Thermal ablation of peripheral lung cancer: A narrative review of the role of bronchoscopic thermal ablation

Chayanon Songsomboon M.D.
Kamontip Kunwipakorn M.D.
Supparerk Disayabutr M.D.
Jamsak Tscheikuna M.D.

Division of Respiratory Disease and Tuberculosis, Department of Medicine
Faculty of Medicine Siriraj Hospital, Mahidol University

Introduction

The bronchoscopic techniques for diagnosing peripheral lung nodules have developed over time. The advanced techniques, including a smaller and more flexible bronchoscopy, a device for harvesting biopsies, and guidance techniques such as the use of guide sheath, radial endobronchial ultrasound (R-EBUS), cone-beam computed tomography (CT), fluoroscopy, and an electromagnetic navigation, enhance the diagnostic yield, especially when used simultaneously\(^1\). Bronchoscopic therapies have also been created and are already being used in humans, including Salvage radiation ablation, CT-assisted transbronchial brachytherapy, CyberKnife robotic radiosurgery, and cryotherapy\(^1\text{-}\text{3}\). However, the data on bronchoscopic therapies in lung cancer are limited in contrast to percutaneous CT chest guiding approaches, including percutaneous radiofrequency ablation, microwave ablation, and cryoablations\(^4\text{-}\text{6}\). The purpose of this article was to ascertain the development of peripheral lung cancer therapy using an endoscopic method, based on the current evidence of percutaneous CT-guided thermal ablation.

Biological mechanisms of thermal ablation

Thermal ablation therapy began in 1850 with the introduction of frozen saline solutions for the treatment of advanced cancers of the prostate and uterus. Then, in 1926, radiofrequency ablation was used to resect brain tumors, and in 1990, percutaneous radiofrequency ablation was utilized to treat liver tumors for the first time\(^6\). Thermal ablation has significant advantages over surgery in terms of reduced morbidity, improved preservation of surrounding tissue, lower cost, shorter hospital stay, and intra-procedure visibility. While key limitations included the potential of incomplete ablation or recurrence, a less favorable treatment outcome, and the lack of comparable randomized controlled trials (RCT)\(^4\text{-}\text{6}\).
Thermal ablation techniques can be classified into two categories: those that use high- and low-temperature. In the group of high-temperature modalities, there are radiofrequency ablation (RFA), microwave ablation (MWA), and emerging technologies such as high-intensity focused ultrasound (HIFU) and laser ablation, as well as low-temperature modalities such as cryoablation. Only RFA, MWA, and cryoablation will be discussed in this section because they have several supported data.

Heat and cold temperatures will influence the tissues of the tumor and its surrounding areas by destroying and inhibiting tumor growth. The temperature change zone is divided into the central zone, the peripheral or transitional zone, and the surrounding tissue zone. The effect on each zone is different, with the central zone being directly affected by temperature changes, resulting in central necrosis, whereas the peripheral and surrounding zones are affected by indirect injury, which cells in the peripheral zone experiencing apoptosis or recovery, and cells in the surrounding zone being unaffected but potentially affected by the subsequent immunological change.

Thermal energy delivering by the probe or applicator tip causes the tissues to reach temperatures greater than 50-100°C. These result in loss of cell membrane integrity and permeability and mitochondrial dysfunction. Intracellular proteins and DNA are incapable of self-repair and thus harm the DNA polymerase enzyme leading to cell cytolysis. The peripheral zone is cooler than the central zone at 41-45°C. This heat can cause local damage, denaturation of hyaluronic acid, and chemokines, resulting in the secretion of various cytokines that stimulate inflammatory cells such as neutrophils, dendritic cells, and T cells to migrate to the area of local damage. Additionally, heat shock protein-70 (HSP70), which is normally found inside the cell, acts as an anti-apoptotic factor. However, when HSP70 is pushed further out of the cell, it has the ability to bind to tumor antigens and present them to dendritic cells for further destruction. Heat also causes vascular permeability in the surrounding zone. Vasodilation and subsequent reperfusion injury result in increased oxygen consumption and responsiveness of tissue in the area to oxygen-free radicals. Tumor antigen released following cell death is transported through the lymphatic system to normal tissue areas via the lymphatic system. To stimulate the immune system, immature dendritic cells bind to antigens and present them to naïve T cells for further degradation of foreign matter. The zone of hyperthermic ablation is shown in Figure 1.

