# Lung Cancer Ablation: What Is the Evidence?

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## Abstract

Percutaneous ablation of small non–small cell lung cancer (NSCLC) has been demonstrated to be both feasible and safe in nonsurgical candidates. Radiofrequency ablation (RFA), the most commonly used technique for ablation, has a reported rate of complete ablation of ~90%, with best results obtained in tumors <2 to 3 cm in diameter. The best reported 1-, 3-, and 5-year overall survival rates after RFA of NSCLC are 97.7%, 72.9%, and 55.7%, respectively. It is noteworthy that in most studies, cancer-specific survival is greater than overall survival due to severe comorbidities in patients treated with RFA for NSCLC. Aside from tumor size and tumor stage, these comorbidities are predictive of survival. Other ablation techniques such as microwave and irreversible electroporation may in the future prove to overcome some of the limitations of RFA, namely for large tumors or tumors close to large vessels. Stereotactic body radiation therapy has also been demonstrated to be highly efficacious in treating small lung tumors and will need to be compared with percutaneous ablation. This article reviews the current evidence regarding RFA for lung cancer.

**Keywords**
- lung cancer
- non–small cell lung cancer
- radiofrequency ablation
- interventional radiology

**Objectives:** Upon completion of this article, the reader will be able to discuss the currently available evidence supporting the role of RFA in the treatment of lung cancer.

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Surgical resection is the current standard of care for patients with stage I or II non–small cell lung cancer (NSCLC). However, even in the early stage of the disease, a subset of patients with NSCLC are ineligible for surgery due to severe medical comorbidities. If left untreated, survival of patients with stage I or II NSCLC have a median overall survival of 14.2 months, with 53% of patients dying from their cancer.[1] Percutaneous image-guided ablation, including radiofrequency ablation (RFA),is a therapeutic option in such nonsurgical patients. Current published data are composed of retrospective studies in heterogeneous populations, with many series including both NSCLC and lung metastases, making analysis of the currently available data difficult.

## Rationale

Local efficacy of RFA in destroying lung tumors has been demonstrated in animals where RFA has been applied to lung VX2 tumor models to demonstrate feasibility of ablation and possibility of complete ablation.[2] More recently, histologic proof of complete tumor destruction after a single session of RFA was demonstrated in 9 patients where percutaneous RFA was performed before surgical resection of lung metastases.[3]

The lungs provide a unique environment for RFA under computed tomographic (CT) guidance. First, there is an excellent contrast ratio between tissue of the targeted tumor, aerated lung, and the metal of the needle, which is enhanced by the ability to provide multiplanar imaging for accurate evaluation of needle placement and electrode deployment.

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Second, site-specific differences favor lung tumors for energy deposition due to heat insulation and low electric conductivity provided by aerated lung around the tumor. Indeed, it has been demonstrated that a given quantity of radiofrequency current produces a larger volume of ablation in the lung than in subcutaneous tissues or in kidney.[4] Third, excellent tolerance of RFA applied in NSCLC, with relatively few side effects, allows for aggressive treatment in nonsurgical candidates.

## Results

### Local Efficacy

A review of 17 of the most recent publications of lung RFA including primary lung tumors and lung metastases demonstrated a median reported rate of complete ablation of 90%, with a range of 38 to 97%.[5] According to several reports with a prolonged imaging follow-up, tumors <2 cm can be successfully ablated in 78 to 96% of cases.[6–10] A statistically significant lower success rate of ablation is reported for tumors >2 to 3 cm.[6–9] In one early report of lung RFA, complete necrosis was attained in all 6 tumors (100%) <3 cm, but in only 6 of 26 (23%) larger tumors ($p < 0.05$).[11] All subsequent series confirmed that the risk of incomplete local ablation is linked with tumor size. Moreover, the rate of incomplete ablation is highly dependent on the ratio of the volume of ablation relative to the tumor volume, which has an impact on ablation margins.

It is clear that adequate margins of ablation are a key for success. A ratio between the area of RFA-induced ground-glass opacity and the tumor area before treatment of at least 4:1 is correlated with a significantly higher rate of complete ablation at 18 months than when this ratio is <4:1 (96% and 81% rates of complete ablation, respectively) ($p = 0.02$).[6] Ground-glass opacity margins have been reported absent in 85% of post-RFA CTs of incompletely ablated tumors.[12] In the same study, the receiver operating characteristic analysis constructed from recurrences, according to the minimal ground-glass opacity width after ablation, confirmed the usefulness of the ablation zone as a predictor of recurrence; the threshold of 4.5 mm demonstrated a specificity for local recurrence of 100%. These results clearly emphasize the need for oversizing ablation zones relative to tumor volume to obtain safety margins that guarantee success. Consequently, because RFA tools provide volumes of ablation with a diameter of ~4 to 5 cm, this may provide an explanation of why tumors <3 cm result in a better complete ablation rate.

