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ORIGINAL ARTICLE

Percutaneous radiofrequency ablation for medically inoperable patients with clinical stage I non-small cell lung cancer

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Abstract

Background: A retrospective evaluation of percutaneous radiofrequency ablation (RFA) in medically inoperable patients with clinical stage I non-small cell lung cancer (NSCLC).

Methods: Between 2008 and 2014, 29 medically inoperable patients with clinical stage I NSCLC underwent percutaneous RFA. We evaluated the feasibility, safety, and effectiveness.

Results: There were 18 men and 11 women with a median age of 78.0 years (range 56–85), mean 76.0 years. No procedure-related deaths occurred in any of the 33 ablation procedures. The mean follow-up was 25 months. The incidence of local tumor progression was 21.0% at 25 months of median time to progression after the initial RFA. The mean overall survival (OS) was 57 months (95% confidence interval (CI) 44–70 months). The mean cancer-specific survival CSS was 63 months (95% CI 50–75 months). OS was 90.5% ± 6.4% at one year, 76.4% ± 10.7% at two, and 65.5% ± 13.6% at three years. CSS was 95.2% ± 4.6% at one, 86.6% ± 9.3% at two, and 74.2% ± 13.9% at three years in all patients. The survival for stage IA and IB cancers were 87.5% and 92.3% at one, 87.5% and 73.4% at two, and 87.5% and 58.7% at three years, respectively. Survival rates were not significantly different between the two groups ($P = 0.596$), with mean survival times of 65 (95% CI: 51–79 months) and 55 months (95% CI: 38–71 months), respectively.

Conclusion: Percutaneous RFA is a safe, feasible, and effective procedure in medically inoperable clinical stage I NSCLC patients.

Lung cancer has increased in incidence and is now the most common malignancy and the leading cause of cancer death in the both men and women.[1] Standard surgical resection and lymph node dissection remain the foundation for the treatment of early stage non-small-cell lung cancer (NSCLC); however, in practice only about one-third of patients are eligible for surgical intervention. Percutaneous radiofrequency ablation (RFA) is a minimally invasive technique used to treat solid tumors. Because of its ability to produce large volumes of coagulation necrosis in a controlled fashion, this technique has gained acceptance as a viable therapeutic option for unresectable malignancies. The first clinical reports on ablation of lung tumors began with a study of three patients by Dupuy *et al.* in 2000.[2] Furthermore, there are retrospective reports[3–6] and prospective intention-to-treat studies,[7,8] with an emphasis on stage I NSCLC.

To our knowledge, RFA can provide controlled regions of coagulation necrosis with a single application to an area as large as 3.0 cm. However, it is very difficult to induce such a symmetric ablation of the tumor in lesions larger than 3.0 cm because of the large dimension and asymmetric shape of the tumor. In this paper, we retrospectively evaluated our results with the use of computed tomography (CT)-guided RFA for the treatment of medically inoperable stage I NSCLC patients from 2008 to 2014.

Materials and methods

Selection of patients

We retrospectively evaluated our experience with percutaneous RFA for the treatment of medically inoperable stage I

NSCLC patients at the Xuanwu Hospital from 2008 to 2014. The institutional review board at the Xuanwu Hospital approved the study.

Criteria for inclusion in the study were: patients with biopsy-proven NSCLC; patients with clinical stage I NSCLC; patients who were considered medically inoperable, rejected or refused surgical resection; and tumors accessible by percutaneous route.[9]

Exclusion criteria were: patients who were considered high-risk for RFA; Eastern Cooperative Oncology Group (ECOG) performance status of more than 2; central tumors (tumors located less 1 cm from trachea, main bronchi, esophagus, aorta, aortic arch branches, main, right or left pulmonary artery, and heart); tumors associated with atelectasis or obstructive pneumonitis; active clinically serious infection; and uncorrectable coagulopathy with an international normalized ratio greater than 1.5 and a platelet count of less than 100×109/L.

The presence of a cardiac pacer or metallic prosthesis was not considered an exclusion criterion. All patients were evaluated by a thoracic surgeon to determine inoperability and suitability for RFA.

