Image guided thermal ablation in lung cancer treatment

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Abstract: Lung ablation has been introduced into lung cancer treatment for about two decades. Currently, 3 main choices of thermal energy for lung ablation are radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation. As a mostly palliative, occasionally curative intent local treatment, the feasibility and safety of lung ablation have been validated in small size lung cancer treatment, especially in lung tumor ≤3 cm. Improved techniques and experience in recent years help render outcomes much better than before for lung cancer patients who are medically inoperable with early stage primary lung cancer, and patients with oligometastasis or local recurrence. For stage IA non-small cell lung cancer (NSCLC) patients underwent RFA, 1- and 2-year overall survival rate were reported as 86.3% and 69.8%. And 1- and 2-year local recurrence rate were reported as 68.9% and 59.8%. Limitations, including heat sink, skin burn, and inconsistent heat conduction, are observed in the first applied ablation technique, RFA. MWA and cryoablation are developed to overcome these limitations and achieve the goal of less morbidity. Generally, imaged guided thermal ablation has a good safety profile, with pneumothorax as the most common morbidity. This article will mainly discuss the current features and application of these ablation techniques in lung cancer treatment.

Keywords: Lung ablation; lung cancer; thermal ablation; radio frequency ablation; microwave ablation (MWA); cryoablation

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Introduction

Lung cancer is one of the most common cancers, and also one of the leading cause of cancer death around the world (1). According to the World Health Organization, lung cancer is responsible for an estimated 1.76 million deaths in 2018 worldwide (2).

Radical resection is the first choice for surgical candidates, and has the best outcomes compared with other therapies. However, only 20–30% of patents with lung cancer are operable (3). Other patients have to seek non-surgical treatments, including image guided thermal ablation, SBRT, chemotherapy, radiotherapy, chemoradiotherapy, and immunotherapy.

As one of the local therapies, image guided lung thermal ablation, was first introduced as a lung cancer treatment about two decades ago (4), and represents a collection of different techniques. It is applied in medically inoperative patients with early stage primary lung cancer, and patients with oligometastasis or local recurrence (5,6). Radiofrequency ablation (RFA) and microwave ablation (MWA) are two most widely used thermal ablation for inoperable lung cancer patients. Cryoablation, which induces cell death through extremely low temperature, is now practiced worldwide, and seems promising according to current data. Other techniques, including laser ablation and irreversible electroporation (IRE), are not widely used in lung ablation due to lack of clinical data.

Indications

Image guided thermal ablation has been practiced in many centers all over the world, and has been proven to be cost-effective with good patient experience (6).

The first indication is local therapy for medically inoperable patients with early stage primary lung cancer (5). For surgical candidates, radical surgery is always the best choice. However, for inoperable patients with severe morbidities, poor performance status level, limited lung function, and/or unwillingness to undergo surgery, local treatment and local control of tumor spread needs to be addressed by alternative means. In rare cases, cure can be achieved with image guided thermal ablation. Local recurrence is a major risk of lung ablation. If a patient has local recurrence after ablation, up to 3 repeated ablations is an option in our experience.

The second indication is treatment for multiple lung cancers when definitive local therapy is possible (7). Surgical resection is sometimes impossible because of poor preoperative pulmonary function or predicted massive loss of lung parenchyma. Lung ablation can preserve more normal tissue than surgery, resulting in preservation of post procedural patient quality of life and lung function.

Pulmonary oligometastasis is another indication for imaged guided thermal ablation (8). Lung is the most common target for cancer metastasis compared to other organs. Patient outcomes can be improved if all oligometastasis are removed or inactivated in certain kinds of cancers, for instance, hepatocellular carcinoma and colorectal adenocarcinoma. In the circumstances when surgical resection is not feasible, lung ablation can be a viable alternative.

Local therapy should also be considered when asymptomatic progression is observed in patients with chemo-, radio- or immunotherapy (6). For limited lesions that do not response well to systemic treatment, image guided thermal ablation can be used as definitive local therapy to achieve complete tumor eradication.

However, in order to render a comprehensive and best treatment model for patients, every case should be submitted to multidisciplinary tumor boards with inputs from surgery, interventional and diagnostic radiology, medical and radiation oncology before treatment is applied.

