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ORIGINAL ARTICLE

Radiofrequency ablation of primary non-small cell lung cancer: A retrospective study on 108 patients

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Summary

Purpose: *To retrospectively analyze the factors influencing response, local progression, local progression-free survival (LPFS), and overall survival (OS) in patients with primary non-small cell lung cancer (NSCLC) after computed tomography (CT)-guided radiofrequency ablation (RFA).*

Methods: *From August 2012 to October 2017, 108 lesions of 108 patients who had undergone CT-guided RFA were analyzed in this study. Patients were followed after RFA continuously. Meanwhile, technical success rate, incomplete ablation rate, local progression, LPFS and OS were assessed.*

Results: *In all patients, 100% technical success rate was achieved. Incomplete ablation rate was 9.26% (10 of 108). Maximum diameter of lesions was associated with incomplete ablation. Maximum diameter of lesions, clinical stage, solitary lesion in the lung and treatments after initial RFA were significantly related to LPFS. Maximum diameter of lesions clinical stage, solitary lesion in the lung, histologic types and treatments after initial RFA were significantly related to OS.*

Conclusions: *Maximum diameter of lesions ≤3cm, early clinical stage, solitary lesion in the lung and RFA combined with cisplatin and carboplatin chemotherapy and/or tyrosine kinase inhibitors (TKI) all were positive factors of local efficacy and survival after RFA of primary NSCLC.*

Key words: *radiofrequency ablation, non-small cell lung cancer, local progression-free survival, overall survival, retrospective study*

Introduction

Lung cancer (LC) is the most common cancer and the leading cause of cancer-related death worldwide [1,2]. According to Jemal et al. [3], the annual incidence of LC is 1.6 million, and about 1.4 million patients with LC die each year. In terms of treatment, surgical resection is considered the gold-standard for treatment for primary non-small cell lung cancer (NSCLC) [4]. Even at the early stages of disease, however, 2/3 of patients with primary NSCLC may not be candidates for lobar or sublobar resection because of age problems, cardiorespiratory disease and so on [5,6]. There are some alternative treatments which could be considered in these patients, including chemotherapy [7], targeted therapy [8], radiotherapy [9], and tumor thermal ablation [10]. Although lung cancer chemotherapy and radiotherapy have improved significantly in recent years, the overall effect is still less than satisfactory. Thus, tumor thermal ablation becomes a good option, especially percutaneous radiofrequency ablation (RFA),

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which has been widely applied in the treatment for solid organs [11]. Since 2000, RFA has become one of the preferred treatments for NSCLC [12,13].

The primary purpose of this study was to retrospectively describe the successful application of percutaneous CT-guided RFA in patients with primary NSCLC and analyze the factors influencing the local efficacy and survival of this procedure.

Methods

Clinical data

From August 2012 to October 2017, 108 patients with primary NSCLC sumitted to CT-guided RFA in our hospital were collected. According to the International Staging System of Lung Cancer [14], all patients were divided from stage I to stage IV. All patients were divided into two groups: early-stage group, including stage I and/or stage II; and advanced-stage group, including stage III and/or stage IV. All patients signed informed consent, and the Ethics Committee approved this study.

The histologic diagnosis of the lesion was performed in all patients by percutaneous puncture biopsy. Patients were excluded from surgical resection due to some medical causes including older age, poor cardiopulmonary status, poor mental status, and impaired renal function and liver function.

Pre-operative preparation

All patients should cease taking anticoagulative or antiplatelet medications before undergoing RFA. CT scans of the chest and upper abdomen, cardiopulmonary function assessment, and coagulation function tests were assessed before the procedure. A previous study by Dupuy et al. [12] established the inclusion criteria of RFA in the treatment of patients. Patients were asked not to eat any food 12 h before the procedure. Oral antitussive and surgical skin preparation before local anesthesia also should be established. Local anesthesia (subcutaneous 1% lidocaine hydrochloride injection) was used for each patient.

