

ORIGINAL ARTICLE

Safety and efficacy of thermal ablation for subpleural lung cancers

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Keywords

Complication; efficacy; subpleural lung cancer; thermal ablation.

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Abstract

Background: The study was conducted to assess the safety and efficacy of thermal ablation for the treatment of subpleural lung cancer.

Methods: Eighty-nine patients with 101 subpleural lung cancers were identified between January 2012 and July 2018 in our database and included in this study. Tumors were classified as adhering to cervical, costal, diaphragmatic, and mediastinal pleurae. Lesions were categorized based on their relationship to the pleura: close to the pleura, causing pleural indentation, and involving the pleura. The complete ablation rate, local progression-free survival, complications, and associated factors were analyzed.

Results: Subpleural lung cancers included lesions located under costal ($n = 69$), mediastinal ($n = 17$), cervical ($n = 8$), and diaphragmatic ($n = 7$) pleurae. The rate of complete ablation was 87.1% and the local progression-free survival rates at 3, 6, 12, and 24 months were 86%, 77%, 75%, and 64%, respectively. Tumor size was the most important factor influencing technique efficacy ($P < 0.05$), with a complete ablation rate of only 55.6% in lung cancers measuring > 30 mm. There were nine (10.11%) major complications, including one chest abscess, five cases of pneumothorax, and three cases of hemothorax. The occurrence of major complications was associated with increased levels of pain within 48 hours post-procedure ($P < 0.05$).

Conclusion: Local thermal ablation is a safe and effective treatment for subpleural lung cancers. Tumor size was the most significant factor affecting technique efficacy. Post-procedure pain indicated the possibility of major complications.

Introduction

Lung cancer incidence is increasing worldwide.^{1,2} Primary lung cancer is one of the most common cancers and the leading cause of cancer-related death. The lungs are also the second most frequent sites of malignant tumor metastases.³ Although the number of basic and clinical studies being conducted is rapidly increasing, the five-year overall survival rate of patients with lung cancer has not significantly improved.^{1,2} Surgical resection is the best treatment choice for early-stage lung cancer and may improve patient survival. However, more than 20% of early-stage lung cancer patients are inoperable.^{4,5} Therefore, a number of

alternative therapies are available to patients with unresectable disease, including stereotactic radiation therapy (SBRT), chemotherapy, and thermal ablation.

Thermal ablation is a minimally invasive method and is widely used as an effective and safe therapy for liver cancer.⁶ It was recently shown as an appropriate alternative for patients with lung cancer who refuse surgery or who are at high risk of post-thoracotomy morbidity.^{7,8} Thermal ablation, including radiofrequency ablation (RFA) and microwave ablation (MWA), has emerged as a promising treatment for unresectable lung cancer, in line with several recent studies on the ablation of lung cancers.^{9,10} However,

many issues concerning thermal ablation still need to be addressed. For example, tumor location is an important risk factor of major complications or insufficient local therapeutic efficacy.¹¹

Although subpleural tumors have not been clearly defined, they are generally described as tumors within 5 mm of the pleura.^{12,13} Thermal ablation of the subpleural tumor often induces severe pain during and following the procedure. Ablation-induced pain can influence the time, power, and electrode repositioning required for successful ablation. In addition to injury to the pleural and chest wall, the procedure may cause other complications, such as pneumothorax, hydrothorax, and bronchopleural fistula.¹⁴ However, only few studies on ablation of subpleural lung cancer with small sample sizes have been reported. Therefore, to our knowledge, the present study is the first to classify subpleural lung cancer based on its location in the thorax, assess the technical efficacy and complications of computed-tomography (CT)-guided percutaneous thermal ablation of subpleural lung cancer, and discuss the associated factors.

Methods

Patients

This retrospective study was approved by our institutional review board, which waived the requirement for informed consent. Between January 2012 and July 2018, 110 consecutive patients with lung cancer in our database who received local thermal therapy were reviewed. Subpleural lung cancer was defined as cancer within 5 mm of the pleura at any distance. The inclusion criteria were: (i) lung cancers close to the pleura, (ii) fewer than three unilateral and five bilateral lesions, (iii) single tumor < 5 cm, and (iv) patients who refused or were not candidates for surgical resection. The exclusion criteria were: (i) poorly-controlled infection, (ii) severe coagulation dysfunction, (iii) lung failure, (iv) an Eastern Cooperative Oncology Group performance score > 3, and (v) chest wall muscle involvement.¹⁵ Eighty-nine patients (59 men and 30 women, mean age 54.2 years) with 101 lung tumors were finally included in this study.