It is known from pathologic evaluation of microscopic tumor extension in 354 NSCLCs that the ablation margin needed for different histologies of NSCLC differ.[13] A 5-mm margin covers 80% of the microscopic extension for adenocarcinoma and 91% for squamous cell carcinoma. To account for 95% of the microscopic extension, a margin of 8 mm and 6 mm must be used for adenocarcinoma and squamous cell carcinoma, respectively.[13] No difference has been demonstrated in regard to the relative risk of local progression for a given tumor type as demonstrated in a series of RFA for 252 lung tumors that included lung cancer ($n = 35$) and metastasis from colorectal cancer ($n = 117$), renal cell carcinoma ($n = 49$), lung cancer ($n = 23$), and hepatocellular carcinoma ($n = 28$).[14]

In treating large tumors, one of the limitations of RFA is that only one probe can be activated at any given time; consequently, overlapping ablation zones with subsequent probe repositioning are needed to create larger volumes of ablation. Microwave ablation (MWA), introduced relatively recently for lung ablation, carries the advantage of simultaneous delivery of energy through several probes activated at the same time. Additionally, a single probe has been shown to create slightly larger volumes of ablation when compared with RFA. In one animal study, a mean diameter of ablation of 32.7 ± 12.8 mm perpendicular to the feeding point of the MWA antenna was demonstrated.[15] In the same study, simultaneous activation of three antennae provided an ablation zone measuring 54.8 ± 8.5 mm perpendicular to the feeding point.[15] Such large ablation volumes offer hope for improvement of local tumor control rates for larger tumors. Wolf et al evaluated 50 patients including 30 with NSCLC who received 66 ablation sessions for tumors up to 5 cm in diameter (mean size: 3.5 cm ± 1.6) that included the use of multiple antennae in 47% of tumors >2 cm (two antennae were used in 5%, three antennae in 27%, four antennae in 9%, and multiprobe loop antenna in 6%). In this study, the overall local recurrence rate was 26%, but tumors >3 cm remained a predictive factor for recurrent disease ($p = 0.01$).[16]

Contact between targeted tumors and a large adjacent vessel (>3 mm) has been reported by several authors as a negative predictive factor for complete tumor ablation in lung.[7,17] Percutaneous balloon occlusion of the involved pulmonary artery branch during lung RFA has been reported in animal studies to improve the shape and volume of ablation.[18] To our knowledge, the only clinical series consisting of five patients receiving percutaneous lung RFA with balloon occlusion of the segmental pulmonary artery reported poor tolerance, with lung atelectasis occurring the month following RFA in three patients (60%), need for hospital readmission in two patients (40%), and persisting occlusion of the balloon occluded vessel at 3 months in four patients (80%). Positron emission tomography (PET)/CT at 12 months, however, demonstrated, complete ablation in five of five tumors.[19] By working at higher temperature,[20] MWA has been demonstrated to lower convective cooling close to large vessels in animal studies,[21,22] which could be a solution to the difficulties in obtaining complete ablation close to large vessels. Such benefit has yet to be demonstrated in clinical practice.

Electroporation is a nonthermal ablation process that results in apoptosis by irreversibly opening cell pores by delivering a short electric pulse of high voltage (1500 V/cm) to the target region.[23] Because electroporation provides a nonthermal lethal zone, the ablation zone is not impacted by convection cooling resulting in no thermal damage to vulnerable structures as demonstrated in animal studies performed in healthy lung parenchyma.[24,25] Studies on lung tumor models are lacking, but investigators are hopeful that additional studies will be able to reproduce the promising results obtained in the liver and pancreas.[26–28] Early clinical results have

been reported on patients with lung metastases with some late recurrences in the ablation zone.[29]

## Survival

Survival data for RFA of NSCLC are scarce due to the relative novelty of the technique that was first reported in the lung in 2000.[30] One of the earliest reports of 75 primary NSCLC patients (75% stage IA and 25% stage IB) demonstrated a median survival of 29 months (95% confidence interval [CI], 20 to 38 months) with a 1-, 2-, 3-, 4-, and 5-year overall survival of 78%, 57%, 36%, 27%, and 27%, respectively.[31] Median survival for stage IA was 30 months, and 25 months for stage IB. Better survival was reported for tumors $\leq$3 cm, with a survival rate close to 50% at 5 years.[31] The same team reported combined radiation therapy and RFA in 41 patients with NSCLC (stage IA, $n = 21$; stage IB, $n = 1$; stage IIB, $n = 3$). In this study, the 27 patients with the largest tumors received external-beam radiation (66 Gy) and the 14 patients with tumors <3 cm received brachytherapy through the puncture tract used for RFA. This combination treatment seems to improve results in NSCLC, with 57% survival at 3 years. The median survival was 34.6 $\pm$ 7 months for tumors >3 cm, and 44.4 $\pm$ 5.4 months for tumors $\leq$3 cm ($p = 0.08$).