Course of operation

Each RFA was carried out by two or three experienced radiologists and a radiology technician assisted with the CT scan. Under the guidance of CT, the tip of the RF needle was inserted accurately into the focus.

Table 1. Clinical characteristics of 108 patients in this study

Characteristics (n=108)	*No. (%)*
Sex	
Men	77 (71.30)
Women	31 (28.70)
Age (y), mean±SD	64.99 ± 11.977
Maximum diameter (cm), mean±SD	4.08 ± 2.278
≤ 3	41 (37.96)
> 3	67 (62.04)
Location of lesion	
Right upper lobe	33 (30.56)
Right middle lobe	11 (10.19)
Right lower lobe	27 (25.00)
Left upper lobe	21 (19.44)
Left lower lobe	16 (14.81)
Histologic type	
Squamous-cell carcinoma	37 (34.26)
Adenocarcinoma	63 (58.33)
Other types	8 (7.41)
Clinical stage	
Early stage	30 (27.78)
Advanced stage	78 (72.22)
Solitary lesion in the lung	
Yes	70 (64.81)
No	38 (35.19)
Post-ablation therapy	
No	17 (15.74)
Chemotherapy	74 (68.52)
Chemotherapy + TKI	17 (15.74)
Follow-up (months), mean±SD	21.97 ± 12.331

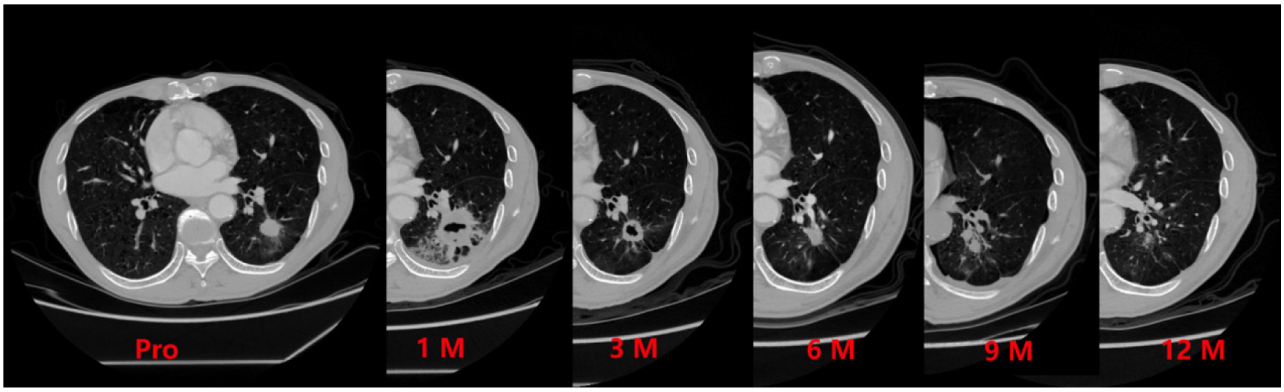

Figure 1. Primary non-small cell lung cancer (NSCLC) located in the left lower lobe. The 1-month computed tomography (CT) scan showed a large area of cavitation, and the size of the ablated lesion in the 3-month was larger than that before ablation. The 6-, 9-, and 12-month CT images demonstrated the progressive reduction in size of the ablated lesion (M: month).