Pre-treatment assessments

Eligible patients were asked to provide written informed consent after the procedure had been fully explained. The informed consent document was signed before any study-related procedures were performed. During the screening period, within 28 days of treatment, the following were performed: physical examination and collection of data on vital signs, demographics, and medical history; recording of ECOG performance status; routine staging with thoracic CT, abdominal ultrasound, brain magnetic resonance imaging, isotopic bone scanning, and alternative positron emission tomography (PET) or single-photon emission computed tomography (SPECT) scan; tumor biopsy; and electrocardiography and pulmonary function testing. Within seven days of treatment, a complete blood count, measurement of electrolyte panel, chemistry panel, coagulation panel, and tumor marker were also performed. Patients with hilar or mediastinal nodes greater than 1 cm in short axis diameter on CT scan underwent a PET or SPECT scan to exclude N1 or N2 disease. Patients meeting all eligibility criteria were enrolled and scheduled for treatment. Patients taking anticoagulation and antiplatelet medications were advised to stop these medications five to seven days before the procedure.

Pre-treatment preparation

Patients were required to fast for two hours before undergoing the RFA procedure. The patient was positioned on the CT table according to the location of the lesion so that they were as comfortable as possible, preferably with the shortest and safest route to the tumor.

Continuous electrocardiography and pulse oximetry with blood pressure monitoring was performed every five minutes throughout the procedure with continuous oxygen administration. Two large dispersive electrodes (ground pads) were placed on the patient's lumbar, gluteal region or thighs, according to the position of the lesion to be treated.

Treatment protocol

All patients underwent chest CT immediately prior to the procedure. The skin entry site that allowed the shortest path that avoided bullae, interlobar fissures or pulmonary vessels was chosen. The procedure was conducted under sedation using pethidine hydrochloride or morphine injected intramuscularly. After the skin was cleansed with iodine and alcohol and draped in a sterile fashion, local anesthesia was administered with 5–15 mL 1% lidocaine, from the skin, intra-dermal, and subcutaneous down to the pleura along the predetermined puncture site. The needle was placed into the target tumor and its correct placement was checked by use of multiplanar image reconstructions.

We used a radiofrequency generator able to provide monopolar energy to perform coagulation and ablation of soft tissue (RITA Medical Systems Model 1500X; AngioDynamics, Manchester, GA, USA). This is an automatic device with a maximum power output of 250 W operating at 460 MHz. The generator has a display where temperatures (set to a target temperature of 90°C), impedance, and power are continuously monitored. The energy was transferred into the lesion by a deployable array (RITA Medical System StarBurst XLi; StarBurst Talon; AngioDynamics, USA) with a perfusion system. It consists of a 14-gauge needle cannula with five to nine deployable electrodes. On the handle of the device there are markings to indicate the amount of electrode deployment from the trocar. At maximum deployment, the device induces an ablation sphere of 5 to 7 cm in diameter. Five electrodes have a thermocouple on the tip, which allows continuous measurement of treatment temperature. The maximum power output of the radiofrequency generator, amount of electrode array deployment from the trocar, and duration of the effective time of the ablation depended on the desired volume of ablation. The ablation protocol was always planned with the aim to destroy the visible tumor mass plus at least a 0.5 cm of non-diseased pulmonary tissue to ensure adequate tumor margins.

At the end of the procedure, after the automatic cool down of the radiofrequency system, the tines were retracted and the generator was reactivated to ablate the track from the tumor to the subcutaneous tissue to prevent bleeding or tumor seeding.

After completion of the procedure, a CT scan of the chest was obtained to assess technical success and to detect any complications. The presence of a ground glass opacification, regarded as pulmonary hemorrhage or hyperemia, surrounding the tumor and completely enveloping the lesion is said to indicate complete ablation.

Post-treatment care

After the procedure, patients were instructed to stay in bed for two to four hours in the supine position. Chest radiographs to detect and monitor pneumothorax and other complications were obtained 12 hours after treatment and daily until discharge of the patient from the hospital.

Prophylactic antibiotics and hemostat were not routinely administered. Patients had adjuvant therapies, such as chemotherapy or target therapy (epidermal growth factor receptor-mutant) after RFA. All patients orally took traditional Chinese medicine.

Data collection

Patients were followed up one and three months after treatment, and then at three month intervals with: a physical examination; radiological imaging for tumor assessment, including CT of the chest, by use of the same technique as that used at baseline; and selectively, with PET or SPECT scans. The primary end points of this study were time to progression (TTP) and patient death, calculated from the date of the RFA procedure. We evaluated technical success, safety, technique effectiveness (complete ablation), TTP, overall survival (OS), and cancer-specific survival (CSS). Because the aim of radiofrequency ablation was to produce a volume of coagulation necrosis exceeding that of the native tumor, the one-month follow up CT scan (in which the high-density area representing the ablation zone was usually larger than the native tumor) was taken as a term of reference.[7]

Technical success was defined as correct placement of the ablation device into all target tumors with completion of the planned ablation protocol – that is, maintenance of the target temperature of 90°C for the required time according to tumor size.

