Efficacy Evaluation and Prognosis Analysis of CT-Guided Radiofrequency Ablation for Non-Small Cell Lung Cancer

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Research

Keywords: Lung cancer, CEA, carcinoembryonic antigen, RFA, targeted therapy

Posted Date: November 3rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1020213/v1

Abstract

Background: Lung cancer has a high morbidity and mortality, and has the highest incidence of all malignancies in men in China. In recent years, radiofrequency ablation (RFA) has become the fourth promising treatment for lung cancer.

Method: We followed up patients with non-small cell lung cancer in the First Affiliated Hospital of Anhui Medical University to investigate the survival, complications and prognosis of RFA.

Results: Among 34 patients, there were 25 men and nine women (age range 22–84 years; 64% aged 60–80 years. The mean diameter of lung lesions was 2.46±0.89 cm. The pathological types were adenocarcinoma (27/34, 79.41%) and squamous cell carcinoma (7/34, 20.59%). Half of the patients had reached stage IV at the time of the study. Sixteen patients had elevated carcinoembryonic antigen (CEA). Six patients did not receive any further treatment after RFA and nine received chemotherapy combined with targeted therapy. The median follow-up period was 18 (7.0–33.5) months. Complications of RFA were reported in 15 patients (44.12%) and the most common were pneumothorax and pleural effusion. The risk of complications was higher in smokers than in non-smokers ($P<0.05$). The median overall survival was 22 (2.58–41.42) months, and the overall survival rate was 69.78% (1 year), 59.10% (18 months) and 48.85% (2 years). The survival rate of patients with lung lesions diameter ≤2 cm was significantly higher than that of patients with lesion diameter >2 cm ($P<0.05$). The annual survival rate of patients with elevated serum CEA before RFA was significantly lower than that of patients with normal serum CEA ($P<0.05$). Patients with chemotherapy combined with tyrosine kinase inhibitors (TKIs) had significantly higher survival rates compared with patients with only chemotherapy or TKI/no treatment ($P<0.05$).

Conclusion: CT-guided RFA is a safe and effective treatment for lung cancer. Small lesions and combined therapy can result in longer survival. Patients with serum increased CEA have poor survival.

Introduction

Increased air pollution from social and industrial development, along with increased awareness of physical examination, have resulted in an increase in the detection rate of pulmonary nodules. Studies have shown that most pulmonary nodules are benign, while about 3.7–5.5% of those will develop into early-stage lung cancer[1]. According to a report of a large health examination survey on pulmonary nodules in the United States in 2015, the detection rate of pulmonary nodules increased from 3.9 per 1,000 person-years in 2006 to 6.6 per 1,000 person-years in 2012[2], showing a significant upward trend. A survey carried out by World Health Organization on new tumors in 2018 showed that lung cancer ranked first among new tumors in China in terms of morbidity (18.1%) and mortality (24.1%), first among all malignant tumors in men, and second only to breast cancer in women[3]. Lung cancer has the highest morbidity and mortality worldwide[4]. Subsolid nodules, short burrs, vacuoles, pleural depression, and other signs all indicate the possibility of malignancy, which helps with early diagnosis of malignant

nodules[5]. However, when lung cancer is diagnosed, more than two-thirds of patients have lost the opportunity for surgery because of lymph node or distant organ metastases. Meanwhile, many patients cannot tolerate the adverse effects of radiotherapy or chemotherapy, such as radiation damage and bone marrow suppression. Tumor thermal ablation technology has now become a promising treatment of malignant tumors and can effectively reduce the local tumor load. Tumor thermal ablation technology mainly includes radiofrequency ablation (RFA) or microwave ablation (MWA)[6].

RFA is a type of precise interventional therapy for lung tumors. The treatment involves the use of CT three-dimensional reconstruction for accurate positioning. Under imaging guidance, radiofrequency electrodes (needles) with a diameter <2 mm are accurately punctured into the lung tumor tissue. The heat energy released by the electrodes destroys the tumor tissue, resulting in short operation time, low trauma, and rapid recovery[6]. Since the advent of RFA to treat lung tumors in 2000[7], the technology has developed further, and many studies have explored its efficacy, safety and prognosis. RFA can be used to treat primary lung cancer and lung metastases[8]. A recent survey showed that the overall 5-year survival rate for lung cancer with an intensive intervention was only 15–17%[9]. RFA can extend the survival time of patients. At the same time, RFA reduces the symptoms caused by local lesions[10]. Complications such as bleeding, pneumothorax, and skin burn may occur during the procedure but can be controlled by symptomatic treatment. We investigated the efficacy and prognosis of RFA in patients with non-small cell lung cancer (NSCLC) in the First Affiliated Hospital of Anhui Medical University, to provide guidance for the development of RFA in the future.

Methods

Participants

We enrolled lung cancer patients who underwent RFA in the Department of Geriatric Respiratory and Critical Care Medicine of the First Affiliated Hospital of Anhui Medical University between March 2015 and January 2021. The inclusion criteria included: (1) clear pathological diagnosis of lung cancer; (2) lung lesion diameter <4 cm; and (3) patients who cannot tolerate or refuse to undergo surgical treatment for their own reasons (such as severe impaired cardiopulmonary function) and who exceed the surgical indications. Exclusion criteria included: (1) small cell lung cancer; (2) patients who underwent two or more RFAs; and (3) lung metastases.