**Figure 1.** The zone of hyperthermic ablation: The probe or applicator tip heats tissues to 50-100°C.

- a) Central zone, temperature changes in the central zone cause necrosis;
- b) Peripheral zone and
- c) Surrounding tissue zone, indirect injury causes apoptosis or recovery in peripheral zone cells while surrounding zone cells remain unaffected but may be affected by the subsequent immunological change.
Hypothermic ablation affects tissues in three zones as shown in Figure 2. The cold induces coagulation necrosis in the central zone via a solution-effect cell injury mechanism. When the cell is cooled to negative temperatures, the extracellular fluid crystallizes before the intracellular fluid due to the lipid bilayer covering the intracellular content. Extracellular fluid crystallization results in cell dehydration and a high extracellular solute concentration, resulting in the expulsion of intracellular content and eventually coagulation necrosis. When the cell’s exogenous intracellular content interacts with the immune system, it induces the release of a large number of cytokines, most notably IL-6, IL-1, and TNF, which can result in systemic inflammatory response syndrome (SIRS), multiorgan syndrome (MOS), and death. This phenomenon is referred to “cryoshock” \(^\text{2-8}\).

In peripheral zone, cold can injure the vascular system, resulting in platelet aggregation, microthrombosis, and local ischemia, as well as vasoconstriction, resulting in coagulation necrosis that is expanded. Moreover, if the blood supply reduced, the cells are ongoing apoptosis. In the surrounding tissue, the cells may be affected by reduced the blood flow causing cell hypoxia and causing cell injury. Whether a cell is damaged by necrosis or apoptosis (which is the death of cells naturally), it has different effects on the immune system. When cells necrose, the release of DNA, RNA, uric acid, HSP70, and HMGB1 stimulate DC activation and proliferation of activated T cells. These are immunostimulatory effects. Whereas apoptosis is simulated by DC, anergy and clonal deletion occur in the absence of T cell stimulation, thereby acting as immunosuppression \(^\text{6}\).

**Figure 2.** The zone of hypothermic ablation:

- **a)** Central zone, the cold causes coagulation necrosis.
- **b)** Peripheral zone, the cold can cause platelet aggregation, microthrombosis, and local ischemia.
- **c)** Surrounding tissue zone, the cold reduced vascular supply to cells, causing hypoxic injury. Whatever the cell injury that results in “necrosis,” “apoptosis,” or “hypoxia,” these alert the innated immune system to the systemic effect of hypothermic ablation.

Both heat and cold treatments can have an indirect effect on tumor cells by stimulating the immune system. This phenomenon is referred to “post ablative immunogenicity”. Because heat destroys the released intracytoplasmic material, it has a lower ability to stimulate the immune system while the intracytoplasmic content released after cooling was unaltered as a result, can boost the immune system more. Thermal ablation causes not only tumor destruction, but also immunomodulation, in which local inflammation stimulates the immune system, including induced systemic cytokine and stress response, recruitment and activation of immune effector cells, and activated antitumor adaptive immunity (CD4+, CD8+ T cells) in both animal and human studies \(^\text{6,8}\). Immunotherapy
is currently being employed, such as naïve DC injection to produce DC, ipilimumab to suppress T cell proliferation, and OK-432 to stimulate tumor-specific T cells and to induce greater T cell activation and proliferation, in combination with thermal ablation to boost therapeutic efficiency.\(^6\)