MedSphere Needle Electrodes (MedSphere International, Inc, Fremont, CA, USA) were used. They consist of 9 deployable electrode tracts. The diameter of electrode tracts of different needles were different, the maximum diameter was 5 cm. The paths of the electrode tracts were evaluated in advance, to avoid large vessels, bronchi and fissures. Once RF needle position was achieved, the electrode tracts were deployed and attached to a Radio Therapeutics RF generator (S-1500, MedSphere International, Inc, Fremont, CA, USA). In all cases, CT imaging was used to change position of the needle and to monitor the effects of the ablation. For most lesions, RFA was performed for small lesions (eg, ≤5 cm) with a single point radiofrequency catheter, while RFA was performed for large lesions (eg, >5 cm) with single or multiple ablation needles through multiple points. Depending on the size of the tumor, ablation was performed no more than 6 times. The maintained target temperature was 90-100°C, and the ablation time varied between 12 and 25 min. It took longer to ablate larger lesions. Ablation ended after control CT when a small rim of approximately 1 cm around the lesion became visible. Before pulling out the needle, a needle passage ablation was conducted to prevent tumor seeding. A CT scan was performed immediately after ablation to observe if there was bleeding and other complications. If the patient had normal heart rate, blood pressure, blood oxygen saturation and no complications, then he/she would be allowed to return to the ward.

Postoperative follow-up

Patients were followed by enhanced CT scans at 1, 3, 6, 9, and 12 months after RFA and then at an interval of 6 months in order to evaluate the ablation efficacy (Figure 1). CT scan evaluation was performed by a radiologist and a thoracic surgeon. Postoperative CT images of the lesion at 1 month were defined as the baseline to assess the effects of treatment [4]. According to the improved Response Evaluation Criteria In Solid Tumors (RECIST) [15], the treatment response was considered to include four levels: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD).

After continuous follow-up, the technical success, incomplete ablation, local progression, LPFS and OS were assessed. Previous studies have reported that the size of ablated lesions usually exceeds the size of lesions before ablation in the first 3 months; during this period, the size of ablated lesions cannot be used to evaluate the effect, but contrast enhancement CT can evaluate the effect [16,17]. Technical success was defined as the target lesion being treated according to protocol and covered

Table 2. Correlation between response to RFA and clinical characteristics

Characteristics	*Complete ablation*	*Incomplete ablation*	*p value*
	(n=98)	*(n=10)*	
Sex			0.410
Men	69	8	
Women	29	2	
Age (y)			0.531
≥ 65	53	5	
< 65	45	5	
Maximum diameter (cm)			0.012
≤ 3	57	10	
> 3	41	0	
Location of lesion			0.991
Right upper lobe	30	3	
Right middle lobe	10	1	
Right lower lobe	24	3	
Left upper lobe	19	2	
Left lower lobe	15	1	
Clinical stage			0.059
Early stage	30	0	
Advanced stage	68	10	
Solitary lesion in the lung		0.087	
Yes	66	4	
No	32	6	
Histologic type			0.603
Squamous-cell carcinoma	35	2	
Adenocarcinoma	56	7	
Other types	7	1	

completely (ie, ablation zone completely overlaps or encompasses target lesion plus an ablative margin) [18]. Complete ablation was defined as no imaging findings of tumor growth in the ablated zone, or complete cavernous formation, when enhanced CT scan was performed at 1 month after RFA [19]. Local progression was defined as the appearance of tumor foci at the edge of the ablation zone, after at least one contrast-enhanced follow-up CT scan has confirmed adequate ablation and absence of viable tissue in the target lesion [18]. LPFS was defined as the time between RFA and the first radiologic evidence of the lesion local progression [20]. OS was defined as the time between RFA and death from any cause [20].

Statistics

Fisher's exact test or the x^2 test were used to analyze the association between categorical variables. The Kaplan-Meier method was used for survival analyses (LPFS and OS) accompanied with log-rank test to compared differences between groups. SPSS 19.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. P values <0.05 were considered statistically significant.

Results

Clinical characteristics

108 patients in total with primary NSCLC underwent CT-guided RFA. There were 77 men and 31 women with a mean age of 64.99±11.977 years (range 33-85). The mean follow-up duration of these patients was 21.97±12.331 months (range 2-54). The demographics and tumor characteristics of all patients are summarized in Table 1.