The safety assessment included identification of puncture-related and ablation-related complications. Complications were those occurring within 30 days of treatment and were assessed on a per-procedure basis. Minor complications were defined as those resulting in no sequelae or needing nominal treatment or a short hospital stay for observation. Major complications were defined as those resulting in re-admission to the hospital for treatment, an unplanned increase in the level of care, extended hospitalization, permanent adverse sequelae or death.

Technique effectiveness should, therefore, refer to a prospectively defined time point (i.e. 1 month after treatment), at which point "complete ablation" of the macroscopic tumor as evidenced at imaging follow-up was achieved.[10]

Local tumor progression is the preferred term over local recurrence. Assessment of target tumor response was based on CT analysis of lesion size, geometry, and enhancement in comparison with the baseline diameter.[7] Areas of hypoattenuation that did not enhance were considered to represent the ablation zone. Focal enhancement of soft tissue of more than 15 HU when compared with the initial post-ablation non-enhanced series was considered to indicate local tumor progression. A second session of RFA was performed.

Statistical analysis

Information on patient demographics, tumor characteristics, treatment, and comorbidities was collected.

Survival probabilities were estimated by the Kaplan-Meier method. OS and CSS were defined as the time from the beginning of treatment to the last follow-up visit or death from any cause; deaths resulting from causes other than cancer progression were censored. TTP was defined as the time from the beginning of treatment to cancer progression. A value of P less than 0.05 was considered to indicate a statistically significant difference. All analyses were performed from the time of the first RFA session.

Results

Patient characteristics

In the period 2007–2014, we performed more than 700 RFAs of lung tumors. Twenty-nine patients with medically inoperable clinical stage I NSCLC were enrolled. There were 18 men and 11 women with a median age of 78.0 years (range 56–85 years), mean 76.0 years. The 29 patients with stage I NSCLC disease were grouped according to the diameter of the index tumor ablated, resulting in nine patients with stage IA disease and tumors of 3 cm or smaller, and 20 patients with stage IB disease and tumors larger than 3 cm in greatest diameter. Patient pathology was obtained via percutaneous transthoracic needle biopsy, and included squamous-cell carcinoma ($n = 7$), adenocarcinoma ($n = 16$), and not otherwise specified (NOS) ($n = 6$). Table 1.

The most common reason for RFA was poor pulmonary function, increased cardiac risk, multiple comorbidities, and rejection or refusal of surgical resection, according to institutional guidelines.

Feasibility

Overall, 33 treatment procedures were required. Treatment was successfully completed in all patients. Median tumor size was 3.0 cm (range 1.5–4.8 cm; mean 3.1 ± 0.8 cm). The

Table 1 Patient characteristics

Gender (male/female)	18/11
Age (years)	
Median	78
Range	56–85
Lesion size (cm)	
Mean	3.1
Range	1.5–4.8
Clinical stage	
T1N0(IA)	9
T2aN0(IB)	20
Histologic type	
Squamous	7
Adenocarcinoma	16
Not otherwise specified (NOS)	6
Lobar location	
RUL/RML/RLL	7/2/2
LUL/LLL	8/10

LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

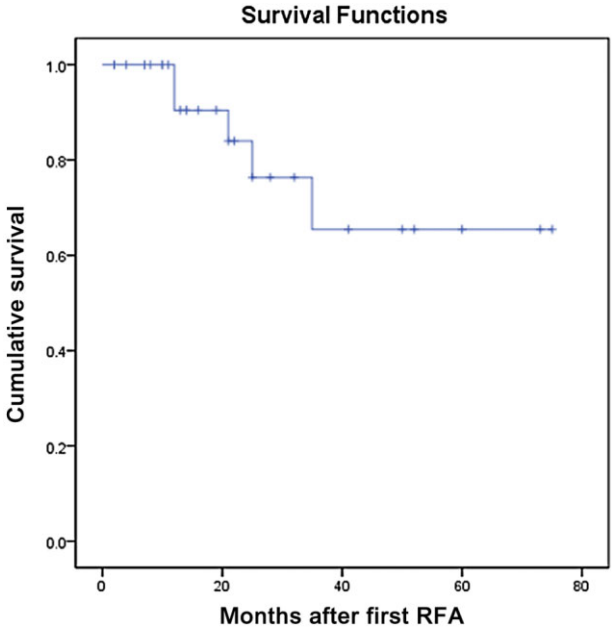

Figure 1 Kaplan-Meier analysis of overall survival of medically inoperable stage I non-small cell lung cancer patients. RFA, radiofrequency ablation. ⌐¬, survival function; ⊣⊢, censored.