**Table 1.** Comparisons between percutaneous radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation

<table>
<thead>
<tr>
<th></th>
<th>RFA</th>
<th>MWA</th>
<th>Cryoablation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Principle of action</strong></td>
<td>Oscillating currents created tissue heating</td>
<td>Direct microwave energy created tissue heating</td>
<td>Gas cooling created ice crystal formation and osmotic shock</td>
</tr>
<tr>
<td><strong>Electromagnetic frequency</strong></td>
<td>3-300MHz</td>
<td>900-2,500 MHz</td>
<td>-</td>
</tr>
<tr>
<td><strong>Energy source</strong></td>
<td>EM energy</td>
<td>EM energy (dielectric hysteresis)</td>
<td>Argon or Nitrogen gas</td>
</tr>
<tr>
<td><strong>Ablation function</strong></td>
<td>Heating</td>
<td>Heating</td>
<td>Cooling</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>60-100 °C</td>
<td>&gt;100°C</td>
<td>&lt; -40°C</td>
</tr>
<tr>
<td><strong>Function</strong></td>
<td>Coagulation necrosis</td>
<td>Coagulation necrosis</td>
<td>Protein denaturation</td>
</tr>
<tr>
<td><strong>Ablation lesion</strong></td>
<td>Single lesion</td>
<td>Multiple lesion</td>
<td>Multiple lesion</td>
</tr>
<tr>
<td><strong>Procedural time</strong></td>
<td>-</td>
<td>Shorter than RFA</td>
<td>Longer than RFA</td>
</tr>
<tr>
<td><strong>Ablation volume</strong></td>
<td>-</td>
<td>More than RFA</td>
<td>More than RFA</td>
</tr>
<tr>
<td><strong>Procedural pain</strong></td>
<td>-</td>
<td>Less than RFA</td>
<td>Less than RFA</td>
</tr>
<tr>
<td><strong>Grounding pad injury</strong></td>
<td>Potential occurs</td>
<td>No pad used</td>
<td>No pad used</td>
</tr>
<tr>
<td><strong>Advantage</strong></td>
<td>- effective and safe</td>
<td>- More effective for cystic masses</td>
<td>- Larger ablation volume</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Less heat sink effect</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Less tissue charging</td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantage</strong></td>
<td>- Not suitable for mediastinum or lung apex due to non-target injury to neuro-vasculature structure and airway</td>
<td>- Limited data in safety and efficacy</td>
<td>- Limited data in safety and efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Longer procedural time due to freeze-thaw-freeze cycle</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Higher hemorrhagic risk secondary to lack of tissue cauterization</td>
</tr>
<tr>
<td><strong>Pneumothorax</strong></td>
<td>6-47%</td>
<td>3-64%</td>
<td>1-64%</td>
</tr>
</tbody>
</table>

**Thermal techniques**

The use of radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation, which have been available for some time, will be discussed and reviewed in both the percutaneous and bronchoscopy approach ablation using currently available data in this publication (Table 1 and 2).
Table 2. Comparisons between bronchoscopic radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation CT, computed tomography; ENB, electromagnetic navigation bronchoscopy; NA, no data available; VBN, virtual bronchoscopic navigation

<table>
<thead>
<tr>
<th></th>
<th>RFA</th>
<th>MWA</th>
<th>Cryoablation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current evidence</strong></td>
<td>- Animal studies</td>
<td>- Animal studies</td>
<td>- Animal studies</td>
</tr>
<tr>
<td></td>
<td>- Fresh human specimen</td>
<td>- Human (case report, series)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Human (case report, series)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Studies field</strong></td>
<td>Stage I NSCLC, Mediastinal LN Transbronchial Transparenchyma</td>
<td>Stage I NSCLC, Metastasis Transbronchial Transparenchyma</td>
<td>Transbronchial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Device</strong></td>
<td>Single or multiple electrodes</td>
<td>Single antenna</td>
<td>Single antenna</td>
</tr>
<tr>
<td><strong>Diameter</strong></td>
<td>1.3-3.0 mm</td>
<td>2.0 mm</td>
<td>2.4 mm</td>
</tr>
<tr>
<td><strong>Guidance</strong></td>
<td>ENB, VBN, radial EBUS, low dose CT</td>
<td>ENB, cone-beam CT, Fluoroscopy</td>
<td>ENB, cone-beam CT</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>70-100°C</td>
<td>60-100°C</td>
<td>- 130°C</td>
</tr>
<tr>
<td><strong>Procedural time</strong></td>
<td>20 min</td>
<td>20 min</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Ablation volume</strong></td>
<td>NA</td>
<td>Depending on the contraction percentage</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Procedural pain</strong></td>
<td>Fever, chest pain</td>
<td>Chest pain</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>- Local recurrence rate 82.6%</td>
<td>No recurrence</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>- Median progression free interval 35 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Overall survival 61.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Complication</strong></td>
<td>None</td>
<td>Pneumothorax (6.7%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Radiofrequency ablation