Radio-frequency ablation

Radio-frequency ablation is one kind of hyperthermal approaches, and was the first applied ablation technique in the lungs. In RFA targeted area, an active electrode oscillates at a frequency of approximately 400 kHz to induce an electrical current which in turn generates heat. Subsequent protein denaturation and coagulation necrosis can be induced under high temperature, which is generally above 55 ℃ (9). Although only one probe works at a time in RFA, researches of multiple-electrode switching system are ongoing to evaluate its clinical efficacy and safety (10,11). Tissue electrical conductance is an important factor for heat generation. Malignant tissue has higher electrical conductance than normal tissue, thus most electrical current passes through the malignant tissue, resulting in heat accumulation in this area. Malignant tissue also has higher heat conductance than normal tissue, which also helps to trap heat in this area and spare adjacent normal parenchyma. There are several limitations of RFA (12). First, various available devices for RFA operate in a monopolar mode, with grounding pads attached to the skin, allowing for possible skin burns. Feasible solutions include increased surface area of pad, increased number of pads and sequential activation, simultaneous skin temperature monitoring (13). Secondly, electrical and heat conductance is affected by possible charring tissue formed during ablation around the electrode. Improved protocols and devices might help to avoid the rapid rise of temperature and therefore reduce charring. ‘Heat sink’ phenomenon is another problem (*Figure 1*). Large blood vessels and airways near the ablation zone can drain heat, decreasing the temperature to sublethal threshold and adversely affecting the ablation effectiveness. When vessel is greater than 4 mm, heat sink would be remarkable (14). More intense heating may be a solution for this problem in RFA. However, switching to MWA or cryoablation which is less sensitive to ‘heat sink’ is recommended when treating lesion adjacent to large vessels or airways. Tumor size >3 cm is a predictor of higher recurrence rate in RFA (5). In order to achieve homogeneous necrosis and 1 cm margin, overlapping spheres are required when tumor size is larger than 3 cm in diameter (15). The linear increase of tumor size leads to exponential increase of the number of overlapping spheres. And it results in longer procedure time, higher chance for complications, and higher incidence of leaving behind viable tumor islands (16).

MWA

MWA is another kind of hyperthermal approach,

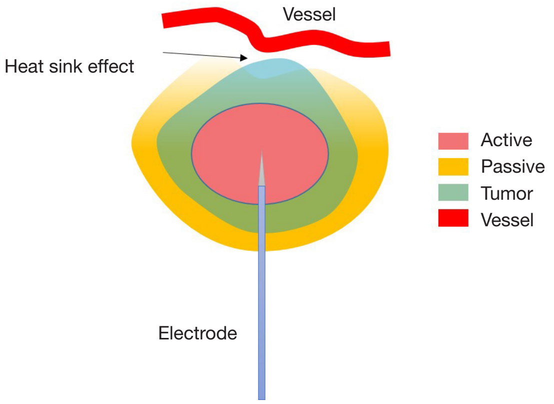

Figure 1 Heat sink in radiofrequency ablation. In RFA, large blood vessels and airways near the ablation zone can drain the heat, decreasing the temperature to sublethal threshold and adversely affecting the ablation.

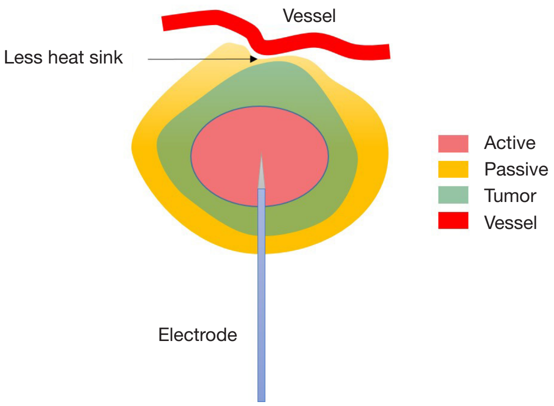

Figure 2 Heat sink in Microwave ablation. Microwave ablation is less sensitive to heat sink than RFA, and can be applied to tumor located near large vessels or airways.

using electromagnetic waves in the microwave energy spectrum to generate heat (17). Unlike RFA, electric current and cutaneous grounding pad are not needed, and multiple probes are allowed in MWA. The oscillation of electromagnetic field around the MW antennas induces constant realignment and agitation of water molecules, which leads to increased kinetic energy, ultimately resulting in heat generation. MWA is not restrained by tissue electric and heat conduction, and can reach a larger ablation volume than RFA. It is also less sensitive to the 'heat sink' phenomenon due to greater heat generation from microwave energy, larger zone of active heating, and less dependence on thermal conduction than RFA (*Figure 2*) (18,19). Therefore, MWA can be applied in tumors adjacent to large vessels and airways. The shape of MWA ablation zone is oblate, not spherical. This feature impairs the predictability of the size and shape of the ablation zone.