All tumors were diagnosed based on CT-guided tumor biopsy findings or typical clinical features and radiological evidence. The pleura was classified as cervical, costal, diaphragmatic, or mediastinal according to the location in the thorax. Cervical pleurae were located at the apex of the lung at a level higher than that of the manubrium. Costal pleurae were located behind the inner surfaces of the ribs and intercostal muscles. Diaphragmatic pleurae were located on the convex surface of the diaphragm. Finally, mediastinal pleurae were located outside the mediastinum. We developed four subpleural cancer classifications

according to their locations (Fig 1). Three classifications were developed to further characterize the relationships between the lesions and pleurae. The first was defined as lesions close to the pleura, the second as lesions causing pleural indentation, and the third as lesions involving the pleura (Fig 2).

Treatment plan and ablation procedures

The ablation procedures were mainly performed by interventional radiologists with more than 10 years of experience in RFA and MWA. Ablation was always performed percutaneously by real-time CT. The patients were placed in supine or prone body positions during the procedures. All treatments were performed according to standard protocols using MWA (FORSEA, Vision Microwave Electronic Institute, Nanjing, China) or RFA (STARmed, Gyeonggi-do, South Korea; Cool-Tip, Valley lab, Boston, MA, USA) systems. For tumors 3–5 cm, either two microwave antennas were used or the antenna paths were adjusted during the procedure. The ablation parameters were chosen based on tumor size, location, morphology, adjacent structures, and access route.¹⁶ The routes of the needles were designed to avoid the pulmonary bullae, intercostal artery, large vessels, and the bronchus and pericardium. To protect the pleura and reduce pain, all needles were inserted parallel to the pleural surface.¹⁶ Intravenous anesthesia (remifentanyl 0.05–0.10 µg/kg/minute continuous intravenous infusion, flurbiprofen 50 mg, palonosetron 0.25 mg) was used during the entire procedure. When the patient could not tolerate the pain, the dose of remifentanyl was adjusted to no more than 0.2 µg/kg/minute. After the procedure, CT scans were immediately performed to determine if the ablation zone was sufficient to cover the lesion and whether the procedure should be continued.

Follow-up and outcomes

Clinical, routine blood, and biochemical examinations, as well as chest radiography, were usually performed the next day to rule out complications, including pneumothorax, bleeding, pleural effusion, and infection. Major complications can cause hospitalization, disability, and even death, and should be treated immediately. Minor complications were common and generally did not require treatment; however, close observation was necessary to avoid their development into major complications. Nurses used a visual analog scale (VAS) to assess patient pain 0–48 hours after the ablations. Analgesics administered within 48 hours were also recorded. The level of pain was classified as mild (VAS 0–4), moderate (VAS 5–7), or severe (VAS 8–10).

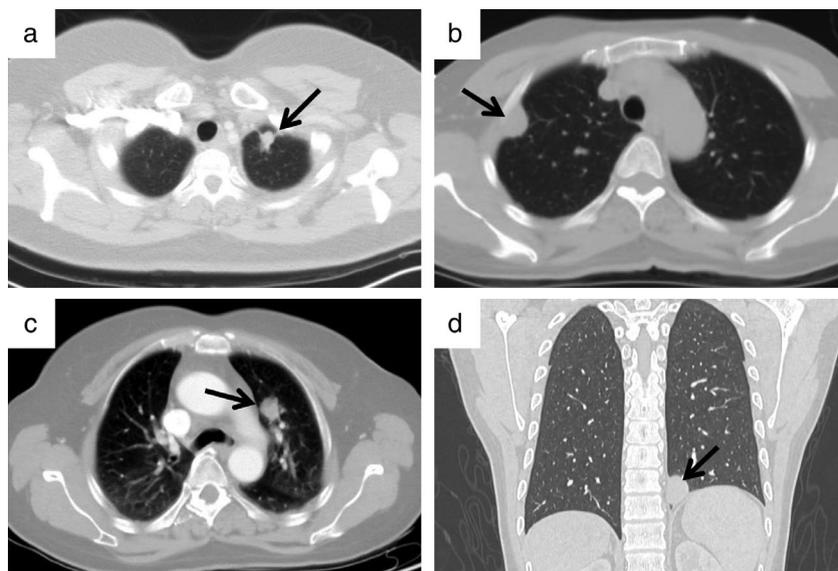


Figure 1 Lung cancers (black arrows) were classified according to location as beneath the (a) cervical, (b) costal, (c) mediastinal, or (d) diaphragmatic pleurae.