ablation time varied from 12.6 to 32 minutes (mean 22 ± 7.5 minutes). The total procedure time ranged from 15 to 120 minutes (mean 39 ± 12 minutes) depending on the difficulty of accessing the lesion and the patients' cooperation. The mean time to reach the target temperature was four minutes (range 2–6 minutes).

Safety

No procedure-related deaths occurred, with no 30-day mortality. In three of the procedures, a large or symptomatic pneumothorax needing drainage was a major complication. In all instances, a pneumothorax was detected on CT scans obtained at the end of the procedure after having retrieved the ablation device, and, therefore, did not prevent completion of the planned ablation protocol. Minor complications included: pneumothorax ($n = 5$) not needing treatment, chest pain in eight patients, and a cough in one patient. Side effects (moderate-grade fever <38.5°C, and/or chest pain) were the most common complications; however, most of these were cured within a couple of days. The median hospital stay was three days (range 2–5).

Effectiveness

During follow-up, locoregional recurrence occurred in nine of the 33 treatments (27.2%), within a mean of 25 ± 11 months (range 4–35 months) after the first session. Local progression of the treated lesion occurred in seven of 33 (21.0%), and regionally in two of 33 (6.0%). Four recurrent lesions were treated with repeat RFA, and five recurrent lesions were treated with radiotherapy.

The mean follow-up was 25 months (median 19 months; range 2–75 months). At the end of the study, 24 patients were alive and five had died. Three patients died as a result of tumor progression; one died of myocardial infarction, and one died of stroke. OS was 90.5% ± 6.4% at one year, 76.4% ± 10.7% at two, and 65.5% ± 13.6% at three years (Fig. 1). CSS was 95.2% ± 4.6% at one year, 86.6% ± 9.3% at two, and 74.2% ± 13.9% at three years (Fig. 2). The mean overall survival was 57 months (95% confidence interval [CI] 44–70 months). The mean cancer specific survival was 63 months (95% CI 50–75 months).

The survival rates for stage IA and IB cancers were: 87.5% and 92.3% at one year, 87.5% and 73.4% at two, and 87.5% and 58.7% at three years, respectively (Fig. 3). The survival rates were not significantly different between the two groups ($P = 0.596$), with mean survival times of 65 (95% CI: 51–79 months) and 55 months (95% CI: 38–71 months), respectively.

Discussion

Surgical resection remains the cornerstone of therapy for patients with early stage NSCLC. Lobectomy with hilar and mediastinal lymphadenectomy is the standard surgical treatment for stage I disease and offers the best chance for cure. Five-year survival rates of between 57–85% for stage I disease are reported.[11,12] Despite the effort to minimize surgical impact, even with less-invasive surgical approaches

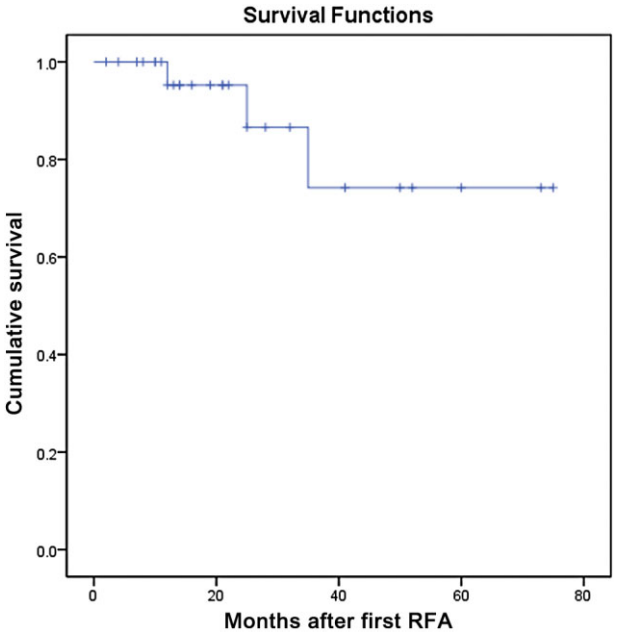

Figure 2 Kaplan-Meier analysis of cancer-specific survival of medically inoperable stage I non-small cell lung cancer patients. RFA, radiofrequency ablation. ⌐¬, survival function; ┼, censored.