Cryoablation

Cryoablation has different underlying mechanism inducing cell death compared to RFA and MWA. Pressurized argon gas is distributed through an orifice in the probe to achieve a subzero temperature in Celsius (20). Multiple studies have proved that temperature below −40 ℃ should be achieved to induce cryogenic destruction and complete cell death (21). Cryoablation is based on the Joule-Thomson effect, which means higher initial gas pressure is related with lower ablation temperature and formation of larger ice balls (22). Several cycles of freezing and thawing can lead to protein denaturation, cell membrane disruption and cell rupture due to osmotic shifts, and tissue ischemia due to microvascular thrombosis. The effects of cryoablation can be affected by many factors, including the number of cycles, duration of procedure, different auxiliary warming devices, tumor location, and regional blood flow. Another possible effect of cryoablation is its pro-immune function. Tumor cell content is not damaged during cryoablation and may be presented to immune cells after cell rupture and therefore triggering an antitumor immune reaction. Such antitumor immune reaction may also help enhance efficacy of subsequent immunotherapy. In addition to cell contents, collagenous architecture is also preserved in cryoablation. This is helpful for tumors locating near the central airways. An additional benefit of MWA is that more than 1 probe can be used at a given cryoablation session, which shortens the procedure time and improves patient experience. Cryoablation induced hypothermic injury is also believed to be better tolerated than hyperthermic injury from RFA and MWA (23).

Comparison among RFA, MWA, and cryoablation

There are very limited data comparing survival and recurrent rates among different contemporary ablation techniques. We herein provide a brief comparison between RFA, MWA, and cryoablation (*Table 1*) according to current studies.

RFA was first introduced for clinical treatment in 2000 (4), with the longest history and thus the most experienced

Table 1 Comparison between RFA, MWA, and cryoablation

Features	Radiofrequency ablation	Microwave ablation	Cryoablation
Advantages	Many publications	Low sensitivity to heat sink	Low sensitivity to heat sink
	Experienced physicians	Easy set up	Pro-immune response
	Comparable oncological outcomes	Short procedure duration	Multiple probes
		Multiple probes	Malignancies with large size or special location (near mediastinum, chest wall, or pleural)
Disadvantages	Heat sink	Oblate ablation zone	Limited experience and data
	Possible skin burn	Tumor size limitation	Long procedure duration
	Tumor size limitation		Complex set up
	Interaction with cardiac pacemaker and ICD		Increased risk of bleeding
	1 working probe at a time		

RFA, radiofrequency ablation; MWA, microwave ablation.

operators compared to other modalities. One disadvantage is that RFA cannot be utilized when the tumor is located next to large vessels, airway, and other important structures due to potential thermal injury. Other limitations include heat sink phenomenon and rapid charring.

MWA uses a different mechanism to generate heat from RFA, and is less likely to be affected by thermal and electrical impedance. Theoretically, MWA can achieve larger ablation volume and higher temperature than RFA. However, most comparisons of outcomes between MWA and RFA indicate they have similar effects. The disadvantages of RFA do not compromise its oncological outcomes when compared with MWA. Possible reason is their similar mechanism of action, leading to similar outcomes. The randomized controlled trial LUMIRA evaluated the effectiveness of RFA and MWA in lung tumors with 12 months of follow-up (24). It showed no significant differences of overall survival between RFA and MWA. Less intraoperative pain and a significant reduction in tumor mass were observed in the MWA group. Another retrospective, case-controlled observational study enrolled 238 patients, proved similar median progression-free (RFA *vs.* MWA: 12.5 months, *vs.* 9.5 months, P=0.673) and overall survival (RFA *vs.* MWA: 33 months, *vs.* 30 months, P=0.410) between the RFA and MWA groups (25).

Cryoablation is a relatively new and promising modality. It does not ruin the collagenous architecture of the target area, helps promote immune response by preserving and presenting cancer cell contents. Disadvantages include long procedure duration, increased risk of bleeding, and complex preparation. Moore and colleagues reported a 5-year survival rate of 67.8%±15.3%, cancer-specific survival rate at 5 years of 56.6%±16.5%, 5-year progression-free survival rate of 87.9%±9% (26) in 45 patients with stage I NSCLC after cryoablation. Their results were very encouraging and were comparable to another thermal ablation. Contrarily, a meta-analysis performed by Jiang *et al.* reported worse outcomes from cryoablation compared to RFA and MWA (27). Therefore, it is still controversial regarding cryoablation's superiority over RFA and MWA. Randomized controlled trial with large volumes is required.

