



REVIEW / *Interventional imaging*

# Percutaneous thermal ablation of lung tumors – Radiofrequency, microwave and cryotherapy: Where are we going?



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## KEYWORDS

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**Abstract** Main indications of percutaneous pulmonary thermal ablation are early stage non-small cell lung carcinoma (NSCLC) for patients who are not amenable to surgery and slow-evolving localized metastatic disease, either spontaneous or following a general treatment. Radiofrequency ablation (RFA) is the most evaluated technique. This technique offers a local control rate ranging between 80 and 90% for tumors <3 cm in diameter. Other more recently used ablation techniques such as microwaves and cryotherapy could overcome some limitations of RFA. One common characteristic of these techniques is an excellent tolerance with very few complications. This article reviews the differences between these techniques when applied to lung tumors, indications, results and complications. Future potential associations with immunotherapy will be discussed.

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In the last 20 years, different technologies have been developed and used for image-guided percutaneous thermal ablation of tissue including mainly radiofrequency ablation (RFA), microwave ablation (MWA) and cryotherapy [1]. These image-guided ablation techniques have emerged as a safe,

cost-effective, minimally invasive treatment alternative for patients who do not require surgery. Since 2000, RFA has been the first-choice technique to be proposed for lung tumors and to date, it has been the most evaluated technique.

Despite apparent drawbacks such as insulating effects intrinsic to lung tissue, these techniques treat lung tumors particularly well. Another positive point to underline with lung is the excellent tumor visualization due to the important differences in density between the tumor and the non

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tumoral lung parenchyma. Targeting and device positioning can be optimal and then accurately assessed on multiplanar reconstructions.

In this article, we review the main results obtained using RFA, MWA and cryotherapy in patients with primary and secondary lung tumors and discuss future potential association with immunotherapy.

## Basic concepts of RFA, MWA and cryotherapy

RFA is an electric current-based technique that heats tissue due to fractioning electrons at a frequency of 400 KHz. This electronic agitation is mainly present at the interface with the device. The thermal effect is due both to active heating along the device and passive progressive diffusion of the temperature through to the target. The conduction of heat is crucial to be able to treat a sufficient volume. In lungs, the air-filled spaces insulate the heated volume thermally and electrically therefore, thermal inertia is low and electrical impedance is high compared to other tissues. It has been demonstrated that tissue characteristics affect ablation outcomes, for example, ablation volume is larger for a given quantity of energy in the lung than in the kidney or soft tissues [2]. An expandable multitined array with an electrode diameter at least 10 mm larger than the target tumor has been shown to successfully ablate tumors with < 10% local recurrence. Conversely, an array diameter < 10 mm larger than the target tumor resulted in 30% local recurrence [3].

MWA is a field-based technology. The electromagnetic field created around the ablation device varies from 915 MHz to 2450 MHz, which heats tissue through rotating water molecules, resulting in frictional heat. In contrast to RFA, temperature rises higher and more rapidly due to the friction of water molecules, and the active heating zone is wider allowing better thermal build-up. Consequently, this type of thermal ablation relies less on conduction into tissues, and may not be influenced as much by the heat-sink effect that limits RFA thereby yielding a more uniform ablation zone [4].

Cryotherapy damages and kills tumoral cells through a complex combination of different mechanisms during tissue freezing and thawing. At  $-20^{\circ}\text{C}$ , cells are killed by protein denaturation and membrane disruption. The successive repetition of the freeze-thaw cycles increases cellular injury with formation of both intra- and extra-cellular ice crystals. Indirect actions include vasoconstriction and occlusion of blood vessels, secondary osmotic changes and local tissue edema resulting in hypoxic tissue injury and coagulative necrosis. The alveolar structure, mostly composed of air, can interfere with the creation of the ice ball, limiting the freezing. This could be resolved by water; consequently, to increase the water content in the area of treatment, a first short freezing and thawing is carried out. Following that, fluid and hemorrhage replace the air and fill the alveoles resulting in an estimated 20-fold increase of thermal conductivity [5]. This results in a larger ice ball during subsequent freezing phases. Hence, a triple-freeze cycle are recommended by Hinshaw et al. [5]. The authors also noted that a triple-freeze protocol could be exploited not only to create larger zones of ablation but also to shorten the overall procedure time.

