XRT) has been traditionally administered to such patients. A meta-analysis of patients with stage I NSCLC treated by conventional XRT revealed mean overall and cause-specific survivals at 3 years of 34% and 39%, respectively.¹ Because such survival outcomes after XRT are unsatisfactory, various alternative modalities have been the focus of many studies. For example, stereotactic radiation therapy shows favorable survivals for patients with stage I NSCLC: 56% to 60% at 3 years.²⁻⁴ Radiofrequency ablation (RFA) has received considerable attention as a local therapy mainly for hepatic cancer. The

favorable outcomes of RF ablation of hepatic cancer have facilitated the application of this technique to lung cancer. Currently, RFA is gaining popularity as a treatment of lung cancer. The purpose of this study was to retrospectively evaluate the outcomes of RFA on nonsurgical candidates with clinical stage I NSCLC.

MATERIALS AND METHODS

Study Population

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 for our retrospective study. From July 2002 to September 2009, we treated 56 patients with clinical stage I primary lung cancer at Okayama University Medical School. We excluded 6 of these patients, because the tumor was also treated with adjuvant radiation therapy (n = 4), the patient was lost to follow-up (n = 1), or the tumor was not histologically proven (n = 1). Thus, this study consisted of 50 patients with histologically proven clinical stage I NSCLC. Twenty patients who were previously reported in the literature⁵ were included in this study, although their follow-up information was updated. Two patients had synchronous double primary lung cancers; thus, a total of 52 tumors were treated with 52 ablation sessions.

For clinical staging, chest and abdomen computed tomography (CT) scans were performed in all patients; positron emission tomography (PET) scanning was performed in 29 patients, and brain magnetic resonance imaging was performed in 26 patients. Lymph node metastasis was considered absent, because none of the lymph nodes were larger than 1.0 cm in short-axis diameter and there was no more accumulation of ¹⁸F-fluorodeoxy glucose in the lymph nodes than mediastinal structures when PET was performed. This led to the diagnosis of clinical stage IA and IB cancers in 38 and 12 patients, respectively.

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Abbreviations and Acronyms

CT	= computed tomography
NSCLC	= non-small cell lung cancer
PET	= positron emission tomography
RFA	= radiofrequency ablation
XRT	= external beam radiation therapy

The characteristics of the 50 patients and the 52 tumors are summarized in Table 1. There were 29 men and 21 women (mean age, 74.7 years; range, 52–88 years). Sixteen patients had a history of surgery for the following types of cancer: lung cancer (n = 9), esophageal cancer (n = 2), cholangiocarcinoma (n = 2), hepatocellular carcinoma and pulmonary metastasis (n = 1), breast cancer (n = 1), and colon, uterus, and ureter cancer (n = 1). The mean long-axis tumor diameter was 2.1 cm (median, 1.8 cm; range, 0.7–6.0 cm). There were 41 adenocarcinomas and 11 squamous cell carcinomas. Eleven tumors in 10 patients were adenocarcinomas showing pure ground-glass opacity on CT images.

Patients were first referred to the department of thoracic surgery. All patients were determined to be nonsurgical candidates by a surgeon because of one or more of the following reasons: poor pulmonary function (predicted forced respiratory volume in 1 second $\leq$ 1000 mL), poor cardiac function (New York Heart Association class $\geq$ III), advanced age ($\geq$ 80 years), poor performance status ($\geq$ 2), substantial comorbidity, or refusal to undergo surgery. Fourteen patients had poor pulmonary function, 1 patient had poor cardiac function, 7 patients had advanced age, 1 patient had poor performance status, 7 patients had substantial comorbidity, and 9 patients had combinations of 2 of those reasons. The remaining 11 patients were deemed operable but refused to undergo surgery. For the 27 patients whose vital capacity was examined before RFA, the mean value was 2.53 L (range, 1.06–3.97 L); for the 30 patients whose forced expiratory volume and volume percentage in 1 second were examined before RFA, the mean values were 1.68 L (range, 0.41–3.19 L) and 68.6% (range, 42.3%–96.3%), respectively. No patient received concurrent or adjuvant therapy.

Radiofrequency Ablation Technique

RFA was always performed percutaneously using CT fluoroscopy (Asa-teion; Toshiba, Tokyo, Japan). Intraprocedural pain was treated by using local anesthesia or epidural anesthesia along with conscious sedation with an intravenous drip infusion of 0.3 mg fentanyl and an intramuscular injection of 25 mg hydroxyzine. In the case of expected severe procedural pain, for example, when the tumor was close to the pleura, or if the patient asked for it, epidural anesthesia was administered. Thus, epidural anesthesia was used in 15 sessions (15 patients). General anesthesia was not used for any of the patients.