The use of vibrational frequencies to generate heat energy is known as radiofrequency ablation. Based on the physical principle of the electromagnetic spectrum, which has frequencies ranging from 3 Hz to 300 GHz. A tiny electrode cannot generate heat; instead, it vibrates and turns it into heat energy via dipole vibration, which conducts current through body tissues. As a result, the system must incorporate a generator to generate electromagnetic energy as well as a grounding pad located on the body to allow the tissues to act as a medium for carrying current.

According to the mechanism described above, RFA can destroy the tumor by causing tumor necrosis. The zone of ablation is determined by a variety of factors. Factors influencing coagulation necrosis include: tumor-related factors (size, site orientation, organ, and histology and biology) and technical factors (electrode, generator power, heat sink effect, and duration of ablation).

The zone of ablation is affected by the rate of temperature rise. A gradual increase in thermal energy results in a greater dead area than a rapid increase in heat energy. This is because the rapid increase in temperature rise.
temperature results in instantaneous tissue necrosis, and the scorched area acts as a heat insulator. The energy that accumulates in the subsequent time act as Desiccation or the energy that the subsequent charring is unable to extend, resulting in a smaller necrosis zone. Whereas a gradual increase in temperature will result in the expansion of necrosis zones. This is because the energy is gradually released from nearby tissues.

The zone of ablation is also affected by exposure to higher or lower temperatures. Such as 100°C for 1 minute versus 45°C for 15 minutes, may result in an even zone of necrosis, but overheating accelerates boiling, vaporization, and carbonization, and reduces energy transmission.

The types such as triaxial, slotted, and choked, the size and power such as 14-18 gauge, 200-250 W, 460-500 kHz power, and the number of electrodes, single or multi-tined RF electrodes, or the new technology such as internally cooled electrodes, which are cooled flanking the electrode, allowing for better temperature control, all affect the ablation zone. Using a single or multiple electrodes, a zone of necrosis typically occurs within a 1 cm surgical margin, but this is not always due to Induced coagulation necrosis = (energy deposit x local tissue interaction) – heat loss, where heat loss is caused by a phenomenon known as the heat sink effect, which occurs when heat is dissipated through a vessel that supplies that tissue, which frequently occurs in hypervascular tumors or with an abuts vessel greater than 3 mm. To overcome the heat sink effect, intravascular clamping, atrial embolization balloons, coils particles or lipiodol agents, transarterial chemoembolization, and pharmacological agents that slow blood flow, such as arsenic trioxide or halothane, can be used. Additionally, therapies to augment the efficacy of RFA are being developed, including anti-angiogenic agents such as soratinib, synergy with conventional therapies such as adjuvant chemotherapy, nanoparticle-deliver chemotherapies, thermosensitive liposomal doxorubicin, and radiotherapy.

Percutaneous RFA has been studied in patients with primary lung cancer, as well as those with secondary or metastatic lung cancer. Using changes in tumor size following RFA to determine a response to treatment should be interpreted cautiously. This could be because the nodule may grow larger in the first two months following the procedure. Generally, nodules are not significantly smaller or do not change over several years of follow-up. Following a 12-month follow-up period, the nodules were either 50.5% of fibrosis or 44.8% of nodules. The initial size of the nodule is predictive of its tendency to change. Therefore, it is important to remember that nodules can change after at least two months, and that treatment should be followed by continuous radiographic monitoring for a minimum of 12 months to assess response to treatment.