Clinical data

We collected the basic information of patients through the electronic medical record system of the hospital, including age, gender, smoking history, comorbidity, intraoperative complications, and obtained preoperative serum tumor indicators [carcinoembryonic antigen (CEA), cytokeratin fragment 19 (CYFRA21-1), and neuron-specific enolase (NSE)], size and location of lung lesions by referring to the laboratory examination and chest CT of patients. All patients underwent general examinations (PET/CT or abdominal ultrasound, head MRI and bone scan) to assess lymph node or distant organ metastasis. We divided these patients into corresponding clinical stage according to the tumor node metastasis

(TNM) classification (8th edition)[11]. We collected the clinical data with the informed consent of the patient or their representative. The study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University.

Procedures for RFA

Prior to RFA, all patients underwent routine blood tests, coagulation function test and chest CT to rule out surgical contraindications. Antiplatelet and anticoagulant drugs should be suspended in patients with cardiovascular and cerebrovascular diseases. All RFA procedures were performed percutaneously with CT guidance by one senior interventional radiologist, who had >10 years of experience with RFA of lung lesions. After the location of the lesion was determined according to the preoperative imaging data of the patient, the appropriate surgical position was selected, which was based on the principle of the shortest puncture distance, and avoidance of crossing important structures (major blood vessels, bones, interlobar fissure, and pulmonary bulla). During the course of treatment, all patients received ECG monitoring of heart rate, blood pressure and oxygen saturation. At the same time, we paid attention to whether patients had any discomfort (e.g., cough, hemoptysis or chest pain). Iodine was used to disinfect the surgical field and aseptic towels were laid. The puncture site was anesthetized with local infiltration of 2% lidocaine up to the pleura. All patients were treated with a Beijing Welfare WE7568-II radiofrequency tumor ablation instrument (Figure 1A), and the electrode was a Beijing Welfare WHK-1 or WHK-3 multifunctional ablation electrode. The ablation temperature was set to 90℃ (Figure 1B). A high temperature solidification zone was formed after expanding the electrode. The number of targets was determined according to the size of the lesion and the treatment time of each target was 3–5 minutes. Radiofrequency electrode coverage included the lesion and surrounding lung tissue of 0.5–1.0 cm (Figure 2A–C). When the needle was withdrawn, the electrocoagulation mode was turned on to prevent tumor cell transfer and bleeding from the needle path. Chest CT scan was performed to ensure that the ablation lesions showed halo signs after treatment (Figure 2D).

The incidence of complications associated with RFA, such as pneumothorax, pleural effusion, hemoptysis, fever, and skin burns, was recorded.

Follow-up

The follow-up period was from the date of enrollment in the RFA procedure until death or last visit. Patients that started treatment between March 2015 and January 2021 were enrolled, and follow-up was conducted until August 2021. We calculated overall survival (OS) through telephone follow-up.

Statistical analysis

We denoted categorical variables by frequency (percentage), and they were expressed by mean (standard deviation) or median [interquartile range (IQR)] depending on whether the variables were normally distributed. Kaplan–Meier analysis for OS was performed. Fisher's exact test was performed to analyze risk factors associated with complications. $P<0.05$ indicated a significant difference. All statistical analyses were carried out by SPSS version 25.0 software.

Results

Clinical features

Table 1 shows the clinical characteristics of the patients. We enrolled 34 patients (25 male, nine female). The age range was 22–84 years, and the median age was 66 years (IQR, 54.75–76.0 years). Patients aged 60–80 years accounted for 64.7% (Figure 3). Only about one third of the patients had a history of smoking, and two thirds had chronic underlying diseases, including 13 with cardiovascular diseases and seven had poor lung function. The lung lesions were all single with a diameter <4 cm (mean 2.46±0.89 cm). There were eight patients with lung lesions diameter >3 cm. The distribution of lung lesions was nonspecific, with lesions situated in the upper lobe of the left lung in 10 patients and the middle lobe of the right lung in only three patients. The pathological types included NSCLC, including 27 adenocarcinomas and seven squamous cell carcinomas. According to TNM classification, half of the patients reached stage IV. The serum tumor indicators of patients before RFA were analyzed, which showed that 16 patients had elevated CEA, 18 had elevated CYFRA21-1, and nine had elevated NSE. Six patients did not receive any further treatment after RFA due to physical conditions or personal choice. On the contrary, nine patients sought aggressive treatment and underwent chemotherapy combined with targeted therapy. The median follow-up period was 18 (IQR, 7.0–33.5) months.

Table 1
Clinical features of 34 patients in this study.