Patients were placed in a supine or prone position according to the location of the tumor, and grounding pads were placed on their thighs. An initial CT examination was scanned to identify the precise location of the tumor and decide the pathway of electrode insertion. The skin at the entry site of the electrode was sterilized. After the administration of anesthesia, the electrode was introduced into the tumor and connected to a generator. The electrodes that were used for the ablation included a multitined expandable electrode (LeVeen; Boston Scientific, Natick, Mass) with an array diameter of 2 cm (n = 15), 3 cm (n = 15), 3.5 cm (n = 4), or 4 cm (n = 2); a single internally cooled electrode (Cool-tip; Valleylab, Boulder, Colo) with a 1-cm (n = 3), 2-cm (n = 7), or 3-cm (n = 4) noninsulated tip; or a cluster internally cooled electrode (n = 2) (Cool-tip; Valleylab). In the case of the Valleylab device, radiofrequency energy was applied with an impedance control algorithm for 12 minutes during the internal cooling of the electrode. The temperature of the tumor at the electrode tip was measured immediately after the generator was turned off. When the tempera-

ture failed to reach 60°C, additional application at the same site was then required. When using the Boston Scientific device, the energy was applied until the impedance showed a rapid increase or an automatic shut-off occurred after 15 minutes; this was repeated once at each site. To obtain the ablative margin, multiple overlapping ablation zones were created whenever deemed necessary.

A chest CT scan was performed immediately after the procedure to evaluate ablation zone and procedural complications. A chest radiograph was obtained 3 hours later and the following morning to assess the occurrence of complications, such as pneumothorax, hemothorax, and pleural effusion. A complete blood count and blood biochemistry were examined at 1 and 3 days after RFA.

Follow-up

The patients were followed up, whenever possible, at 1, 3, 6, 9, and 12 months, and thereafter at 6-month intervals. At every follow-up session, a chest CT scan was performed with 5-mm collimation before and 30 and 90 seconds after the intravenous administration of a contrast medium (iopamidol, Iopamiron 300; Nihon Schering, Osaka, Japan) at a rate of 3 mL/s to assess local efficacy. The size of the ablated lesion usually exceeds the preprocedural tumor size on CT images for the first 3 months after RFA, because the ablated lesion is detected together with the ablated marginal parenchyma.⁶ During this period, thus, the effectiveness of RF ablation cannot be determined by comparing the tumor size but can be determined by contrast enhancement. That is, the tumor is considered to be completely treated when the entire ablation zone is not contrast-enhanced or when the ablation zone exhibits contrast enhancement; however, the enhancement zone is peripheral, concentric, symmetric, and uniform with smooth inner margins. Such enhancement zone is considered to correspond to reactive hyperemia, inflammation, or granulation at the marginal parenchyma.⁷ Thereafter, local efficacy was evaluated by comparing the size and geometry of the ablation zone in the previous CT images. Local progression was defined as tumor progression at the ablation zone and considered to have occurred when the ablation zone was circumferentially enlarged or an irregular, scattered, nodular, or eccentric focus in the ablation zone appeared. The focus generally exhibited some degree of contrast enhancement, and thus contrasted against the unenhanced necrotic tumor tissue.

For the assessment of hematogenous metastasis, an abdominal CT scan was generally performed with a contrast medium at 6-month intervals. Although PET was not included in our routine follow-up modalities, for 29 patients, PET examinations were also performed to evaluate the outcomes of RFA and hematogenous metastasis. When symptoms suggesting brain or bone metastasis were observed, a radiologic examination such as magnetic resonance imaging or a bone scintigram was performed.

Study End Points and Statistical Analysis

The study end points included toxicity, local efficacy, and patient survival. Toxicity was evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0, and adverse events of grade greater than 1 were noted. The forced expiratory volume in 1 second 1 to 3 months after RFA was compared with that before RFA by using the paired *t* test. Local efficacy was evaluated by the presence of local tumor progression, which was diagnosed with the aforementioned criteria. The overall local progression rates and the local progression rates according to tumor size were calculated. Further, the local progression rates according to type of electrode used (internally cooled electrode or multitined expandable electrode) were compared by using the log-rank test. In addition to local progression, parenchymal recurrence (defined as recurrence in the same lobe but away from ablation zone), regional recurrence (defined as hilar and ipsilateral mediastinal lymph nodes recurrence), and distant recurrence (all other recurrences) were also evaluated.

