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# Percutaneous thermal ablation of primary lung cancer

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**Abstract** Percutaneous ablation of small-size non-small-cell lung cancer (NSCLC) has demonstrated feasibility and safety in nonsurgical candidates. Radiofrequency ablation (RFA), the most commonly used technique, has an 80—90% reported rate of complete ablation, with the best results obtained in tumors less than 2—3 cm in diameter. The highest one-, three-, and five-year overall survival rates reported in NSCLC following RFA are 97.7%, 72.9%, and 55.7% respectively. Tumor size, tumor stage, and underlying comorbidities are the main predictors of survival. Other ablation techniques such as microwave or cryoablation may help overcome the limitations of RFA in the future, particularly for large tumors or those close to large vessels. Stereotactic ablative radiotherapy (SABR) has its own complications and carries the risk of fiducial placement requiring multiple lung punctures. SABR has also demonstrated significant efficacy in treating small-size lung tumors and should be compared to percutaneous ablation.


Surgical resection is the current standard of care for patients with stage I or II non-small-cell lung cancer (NSCLC). Even in the early stages of the disease, however, a subset of patients with NSCLC is ineligible for surgery due to severe medical comorbidities, primarily associated with deterioration in lung function curtailing the necessary resection. Minimally invasive therapy has been developed to give these nonsurgical candidates a curative treatment option, including stereotactic ablative radiotherapy (SABR), percutaneous

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image-guided ablation including radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, and irreversible electroporation (IRE). RFA has been the primary technique used and reported for thermal ablation of the lung, with numerous publications and a large volume of data. MWA, IRE, and cryoablation are more recent treatment options.

## Rationale

The local efficacy of RFA in destroying lung tumors has been shown in animals when RFA has been applied to VX2 lung tumor models to demonstrate the feasibility of ablation and the possibility of complete ablation [1]. More recently, histological evidence of complete tumor destruction after a single session of RFA has been provided for nine patients for whom percutaneous RFA was performed before surgical resection of the lung metastases [2].

The lung provides a unique environment for RFA under computed tomography (CT) guidance. Firstly, there is an excellent contrast ratio between the targeted tumor tissue, aerated lung, and metal of the needle, making it possible to provide multiplanar imaging for accurate assessment of needle placement and electrode deployment. Secondly, site-specific differences within lung tumors facilitate energy deposition due to the heat insulation and low electric conductivity provided by the aerated lung around the tumor. It has been demonstrated that a certain amount of RF current produces a larger volume of ablation in the lung than in subcutaneous tissue or the kidney [3].

## Treatment and image guidance

CT is currently the most accurate image-guidance technique for lung RFA, with real-time CT enabling quick needle placement and making the procedure more comfortable for the operator. A shorter procedure time has been reported for cone-beam CT (CBCT) [4] but it does not enable rapid acquisition/reconstruction and can be problematic when a moving target tumor is displaced by the needle or a pneumothorax. Multiplanar reconstruction is required to assess the appropriate needle positioning relative to tumor margins in all planes. When the needle was deemed to be centered on axial CT image, multiplanar and volume-rendered analysis reclassified the needle position from centered to marginal or from marginal to outside in 44% of RF procedures [5]. When using needles with expandable electrodes, puncturing the tumor with the electrode shaft is not necessary for small tumors provided that the deployed arrays are encompassing the tumor, with one array through the tumor and an ablation volume containing the tumor. A carbon dioxide injection between the parietal and visceral pleura can be used to separate a sub-pleural tumor from the parietal pleura or mediastinum to avoid collateral damage during ablation of sub-pleural tumors.

Usually, the lungs are treated separately a few weeks apart to avoid life-threatening complications from bilateral adverse events, such as bilateral massive hemorrhage or pneumothorax. Single-session bilateral treatment has been reported in patients who completed treatment of the first lung with no CT-depicted complications.

The use of conscious sedation was associated with peri-procedural pain in 29% of cases with 3% of treatments being interrupted due to pain [6], and stopped due to intractable coughing in 5/30 patients [7]. The technique's feasibility under general anesthesia is reported to be as high as 97% [8].