Features (n=34)	Frequency (%)
Gender	25 (73.50%)
Male	9 (26.50%)
Female	
Age, years, median (IQR)	66 (54.75~76)
Range	22 years~84 years
≤50	6 (17.65%)
(50,60]	6 (17.65%)
(60,70]	11 (32.35%)
>70	11 (32.35%)
Smoking history	12 (35.30%)
Comorbidity	23 (67.65%)
Maximum diameter (cm), mean±SD	2.46±0.89
≤2	10 (29.41%)
(2,3]	16 (47.06%)
(3,4]	8 (23.53%)
Location of lesion	8 (23.53%)
Right upper lobe	3 (8.82%)
Right middle lobe	7 (20.59%)
Right lower lobe	10 (29.41%)
Left upper lobe	6 (17.65%)
Left lower lobe	
Histologic type	7 (20.59%)
Squamous-cell carcinoma	27 (79.41%)
Adenocarcinoma	
Lymph node metastasis	17 (50.00%)
Distant-organ metastasis	17 (50.00%)

Features (n=34)	Frequency (%)
Clinical stage	10 (29.41%)
I stage	1 (2.94%)
II stage	6 (17.65%)
III stage	17 (50.00%)
IV stage	
Serum tumor marker, median (IQR)	4.40 (1.975~8.975)
CEA, ng/ml, (normal range <5.0)	16 (47.06%)
Increased	3.81 (2.002~6.275)
CYFRA21-1, ng/ml, (normal range <3.3)	18 (52.94%)
Increased	14.15 (11.413~16.728)
NSE, ng/ml, (normal range <16.3)	9 (26.50%)
Increased	
Post-ablation therapy	6 (17.65%)
No	17 (50.00%)
Chemotherapy only	2 (5.88%)
TKI only	9 (26.50%)
Chemotherapy + TKI	
Follow-up (months), median (IQR)	**18 (7.0~33.5)**

Complications and risk factors

Complications of RFA were reported in 15 patients (44.12%), which were all minor and improved after symptomatic treatment, and no fatal complications occurred. The common complications were pneumothorax and pleural effusion (both five; 14.7%) (Table 2). Other complications include hemoptysis, skin burns, and fever. The risk of complications was significantly higher in smokers than in non-smokers ($P<0.05$). However, gender, age, lesion size and location had no significant effect on the occurrence of complications ($P>0.05$) (Table 3).

Table 2
Complications during and after RFA.

Complications	Frequency (%)
Overall	15/34 (44.12%)
Pleural effusion	5/34 (14.70%)
Pneumothorax	5/34 (14.70%)
Hemoptysis	3/34 (8.82%)
Fever	2/34 (5.88%)
Skin burns	1/34 (2.94%)

Table 3
Risk factors for complications during and after RFA.

Features (n=34)	Frequency (%)		P value*
	Complications (n=15)	No complications (n=19)	
Gender	12 (80.00)	13 (68.42)	0.697
Male	3 (20.00)	6 (31.58)	
Female			
Age (years)	5 (33.33)	7 (36.84)	>0.999
≤60	10 (66.67)	12 (63.16)	
>60			
Smoking history	8 (53.33)	3 (15.79)	**0.030**
Yes	7 (46.67)	16 (84.21)	
No			
Maximum diameter (cm)	4 (26.67)	6 (31.58)	>0.999
≤2	11 (73.33)	13 (68.42)	
>2			
Location of lesion	2 (13.33)	6 (31.58)	0.778
Right upper lobe	1 (6.67)	2 (10.53)	
Right middle lobe	4 (26.67)	3 (15.79)	
Right lower lobe	5 (33.33)	5 (26.32)	
Left upper lobe	3 (20.00)	3 (15.79)	
Left lower lobe			

OS

Some patients were lost to follow-up; therefore, we followed 29 patients for survival analysis. The median OS was 22 (2.584–41.416) months, and the OS rate was 69.78% (1 year), 59.10% (18 months) and 48.85% (2 years). The 1-year, 18-month and 2-year survival rates for patients aged <60 years were 83.78%, 68.20% and 62.72%, respectively (Table 4). The survival rate of patients aged >60 years was lower than that of patients aged <60 years, but the difference was not significant (Figure 4B). The same result was found for patients at different clinical stages (Figure 4F). The corresponding survival rate of patients with early-stage cancer was higher than that of patients with advanced stage (1 year 91.37% vs 53.18%, 18

months 86.43% vs 45.0%, 2 years 81.50% vs 30.0%) (Table 4), but there was no significant difference. The survival rate of patients with lung lesions <2 cm and >2 cm in diameter differed significantly (1 year 91.37% vs 53.18%, 18 months 86.43% vs 45.0%, 2 years 81.50% vs 30.0%) ($P<0.05$) (Figure 4D). There was no significant difference in survival rate between squamous cell carcinoma and adenocarcinoma after RFA. The annual survival rate of patients with elevated serum CEA before RFA was significantly lower than that of patients with normal serum CEA (Figure 4G). Moreover, aggressive post-RFA treatment can also improve survival significantly. Patients with chemotherapy combined with tyrosine kinase inhibitor (TKI) had obviously higher survival rates compared with patients with only chemotherapy or TKI/no treatment ($P<0.05$) (Figure 4H).

Table 4
OS rates of 29 patients.