The overall, cancer-specific, and disease-free survivals were estimated with Kaplan-Meier analysis. For estimation of cancer-specific survival

TABLE 1. Characteristics of the 50 patients and the 52 tumors

Patients (n = 50)	
Age (y)	
Mean	74.7
Range	52–88
Gender	
Male	29
Female	21
Vital capacity (L)*	
Mean	2.53
Range	1.06–3.97
Forced expiratory volume in 1.0 s (L)†	
Mean	1.68
Range	0.41–3.19
Stage	
IA	38
IB	12
History of surgery for cancer	
Yes	16
No	34
Tumors (n = 52)	
Diameter (cm)	
Mean	2.1
Range	0.7–6.0
Histology	
Adenocarcinoma	41
Squamous cell carcinoma	11
Lobar location	
RUL/RML/RLL	10/2/12
LUL/LLL	15/13
Electrode used for ablation	
Internally cooled	16
Multitined expandable	36

RUL, Right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe. *Data are available in 27 patients. †Data are available in 30 patients.

and disease-free survival, the terminal event was cancer-related death and any death or cancer recurrence, respectively. The survivals were also estimated according to cancer stage (IA or IB), type of electrode used, and procedure period (first 4 years or later years), and compared between the 2 groups by using the log-rank test. Statistical analyses were performed using the Statistical Package for the Social Sciences software (version 11.0; SPSS Inc, Chicago, IL).

RESULTS

The case of a 79-year-old woman with clinical stage IA NSCLC is shown in Figure 1. Grade 1 pneumothorax occurred after 22 sessions. Grade 2 and 3 adverse events occurred after 6 (12%) and 3 (6%) of the 52 sessions, respectively, whereas no grade 4 or 5 adverse events occurred. The grade 2 adverse events included pneumothorax that required chest tube placement after 1 session, pneumonitis that required medical therapy after 3 sessions, and both of those after 2 sessions. The grade 3 adverse events included pleural effusion that required chest tube placement after 1 session, bronchopleural fistula that required surgical inter-

vention to cover the pleural orifice of the fistula in 1 session, and pleural infection that required radiologic chest tube placement after 1 session.

Among the 30 patients in whom forced expiratory volume in 1 second was examined before RFA, this test was repeated 1 to 3 months after RFA in 22 patients. The mean forced expiratory volume in 1 second after RFA for the 22 patients was 1.58 L (range, 0.68–2.74 L); the volume was not significantly different ($P = .17$) than the volume before RFA. Local progression was observed in 16 (31%) of the 52 tumors at a median of 15 months after the session. Five of the 16 locally progressing tumors were confirmed by biopsy. The local progression rate according to tumor size was 33% (10/30) for tumors 2.0 cm or less, 40% (4/10) for tumors 2.1 to 3.0 cm, and 17% (2/12) for tumors greater than 3.0 cm. The local progression rates were not significantly different according to type of electrode ($P = .10$). Six of the 16 locally progressing tumors were treated again in 1 or 2 repeat sessions; 4 tumors were completely treated and the other 2 tumors progressed again. Finally, local control was achieved in 40 (77%) of the 52 tumors at the time of this report. Regional, parenchymal, and distant recurrence occurred in 2, 7, and 8 patients, respectively.

The median follow-up period of the 50 patients was 37 months (mean, 39 months; range, 2–88 months). The survival outcomes of the 50 patients are summarized in Figure 2. Of the 50 patients, 19 died and 31 were surviving at the time of this report. Of the 19 patients who died, 12 died of cancer progression and the remaining 7 died of other causes. Of the 7 patients who died of other causes, 2 had local progression and 5 were free from cancer. Of the 31 patients who survived, 20 were free from cancer since RFA. Local progression or intrapulmonary metastasis developed in 5 patients, who were then completely treated with a partial resection or repeat RFA. At the time of this report, these 5 patients were free from cancer. The remaining 6 patients showed recurrence, such as local progression, intrapulmonary metastasis, or lymph node metastasis.