Other technologies—IRE and laser ablation

IRE is a relatively new ablation technique using pulsed electric fields to induce reversible or irreversible opening of pores along cell membranes which ultimately leads to apoptotic cell death (28,29). Disrupted lipid bilayer by high electrical voltage and destabilized electrical potential on cell membrane are reasons for pore formation. This technique is first used in 2005 in liver ablation by Davalos *et al.* (30). However, due to poor local control rates in lung cancer demonstrated by the ALICE trial (31), IRE is not recommended in lung ablation.

Laser ablation is another kind of thermal ablation, using catheter delivered laser energy to the target area. However, due to limited available data, its application in lung cancer has not gained much attention.

Trans-bronchial peripheral ablation

Most ablation are performed through percutaneous

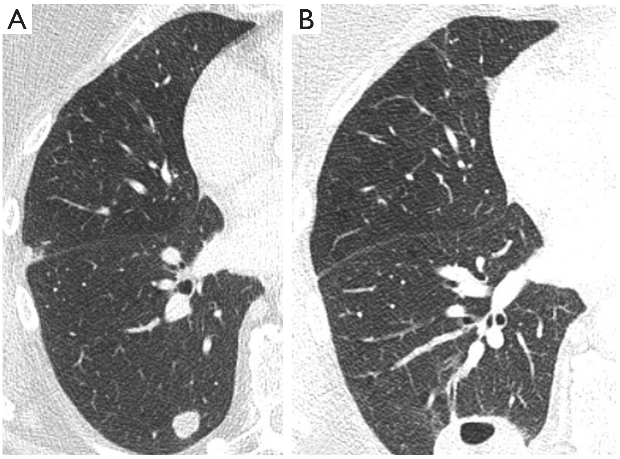

Figure 3 Post ablation nodule cavitation. (A) Pre-ablation CT demonstrated a 1.3-cm solid noncalcified right lower lobe nodule; (B) 1 month CT after cryoablation of the same nodule demonstrated peri-nodular post ablation changes and new cavitation.

puncture. Trans-bronchial ablation is a new approach developed in recent years (32). It does not violate the pleural space, so as to avoid certain complications, such as pneumothorax, bronchopleural fistula (BPF), and pleural effusion. RFA and MWA ablation have been applied in this approach. Relevant data is still limited. Several clinical trials are underway, and results should be available soon.

Complications from image guided ablation

Generally, imaged guided thermal ablation has a good safety profile, with very low morbidity and mortality. A national data analysis indicated that in-hospital mortality rate is as low as 1.3% (33). The median hospital stay is reported to be 1 day (33).

Pneumothorax is the most common complication in lung ablation. The incidence can be as high as 40% in lung ablation (33,34). However, only less than 2% of pneumothorax cases were considered as Grade III complication, requiring interventions in Kashima *et al.*'s study (34). More than half of these pneumothorax patients did not need any treatment. Chest tube placement and surgical intervention are only necessary in a relatively small number of these patients.

BPF is a much more severe complication and could be occasionally observed (35). The incidence of BPF after ablation is reported as 0.4–0.6% (36). The reason is ablation induced tissue necrosis and subsequent sloughing between the pleural space and bronchus. Intractable or recurrent pneumothorax after ablation is an important sign of BPF, which sometimes cannot be diagnosed until even 2 months after ablation (37). Treatment for BPF is challenging, and may not be effective at times. Surgical repair, endoscopic intervention, and pleurodesis are possible choices.

The incidence of hemorrhage is less than 20% (36). Parenchymal hemorrhage and haemothorax are two different forms of hemorrhage. Risk factors include small lesion, lesion located in the basal and middle lung zones, long needle track, traversing vessels in the track, coagulation disorders, and the use of multi-tined electrodes (37). Most cases are self-limiting, and do not require blood transfusion or other interventions. Hemorrhage is much more common in cryoablation than in RFA or MWA (38). A possible reason is the greater number of probes in cryoablation.

Infectious complications should be treated carefully as deaths from post ablation interstitial pneumonitis or lung abscess have been reported (34). Aseptic pleural effusion may happen in less than 20% of patients, and only require conservative treatment for most of the time. Other rare complications include needle track seeding, thermal injury to nearby organ, pulmonary necrosis resulting in cavitation (*Figure 3*), nerve injury, rib fracture.