More recent reports tend to demonstrate improvement in survival when compared with earlier series. This improvement can be explained by multiple factors such as improvement in techniques, increase in experience by operators, and better patient selection. Indeed, Kodama et al published impressive results with 1-, 3-, and 5-year overall survival rates of 97.7%, 72.9%, and 55.7%, respectively, in 44 consecutive patients treated with RFA for 51 recurrent NSCLCs after surgery. Mean lesional diameter of 1.7 $\pm$ 0.9 cm (0.6 to 4.0) was reported in this study.[32] Size as a prognostic factor was confirmed with 1-, 3-, and 5-year overall survival rates of 100%, 79.8%, and 60.5%, respectively, in patients with tumors measuring <3.0 cm, compared with 1-year and 3-year overall survival rates of 83.3% and 31.3% in patients with tumors measuring 3.1 to 4.0 cm. Palussière et al reported results in the same range in 135 patients with 135 NSCLCs, including 124 tumors with histologic proof.[33] The 1-, 3-, and 4-year overall survival rates were 89.6%, 57.8%, and 55.2%, respectively. Lesional size was predictive of disease-free survival, with a hazard ratio of 1.6 for a threshold of 2 cm, and interestingly, patients >70 years of age demonstrated a significantly better disease-free survival than younger patients, with a hazard ratio of 0.62 for patients <70 years of age. This unexpected result of longer survival for older patients is likely explained by selection criteria, with younger patients having more associated comorbidities and older patients more frequently referred for RFA. Indeed, lung RFA for NSCLC is usually performed in nonsurgical patients with severe comorbidities; it is important to note that deaths reported in the literature are not typically related to cancer progression but to comorbidities. Simon et al reported 40 deaths during the follow-up 82 RFA for NSCLC, with only 19 deaths (47.5%) related to tumor progression.[34] In the RAPTURE multicenter study, comorbidities explain the gap between overall survival and cancer-specific survival.[10] Indeed, overall survival was 70% (95% CI, 51 to 83%) at 1 year and 48% (30 to 65%) at 2 years, whereas cancer-specific survival was 92% (78 to 98%) at 1 year and 73% (54 to 86%) at 2 years in patients with NSCLC treated with RFA.

It has been recently demonstrated that the Charlson Comorbidity Index (CCI) is a strong predictive factor for survival in patients treated with RFA for NSCLC.[34] The index is one of the most widely used clinical indices for the evaluation of comorbidities (►**Table 1**).[35] Using this index, Simon et al retrospectively reviewed a group of 82 patients treated with RFA and demonstrated a 3-year overall survival (OS) of 50.6%.[34] Gender, stage, histology, and high CCI scores were each associated with significantly impaired survival ($p < 0.001$ in all cases). When factoring in covariables such as age, tumor stage >IB, squamous histology, and gender, multiple Cox regressions showed that an increasing CCI score was significantly associated with an increased risk of death (hazard ratio 1.3). A CCI score $\geq$5 (OS: 10.43 months; 95% CI, 7.61 to 19.85) was associated with significantly impaired mortality, compared with patients who had a CCI grade of 1 to 2 (OS: 55.5 months; 95% CI, 39.46 to 64.02) or a CCI grade of 3 to 4 (OS: 36.62 months; 95% CI, 25.54 to 58,29). No significant difference was observed between CCI grades 1 to 2 and 3 to 4.[34]

**Table 1** Charlson Comorbidity Index scoring system

| Condition | Score |
|---|---|
| Myocardial infarct* | 1 |
| Congestive heart failure | 1 |
| Peripheral vascular disease | 1 |
| Cerebrovascular disease | 1 |
| Dementia | 1 |
| Chronic pulmonary disease | 1 |
| Connective tissue disease | 1 |
| Ulcer disease | 1 |
| Mild renal disease | 1 |
| Mild liver disease | 1 |
| Diabetes without end-organ damage | 1 |
| Hemiplegia | 2 |
| Moderate to severe renal disease | 2 |
| Diabetes with end-organ damage | 2 |
| Any tumor or prior history of tumor† | 2 |
| Leukemia | 2 |
| Lymphoma | 2 |
| Moderate to severe liver disease | 3 |
| Metastatic solid tumor | 6 |
| Acquired immunodeficiency virus | 6 |

Note: A score >5 has been associated with significantly worse mortality rates.

*Myocardial infarction includes coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and angina pectoris.

†Except basal cell carcinoma.