There is some evidence that percutaneous RFA is beneficial in the treatment of patients with stage I non-small cell lung cancer (NSCLC). The previous study has reported that stage I NSCLC patients undergoing percutaneous RFA had a treatment-specific 5-year survival rate of 27%, while surgical intervention and conventional radiotherapy had treatment-specific 5-year survival rates of 64.6% and 32%, respectively. Another retrospective study found that 1-year survival rates in primary lung cancer ranged between 78 and 83%. Percutaneous RFA appears to have a lower survival rate in patients with primary lung cancer.

The ALLiance trial enrolled 51 patients with inoperable stage IA NSCLC in 16 centers in the United States (US). They have reported an overall survival rate of 86.3% at one year and 69.8% at two years. Local
tumor recurrence–free survival rates were 68.9% at one year and 59.8% at two years, and were significantly lower for tumors > 2 cm\textsuperscript{20}. According to 3 prospective clinical studies which included 55 patients in the radiation therapy oncology group, 211 patients in the American College of Surgeons Oncology Group, and 51 patients in radiofrequency ablation, there was no difference in early morbidity, post-treatment adverse events, or overall 90-day mortality\textsuperscript{16}. These findings established that RFA is a single minimally invasive procedure that is well tolerated in medically inoperable patients and achieves a 2-year overall survival rate comparable to stereotactic body radiotherapy.

In terms of long-term safety and efficacy, research has indicated the benefit of percutaneous RFA for both primary lung cancer and lung cancer metastasis. A retrospective study of 153 patients admitted to a tertiary care hospital demonstrated that overall 1- and 5-year survival rates for stage I NSCLC were 78% and 27%, respectively, and rates for colorectal pulmonary metastasis were 87% and 57%, respectively\textsuperscript{24}. The RAPTURE study, a prospective cohort study in 7 centers across the US, Europe, and Australia, has reported overall survival of 70% at one year and 48% at two years in patients with NSCLC, and overall survival of 89% at one year and 66% at two years in patients with colorectal metastases, and 92% at one year and 64% at two years in patients with other metastases\textsuperscript{25}. A metastatic lung cancer study of 566 patients with 1037 metastases discovered a median overall survival of 62 months, where primary origin, disease-free interval, metastasis size, and number were all associated with overall survival in multivariate analysis, indicating that radiofrequency is a viable option for treating small lung metastases, defined as those less than 2-3 cm in diameter\textsuperscript{17}. Additionally, a prospective open-label trial of RFA was initiated on 148 nonsurgical candidates with lung metastases and revealed that 46% had a complete response, 26% had a partial response, 39% had stable sickness, and 16% had progressive disease. These findings established that RFA of lung metastases is associated with a high rate of long-term survival in non-surgical patients\textsuperscript{15}.

The primary complication rate of RFA was 9.8% in a single center experience study after 1,000 RFA sessions in 420 patients. The most common severe complications were aseptic pleuritis (2.3%), pneumonia (1.8%), lung abscess (1.6%), hemorrhage necessitating blood transfusion (1.6%), and pneumothorax necessitating pleural sclerosis (1.6%)\textsuperscript{26}.

**Bronchoscopic RFA**

Only a few researches refer to bronchoscopic RFA. The initial study aimed to create a device adapted from percutaneous RFA. Internal cooled electrodes with a 4-mm active tip (ablation tip of 4 mm and diameter of 1.67 cm) were created in 2007, allowing this type of electrode to avoid overheating and injuring normal tissue. The investigations determined that the cooled-RFA operated optimally at a power output of 30 W and a flow rate of 30 or 40 mL/min\textsuperscript{1}. As a result, it appears as though the internal cooled electrode could be a novel therapeutic tool for bronchoscopy\textsuperscript{27}. Additionally, a novel bronchoscopic catheter for transbronchial RF ablation of pulmonary nodules was tested in the ablation zones of tumor specimens utilizing a monopolar RF catheter in a working channel of 2.0 mm or bigger\textsuperscript{28}. At the distal end of the device, an 18-mm-long, uncooled, active electrode demonstrates that these electrodes are capable of creating ablation zones that are confined locally inside ex vivo human malignant lung tissues.