Patient with cardiac pacemaker or implantable cardioverter defibrillator (ICD) should not undergo RFA, because the electrical current and high frequency signals generated by RFA can possibly interact with and disrupt pacing or ICD therapy (39,40). MWA and cryoablation are possible choices in this circumstance.

Ablation versus other local therapy

Lung ablation aims to fully ablate the mass along with adequate margin. However, it is not a curative treatment for lung cancer patients. For patients with early stage primary lung cancer, surgical lobectomy is always the best choice when patients are surgical candidates. For patients who are not willing to or cannot undergo radical surgery, compromised local therapies includes sublobar resection (SLR, wedge resection or segmentectomy), stereotactic body radiation therapy (SBRT), and ablation.

Sublobar resection preserves more lung parenchyma than lobectomy, and is believed to have better outcomes than SBRT or ablation. A propensity matched analysis enrolled 53,973 stage I NSCLC patients from the National Cancer Database to compare the long-term outcome of SLR, SBRT, and ablation (41). After propensity match, a significant difference in overall survival was observed in the SLR group compared to the SBRT or ablation groups.

Data comparing survival outcomes between SBRT and ablation is diverse because of the heterogeneity on study groups and protocols. Bilal *et al.* reviewed 16 related studies, and indicated that SBRT offers a higher 5-year survival rate (47% versus 20.1–27%) and lower local progression rate (3.5–14.5% *vs.* 23.7–43%) than ablation (42). They also found that larger tumor is related to worse outcome in ablation, suggesting 3 cm as the cut off diameter for ablation. Another study analyzed data from Surveillance, Epidemiology, and End Results database, including stage IA lung cancer patient data from 2004 to 2015, concluded that there is no significant differences of overall survival between SBRT and ablation (43). A prospective clinical trial (ACOSOG Z4033) reported 86.3% overall survival rate at 1 year and 69.8% at 2 years for stage IA patients who had undergone RFA (44). Local recurrence rate was 68.9% at 1 year and 59.8% at 2 years, and worse for tumors >2 cm than tumors ≤2 cm. Their data is comparable to data reported in SBRT studies with similar patients. Currently, National Comprehensive Cancer Network guidelines recommend that SBRT should be first considered because of its possible better outcome, and ablation is appropriate for medically inoperable patients when local control is not considered as the highest priority (7). Randomized controlled study with large volume is still necessary to reach a clear conclusion.

Post ablation surveillance

Follow-up is commonly required after lung ablation. The purpose is to find early signs of local recurrence and tumor progression. Most patients are being surveilled every 3 months in the first year, followed by every 6 months thereafter. Individualized plan may vary due to different tumor type and stage. Multidisciplinary tumor board determines the exact time interval and time span for each patient.

Contrast enhanced computed tomography (CT), and positron emission tomography – computed tomography (PET-CT) are viable surveillance choices. High resolution CT provides morphologic information regarding post ablation parenchymal changes, local tumor growth or recurrence as well as metastatic status. Intravenous contrast provides further information regarding tumor perfusion. PET-CT is recommended by many experts because it provides metabolic information not gleaned from CT. However, one must be cognizant that the CT performed along with PET is limited in resolution and is suboptimal for morphologic evaluation. Baseline and one-month post ablation follow-up PET imaging (to establish new baseline) is typically obtained.

One needs to be aware of the slow morphologic evolution of the ablation zone, potentially resulting in false positive results for tumor recurrence during follow-up. Five post ablation CT patterns have been describe by Palussière *et al.* (45): fibrosis, cavitation, nodule, atelectasis, and disappearance. It is imperative to distinguish these normal evolutions from local disease progression as subsequent management differs between these situations.

Limitations

There are several limitations of image guided thermal ablation. Local recurrence is a major concern of lung ablation compared to surgery. Moreover, ablation is limited to regional disease control, while SBRT or segmentectomy can eliminate metastases such as nodal disease concomitantly. Tumor size and location may affect the outcome of ablation, especially in RFA. 'Heat sink' phenomenon can affect the outcome for tumors adjacent to large vessels or airways. Repeated punctures are required in large tumors.

Conclusions

Image guided thermal ablation has been proven to be a safe and feasible alternative to surgery with acceptable morbidity and mortality rate in medically inoperable lung cancer patients. As a minimally invasive technique, lung ablation has several advantages over surgery, including high local control rates, shorter in-hospital stay, comparatively lower cost and better patient tolerance. RFA, MWA, and cryoablation are currently acceptable techniques for lung ablation. Continue technological advances are bringing forth more ablation methods, including laser ablation and IRE. Large randomized controlled trials remain necessary to further validate their application in lung cancer.

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