(e.g. muscle-sparing thoracotomy, video-assisted thoracic surgery), it is estimated that up to one-fifth of patients with early-stage NSCLC are unsuitable for surgical treatment because of comorbidities.[11] Alternative local therapies, such as RFA or stereotactic body radiation therapy, may be beneficial to this high-risk patient population.[9] RFA is administered via a thermal energy delivery system that applies an alternating current supplied by a radiofrequency energy generator, delivered through a needle electrode into the surrounding tissue creating ionic agitation and generating heat that can reach 90°C. The needle electrode is introduced percutaneously under CT guidance and the tines are deployed within the tumor. This allows for maximal distribution of energy, leading to coagulative necrosis and tissue destruction in the area of the needle electrode.

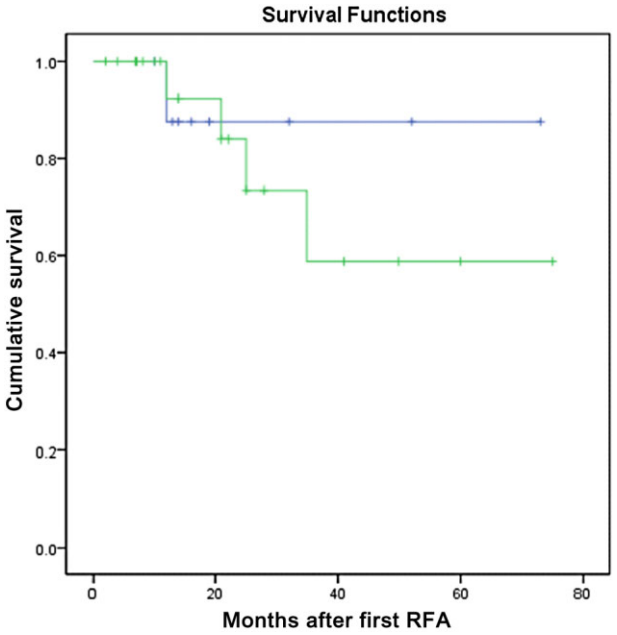

Figure 3 Kaplan-Meier analysis of survival estimate for patients with stage IA *versus* those with stage IB non-small cell lung cancer. RFA, radiofrequency ablation. ⌐¬, IA; ⌐¬, IB; ┼, IA-censored; ┼, IB-censored.

Recently, clinical investigations have shown the safety of percutaneous RFA procedures in human beings and have suggested that the treatment, as a minimally invasive tool for local disease control, can achieve high proportions of tumor response with negligible mortality, low morbidity, short hospital stay, and improved quality of life.[2–10] Survival rates of clinical stage I NSCLC patients after RFA were reported as 78–100% at one year, 57–84% at two, and 36–74% at three years.[3–8] In our trial, OS was greatly affected by the recruitment of patients with severely impaired pulmonary function and/or considerable comorbidities, who were unsuitable for surgery. This is probably the reason why, in our series and also in those reported in the literature, a substantial difference between OS and CSS was noted, because most deaths were not related to cancer progression. Nevertheless, the 86% two-year CSS obtained in stage I NSCLC patients is promising and in agreement with recent published findings (Table 2). As expected, the survival of patients with stage IA cancer was 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.

The mortality, and major and minor complication rates associated with lung RFA have been reported as 0–5.6%, 3.0–24.5%, and 21.3–64.9%, respectively.[13] We reported a technical success of 100%, with no 30-day mortality, and a low morbidity rate.