A comparative study of the properties of
internally cooled RFA electrodes in 10 patients with stage I NSCLC was conducted using three different catheters for CT imaging-bronchoscopy-guided RA. They compared electrode diameters of 10 mm, 8 mm, and 5 mm. The results indicate that when the 10-mm active tip was used, the ablated areas were significantly larger than when the 5-mm tip was used without complications during RFA. According to this study, the ablated patches grew in size when the tip length and ablation duration were increased. It may be concluded that CT imaging-guided, internally cooled RFA is a safe and practical therapy for local control in medically inoperable patients with stage I NSCLC39.

Following the development of a novel internally cooled RFA electrode appropriate for forceps channel bronchoscopy, a clinical experience with bronchoscopy-guided RFA under computed tomography (CT) monitoring was published for patients with peripheral-type NSCLC without lymph node involvement and distant metastases (T1N0M0), who were not candidates for surgery. Two of the three patients remained stable for 4 and 3 years, respectively, following bronchoscopy-guided RFA. One patient exhibited progressive illness. RFA was repeated in the same lesion and resulted in no change during a 1-year period. According to the case report, bronchoscopy-guided RFA is a safe and practical technique that may be effective for local control in medically inoperable patients with stage I NSCLC30.

In 2015, a study to determine the safety, efficacy, and feasibility of CT-guided bronchoscopy cooled RFA in patients with medically inoperable NSCLC using a cooled electrode catheter with a 10-mm active tip filled with five beads (diameter 1.67 mm) was conducted. A total of 28 bronchoscopy-guided cooled RFA operations were performed in 20 patients, yielding an 82.6 % local control rate, a median progression-free survival of 35 months, and a 5-year overall survival rate of 61.5 %. Although three individuals suffered an acute ablation-related response, including fever and chest discomfort, they recovered with conservative treatment without experiencing any further complications. It may be concluded that CT-guided bronchoscopy cooled RFA is a viable alternative therapy for patients with stage I NSCLC who are medically inoperable31.

Several studies demonstrated the use of bronchoscopic RFA in conjunction with other methods. Navigation bronchoscopy-guided RFA is a safe and effective treatment option for individuals who are not surgical candidates for stage IA lung cancer or lung metastases32. Three individuals had nonsurgical peripheral pulmonary tumors treated with a navigation bronchoscopy-guided RFA. Three months after RFA, two patients had a partial response, while another patient had a complete response. Six months after RFA, however, one patient with initial partial response progressed, but the remaining 2 patients lived one-year progression-free. None of the three people had any significant problems. Additionally, animal experiments were undertaken to establish strategies that may be applied in bronchoscopic RFA, such as percutaneous RFA in conjunction with transbronchial saline injection expanded the region of ablation in experimental research in swine using a single internally cooled electrode RFA (2-cm active tip, 17-gauge, and 15 cm in length). In comparison to percutaneous ablation, the volume of the coagulated region was substantially greater in the saline-injected group than in the conventional group33. Recently, a study in animal models demonstrated that EBUS-guided bipolar RFA is viable and capable of ablation of lung tumors and mediastinal lymph nodes under real-time ultrasound guidance34. Furthermore, a recent study published in 2021 discovered that the
innovative RFA system and catheter, when combined with automated saline microperfusion, is safe and viable. Additionally, bronchoscopic transparenchymal nodule access (BTPNA) may be beneficial in the treatment of lung cancers but required future research

Microwave ablation

MWA is a microwave ablation operation that utilizes the EMW 915 or 2,450 MHz frequency range, which lies between radio waves and infrared radiation. Microwave waves have the ability to penetrate tissue and alternate the intrinsic dipoles of molecules. Because the water molecule is strongly polar, it may flip 2-5 billion times every second, generating a temperature more than 60°C. Dielectric hysteresis is the term used to describe the interaction between water molecules and microwaves. The best electromagnetic absorbers are composed primarily of water, which is found in the majority of solid organs and tumors.