## Local efficacy

A review of 17 reports of lung RFA, including primary lung tumors and lung metastases, demonstrated a 90% median reported rate of complete ablation, although the figures range from 38% to 97% [9]. Tumors of less than 2 cm can be completely ablated in 78—96% of cases according to several reports with extended imaging follow-up [8,10—14], while lower success rates are reported for larger tumors [8,10—12]. The ablation safety margins are key to success. A ratio of RFA-induced ground glass opacity to tumor area of 4 or more is correlated with a significantly higher rate of 96% complete ablation versus 81% when this ratio is below 4 [8]. The ROC analysis constructed from recurrences, according to ground glass opacity minimal width after ablation, confirmed the ablation zone's usefulness as a predictor of recurrence, with an estimated cutoff of 4.5 mm for a specificity of 100% (i.e. no local recurrence). When using an expandable multi-tined needle array, finally, a diameter of electrode array at least 10 mm larger than the target tumor has been reported as a predictor of success with less than 10% local recurrence for arrays at least 10 mm larger and approximately 30% local recurrence when the array was less than 10 mm larger than the target tumor [15]. The aforementioned results clearly show the need for oversizing the ablation zone relative to tumor volume in order to obtain safety margins that guarantee success. It is known from pathologic evaluation of 354 cases of NSCLC that a 5 mm margin covers 80% of the microscopic extension for adenocarcinoma and 91% for squamous cell carcinoma, and that to take into account 95% of the microscopic extension, margins of 8 mm and 6 mm must be chosen for adenocarcinoma and squamous cell carcinoma respectively [16].

One of the drawbacks of monopolar RFA is that only one probe can be activated at one time, and so overlapping ablation zones with subsequent probe placement are needed to create a larger ablation volume. Microwave ablation offers the advantage of simultaneous energy delivery through several probes activated at the same time, if needed. A single MWA probe covered a slightly larger ablation volume when compared to RFA in an animal study that demonstrated a mean ablation diameter of $32.7 \pm 12.8$ mm perpendicular to the feeding point of the MWA antenna [17]. In this study, simultaneous activation of three antenna provided an ablation zone measuring $54.8 \pm 8.5$ mm perpendicular to the feeding point [17]. 50 patients, including 30 with NSCLC, received 66 microwave ablation sessions for tumors up to 5 cm (mean size $3.5\ \text{cm} \pm 1.6$) including multiple antenna in 47% of tumors larger than 2 cm (two antennae were used in 5% of cases, three antennae in 27%, four antennae in 9%, and multi-probe loop antenna in 6%) [18]. The overall local recurrence rate was 26%, but a diameter larger than 3 cm remains a predictive factor for recurrent disease ($P = 0.01$). One difficulty of MWA is that a single system provides different ablation volumes and shapes for a given power and treatment time and the ablation volumes are not round in shape [19]. In addition, first-generation MWA lacks reproducibility because MWA is highly dependent on tissue parameters including permittivity and this permittivity even changes during delivery of the ablation. Some recent improvements in the technology are making MWA more reproducible and rounder in shape [20].

Cryoablation has been explored more recently in lung tumors and treatment algorithms have been improved with the use of triple-freeze treatment, which allows for a larger iceball [21,22]. Recently, cryoablation of lung metastases showed promising local tumor control (94.2%) at 12 months in a phase II multicenter study, including 40 patients with 60 metastases measuring $1.4 \pm 0.7$ cm (range 0.3—3.4) [23]. A further benefit of cryoablation is the relatively fast scaring of the ablation zone when compared with RFA. Of 79 tumors monitored by CT following cryoablation, all the ablation zones were enlarged on day 0, and the size transition varied on day 1 and at week 1, but 86% of the tumors (68 of 79) showed continuous size reduction after 1 month. Ten of the eleven ablation zones that showed significant enlargement greater than 1.25 times the initial size of the ablated tumor after six months were later proven to be local progression [24].

Contact between the targeted tumor and a large vessel (>3 mm) has been reported by several authors as a negative predictive factor of complete tumor ablation in the lung [10,25]. Percutaneous balloon occlusion of the relevant pulmonary artery branch during lung RFA reported in a small clinical series of five patients resulted in poor tolerance, although PET-CT at 12 months demonstrated complete ablation in all five tumors [26]. MWA, by working at higher temperatures [27], has been associated with lower convective cooling close to large vessels in animal studies [28,29] and could overcome the difficulties in obtaining complete ablation close to large vessels, but such benefits have not been demonstrated in clinical practice.

Electroporation is a non-thermal ablation process that creates apoptosis by irreversibly opening the cell pores with an electric pulse of high voltage (1500 V/cm) and short duration [30]. Irreversible electroporation for 23 tumors close to large vessels has a 61% local recurrence rate in one report. The authors hypothesize that the energy distribution with current IRE probes is highly sensitive to air exposure, resulting in uneven distribution of the electric energy in the tumor tissue [31].