Features (n=29)	OS rate (%)		
	12 months	18 months	24 months
Age (years)	83.78	68.20	62.72
≤60	57.65	53.50	38.20
>60			
Maximum diameter (cm)	91.37	86.43	81.50
≤2	53.18	45.00	30.00
>2			
Histologic type	44.04	36.88	16.70
Squamous-cell carcinoma	74.80	60.60	57.12
Adenocarcinoma			
Clinical stage	81.28	76.20	63.50
Early stage	60.94	51.20	41.70
Advanced stage			
Serum CEA	88.43	75.80	66.30
Normal	42.70	38.50	28.23
Increased			
Post-ablation therapy	13.32	0	-
No	61.02	56.60	48.50
Chemotherapy/TKI	91.83	79.57	68.80
Chemotherapy + TKI			
Overall	69.78	59.10	48.85
Overall survival (months), median (IQR)	**22 (2.584~41.416)**		

Discussion

Lung cancer has always been a major challenge for human health. Many patients have advanced lung cancer by the time they are diagnosed, which brings serious economic and social burdens at the same time. Early lung cancer is mainly treated by surgery[12], but surgery cannot be performed for patients with advanced lung cancer. Traditional radiotherapy and chemotherapy are faced with a series of adverse

effects, such as radiation pneumonia and bone marrow suppression. Despite the rapid development of targeted therapy and immunotherapy in recent years, expensive drugs are beyond the reach of patients in developing countries. Nevertheless, it remains the leading cause of cancer death and the median OS has not improved significantly[13, 14]. In recent years, many studies have shown that RFA is a feasible and safe treatment for patients with inoperable early lung cancer, lung metastases and patients with advanced lung cancer.

The median OS of patients in the present study was 22 months. The 1-year survival rate was 81.28% in patients in the early stage. A recent meta-analysis of surgical resection versus CT-guided percutaneous ablation for stage I NSCLC showed that there were no significant differences in 1–5-year OS or cancer-specific survival between surgery and ablation. However, the difference in early disease-free survival was significant. Therefore, RFA is an effective treatment for patients with inoperable stage I NSCLC[12].

MWA cannot be ignored for thermal ablation of tumors. The principle of MWA is different from that of RFA. MWA inactivates tumors by microwave energy[15]. There is still controversy about the efficacy of the two techniques in treating lung cancer. A previous study has suggested that MWA can be used for a wider range of indications with larger-diameter lesions than RFA can[16, 17]. In the present study, the maximum diameter of the lesion for RFA was 4 cm. Other studies have shown that patients with lesion diameter <3 cm treated with RFA can achieve long progression-free survival (PFS) and OS[18]. Xu Feng's study[19] proved that the local tumor control rate (90.6% vs 78.1%) and PFS (10.4 vs 9.2 months) of MWA were better than those of RFA ($P<0.05$), and the OS was different (MWA vs RFA, 15.2 vs 14.6 months) ($P>0.05$). There was no significant difference in disease control and objective response rates. Nevertheless, a meta-analysis[20] showed that the OS rate of RFA-treated patients was higher than that of MWA-treated patients. In addition, median survival of patients with lung metastases treated by RFA was higher than that of patients treated with MWA. Nevertheless, MWA was superior to RFA in PFS rate and local tumor PFS rate, without a significant difference, except for 3-year progression-free survival rate ($P=0.028$). Therefore, multicenter, large-sample studies are needed to compare the clinical efficacy between RFA and MWA.

We found that, in patients with lesions <2 cm in diameter, combined chemotherapy/targeted therapy improved prognosis, while patients with elevated serum CEA before RFA had poor prognosis. In line with previous research, post-ablation therapy has a significant impact on the survival, and combination of multiple treatments is more effective. Xu et al.[21] proved that patients treated with RFA combined with chemotherapy fared better than those treated with RFA alone, with increased PFS and OS. Serum tumor marker levels decreased significantly after treatment. Besides, it is noteworthy that the effect was better in patients with lung adenocarcinoma than in patients with squamous cell carcinoma/small cell lung cancer. In contrast, different age and clinical stage of patients in our study had no significant effect on survival, which was not consistent with previous studies. This may have been related to the small sample size in our study. Also, some patients with advanced lung cancer were young and sought active treatment, which may have affected the results.

RFA is an effective palliative treatment for patients with inoperable advanced lung cancer. Many patients suffer from cancer pain and have to take opioids for pain relief for a long time. A new study showed that RFA can relieve cancer pain in patients with advanced lung cancer by 70%[22], and can also reduce the frequency and dose of opioids, thereby improving the quality of life of patients with advanced lung cancer. We did not study remission of cancer pain, which can be followed up in the future.

Related studies have shown that the complications of RFA of lung cancer are divided into two types; one is puncture-related and the other is melt-related. Pulmonary hemorrhage, hemothorax and pneumothorax belong to puncture-related complications. Pleural reaction, skin burns and chest pain pertain to melt-related complications[23, 24]. These complications can be resolved by symptomatic treatment, and the possibility of a fatal complication is extremely low. In the present study, the rate of complications was 44.12% (15/34), which is higher compared with previous studies[25, 26]. The most common complication during RFA was pleural effusion. In addition, chest CT re-examination after ablation showed spontaneous absorption of pleural effusion without therapeutic drainage. Therefore, RFA is a safe treatment. In the future, we should pay more attention to the position and angle of needle insertion to avoid unnecessary injury. We demonstrated that smoking history was a risk factor for complications, which may be related to structural pulmonary lesions such as emphysema caused by long-term smoking. However, there was no relationship between age, gender, lesion size, lesion location and complications. In the future, we need a larger sample of cases.