Chest-enhanced CT was performed one month later to evaluate technique efficacy. A complete lack of enhancement in the ablation zone was defined as technical success. Irregular nodular enhancement in the ablation zone was considered recurrence or a residual tumor. These patients were requested to undergo repeated chest-enhanced CT every three months.¹⁷ Local progression-free survival (LPFS) was used to describe the absence of progression of the treated lesion. Local tumor progression was defined as the appearance of tumor foci at the edge of the ablation zone on contrast-enhanced chest CT. The LPFS rates of incompletely ablated lesions were evaluated according to the modified Response Evaluation Criteria in Solid Tumors.

Statistical analysis

Pearson chi-square and Fisher’s exact tests were used for categorical variables and Mann–Whitney *U* tests for continuous variables. SPSS version 20.0 was used for statistical analysis. *P* values < 0.05 were considered statistically

significant. All data used in this study are recorded at Sun Yat-sen University Cancer Center for future reference (number RDDA2019001001).

Results

Patient characteristics

A total of 89 patients (59 men, 30 women) with 101 lung cancers were treated with local thermal ablation. The mean age of the patients was 54.2 (range: 19–85) years. Twenty-four patients with primary lung cancer and 77 patients with metastatic lung cancer were included in this study. The majority of the metastatic cancer cell types were liver cancer (*n* = 30), nasopharyngeal carcinoma (*n* = 11), and colorectal cancer (*n* = 16). Lung cancers under the costal pleura (*n* = 69) accounted for most of the subpleural lung tumors, while lung cancers under the mediastinal (*n* = 17), cervical (*n* = 8) and diaphragmatic (*n* = 7) pleurae were relatively less common. The baseline characteristics of the patients are shown in Table Table 1.

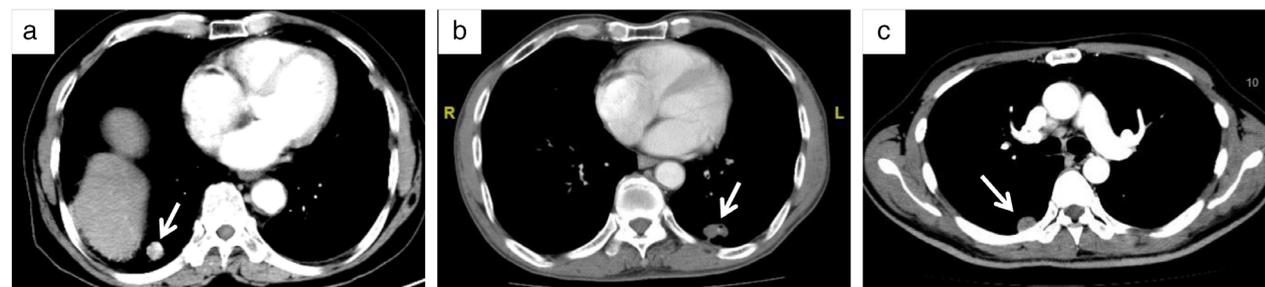


Figure 2 The relationships of the tumors (white arrows) with the pleurae were defined as follows: (a) adhering to the pleura only, (b) adhering to the pleura and with pleural indentation, or (c) adhering to the pleura with pleural involvement.

Efficacy

Evaluation of the efficacy of the technique by contrast-enhanced CT one-month post-procedure revealed that 84 (83.2%) of the lesions were completely ablated in the first ablation. Four patients with unsuccessfully ablated lesions received a second ablation within two weeks; finally, 88 lesions (87.1%) were completely ablated. The other patients did not receive repeated ablations for the following reasons: (i) unable to accept a second ablation; (ii) repeat ablation would not improve patient survival; and (iii) patient had received radiotherapy or systemic therapy and the target tumors were stable. Tumor size was the most important factor influencing technique efficacy ($P < 0.05$). In lung tumors > 30 mm, the complete ablation rate was only 55.6%, while in lung tumors < 30 mm, the complete ablation rate was 90.22%. Other tumor characteristics, including origin, number, location, and relationship to the pleura, were not significantly related to technique efficacy. In addition, there was no statistical significance between the complete ablation rates of patients who received MWA and of those who received RFA. Patients showed local progression including target tumor enlargement ($n = 2$) and the appearance of tumor foci at the edge