### Survival

One of the earliest reports of 75 primary NSCLC patients (75% stage IA and 25% stage IB) demonstrated median survival of 29 months (95% CI: 20—38 months) with one-, two-, three-, four-, and five-year overall survival of 78%, 57%, 36%, 27%, and 27% [32]. Median survival for stage IA was 30 months versus 25 months for stage IB. Better survival was reported for tumors 3 cm or smaller with a survival rate close to 50% at five years [32]. More recent reports tend to demonstrate improvement in survival when compared with earlier series, probably due to technical improvements, more experienced operators and better patient selection. Kodama et al. published impressive results with one-, three-, and five-year overall survival rates of 97.7%, 72.9%, and 55.7% respectively in 44 consecutive patients treated with RFA for 51 recurrent NSCLC after surgery with a mean diameter of $1.7 \pm 0.9$ cm [0.6—4.0] [33]. Size was a prognostic factor with one- and three-year overall survival rates of 100% and 79.8% respectively in patients with tumors measuring less than 3.0 cm, compared to 83.3% and 31.3% for tumors larger than 3 cm. Recently, Palussiere et al. reported results in 87 patients from two comprehensive cancer centers with N0 NSCLC measuring a median of 21 mm (range 10—54 mm) treated with RFA ($n = 82$) or MWA ($n = 5$). The rate of local tumor progression was 21.1% at three years [34]. Five-year OS (overall survival) and DFS (disease-free survival) were 58.1% and 27.9% respectively. Gender ($P = 0.044$), pathology, and tumor size >2 cm were prognostic factors for DFS. In multivariate analysis, pathology and tumor size >2 cm were independent prognostic factors for DFS.

Besides disease characteristics, patients' general condition and comorbidities are highly predictive of survival. Simon et al. reports 40 deaths during RFA follow-up for 82 cases of NSCLC, with only 19 deaths related to tumor progression and the Charlson Comorbidity Index a strong predictive factor of survival [35]. A Charlson Comorbidity Index score $\geq 5$ (OS = 10.43 months) was associated with significantly impaired mortality compared with patients with a grade of 1—2 (OS = 55.5 months) or 3—4 (OS = 36.62 months). No significant difference was observed between Charlson Comorbidity Index grades 1—2 and 3—4.

Comparative studies of RFA with other NSCLC treatments are rare, with many biases and small numbers of patients, thus lowering the studies' power. 64 patients with biopsied stage I NSCLC who were medically unfit for standard resection were offered sublobar resections ($n = 25$), RFA ($n = 12$) or percutaneous cryoablation ($n = 27$) [36]. There were no differences in the probability of three-year survival for sublobar resections, RFA, and cryoablation, which were 87.1%, 87.5%, and 77% respectively. In the same study, no difference was found in three-year cancer-specific and cancer-free survival with 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 the 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 tumor node metastasis stage [37]. The overall survival rates with RFA and surgery were $33.18 \pm 7.90$ months and $45.49 \pm 7.21$ months, with no significant differences ($P = 0.054$) between the two groups.

## Tolerance and complications

Mild to moderate post-procedural pain following lung ablation can be managed with oral analgesics. Mild dyspnea is now a common symptom and may warrant nasal or mask administration of oxygen for a few hours but most patients are discharged the next day if no pleural drain is present. Some patients with compromised respiratory function prior to treatment will experience a temporary worsening of symptoms and require oxygen therapy lasting from one day to three weeks. It is difficult to define a clear lower threshold of respiratory function (spirometry) for lung RFA. There are no changes in the post-ablation respiratory test when evaluated prospectively at one month [8] and twelve months [13], although mild impairments of vital capacity and forced expiratory volume in one second (FEV1) at three months are correlated with severe post-ablation pleuritis and an ablated parenchymal volume >20 $cm^3$ [38].

Patients with an FEV1 down to 0.8 L/s have been treated with no post RFA complications [8].

Chest tube drainage for pneumothorax is necessary in 4—16% of patients.

420 consecutive patients with 1,403 lung tumors who underwent 1000 RFA sessions had 9.8% of grade 3 and 4 complications including aseptic pleuritis (2.3%), pneumonia (1.8%), lung abscess (1.6%), and pneumothorax requiring pleural sclerosis (1.6%) followed by bronchopleural fistula (0.4%) [39]. Previous external beam radiotherapy ($P < 0.001$), emphysema ($P < 0.02$) and age ($P < 0.02$) were significant risk factors for septic complications. They found 0.4% deaths per session including 0.3% interstitial pneumonia and 0.1% hemothorax. These risk factors for septic complications are also hallmarks of NSCLC and explain why NSCLC patients treated with RFA have a higher risk of complications and death when compared to patients with lung metastases of other origins. The use of prophylactic antibiotics before treatment and one day to one week after treatment has been reported but with no proven benefits to infectious complications.