The median and mean survival times were 67 months and 59 months, respectively. The overall survivals were 94% at 1 year, 86% at 2 years, 74% at 3 years, 67% at 4 years, and 61% at 5 years (Figure 3). The survivals for stage IA and IB cancers were 95% and 92% at 1 year, 89% and 75% at 2 years, 83% and 50% at 3 years, 73% and 50% at 4 years, and 66% and 50% at 5 years, respectively (Figure 4). The survivals were not significantly different between the 2 groups ($P = .057$). The survivals were not significantly different according to type of electrode ($P = .35$) or procedure period ($P = .77$). The cancer-specific survivals were 100% at 1 year, 93% at 2 years, 80% at 3 years, 80% at 4 years, and 74% at 5 years (Figure 3). The disease-free survivals were 82% at 1 year, 64% at 2 years, 53% at 3 years, 46% at 4 years, and 46% at 5 years (Figure 3). The median and mean disease-free survival times were both 42 months.

FIGURE 1. RFA for a 79-year-old woman with clinical stage IA NSCLC. A, CT image before the procedure shows a tumor (*arrow*) of 29 mm in maximum diameter in the left upper lobe. B, PET/CT image before the procedure shows marked accumulation of ^{18}F -fluorodeoxy glucose into the tumor (*arrow*). C, CT-fluoroscopic image during the procedure shows that a multitined expandable electrode (*arrows*) is introduced into the tumor. D, PET/CT image 3 months after the procedure shows no obvious accumulation of ^{18}F -fluorodeoxy glucose into the tumor (*arrow*). E, CT image 31 months after the procedure shows considerable tumor involution (*arrow*).

DISCUSSION

RFA is increasingly being used as an alternative local therapy for nonsurgical candidates with lung cancer. A prospective multicenter study of RFA on 106 patients with primary or secondary lung cancer noted technical success in 99% of patients and no procedural-related deaths.⁸ An international survey reported that mortality after RFA of lung tumors was 0.4%.⁹ Our study also confirmed that RFA was a safe procedure with no mortality, only a 6% grade 3 adverse event rate, and no significant effect on pulmonary function.

The local progression rates and survival data after RFA of clinical stage I NSCLC in the literature are summarized in [Table 2](#). Approximately 30% to 40% of the treated tumors progressed locally,¹⁰⁻¹³ which was also observed in our study. A number of studies showed that local efficacy depends on tumor size, that is, larger tumors are at a higher risk of local recurrence.^{10,13-15} In our study, however, the local progression rate did not seem to depend on tumor size. The exact reason for this observation cannot be determined, but 3 groups divided by their tumor size were heterogeneous in terms of the

FIGURE 2. Summary of survival outcomes of 50 patients with clinical stage I NSCLC treated with RFA. RFA, Radiofrequency ablation.

type of electrode used, the period in which the procedure was performed (ie, the issue of a learning curve), and the follow-up period. These factors might bias the outcomes of local efficacy according to tumor size. In view of the relatively high local progression rate, the use of RFA should be limited to patients who are inoperable or operable but refuse to undergo surgery. Further, in the case of RFA, patients should be followed frequently to find local progression as early as possible.

The survivals after RFA of clinical stage I NSCLC were reported as 78% to 100% at 1 year, 57% to 84% at 2 years, and 36% to 74% at 3 years,^{8,10-14} and the overall survivals in our study seem to be equivalent to these results. As expected, the survival of patients with stage IA cancer seemed to be better than the survival of patients with

stage IB cancer, but this did not reach statistical significance in our study, probably because of the small size of the patient population. Although the overall and cancer-specific survivals were promising, the disease-free survival was limited to 53% at 3 years, mainly because of the relatively high rate of local tumor progression. Further, the promising overall and cancer-specific survivals may be partly attributable to the relatively high rate (10/50, 20%) of patients with pure ground-glass opacity adenocarcinoma, which is slow-growing with a doubling time of more than 800 days.^{16,17}

Stereotactic radiation therapy shows favorable local control and survivals for patients with stage I NSCLC, and may rival RFA. According to a Japanese multi-institutional study on the use of stereotactic radiation on 257 patients,² the

FIGURE 3. Overall survivals are 94% at 1 year, 86% at 2 years, 74% at 3 years, 67% at 4 years, and 61% at 5 years. The cancer-specific survivals are 100% at 1 year, 93% at 2 years, 80% at 3 years, 80% at 4 years, and 74% at 5 years. The disease-free survivals are 82% at 1 year, 64% at 2 years, 53% at 3 years, 46% at 4 years, and 46% at 5 years. RFA, Radiofrequency ablation.