The incidence of local tumor progression was significant in this study (20.0%) at 25 months after the initial RFA, as well as in studies by other investigators.[3–8] The proportion of local tumor control was higher than that reported after RFA of tumors of the same histology in the liver. The electrical and thermal conductivities differ between the liver and the lung. In lung tumors, the surrounding normal tissue contains air, which may provide an insulating effect, concentrating the heat inside the tumor. A low thermal conductivity of background tissue has been shown to substantially increase radiofrequency-induced temperatures within a defined ablation target.[14] This lack of conductivity in the surrounding lung tissue may interfere with the margins of ablation and account for the increased incidence of local progression following RFA in lung tumors. There are several factors that

Table 2 Results of RFA treatment of stage I NSCLC in the most significant series in the literature

Study Group	Patient No.	Lesion diameter Mean (cm)	Follow-up Mean (months)	OS (CSS) Median (months)	OS (CSS)%			Disease progression (months)
					1 year	2 year	3 year	
Lanuti *et al*. 2009[5]	31	2.0 (0.8–4.4)	17	30		78	47	31.5
Hiraki *et al*. 2007[23]	20	2.4 (1.3–6.0)	21.8	42	90 (100)	84 (93)	74 (83)	35
Hiraki *et al*. 2011[3]	50	2.1 (0.7–6.0)	37	67	94 (100)	86 (93)	74 (80)	31
Simon *et al*. 2007[4]	75	3.0 (1.0–7.5)	20.5	29	78	57	36	
Pennathur *et al*. 2007[24]	19	2.6 (1.6–3.8)	29	Not reached	95	68		42 (27)
Lencioni *et al*. 2008[7]	13	1.7 (0.5–3.4)	15			75 (92)		
Ambrogi *et al*. 2011[8]	57	2.6	47	33.4 (48.3)	83 (89)	62	40 (59)	49 (26)
Our experience	29	3.1 (1.5–4.8)	25	57 (63)	90 (95)	76 (86)	65 (74)	24 (25)

CSS, cancer-specific survival; NSCLC, non-small cell lung cancer; OS, overall survival; RFA, radiofrequency ablation.

influence local recurrence or progression of disease including tumor size; proximity to vessels, which is associated with a " 'heat sink' " effect; and a satisfactory margin of ablation at least 0.5 cm beyond the edge of the tumor.

A number of studies have shown a higher risk of local recurrence in larger tumors.[4,5,15] In our study, however, the local or disease progression did not seem to depend on tumor size. The exact reason for this observation cannot be determined, but the type of electrode used may be a factor. Over the past several years, advances in delivery mechanisms that can either increase the amount of energy deposited or the conduction of heat through the tissue have increased the sphere of tissue that can be ablated. Multiprobe array electrodes, in which multiple tines apply current simultaneously, achieve coagulation zones of 5–7 cm. Wet electrodes using saline (either isotonic or hypertonic) infused through the electrode into surrounding tissue increase conductivity with greater amounts of infusion of ions in the tissue, increasing current flow and, thus, allowing longer duration of current flow and increasing volume of coagulation.[16,17] In an interesting study, Hiraki *et al*. evaluated the risk factors for local progression after RFA in a series of 128 patients with lung tumors.[15] Multivariate analyses showed that a multi-tined array probe enabled favorable local control compared with the use of an internally cooled electrode in lung tumors.

Several strategies have been developed to decrease tumor tolerance to heat and increase the effectiveness of thermal ablative techniques. The "heat-sink" effect created by the proximity of tumors to large vessels that can dissipate heat is a primary mechanism by which the extent of thermal injury can be limited. A synergistic effect between neoadjuvant transarterial chemoembolization decreasing blood perfusion and RFA in the treatment of lung cancer has also been demonstrated.[18,19]

The important technical issues include the degree of ablation, whether complete ablation is achieved, and the adequacy of the margins of ablation around the tumor. Completeness of ablation has also been evaluated in a few ablate-and-resect studies examining the extent of ablation after RFA. A review of these studies shows that effective 100% ablation varies from 38–67%.[20–22]

Certainly, our study has some limitations. This was a retrospective study with limited patient numbers, possible selection biases (patient population was heterogeneous), and relatively short follow-up. In addition, the use of other therapies in patients treated with RFA confounds the analysis of efficacy of treatment with RFA.

Conclusion

In conclusion, we believe our experience indicates that percutaneous RFA performed by a thoracic surgeon is a safe, feasible, and effective procedure for medically inoperable clinical stage I NSCLC patients. A deployable array probe with a perfusion system (producing an ablation sphere of 5–7 cm in diameter) and adjuvant therapy may be useful in decreasing progression after RFA, and, perhaps, in improving survival. In future, properly designed prospective randomized multicenter trials are necessary to define the role of RFA in comparison with sublobar resection or stereotactic radiosurgery in the treatment of medically inoperable clinical stage I NSCLC patients.

Disclosure

No authors report any conflict of interest.

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