Cryoablation preserves collagenous architecture of the area of ablation [6], which may be advantageous in treating lesions adjacent to the bronchi. As a result, cryotherapy could be recommended for treatment of central tumors. Furthermore, cryotherapy may result in less pain in the treatment of tumors along the pleura and chest wall [7].

## Patient selection and procedure

Main indications of percutaneous thermal ablation of lung tumors are non-small cell lung cancer at early or advanced stages and metastatic disease from different primaries. To date, there are no guidelines regarding the maximum number of pulmonary metastatic tumors that can be treated. Thermal ablation can also be proposed as a salvage therapy when a local recurrence occurs within a previously radiated site [8]. An impaired pulmonary function is not an absolute contraindication. However, severe lung emphysema with bullae is a contraindication due to the risk of intractable fistula and respiratory failure. Ideally, the procedure is performed under general anesthesia, in particular, for subpleural tumors. Interrupted treatments with severe pain in this indication were reported; consequently, epidural anesthesia was often used [9]. General anesthesia with high-frequency jet ventilation allowing repeated breath-holds immobilize the target and may facilitate positioning of ablation probes. When a general anesthesia is not possible or available, cryotherapy that creates less procedural pain due to local anesthetic effects of freezing, could be an interesting option in this indication.

The work-up is generally the same as for all methods of percutaneous thermal ablation. Procedures are performed under computed tomography (CT) or cone beam CT (CBCT) guidance. CBCT with live three-dimensional (3D) needle guidance is a useful and user-friendly technique for percutaneous pulmonary thermal ablation [10].

## Non-small cell lung carcinoma (NSCLC) treatment

Besides surgery, and stereotactic body radiotherapy (SBRT) percutaneous thermal ablation is one of the therapeutic options for early-stage NSCLC [11]. Current American College of Chest Physicians (ACCP) guidelines include percutaneous ablation as a therapeutic option in medically inoperable patients with stage I NSCLC. Thermal ablation techniques do not provide regional control of the disease and hence, do not allow controlling lymph nodes. Surgery that gives access to lymph node resection remains the gold standard for treatment. However, many patients are not candidates for surgery due to co-morbidities and represent indications for non or mini-invasive techniques. SBRT has even been accepted for operable patients. Despite better surveillance and screening, about 30% of NSCLCs are discovered at advanced-stage. With the development of targeted therapies and immunotherapies, improvement in survival have been observed. Consequently, strategies combining an aggressive local treatment to a systemic treatment have become possible for some patients.

## Stage 1 NSCLC

To date, RFA has been the most evaluated technique. Tumor size is a limitation, local efficacy is worse for T2 tumors (largest diameter > 3 cm) [12]. In Beland et al.'s series, an incomplete local treatment resulted in 10.1% recurrence at 1 year and 28% at 2 years [13]. In a retrospective multicenter study, local recurrence per patient was 11.5% at 1 year, 18.3% at 2 years and 21.1% at 3 years [14]. The tumor size was the only significant factor associated with a local failure rate, with tumors > 2 cm in size being approximately 3 times more likely to recur. In the only prospective published series to date, the local tumor recurrence-free rate was 68.9% at 1 year and 59.8% at 2 years and was worse for tumors >2 cm [15].

In a series of 47 patients with stage I medically inoperable NSCLC treated with MWA, the local control rates at 1, 3, 5 years following MWA were 96%, 64% and 48%, respectively [16]. Local control was similar to that of RFA series. In a recent publication by the same group, the Epidermal Growth Factor Receptor (EGFR) status was not related to response to MWA, and response to MWA was a predictor of survival [17]. Zhang et al. reported the results of cryoablation in 46 patients with NSCLC [18]. Among them, 12 had stage I NSCLC and a complete response was achieved in 83.7% patients. In another series, 22 patients with stage I NSCLC were treated with cryotherapy [19]. A total of 25 sessions for 34 tumors (mostly  $\leq 2$  cm) were performed and local progression was observed in one tumor (3%). In this series, majority of the tumors were T1a, which could explain a better local control compared to other thermal ablation techniques.