The primary advantages of MWA over RF lung tumor ablation include bigger ablation zones, faster heating periods, greater intralesional temperatures, less procedural discomfort, and less sensitivity to both intrinsic lung tissue insulating effects and those associated with tissue charring. MWA may create greater temperatures than RFA because they do not suffer from the heat sink effect, which is a significant restriction of RFA. By contrast, microwave transmission is neither impeded by air or the low water content of lung parenchyma, allowing for a more rapid deposition of energy capable of creating greater intratumorally temperatures and consequently a bigger zone of active heating.

Percutaneous MWA is indicated for early-stage primary lung cancer or for patients undergoing necrotic primary lung cancer. For instance, a retrospective analysis of 108 patients who had CT-guided percutaneous MWA for a single lung malignancy discovered a median time to tumor recurrence of 62 months and recurrence rates of 22%, 36%, and 44% at 1, 2, and 3 years, respectively. Complications included pneumothorax (32%), unexpected hospitalization (28 %), discomfort (20%), infection (7%) and post-ablation syndrome (4%).

Bronchoscopic MWA

There are few reports of studies utilizing this technique. However, in 2017, a novel flexible microwave applicator was developed which might be coupled with bronchoscopic imaging and software guidance to broaden the use of MWA as a therapy option. They designed the in vivo investigation, applied the applicator via 2-mm working channel, and evaluated the ablation zone and temperature profile using a two-dimensional-axisymmetric coupled Finite Element Method (FEM) electromagnetic-heat transfer model. They developed a prototype device based on characterizing predicted antenna radiation patterns, ablation size and shape, and optimizing antenna design for lung tissue. They then examined the device in ex vivo tissues to verify simulation results. However, no research on clinical result, safety, and effectiveness have been conducted.

In 2020, an animal study was conducted on bronchoscopically delivered MWA in an in vivo porcine lung model. Virtual bronchoscopy-guided MWA procedures were performed using 24-32 W power (at the applicator distal tip) delivered for 5-10 minutes and identified ablation sites within the lung parenchyma 5-24 mm from the airway wall. There was no evidence of pneumothorax or severe airway hemorrhage.
This study established the technical feasibility of safely ablating the lung parenchyma using microwave ablation under virtual bronchoscopic guidance in an in vivo swine lung model\textsuperscript{45}. The same year, a human study was published in which a 47-year-old woman underwent simultaneous treatment of multiple high-risk pulmonary nodules using a novel method involving MWA guided by electromagnetic navigation bronchoscopy (ENB) and video-assisted thoracoscopic surgery (VATS). MWA was done following the insertion of an antenna into the lesion via the working channel. MWA guided by ENB in combination with VATS was proven to be an alternate therapeutic method for many lung nodules at the same stage of the operation\textsuperscript{46}.

In 2021, case series of 38 patients with advanced NSCLC and lung metastases who had malignant endobronchial obstruction who were treated with transbronchial microwave ablation (TMA) under mild sedation and high FiO\textsubscript{2} was published. They compared two groups of patients with malignant central airway obstruction (CAO) who had respiratory failure at the time of TMA treatment and those who did not. There was no significant difference between groups in terms of the proportion of patients with recovered airway patency following the first session of TMA, the rate of TMA-related complications, and the overall survival. These results suggest that TMA treatment is well tolerated and can be successfully performed in patients with malignant CAO who had respiratory failure\textsuperscript{47}. A retrospective study described the use of TMA in lung nodules, mean size of 15.1 mm, with ENB guidance in 30 patients which resulted in 100% technical success rate. There was no noticeable impact of the heat sink effect. The overall complication was 3.33% which included pain (13.3%), pneumothorax which required drainage (6.67%), post-ablation response (6.67%), pleural effusion (3.33%), and hemoptysis. No progression of the nodules was demonstrated after a median of 12 months of follow-up\textsuperscript{48}.