Table 1 Baseline characteristics of the study patients and lung cancers

Characteristics	Total
No. of patients	89
No. of lung cancers	101
Age, years, mean \pm SD	54 \pm 13
Gender, M/F	59/30
Tumor origin, N (%)	
Primary	24 (27.0%)
Metastasis	77 (73.0%)
Tumor size, mm, mean \pm SD	17.0 \pm 8.7
≤ 10 mm, N (%)	23 (22.8%)
10–30 mm, N (%)	69 (68.3%)
>30 mm, N (%)	9 (8.9%)
Tumor number*, single/multiple	80/21
One lesion	80 (79.2%)
Two lesions	15 (14.9%)
Three lesions	6 (5.9%)
Tumor location	
Cervical pleura	8 (7.9%)
Costal pleura	69 (68.3%)
Diaphragmatic pleura	7 (6.9%)
Mediastinal pleura	17 (16.8%)
Relationship to pleura	
Close to pleura (< 5 mm)	32 (31.7%)
Causing pleural indentation	22 (21.8%)
Involving the pleura	47 (46.5%)
Treatment	
MWA	58 (57.4%)
RFA	43 (42.6%)

MWA, microwave ablation; RFA, radiofrequency ablation; SD, standard deviation. *See Appendix.

of the ablation zone ($n = 16$). At 3, 6, 12, and 24 months, the overall LPFS rates were 86%, 77%, 75%, and 64%, respectively. Technique efficacy and short-duration follow-up of LPFS are shown in Table Table 2. After ablation, 32 (40.0%) patients were administered chemotherapy or targeted therapy and 4 (4.5%) were administered immunotherapy.

Side effects and complications

No ablation-related death occurred. The nine (10.11%) major complications included one chest abscess, five cases of pneumothorax requiring drainage, and three cases of hemothorax requiring blood transfusions and thoracic drainage. Table Table 3 shows the incidence of complications and associated factors. One patient experienced a serious cough with thick sputum and wheezing, shortness of breath, and chest tightness 20 days after ablation. A chest CT performed immediately revealed chest abscesses. A tube was placed to drain the abscesses, and the fungal infection was identified in the drainage liquid. The patient was administered antifungal therapy and the symptoms gradually disappeared. Follow-up CT confirmed the disappearance of the abscess.

Thirty-eight (37.6%) patients experienced fever and 12 patients (31.6%) had temperatures over 38°C. Most fevers were self-limiting within three to five days, but some were not relieved until post-procedure complications were solved. Pain was common within 48 hours from the procedure: 80 patients reported no pain or mild pain (VAS 0–4), 16 patients reported moderate pain (VAS 5–7), and five patients experienced severe pain (VAS 8–10). Patients with mild pain did not receive treatment, while moderate and severe pain was relieved by analgesics. Among the associated factors, the occurrence of major complications was the only significant factor related to an increased level of pain within 48 hours post-procedure ($P < 0.05$). The tumor size, relationship between the tumor and pleura, and tumor location did not impact the pain level post-procedure.

Discussion

Surgery remains the primary therapy for the cure of lung cancer; however, $< 20\%$ of patients are candidates for surgical resection. Previously, patients with unresectable lung cancer could only receive traditional radiotherapy and chemotherapy, but thermal ablation has recently been shown to be safe and effective for the treatment of lung cancer.¹⁵ However, tumor location is closely associated with therapeutic efficacy and complications.^{3,10} Subpleural lung cancers including tumors under the cervical, costal,

Table 2 Technique efficacy and short-duration follow-up of LPFS

Characteristics	Complete ablation		3 months LPFS rate (%)	6 months LPFS rate (%)	12 months LPFS rate (%)	24 months LPFS rate (%)
	rate	<i>P</i>				
Total	88 (87.1%)		86	77	75	64
Tumor origin						
Primary	21 (87.5%)	0.629	83	69	69	60
Metastasis	67 (87%)		87	80	76	67
Treatment						
MWA	49 (84.5%)	0.356	86	78	72	72
RFA	39 (90.7%)		86	76	76	62
Tumor size						
≤ 10 mm	22 (95.7%)	0.008	80	74	65	65
10–30 mm	61 (88.4%)		87	79	79	65
>30 mm	5 (55.6%)		100	75	75	75
Tumor number						
Single lesion	69 (86.3%)	0.724	90	79	76	73
Two lesions	14 (93.3%)		58	58	58	58
Three lesions	5 (83.3%)		100	100	100	100
Tumor location						
Cervical pleura	8 (100%)	0.433	87	87	87	52
Costal pleura	60 (87.0%)		83	68	68	68
Diaphragmatic pleura	5 (71.4%)		100	100	100	100
Mediastinal pleura	15 (88.2%)		92	92	83	73
Relationship to pleura						
Close to pleura (< 5 mm)	30 (93.8%)	0.204	87	87	81	61
Causing pleural indentation	20 (90.9%)		78	60	60	60
Involving the pleura	38 (80.9%)		88	77	69	69