An early publication on RFA reported a 5-year overall survival (OS) rate of 27% [12], which subsequently reached 58.1% in a latter study [14] probably due to better selection of patients and more technical experience. The results of the American prospective trial, Z4033 from American college of surgeons oncology group [15], demonstrated an OS rate of 86.3% at 1 year and 69.8% at 2 years. In the same study, patients with tumors < 2 cm and a performance status of 0 or 1 achieved a statistically significant improved survival of 83% and 78%, respectively at 2 years. Given these results, the ACCP included RFA in their recent recommendations for tumours < 3 cm [20]. Following MWA, the OS rates at 1, 2, 3 and 5 years were 89%, 63%, 43%, and 16%, respectively. Tumors  $\leq 3.5$  cm were associated with better survival than were tumors > 3.5 cm [16]. Following cryotherapy, the 2- and 3-year disease-free survival rates were 78% and 67%, respectively and OS rates of 88% at 2 years and 88% at 3 years were reported [19].

## Other indications in NSCLC

Ablation can also be proposed as a salvage therapy when a local recurrence occurs within a previously radiated site [8]. However, patients who have had prior radiation may be at increased risk of larger ablation zones and possible vascular injury due to radiation-associated vasculopathy. MWA, which is more powerful than RFA, could be cautiously used in this indication. For patients who underwent RFA as a supplemental therapy for tumors in partial response or stable diseases after first-line chemotherapy, a lengthened progression-free survival was observed [21].

The survival of patients with advanced NSCLC has increased with the development of targeted therapies. Tyrosine kinase inhibitors (TKIs) target mutant EGFR. However, development of acquired resistance limits the utility of TKI therapy. Yu et al., demonstrated that a local therapy followed by continued treatment with an EGFR TKI is well tolerated and associated with long PFS and OS [22]. A recent study has evaluated MWA's performance as maintenance therapy following first-line treatment for patients with advanced NSCLC [23]. The results showed that patients benefited from MWA as maintenance, both in local control and survival, and that it was superior to conventional maintenance therapy with improved survival and well-tolerated complications [23].

In another study, the curative effect of cryoablation combined with TKI for patients with advanced NSCLC was investigated [24]. Eighteen patients received the TKI gefitinib, while another 18 patients were treated with cryoablation prior to the administration of TKI. There was an improvement in the rates of partial regression, stabilization of disease and progression of disease in the cryoablation + TKI group at the end of the 6 months of TKI treatment. Moreover, the 1-year survival rate in this group was significantly higher than in the group with TKI alone. This suggests that cryoablation therapy combined with gefitinib could improve the effects of treatment and the prognosis of patients with advanced NSCLC.

## Metastatic disease

Lung is a frequent site of metastatic disease in around a 1/3 of cancer patients. A local treatment is given whenever possible, in particular, for primaries with poor response to systemic treatment (thyroid, sarcoma). For colorectal cancer, in the last fifteen years, there has been an improvement in the systemic treatment with new drugs and monoclonal antibodies. This resulted in a better response rate and consequently, the therapeutic strategies have evolved. The indication of a local treatment is not only proposed to patients with a very slow-evolving disease (oligometastatic disease) but also for more advanced disease following a systemic treatment with a good response. The current priority in the management of metastatic patients is to improve the patient quality of life (QoL) while trying to prolong their survival. To this effect, the concept of therapeutic de-escalation that includes the provision of therapeutic pause or maintenance therapy has recently been introduced without deleterious impact on survival [25]. For these patients, a local treatment could maintain therapeutic breaks and lengthen the period without systemic treatment. Until now, prospective randomized studies have not been conducted to demonstrate the benefit of a local treatment in this indication. Therefore, in the recently published ESMO consensus guidelines, such treatments have been recommended for patients with lung-only or oligometastases of the lung [26].

Surgical lung metastasectomy has demonstrated good efficacy with a 5-year-OS rate in colorectal cancer of 53.5% as reported by Lida et al. [27] and 67.8% after R0 resection as highlighted in a literature review [28]. Similar to NSCLC, RFA has been the most evaluated technique. One of the largest published series in 566 patients with 1037 metastases

treated with RFA has shown similar survival results compared to surgery [29]. A median OS of 62 months was obtained after RFA, and 5-year OS was 51.5%. Local tumor progression rates per tumor was 5.9%, 8.5%, 10.2%, and 11.0% at 1, 2, 3 and 4 years, respectively. Size of tumor is predictive of local tumor progression, consequently, RFA is an option for treatment of lung metastases <2–3 cm [30]. Interestingly in this series, 24% of the initially treated patients were retreated by RFA up to four times, resulting in 44.1% 4-year control rate of lung metastatic disease. In the case of oligorecurrent disease, good tolerance of RFA may offer possible multiple sessions of treatment in order to delay a systemic treatment resumption.