Table 3. Local progression-free survival and overall survival

Characteristics	*LPFS (months)*			*OS (months)*		
	Median	*95%CI*	*p*	*Median*	*95%CI*	*p*
Sex			0.346			0.783
Men	12	10.310-13.690		24	19.370-28.270	
Women	13	11.923-14.077		25	21.379-28.621	
Age (y)			0.355			0.253
≥ 65	12	10.439-13.561		24	22.318-25.682	
< 65	12	9.690-14.310		24	18.790-29.210	
Maximum diameter (cm)			0.002			0.002
> 3	10	7.341-12.659		16	11.619-20.381	
≤ 3	15	11.317-18.683		28	24.700-31.300	
Location of lesion			0.186			0.679
Right upper lobe	13	10.588-15.412		24	16.167-31.833	
Right middle lobe	10	2.717-17.283		14	1.053-26.947	
Right lower lobe	12	9.498-14.502		25	16.731-33.269	
Left upper lobe	12	7.514-16.486		24	21.215-26.785	
Left lower lobe	13	9.390-16.610		26	17.325-35.675	
Clinical stage			0.000			0.000
Early stage	18	12.004-23.996		34	29.127-38.873	
Advanced stage	10	7.843-12.157		16	11.249-20.751	
Solitary lesion in the lung			0.000			0.005
Yes	13	11.145-14.855		25	22.801-27.199	
No	7	2.167-11.833		13	5.200-20.800	
Histologic type			0.055			0.021
Squamous-cell	12	9.522-14.478		24	19.225-28.775	
Adenocarcinoma	13	11.483-14.517		26	23.283-28.717	
Other types	7	1.456-12.544		13	6.290-19.710	
Post-ablation therapy			0.010			0.004
No	10	1.933-18.067		20	15.801-32.199	
Chemotherapy	12	10.354-13.646		24	18.575-29.425	
Chemotherapy + TKI	24	19.704-28.296		35	28.567-41.433	
Overall	12	10.685-13.315	/	24	22.630-25.370	/