There were several limitations to our study. First, our hospital has carried out RFA for lung cancer since 2013. Up to now, a total of 67 cases have been successfully performed, which included patients with lung metastases and irregular follow-up, and only 34 cases have met the inclusion criteria, and only 29 patients were followed up. The overall number of cases was low, and it may reduce the statistical power and affect the reliability of survival data. Therefore, further data collection is required to expand the sample size to verify the efficacy of RFA for lung cancer. Second, many patients were not followed up for chest CT in our hospital, on the grounds that it was different to collect chest CT data, so we were not able to analyze the local PFS of patients. Third, we did not compare the efficacy of RFA combined with chemotherapy and intravenous chemotherapy alone, which would be important for exploring whether RFA and chemotherapy have synergistic effects. We will continue to follow up more patients to better understand the long-term prognosis of RFA.

Conclusion

CT-guided RFA is a safe and effective treatment for lung cancer. Smoking is a risk factor for complications. Lung lesions >2cm in diameter and high serum CEA level may be associated with poor prognosis, while active treatment after RFA can effectively improve prognosis.

Abbreviations

RFA: Radiofrequency ablation, MWA: Microwave ablation, NSCLC: non-small cell lung cancer, CEA: carcinoembryonic antigen, CYFRA21-1: cytokeratin fragment 19, NSE: neuron-specific enolase, TNM: tumor node metastasis, TKI: tyrosine kinase inhibitor, OS: Overall survival, IQR: interquartile range, PFS: progression-free survival.

Declarations

Ethics approval and consent to participate: The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University.

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analyzed during this study are included in this paper and its Supporting Information.

Competing interests: The authors declare that there are no conflicts of interest.

Funding: This work was supported by the National Natural Science Foundation of China (U1803126), Geriatrics and Biochemical Molecular Biology Co-construction Project of Anhui Medical University (2020lcxk003), Geriatrics and Epidemiological health statistics Co-construction Project of Anhui Medical University (2021lcxk005) and Hefei Independent Innovation Policy "Borrowing and Subsidy" Project (J2018Y04).

Author contributions: XF designed the study. MP was responsible for collecting and analysising data and writing the paper. YX performed the data collection. All authors were involved in radiofrequency ablation and the management of patients. Moreover, all authors read and approved the final manuscript.

Acknowledgement: We thank all the medical staff who participated in the radiofrequency ablation procedure and all patients enrolled in this study. In addition, we thank International Science Editing (http://www.internationalscienceediting.com) for editing this manuscript.