LPFS, local progression-free survival; MWA, microwave ablation; RFA, radiofrequency ablation.

diaphragmatic, and mediastinal pleura exhibit different characteristics during local thermal ablation. Furthermore, the relationships between the tumors and pleura also influence the procedure. This study analyzed local thermal ablations of all kinds of subpleural lung cancers, observing a complete ablation rate of 87.1%. The LPFS rates were 86%, 77%, 75%, and 64% at 3, 6, 12, and 24 months, respectively.

There is no exact definition for subpleural lung cancer. Hou *et al.* defined nodules at a distance of < 3 cm from the chest wall as subpleural lung malignancy.¹² Okuma *et al.* reported that patients could experience severe pain during RFA when the distance between the tumor and the chest wall was < 1 cm.¹⁸ Gillams *et al.* described peripheral lung cancer as tumors at a distance from the pleura of < 5 mm.¹³ To ensure success, the peripheral margin of the ground-glass opacity should expand > 5 mm beyond the pre-procedure tumor borders during ablation. When the distance between the tumor and pleura is < 5 mm, the pleura may be damaged by the high temperature, resulting in severe pain or other complications. Therefore, our study defined subpleural lung cancer as cancer within 5 mm of the pleura at any distance.

Peripheral tumors reportedly yield better results than those located centrally. Hiraki *et al.* reported increased recurrence in central versus peripheral tumors.¹⁹ Gillams *et al.* reported the best results for ablation of tumors located within 5 mm of the pleura.¹³ They explained that this finding was the result of the relative ease of targeting, the absence of larger vessels, and the reduced possibility of a pneumothorax, which would increase the ablation difficulty. In our study, the complete ablation rate was 87.1%. Tumor size was the most important factor influencing technique efficacy ($P < 0.05$). For lung cancer measuring > 30 mm, the complete ablation rate was only 55.6%. For lung cancer measuring < 30 mm, the complete ablation rate was 90.22%. The reduced power and duration used to protect the chest wall might have contributed to the lower complete ablation rate. When the tumor was adhered to the pleura, the rate was 93.8%, but in the presence of pleural indentation, the rate was 90.9%. Surprisingly, a complete ablation rate of 80.9% was achieved for lung cancer involving the pleura, which is much higher than predicted. This indicates that thermal ablation could be an appropriate treatment even for tumors involving the pleura.

Table 3 Incidences of complications and associated factors

Characteristics	Major complications	Pneumothorax	Pleural effusion	Infection	Bleeding	Moderate and severe pain
Total	9 (10.1%)	20 (22.5%)	31 (34.8%)	5 (5.6%)	3 (3.4%)	21 (23.6%)
Treatment						
MWA	4 (6.9%)	11 (19.0%)	17 (29.3%)	2 (3.4%)	0	10 (17.2%)
RFA	5 (11.6%)	9 (20.9%)	14 (32.6%)	3 (7.0%)	3 (7.0%)	11 (25.6%)
Tumor size						
≤ 10 mm	3 (13.0%)	8 (34.8%)	9 (39.1%)	0	0	4 (17.4%)
10–30 mm	5 (7.2%)	11 (15.9%)	17 (24.6%)	5 (7.2%)	3 (4.3%)	16 (23.1%)
>30 mm	1 (11.1%)	1 (11.1%)	5 (55.6%)	0	0	1 (11.1%)
Tumor number						
Single lesion	8 (10.0%)	17 (21.3%)	24 (30.0%)	5 (6.3%)	2 (2.5%)	19 (23.8%)
Two lesions	0	3 (20.0%)	4 (26.7%)	0	0	2 (13.4%)
Three lesions	1 (16.7%)	0	3 (50.0%)	0	1 (16.7%)	0
Tumor location						
Cervical pleura	0	2 (25.0%)	1 (12.5%)	1 (12.5%)	0	0
Costal pleura	7 (10.1%)	15 (21.7%)	22 (31.9%)	3 (4.3%)	2 (2.9%)	15 (21.7%)
Diaphragmatic pleura	1 (14.3%)	1 (14.3%)	3 (42.9%)	0	1 (14.3%)	2 (28.6%)
Mediastinal pleura	1 (5.9%)	2 (11.8%)	5 (29.4%)	1 (5.9%)	0	4 (23.5%)
Relationship to pleura						
Close to pleura (< 5 mm)	3 (9.4%)	9 (28.1%)	8 (25.0%)	2 (6.3%)	1 (3.1%)	9 (28.2%)
Causing pleural indentation	0	2 (9.1%)	4 (18.2%)	1 (4.5%)	0	3 (13.6%)
Involving the pleura	6 (12.8%)	9 (19.1%)	19 (40.4%)	2 (4.3%)	2 (4.3%)	9 (19.2%)