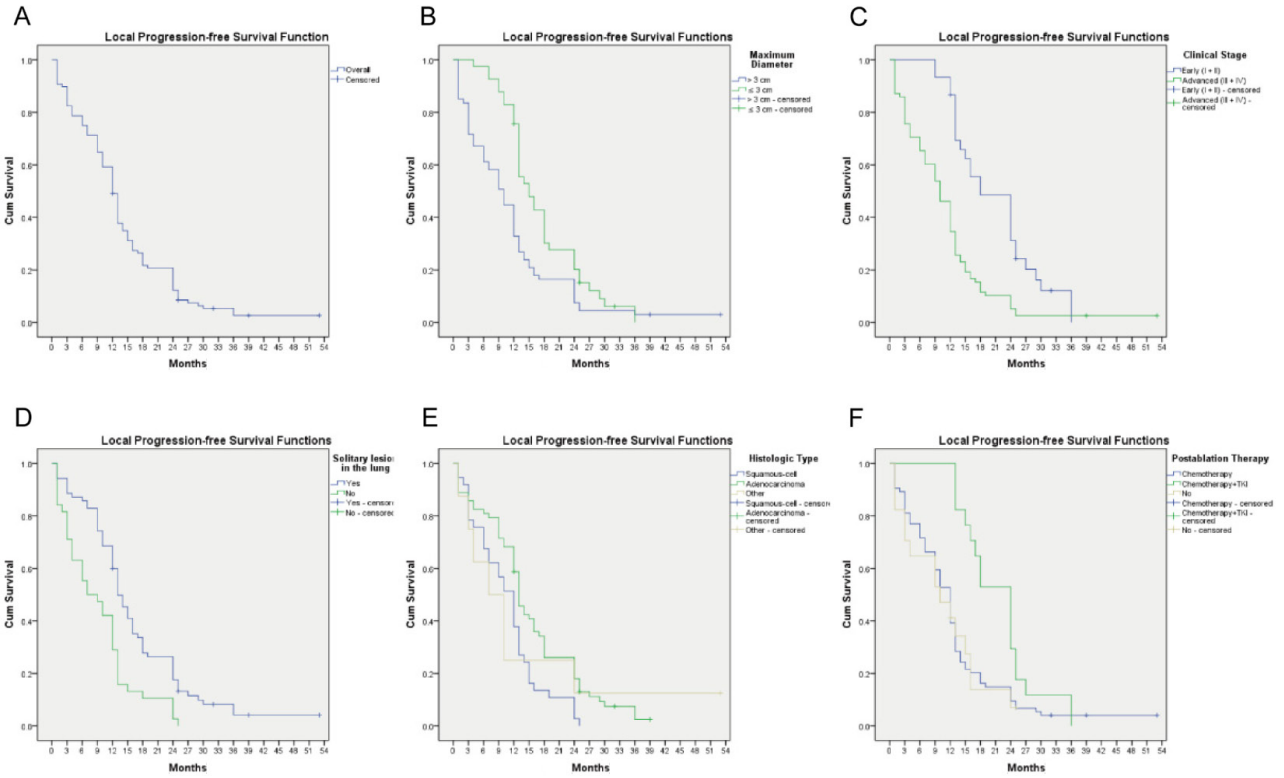

Figure 2. (A): shows the Kaplan-Meier survival analysis of local progression-free survival (LPFS) in all patients with primary non–small cell lung cancer (NSCLC). **(B):** shows the results of comparison between maximum diameter ≤ 3cm and maximum diameter >3cm (p=0.002). **(C):** shows the results of comparison between early stage and advanced stage disease (p<0.001). **(D):** shows the results of comparison between metastasis and no metastasis intrapulmonary (p<0.001). **(E):** shows the results of comparison between different histologic types (p=0.055), and **(F):** shows the results of comparison between different therapeutic methods (p=0.010).

Response to treatment

Complete ablation was observed in 98 patients (90.74%), and incomplete ablation was observed in 10 patients (9.26%). Further analyses showed that the response to treatment did not correlate to some baseline characteristics, including sex (p=0.721), age (p=1.000), location (p=0.991), and histologic type (p=0.603), but was associated with maximum diameter of lesions (p=0.012) and clinical stage (p=0.023) (Table 2).

Complications and treatment

Of all patients in this study, 36 (33.33%) developed postoperative complications within the first week after RFA, including low-grade fever, nausea, emesis, feebleness and other complications. Seventeen patients (15.74%) had different grades of pneumothorax after RFA. Five of these cases (4.63%) needed thoracic drainage. Chest X-ray was used to follow-up pneumothorax. The incidence of pleural effusion was 20.37% (22 of 108). All of these complications were improved and cured after symptomatic treatment. In this study, no intraoperative and peri-operative death occurred in any patient.

Local progression-free survival

The results of Kaplan-Meier survival analysis showed median LPFS of 12 months (95% CI 10.69-13.32) (Table 3, Figure 2A). The median LPFS was associated with maximum diameter of lesions (p=0.002); lesions ≤ 3 cm had significantly improved median LPFS of 15 months (95% CI 11.32–18.68) than those with lesions >3 cm (Figure 2B). The median LPFS of all patients was also significantly related to clinical stage (p<0.001), solitary lesion in the lung (p<0.001) and postablation therapy (p=0.010) (Table 3, Figure 2C, 2D, 2F). However, there was no statistical significance in the histologic type (p=0.055) (Figure 2E). The median LPFS of squamous-cell, adenocarcinoma and other types was 12 months (95% CI 9.52–14.48), 13 months (95% CI 11.48–14.52) and 7 months (95% CI 1.46–12.54), respectively (Table 3).