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Figures

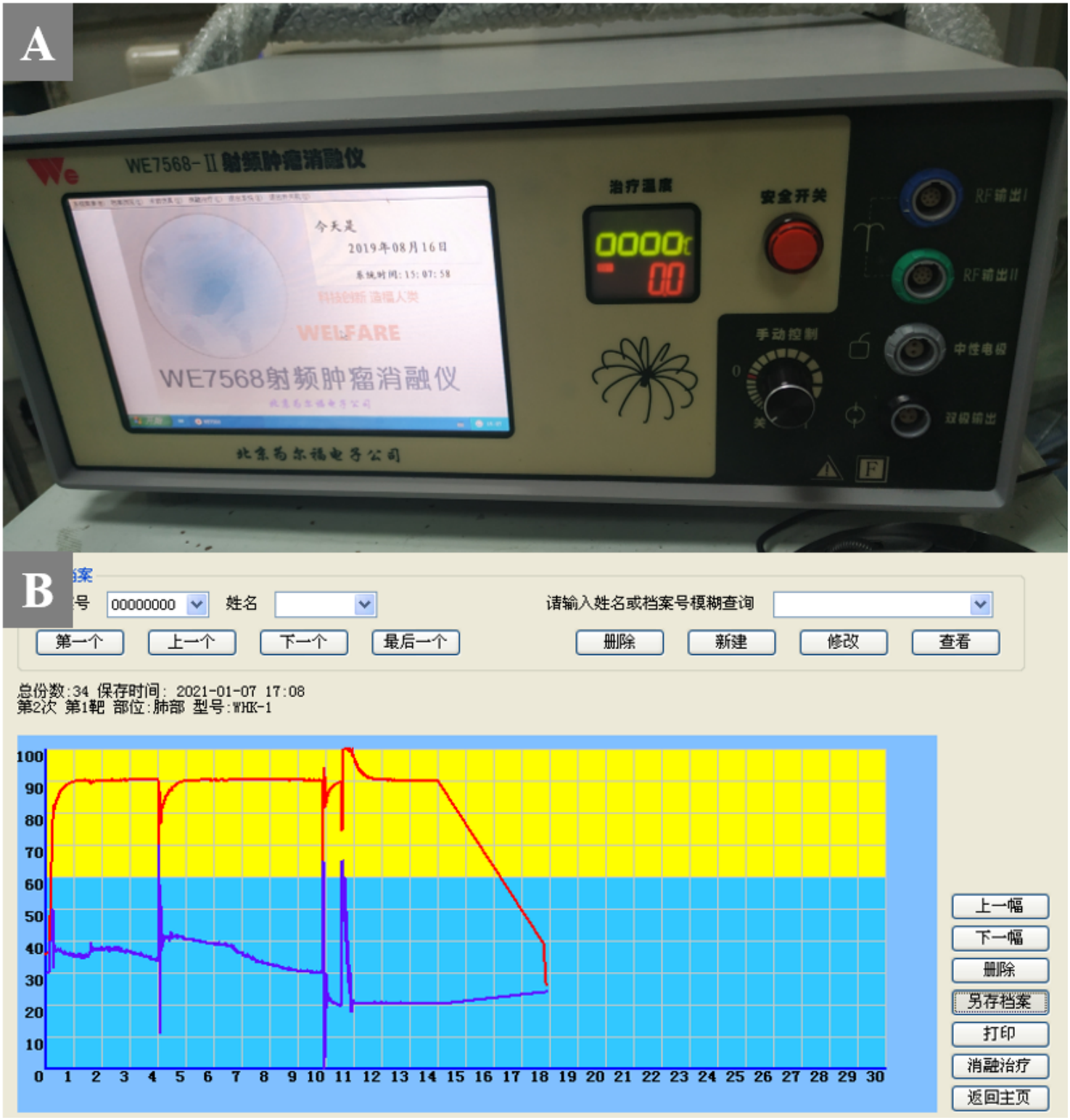

Figure 1

Beijing Welfare WE7568-II radiofrequency tumor ablation instrument and the ablation interface.

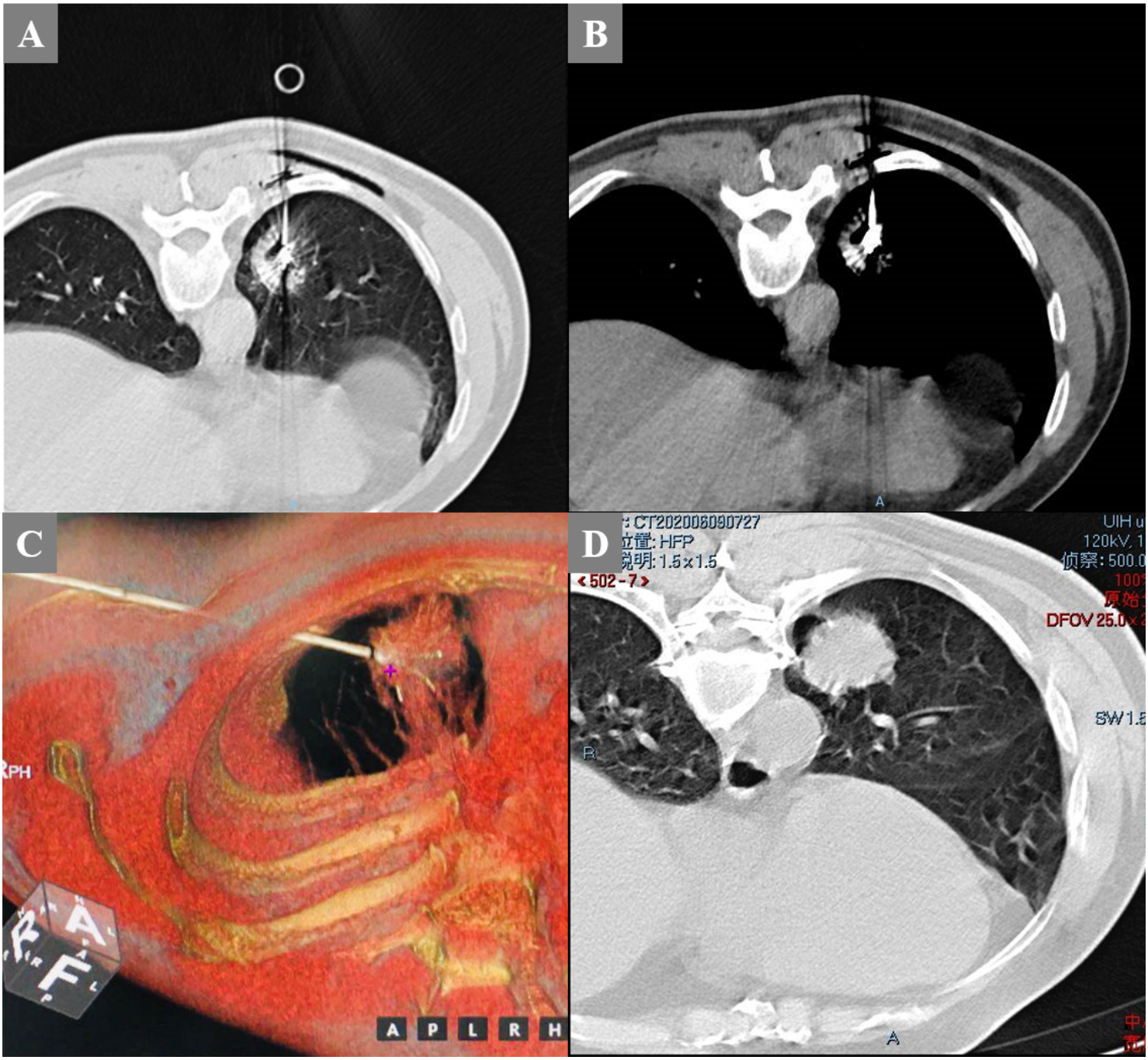

Figure 2

Chest CT during RFA. (A) Lung window. (B) Mediastinal window. (C) Three-dimensional reconstruction. (D) The ablation lesion showed a halo sign after RFA.