MWA, microwave ablation; RFA, radiofrequency ablation.

During and after the procedure, thermal ablation of subpleural tumors can lead to serious pain because of the massive intercostal nerve branches located between the chest wall and the pleura.²⁰ Several studies have attempted artificial pneumothorax under local anesthesia. Hou *et al.* performed MWA in 9 patients with 10 subpleural lung tumors using artificial pneumothorax, and reported that the pain was relieved at an average rate of 94.66% and all lung tumors were ablated successfully.¹² Yang *et al.* compared MWA in 17 patients with and 20 patients without artificial pneumothorax and reported that artificial pneumothorax significantly decreased pain during and after procedures.²¹ Although artificial pneumothorax may decrease pain during thermal ablation, it may also increase the level of difficulty of the procedure. Under artificial pneumothorax, it is not easy to puncture the tumor precisely using a needle and subsequent electrode repositioning requires more time than usual. In our center, experienced anesthetists administered intravenous anesthesia to all patients. Anesthetic dose adjustment allowed all patients to tolerate the pain during the procedure. Among the categorical variables, major complications were significantly associated with post-procedure pain. Therefore, in most situations, severe pain after the procedure might be caused by complications and not by nerve injury. Severe post-procedure pain might be a symptom of major complications, which require careful treatment.

Our study separated subpleural lung cancers into lesions under the cervical, costal, diaphragmatic, and mediastinal pleurae. Because the subclavian and axillary vessels could be confused with muscles when puncturing the tumors in non-contrast enhanced CT, contrast-enhanced CT was necessary in cases of tumors under the cervical pleura to protect the large vessels. Brachial nerve injury was also avoided as it might substantially impair the patient's quality of life. Hiraki *et al.* reported four cases of brachial nerve injury caused by percutaneous RFA of apical lung cancer.²² Tumors under the costal pleura were the easiest location to puncture, with care to avoid damage to the intercostal artery. Many studies have shown that percutaneous ablation can be a safe and effective treatment for lung cancer adjacent to the pericardium.^{10,23} To protect the heart and large vessels, the electrode should be placed parallel to the heart surface. In addition, part of the phrenic and recurrent laryngeal nerves lie lateral to the mediastinal pleura, which may be damaged by the high temperature. Phrenic nerve injury was assumed as the cause of increased diaphragmatic level after ablation, while injury to the recurrent laryngeal nerve results in a hoarse voice or a brassy cough.²⁴ Tumors located in the basal parts of the lungs were the most difficult to successfully ablate because of the greatest excursions during the respiratory cycle.²⁵ In our study, the successful ablation rate was 71.4%, which was lower than in other locations. The diaphragm may also be damaged during the procedure, which could lead to

hernia.²⁶ To protect the diaphragm, power should be reduced in cases in which the treatment may be prolonged.

This study had several limitations. First, the levels of pain during the procedure were not recorded; however, all patients tolerated the pain to complete the thermal ablation under intravenous anesthesia. Second, the survival benefit of these patients was not evaluated because of the various tumor types involved.

In conclusion, thermal ablation therapy is a safe and effective treatment for subpleural lung cancers. Tumor size is the factor most significantly associated with technique efficacy and post-procedure pain indicates the possibility of major complications.

Acknowledgments

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Disclosure

No authors report any conflict of interest.

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Appendix Table 1 Additional data of tumor number

Number of ablated lesions during one ablation procedure†	Total number of patients	Number of subpleural lesions			Total number of subpleural lesions
		1	2	3	
1	77‡	80	/	/	80
2	9	3	6	/	15
3	3	1	1	1	6

†Including 101 subpleural lesions and 6 non-subpleural lesions. ‡Three patients received a second ablation procedure for another new subpleural lesion.

[Correction added on 30 May 2019, after first online publication: Appendix Table 1 has been added to provide more detail about Tumor number]