The 6-, 12-, and 24-month LPFS rates of all patients were 78.70, 59.26 and 20.76%, respectively (Table 4). The 6-, 12-, and 24-month LPFS rates of lesions ≤ 3 cm and > 3 cm were 97.56, 82.93 and 27.72%, and 67.16, 44.78 and 16.42%, respectively. The 6-, 12-, and 24-month LPFS rates of squamous-cell, adenocarcinoma and other types were 75.68,

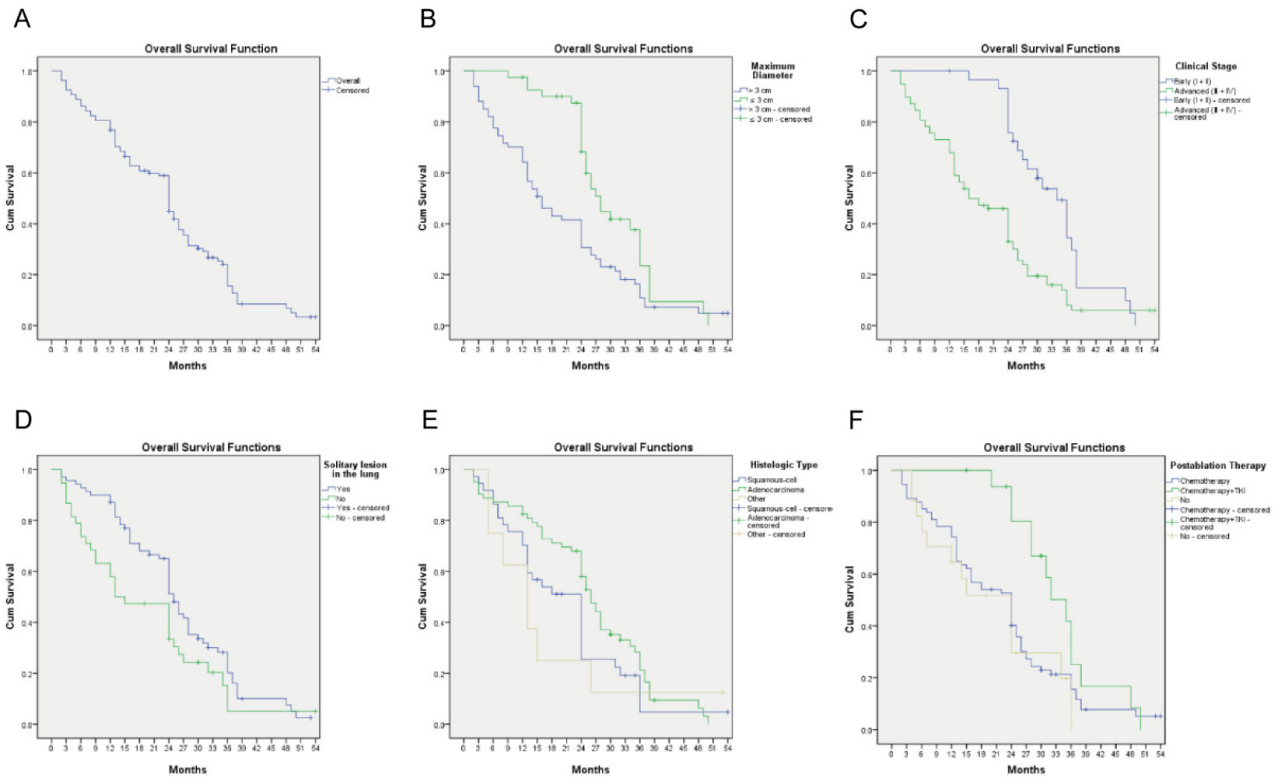

Figure 3. (A): shows the Kaplan-Meier survival analysis of overall survival (OS) in all patients with primary non-small cell lung cancer (NSCLC). **(B):** shows the results of comparison between maximum diameter ≤ 3cm and maximum diameter >3cm (p=0.002). **(C):** shows the results of comparison between early stage and advanced stage disease (p<0.001). **(D):** shows the results of comparison between metastasis and no metastasis intrapulmonary (p=0.005). **(E):** shows the results of comparison between different histologic types (p=0.021), and **(F):** shows the results of comparison between different therapeutic methods (p=0.004).