Several publications have reported efficacy and tolerance of MWA. Most of these series have included both primary and metastatic tumors. Belfiore has shown that four lesions (all >4.3 cm) out of 69 needed to be retreated 20 days after the ablation due to peripheral focal areas of residual tumor [31]. In a retrospective study, the results of laser-induced thermotherapy, RFA and MWA were compared [32]. Data were collected from 231 CT-guided ablation sessions performed on 109 patients presenting with lung metastases from colorectal cancer. Local tumor control was achieved in 69.2% of the lesions treated with RFA, and in 88.3% of the lesions treated with MWA. Local tumor control revealed a potential advantage in using MWA, however RFA local control in this series was slightly inferior to ones obtained in other series [29,33]. Moreover, Vogl et al., have shown that whatever the ablation method, the local control of tumors located <5 cm from the hilum was worse than the local control of tumors located >5 cm [32].

A prospective multicentre trial with cryotherapy was carried out to treat 60 metastatic lung lesions in 40 patients, with a mean tumour size of  $1.4 \pm 0.7$  cm [34]. The local tumor was controlled in 56/58 (96.6%) and 49/52 (94.2%) at 6 and 12 months, respectively. One-year overall survival rate was 97.5%.

## Follow-up

Different to resection, the ablation zone will remain in the lung and a careful long-term follow-up is required to monitor its evolution and detect a possible incomplete ablation. The extent of the ablation area and inflammatory reactions are visible immediately in adjacent normal lung tissue and appear as ground glass opacities. It has been demonstrated that the extension of ground glass opacities with a margin of at least 5 mm is predictive of an effective RFA [35].

Interestingly, cryoablation shows a rapid involution in the ablation zone size on CT [36]. Identification of incomplete ablation or local treatment failure is possible by 6 months.

Following RFA, ablation zones may appear as nodular to fibrous scar depending on the initial diameter of the treated tumor [37]. Cavitation, a consequence of a bronchial fistula, accounts for 10–30% of the evolution [37,38].

## Complications

Irrespective of the technique, pneumothorax is the most frequent complication with a chest tube drainage varying from

10–50% following RFA procedures. Delayed pneumothorax is rare and often is a sign that a broncho-pleural fistula has occurred. The use of multiple devices (cryotherapy, MWA, multipolar RFA), increases the theoretical risk of pulmonary complications.

In large series, complications for each RFA session in 420 consecutive patients who underwent 1000 RFA sessions in a single center have been assessed [39]. Grade 3 and 4 complications (9.8%) were noted 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%). Puncture number ( $P < 0.02$ ) and previous systemic chemotherapy ( $P < 0.05$ ) were significant risk factors for aseptic pleuritis. Previous external beam radiotherapy ( $P < 0.001$ ), emphysema ( $P < 0.02$ ) and age ( $P < 0.02$ ) were significant risk factors for septic complications. Emphysema was a significant risk factor for pneumothorax requiring pleural sclerosis ( $P < 0.02$ ). The risk factors (previous external beam radiotherapy, emphysema) for septic complication and pneumothorax are more frequent in patients with primary lung cancer, and explain why they have higher risk of complications and death when compared to metastatic patients. In these fragile patients, MWA may be used cautiously given the higher temperatures, to avoid potential risks of persistent air leak and bronchopleural fistula. As highlighted by Hinshaw et al., an awareness of the asymmetric long ablation zone associated with certain MWA devices is important to avoid extension of the ablation zone into the chest wall and consequently pain, pleural fistula and skin burn [40]. Hence, a longer trajectory through the lung is often preferable to a shorter path.