Reports of severe hemorrhage during ablation involve tumors in contact with the hilum [40,41]. Delayed major hemorrhage has been reported due to false aneurysm of the pulmonary artery successfully treated with coil embolization in one case [18,42]. It is worth noting that after MWA, on follow-up imaging cavity changes were found in 43% cases of ablation and 6% resulted in documented infectious complications including one abscess and one pneumonia [18]. Furthermore, the abscess eroded a mural blood vessel and was responsible for fatal hemoptysis.

Rarely reported complications include two cases of non-fatal major air embolism as a consequence of RF probe placement [43,44]. The embolism was not linked to the RFA delivery but to the electrode insertion creating a bronchovascular pathway. Only one case of cerebral infarction following lung RFA can be found in the literature [45], although asymptomatic micro-bubble embolism shown by duplex ultrasound has been reported during lung RFA in humans [46].

Single-lung patients have been treated with RFA with 2.6% RFA-related deaths [32]. A multicenter trial involving fifteen single-lung patients, including eleven with NSCLC, treated with RFA did not result in major complications [47], but minor hemoptysis (12%), pulmonary infection (6%), and a median hospital stay of three days.

## Other local treatment of NSCLC

Surgery remains the gold standard for NSCLC. In nonsurgical candidates with small-size tumors and negative work-up, percutaneous ablation can compete with stereotactic ablative radiotherapy (SABR). Although SABR has been advocated for being non-invasive, placement of the fiducial marker needed for SABR resulted in a 33.3% rate of pneumothoraces (major, 13.3%; minor, 20%), with 30.5% minor peritumoral alveolar hemorrhage and 2.9% major bleeding when treating 105 patients with lung tumors [48]. Chang et al. pooled the analysis of two independent, randomized, phase III trials of SABR in patients with T1—2a (<4 cm), N0M0, operable NSCLC (ClinicalTrials.gov/STARS: NCT00840749; ROSEL: NCT00687986), which closed early due to slow accrual [49]. 58 patients were enrolled from 38 institutions over a 66.3-month period and randomly assigned (31 to SABR and 27 to surgery). Estimated overall survival at three years was 95% in the SABR group compared with 79% in the surgery group (HR 0.14 [95% CI 0.017—1.190], log-rank $P = 0.037$). Recurrence-free survival at three years was 86% in the SABR group and 80% in the surgery group (HR 0.69 [95% CI 0.21—2.29], log-rank $P = 0.54$). 10% of patients in the SABR group had grade 3 treatment-related adverse events including chest wall pain (6%), dyspnea or cough (3%), fatigue (3%), and rib fracture (3%). Grade 3 events in the surgery group were dyspnea (15%), chest pain (15%), and lung infections (7%) [50]. This publication prompted a flurry of letters to the editor stressing that the study was unpowered, with 11% of patients assigned to surgery not receiving treatment and thoracotomy used instead of VATS.

## Conclusion

Thermal ablation is a promising treatment for small-size NSCLC in nonsurgical candidates and RFA has been studied in a relatively large population. Today, the size of the target tumor remains the main driver of success and patient selection with a limited tumor size allowing for an 89% local control rate, although new technologies may increase the tumor size suitable for local ablation. In the future, ablation should be compared with stereotactic body radiation therapy, which has also demonstrated a high local control rate [51]. Whether RFA can be compared with surgery in very early stage NSCLC remains to be evaluated. The optimal technique will have to demonstrate efficacy, safety, and cost effectiveness, but randomized studies can be difficult, as highlighted by the early closure of clinical trials aiming to compare surgery and SABR in NSCLC.

Today RFA is largely used as a standalone technique, with the main objective being complete destruction of the tumor cells in the targeted volume. Future treatment strategies should investigate combination therapies with radiation therapy or systemic therapies that are highly feasible due to their low invasiveness.

**Take-home messages**

- Complete ablation of RFA is approximately 80—90% in tumors smaller than 2—3 cm in diameter, and is therefore a valid treatment option in nonsurgical candidates.

- The highest one-, three-, and five-year overall survival rates reported following RFA in NSCLC are 97.7%, 72.9%, and 55.7%. It is worth noting that in most studies cancer-specific survival is much greater than OS due to severe comorbidities in treated patients.
- Alternative ablation techniques to radiofrequency, such as microwave and cryoablation, may help to overcome the limitations of RFA in the future, particularly for large tumors or tumors close to large vessels.
- Stereotactic ablative radiotherapy (SABR) has also demonstrated significant efficacy in treating small-size lung tumors, but has its own complications and carries the risk of fiducial placement requiring multiple lung punctures.

## Disclosure of interest

The authors declare that they have no competing interest.

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