**Table 2** Summary of recent publications on radiofrequency ablation of non–small cell lung cancer

| Study | *N* | Tumor size | OS 1 y (5) | OS 2 y (%) | OS 3 y (%) | OS 5 y (%) |
|---|---|---|---|---|---|---|
| Simon et al[31] | 75 | 2.7 (0.6–8.5) | 78 | 57 | 36 | 27 |
| Grieco et al[41] | 41 | NA | 87 | – | 57 | – |
| Lencioni et al[10] | 33 | 2.2 ± 0.7 | 92 | 73 | – | – |
| Palussière et al[33] | 127 | 2.1 ± 0.6 | 90 | 70 | 58 | – |
| Kodama et al[32] | 44 | 1.7 ± 0.9 | 97.7 | | 72.9 | 55.7 |
| Simon et al[34] | 82 | NA | 77.1 | 62.1 | 50.6 | 20.7 |

Abbreviations: OS, overall survival; NA, not applicable.
*Combination of radiofrequency ablation and external radiation therapy or brachytherapy.

Comparative studies of RFA with other treatments of NSCLC are sparse, with most studies containing biases and small populations, lowering study power. Recently, 64 patients medically unfit for standard resection with biopsy-proven stage I NSCLC were offered sublobar resections ($n = 25$), RFA ($n = 12$), or percutaneous cryoablation ($n = 27$).[36] The group found no statistically significant differences in 3-year survival for sublobar resections, RFA, and cryoablation (87.1%, 87.5%, and 77%, respectively). In the same study, no difference was found in 3-year cancer-specific and cancer-free survival rates (90.6% and 60.8% for surgery, 87.5% and 50% for RFA, and 90.2% and 45.6% for cryotherapy). The hospital stay was significantly longer for sublobar resections (6 days) than for RFA (1.8 days) or cryoablation (2 days). Another study compared surgical resection and RFA for treatment of 22 patients with stage I NSCLC including RFA patients ($n = 8$) matched with patients in the surgery group ($n = 14$) on variables such as gender, age, and stage.[37] The overall survival of RFA and surgery were 33.2 ± 7.9 months and 45.5 ± 7.2 months, respectively, with a trend but no statistically significant differences between the two groups ($p = 0.054$). ►**Table 2** summarizes the survival data from the literature.

## Tolerance and Complications

The expected postablation course includes mild to moderate postprocedural pain during the 2 to 7 days following ablation. This pain can be managed with oral analgesics. Mild dyspnea is common, and symptoms may warrant nasal or mask administration of oxygen. Fever with a temperature <38°C is also common the week following ablation. Most patients are discharged the next day if no pleural drain is present.

Tolerance of the technique in terms of respiratory function has been reported to be excellent, with no changes in post-ablation pulmonary function tests when evaluated prospectively at 1 month[6] and at 12 months.[10] Most recently, mild impairments of vital capacity and forced expiratory volume at 1 second ($FEV_1$) at 3 months was correlated with severe postablation pleuritis and an ablated parenchymal volume >20 $cm^3$ as independent risk factors.[38] In the same report, emphysema was significantly associated with larger ablation volume ($p = 0.029$), and a trend was found between emphysema and severe pleuritis ($p = 0.052$). The number of punctures ($p < 0.02$) and previous systemic chemotherapy ($p < 0.05$) were significant risk factors for aseptic pleuritis.[39]

Patients with $FEV_1$ as low as 0.8 L/second have been treated with no post-RFA complications or worsening of respiratory function.[6] Not surprisingly, some compromised patients will have temporary worsening of respiratory function with the need for oxygen therapy from 1 day to 3 weeks. To our knowledge, there have been no reports of patients requiring long-term or permanent oxygen therapy as a result of RFA. Consequently, it is difficult today to place a clear lower threshold of respiratory function for lung RFA.

Reported outcomes and tolerance of single-lung patients treated with RFA are variable. Simon et al reported a 2.6% mortality rate (4 of 153) related to RFA in a series of heterogeneous patients, but it is noteworthy that 2 of the 4 patients who died were single-lung patients.[31] Our group reported specifically about single-lung patients treated with RFA, with a multicenter experience of 15 single-lung patients including 11 NSCLC treated without major complication.[40] A 12% rate of minor hemoptysis and 6% pulmonary infection rate were noted, and pneumothorax was found in 37% of ablations. The median overall hospital stay for this patient population was 3 days.

## Conclusion

RFA is a promising treatment for small size NSCLC in nonsurgical candidates. Treatment of tumors >3 cm might require the use of other ablative techniques still in evaluation today.

In the future, RFA should be compared with stereotactic body radiation therapy, which also demonstrates a high local control rate. Whether RFA can be compared with surgery in very early stage NSCLC remains to be evaluated.

Today RFA is mostly used as a standalone technique, with the main objective of complete destruction of tumor cells in the targeted volume. Future treatment strategies should investigate combination therapies with radiation therapy[41] or systemic therapies; improved tumor control with RFA by combining with targeted therapies has already been demonstrated in animal studies.[42]

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