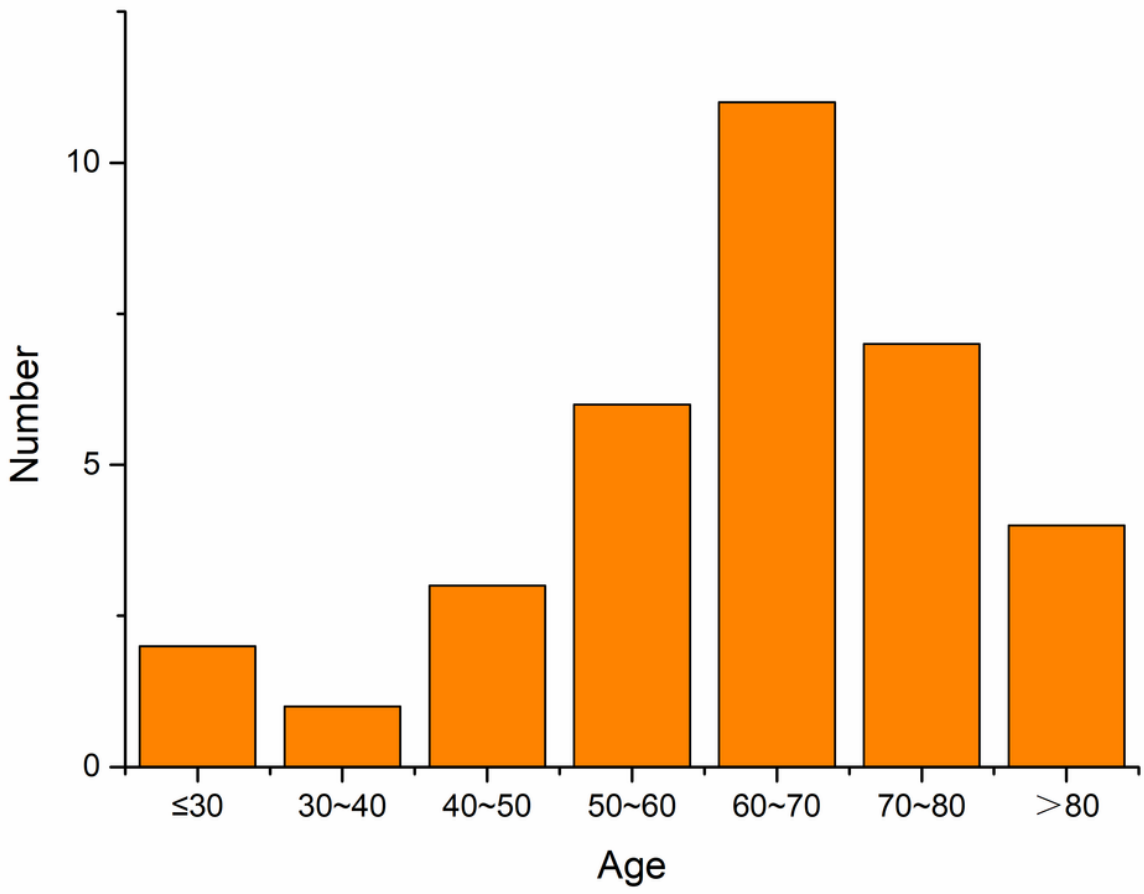

Figure 3

Age distribution of the 34 patients.