**Cryoablation**

Since 1998, cryogens such as, Argon liquid (-185°C), and nitrogen liquid (-195.8°C) have been used via an external probe. Cryotherapy can have an effect on areas other than those treated with local irradiation. It is hypothesized that cryoablation leaves the cancer cells’ intracellular contents intact, allowing the immune system to initiate an immune-specific response, also known as the abscopal effect which termed cryo-immunotherapy.

There was limited evidence in using percutaneous cryoablation in primary and metastatic lung cancer\textsuperscript{49-53}. 187 patients who were not surgical candidates had percutaneous cryotherapy (PCT) guided by CT for treatment of thoracic cancer masses. They compared CT-visualized low-attenuating ice production following PCT. PCT coverage was 99% for peripheral masses less than 4 cm in diameter and 80 % for central masses greater than 4 cm in diameter. Within one week after PCT, area of necrotic cavitation was bigger than the initial size of lung mass in 80% of masses and was almost resolved in 7% of masses after three months. Pneumothorax occurred in 12\%\textsuperscript{53}. A study of 20 patients with metastatic lung cancer have reported 1-year survival rate was 89.4\%\textsuperscript{49}.

A study of 45 patients with NSCLC stage T1N0M0 who was performed ablative treatment using cryoprobes demonstrated 5-year overall survival, 5-year cancer-specific survival and 5-year progression-free survival of 67.8%, 56.6%, and 87.9%, respectively\textsuperscript{52}. A recent multicenter study targeted by interventional cryoablation evaluation (SOLSTICE) in 128 patients with lung metastasis found that the treated tumor had an 85.1% local recurrence-free
response at 12 months and 77.2% at 24 months after the initial treatment. Secondary local recurrence-free response was 91.1% at 12 months and 84.4% at 24 months following a second cryoablation therapy for recurrent malignancy. Overall survival rates at 12 and 24 months were 97.6% and 86.6%, respectively. The most serious complication, pneumothorax required pleural catheter placement, was 26%.

**Bronchoscopic cryoablation**

Bronchoscopic cryoablation has been rarely studied in humans. The recent study was conducted in animal models to determine the safety of procedure. Early experience in transbronchial cryoablation for malignant peripheral lung lesions (PPLs) was published in 2018. Cryoablation were performed on swine lungs using a rigid cryoprobe, 2.4-mm diameter. The probe was inserted into the distal bronchus from the right major bronchus through thoracotomy. The cryoprobe was removed after three freeze-thaw cycles. No major bleeding was noticed bronchoscopically in the airways. The core destruction zone of alveolar tissues was histologically identical to the thermal zone, whereas the conducting bronchus structure and associated pulmonary artery were unaffected.

In 2019, a flexible cryoprobe with a 12-mm-length, 2.33-mm-diameter cryotip and a 1-meter long, 13-gauge flexible catheter was utilized to cryoablate lung parenchyma in six normal female pigs by transbronchial cryoablation. Under virtual bronchoscopic guidance, the cryoprobe was administered to the distal bronchus in the bilateral porcine lungs via the bronchoscopic working channel and validated by real-time CT. Two freeze-thaw cycles were used during the operation. Histopathologic findings indicated the formation of a coagulative necrotic zone along the target bronchus 24 hours after treatment, with apparent vascular blockage and bleeding. The lesions developed fibrosis after 4 weeks after bronchoscopic cryoablation. These two animal studies revealed that bronchoscopic cryoablation of peripheral lung parenchyma is a realistic and safe, implying the possibility for this treatment approach in peripheral lung cancer in humans.

**Conclusions**

Percutaneous thermal ablation has shown to be a safe and effective alternative treatment for lung cancer, especially in patients with early-stage NSCLC who are not candidates for surgery and lung metastasis. Currently, there is limited evidence in using bronchoscopic thermal ablation which needs further studies about efficacy and safety in human uses.

**Reference**