FIGURE 4. Survivals of stage IA and IB cancers are 95% and 92% at 1 year, 89% and 75% at 2 years, 83% and 50% at 3 years, 73% and 50% at 4 years, and 66% and 50% at 5 years, respectively. Survivals are not significantly different between the 2 groups ($P = .057$). RFA, Radiofrequency ablation.

TABLE 2. Summary of data by radiofrequency ablation of clinical stage I non–small cell lung cancer

Author	No. of patients	Follow-up period (mo)	Local progression rate (%)	Survival (%)					Survival time (mo)
				1 y	2 y	3 y	4 y	5 y	
Lencioni and colleagues ⁸	13				75				
Lee and colleagues ¹⁰	10	14 (median)	40	100					
Pennathur and colleagues ¹¹	19	29 (mean)	42	95	68				
Hiraki and colleagues ¹²	20	22 (median)	35	90	84	74			42 (mean)
Lanuti and colleagues ¹³	31	17 (median)	32	85	78	47	47		30 (median)
Simon and colleagues ¹⁴	75			78	57	36	27	27	29 (median)

complication rate for tumors more than grade 2 was 5%, the proportion of patients with local recurrence was 14%, and the overall and cause-specific survivals were 57% and 77% at 3 years and 47% and 73% at 5 years, respectively. A phase 2 North American multicenter study including 55 medically inoperable patients³ showed that the incidence of adverse events for grade 3, 4, or 5 tumors was 13%, 4%, or 0%, respectively, the estimated 3-year primary tumor control rate was 98%, and the disease-free and overall survivals at 3 years were 48% and 56%, respectively. According to another multicenter prospective phase 2 trial including 57 patients in Nordic countries,⁴ grade 3 and 4 toxicity occurred in 28% and 2% of the patients, respectively, the estimated local control rate was 92% at 3 years, and the overall, cancer-specific, and progression-free survivals were 60%, 88%, and 52% at 3 years, respectively. In the future, it would be interesting to compare RFA with stereotactic radiation therapy in a randomized controlled study.

At Okayama University Medical School, stereotactic radiation has been another available therapy for lung cancer. Although selection of the 2 modalities may be difficult sometimes because of the lack of data suggesting which is better, roughly speaking, RFA is performed when performing stereotactic radiation seems hazardous, that is, when a tumor is located near (<3 cm) the hilum, mediastinum, lung apex, and vertebral body, and a tumor is located in the lower lobe in patients with considerable respiratory motion. Given that stereotactic radiation seems more toxic mainly because of radiation pneumonitis, RFA is apt to be selected in patients with severe pulmonary dysfunction. In contrast, considering the limited local efficacy of RFA, especially for tumors greater than 2 cm,¹⁵ such tumors are likely to be treated with stereotactic radiation.

Notable advantages of RFA include its low invasiveness, the preservation of pulmonary function, the freedom to perform the procedure regardless of any previous therapy, and the ability to repeat the procedure whenever required. In contrast, a substantial limitation of this procedure may be its limited local efficacy. To secure favorable long-term survival, the local efficacy needs to be improved. In animal experiments, various attempts have been made to enhance the efficacy of RFA. In the lung, thermal and electrical

conductivities are limited because of alveolar air, and they may be further limited by blood perfusion and ventilation. Thus, successfully enlarged coagulation necrosis was obtained by the modulation of conductivity by infusing saline into the lung¹⁸ and decreasing blood perfusion¹⁹ and ventilation.²⁰

Combining RFA with other therapies may enhance its effects. Dupuy and associates²¹ performed RFA followed by conventional XRT in 24 patients with stage I cancer (mean size, 3.4 cm). The local progression rate of 8% seemed promising despite the relatively large tumor sizes. The continuous evolution of the technology used in RFA may aid in the development of this procedure. Navigation devices that use electromagnetic tracking may facilitate more accurate electrode insertion.²² In addition, other ablative technologies, including microwave ablation and cryoablation, are also being developed.^{23,24} Furthermore, a recent study showed that RFA may be carried out by using a transbronchoscopic approach.²⁵

Study Limitations

Our study had several limitations. This was a retrospective study with possible selection biases. We used 2 types of ablation device, although a previous study indicated that a multitined expandable electrode provided better local efficacy than an internally cooled electrode.¹⁵ PET was not used for cancer staging in 21 patients, which may have affected the reliability of clinical cancer staging. Finally, the follow-up period was not long enough to determine the long-term outcomes.

CONCLUSIONS

RFA of clinical stage I NSCLC is minimally invasive and provides promising patient survivals, although the local efficacy needs to be improved.

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