Table 4. Local progression-free survival rates and overall survival rates

Characteristics	*LPFS rate (%)*			*OS rate (%)*		
	6 months	*12 months*	*24 months*	*12 months*	*24 months*	*36 months*
Maximum diameter (cm)						
> 3	67.16	44.78	16.42	70.15	41.52	16.31
≤ 3	97.56	82.93	27.72	97.56	87.41	37.64
Clinical stage						
Early stage	100	93.33	48.53	100	93.10	49.31
Advanced stage	70.51	46.15	10.26	73.08	45.93	13.96
Solitary lesion in the lung						
Yes	87.14	68.57	26.34	90.00	65.10	28.21
No	63.16	42.11	10.53	63.16	47.37	15.20
Histologic type						
Squamous-cell carcinoma	75.68	51.35	10.81	75.68	51.08	19.16
Adenocarcinoma	82.54	68.25	26.10	85.71	67.97	28.34
Other types	62.50	25.00	12.50	62.50	25.00	12.50
Post-ablation therapy						
No	64.71	47.06	13.73	70.59	51.76	19.72
Chemotherapy	77.03	52.70	14.86	78.38	52.67	21.33
Chemotherapy + TKI	100	100	52.94	100	93.75	41.85
Overall	78.70	59.26	20.76	80.56	58.89	24.03

51.35 and 10.81%, and 82.54, 68.25 and 26.10%, and 62.50, 25.00 and 12.50%, respectively.

Overall survival

The median OS for all patients was 24 months (95% CI 22.63–25.37) (Figure 3A). The median OS was associated with maximum diameter of lesions (p<0.002); lesions ≤ 3 cm had significantly improved median OS of 28 months (95% CI 24.70–31.30) than lesions > 3 cm (Figure 3B). The histologic types were not associated with median LPFS of the entire patient cohort (p=0.055), but it was significantly related to median OS (p=0.021) (Table 3, Figure 3E). The median OS of squamous-cell, adenocarcinoma and other types was 24 months (95% CI 19.23-28.78), 26 months (95% CI 23.28-28.72) and 13 months (95% CI 6.29-19.71), respectively (Table 3). The median OS of all patients was also significantly related to clinical stage (p<0.001), solitary lesion in the lung (p=0.005) and post-ablation therapy (p=0.004) (Table 3, Figure 3C, 3D, 3F).

The 1-, 2-, and 3-year OS rates of all patients were 80.56, 58.89 and 24.03%, respectively (Table 4). The 1-, 2-, and 3-year OS rates of lesions ≤ 3 cm and > 3 cm were 97.56, 87.41 and 37.64%, and 70.15, 41.52 and 16.31%. The 1-, 2-, and 3-year OS rates of squamous-cell, adenocarcinoma and other types were 75.68, 51.08 and 19.16%, and 85.71, 67.97 and 28.34%, and 62.50, 25.00 and 12.50%.

Discussion

This study was conducted to analyze the factors influencing the local efficacy and survival of percutaneous CT-guided RFA in patients with primary NSCLC. As widely recognized in previous studies [21-24], the maximum diameter and clinical stage were significantly associated with the local efficacy and survival of pulmonary RFA. In addition, our study also showed that solitary lesion in the lung, histologic type and post-ablation therapy were related to LPFS and OS of ablated patients with primary NSCLC.

The complete ablation rate was 90.74% in this study, which is comparable to the reported rates of 38-97% (median 90%) for RFA [25]. The larger diameter (> 3cm) remains a risk factor of incomplete ablation [21-23], the complete ablation rate of lesions ≤ 3cm was markedly greater than that of lesions > 3cm. The lesions with completed ablation all have ground-glass opacity (GGO) around them on CT images. In an effort to obtain complete ablation, two antennae or more were used simultaneously for larger lesions in our operations.