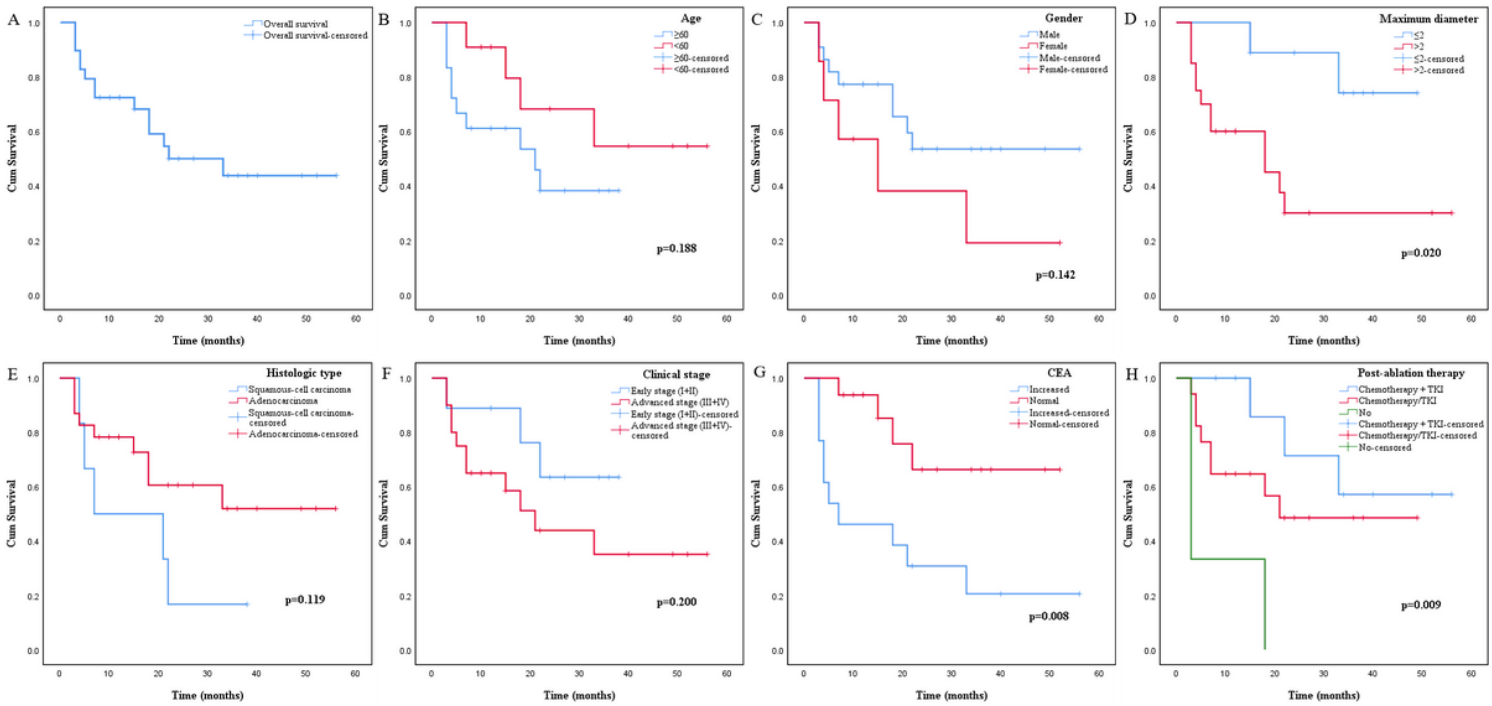

Figure 4

(A) Kaplan–Meier analysis of OS in all patients with primary NSCLC. (B) Comparison between patients aged <60 years and >60 years (P=0.188). (C) Comparison between male and female patients (P=0.142). (D) Comparison between maximum diameter ≤2 cm and >2 cm (P=0.020). (E) Comparison between different histological types (P=0.119). (F) Comparison between early stage and advanced stage disease (P=0.200). (G) Comparison between increased and normal serum CEA (P=0.008). (H) Comparison between different therapeutic methods (P=0.009).

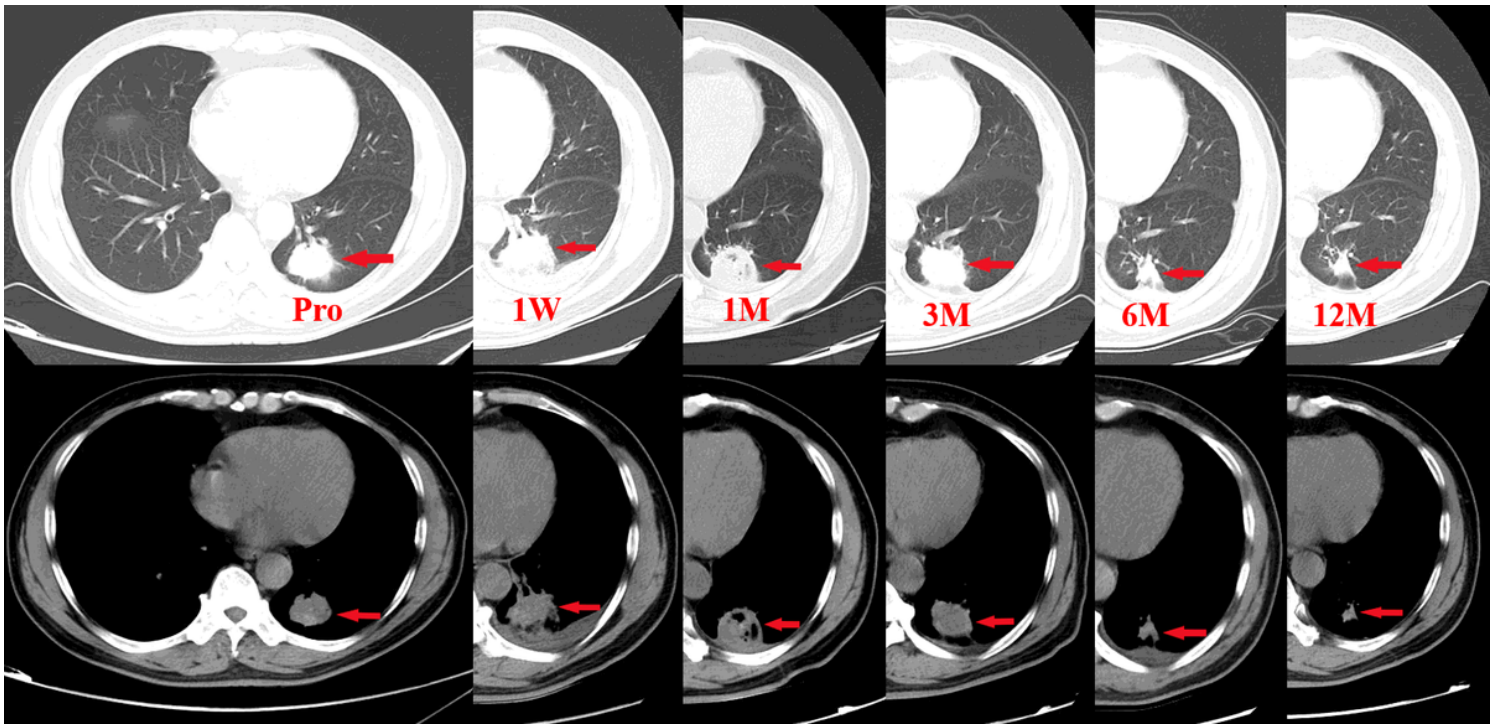

Figure 5

CT images of a 59-year-old man with adenocarcinoma before and after RFA.