Cryotherapy, which is more respectful of the cellular architecture in frozen tissues [6], could be an option in these fragile patients. However, a disadvantage to this technique is that additional probes are often needed. In a study including 193 cryoablation sessions for 396 lung tumors in 117 consecutive patients, a greater number of cryoprobes was a significant predictor of pneumothorax ( $P = 0.001$ ), of pleural effusion ( $P = 0.001$ ) and for hemoptysis ( $P < 0.001$ ) [41]. Higher rates of hemorrhage have been reported in literature regarding lung cryoablation, exposing patients to increased risk for hemoptysis [42].

Freezing is also associated with cell membrane disruption and a release of intracellular contents. A rapid release of cellular debris into the systemic circulation causes the release of cytokines that can result in systemic complications following cryoablation (cryoshock). A similar phenomenon is rare with heat-based ablation. Although mainly described after hepatic cryoablation [43], an excessive inflammatory response with an acute respiratory distress syndrome has been described in a case report following percutaneous cryotherapy for a lung metastase [44]. It is also important to note that this patient presented risk factors with emphysema and a previous radiotherapy for an esophageal cancer.

Some more rare complications with RFA have been described [45], emphasizing the need to be aware of organs at risk especially, the nerves and the diaphragm. To avoid nerve or diaphragmatic damage, a separation from the ablation zone is warranted as much as possible; a systematically created artificial pneumothorax may help. Moreover, lung tumors are generally mobile and when using expandable RFA



electrodes and cryoprobes, it is possible to move the tumor from the vulnerable structure by pulling on the device.

## Future associations with thermal ablation

With the recent development of immunotherapy in the treatment of cancer from various origins, the activation of immune cells by thermal ablation techniques is an interesting area of research. The huge release of antigens during thermal ablation leads to the recruitment, differentiation, and activation of immune cells including T-, B-, Antigen Presenting Cells (APCs), and NK cells. Recruited APCs may uptake the tumor antigens and present them to naive T-cells resulting in the clonal expansion of tumor specific T- and B-cells. Tumor antigen specific T-cells and B cells along with the activation of innate immune cells may help eliminate the residual tumor cells at the ablated as well as distal sites. This native immune response, also called “abscopal effect” (literally, away from the scope), is therefore often insufficient to cause sustained regression of distant metastases.

Interestingly, cryotherapy differs from heat-based methods in their mode of tumor destruction. Cryoablation induces relatively much greater post-ablative immune response than RFA or MWA [46]. Hyperthermia based methods are responsible for protein denaturation that reduced the proportion of intact antigens and tumor material released into the blood circulation. Consequently, antigen loading is higher with cryoablation compared to RFA [47]. Freezing, on the other hand, maintains intact cytoplasmic organelles while disrupting the plasma membrane. As a result, majority of the released antigens are intact and nondenatured [48]. Some animal studies showed that cryotherapy is better than heat-based ablation for immune stimulation [49]. However, it should be considered that the development of the immune response is complex and may be affected by the rate of freezing, the total freezing time and the number of freeze-thaw cycles. A high freeze rate results in a significant increase in tumor-specific T cell numbers. In contrast, low freeze rate cryoablation resulted in an increase in regulatory T cells [50]. Obtaining a synergistic effect through a combinatorial approach with thermal ablation and immunotherapy could be promising and deserves further investigations.

## Conclusion

Local efficacy of RFA, MWA or cryoablation applied to lung tumors, appears comparable even though no randomized studies have been conducted to demonstrate this point. RFA is a robust technique and has the advantage of having been the most evaluated technique with favorable results. The theoretical superiority of microwave: higher and faster peaks of temperature have not shown different results from those already reported for radiofrequency ablation: tumor diameter (>3 cm) and proximity to a large vessel remain risk factors of incomplete treatment. Faster ablations could be achieved with MWA and, with the latest generation of devices, reproducibility of the ablation is better. Cryoablation could be interesting to use in some locations owing to the better preservation of the collagenous architecture. The use of multiple probes can be a disadvantage

for complications, but on the other hand, could be an advantage for larger tumoral volume. In the future thermal ablation should be compared to stereotaxic body radiation therapy, which has also demonstrated high local control rate. Considering the challenge of viewing some cancer as a chronic disease, future strategies should extend the indications in combining thermal ablation with systemic therapies. The low invasiveness and repeatability are major advantages to minimize toxicities. Combining thermal ablation and immunotherapy for a synergistic effect should be promising and deserves further investigations.

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## Disclosure of interest

The authors declare that they have no competing interest.

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