The results of this study also showed that maximum diameter of lesions, clinical stage, solitary lesion in the lung, and post ablation therapy were associated with local progression. These conclusions were reported in other studies [21-23], where smaller diameter, early stage and solitary lesion in the lung were favorable conditions for LPFS. Our data also showed that RFA combined with chemotherapy and/or TKI can effectively reduce local progression [4,26].

In previous reports, the 1-, 3-, and 5-year OS rates after RFA of early-stage NSCLC were 78-100% [17,21], 36-88% [4,16,22], and 25-61% [16,22], respectively. The median survival time ranged from 29 to 67 months [1,4,17]. In our study, and the 1- and 3-year OS rates after RFA of early-stage NSCLC were 100% and 49.31%. Lee et al. [26] reported that the median survival time of NSCLC patients in early-stage was 28.5 months, but in our data this was 34 months. Simon et al. [21] reported that median OS in patients with stage IV NSCLC after RFA was 12 months. Rose [27] reported that the median OS in patients with stage III and IV NSCLC after RFA was 6 months. In our study, the median OS for advanced stage was 16 months. Our data was better than that those reported in previous studies, perhaps due to some patients who received RFA combined with chemotherapy and/or TKI. Some published studies demonstrated that percutaneous thermal ablation combined with chemotherapy and/or TKI is well tolerated and associated with long LPFS and OS [26].

In previous reports, the 1-, 3-, and 5-year OS rates after RFA of all-stage NSCLC were 70-100%, 36-77%, and 19-61%, respectively [21,26]. Lencioni et al. [28] reported that 1- and 2-year OS rates in patients with lung tumors were 70% and 48%, respectively. In addition, Dupuy et al. [23] reported that 1- and 2-year OS rates in patients with lung tumors were 86.3 and 69.8%, respectively. Siomn et al. [21] showed a median OS of 29 months in patients with NSCLC. Our results showed 1-year, 2-year, and 3-year OS rates of 80.56, 58.89 and 24.03%, with median OS of 24 months. Compared to these results, the OS in our study was lower due to our older population and a high co-morbidity index. Yet, the OS in our study was greater than that reported by Lencioni et al. [28], due to the selected patients that had primary lesions in our study whereas the selected patients had secondary lesions in their study.

The maximum diameter of lesions and the clinical stage were generally recognized as risk factors related to the OS of patients with NSCLC after RFA [4,21,22,29], and our data support this conclusion. Besides, in this study, histologic type and post-ablation therapy were related to the OS. Zheng et al. [20] reported that squamous-cell carcinoma

was more prone to local progression. In our study, the OS of squamous-cell carcinoma was also lower than adenocarcinoma. It might be that the sensitivity of adenocarcinoma to chemotherapy and/or TKI led to this outcome. From our study, we thought that chemotherapy and/or TKI could prolong the OS in ablated patients with primary NSCLC, especially chemotherapy combined with TKI.

Some limitations should be noted in this study. One of the limitations was the lack of comparison with radiotherapy and other thermal ablation (eg, microwave ablation). An additional limitation was that the follow-up time was short, leading to no 5-year survival in our results. Besides, patients who underwent two or more RFA due to the recurrence of lesions were not included in this study. In addition, limited sample size, lack of control group and retrospective methodology were also limitations.

Conclusions

In conclusion, percutaneous CT-guided RFA is a minimally invasive procedure applied for the treatment of primary NSCLC, which confirmed low mortality and recurrence rates. Maximum diameter of lesions ≤ 3 cm, early stage, solitary lesion in the lung, and RFA combined with chemotherapy and/or TKI are all positive factors of the local efficacy and survival after RFA.

Conflict of interests

The authors declare no conflict of interests.

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