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Editorial

Understanding the possibility of image-guided thermal ablation for pulmonary malignancies

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Introduction

There is a debate regarding the ideal treatment for inoperable patients with pulmonary malignancies. Although surgery has been the gold standard of care for centuries, other local therapies are applicable for patients with early stage non-small cell lung cancer (NSCLC) and oligometastatic disease from various types of malignancies. A variety of image-guided percutaneous thermal ablation technologies have been demonstrated as favorable therapeutic options for patients who are not surgical candidates because of poor cardiopulmonary reserve, anatomic constraints limiting resection, failure of traditional therapies, or refusal of operative approaches. Through case report series and small clinical trials, radio-frequency ablation (RFA), microwave ablation (MWA) and cryoablation have been demonstrated. These interventional thermal ablation techniques have been investigated, showing efficacy, safety, and good local disease control while preserving the normal lung parenchyma. However, we still have been without clinically relevant, statistically significant evidence for several years.

This is an analysis of the article by Mouli and colleagues, which was a review article of image-guided thermal ablation for patients with pulmonary malignancies (1). They evaluated various studies that have reported efficacy and safety for the treatment of both primary and metastatic disease.

Principle mechanism of thermal ablation

Before discussing the feasibility of current thermal ablation technologies, we recommend understanding the mechanism of action and local efficacy of each thermal ablation modality. Here, we summarized the comparison of image-guided percutaneous thermal ablation techniques in *Table 1* (2). The unique characteristics of pulmonary parenchyma promote thermal ablation, including heat insulation and low electrical conductivity. These exclusive characteristics enable a larger volume of tissue to be ablated at a given energy level than in other organ tissues in the body (3). With RFA, an electrode from a generator causes frictional heating, elevating the tissue temperature to 60–100 ℃. This heating effect creates a necrotic zone covering both the tumor and margin of normal lung parenchyma (4). As a weak point, this thermal energy can be limited by the heat-sink effect of adjacent blood vessels and airways (5). An important note for obtaining adequate margins is the ablation zone must exceed the tumor size (6). Therefore, RFA performs best for lesions smaller than 2 cm in diameter, lower success rates are seen with larger tumors (6-9). More specifically, a ratio of RFA-induced ground-glass opacity (GGO) to tumor area of greater than 4 (the bi-dimensional area on axial images) is correlated with a significantly higher rate of complete ablation than a ratio of less than or equal to 4 (6). Nowadays, new technologies have been developed to overcome the limitations of RFA by extending the volume of

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Table 1 Comparison of image-guided percutaneous thermal ablation techniques (RFA, MWA, cryoablation)

Characteristics	RFA	MWA	Cryoablation
Principle of action	Application of oscillating electrical currents resulting in resistive heating surrounding an electrode and tissue hyperthermia	Direct application of a propagating microwave energy level electromagnetic field to induce tissue hyperthermia via dielectric hysteresis	Changes in gas pressures result in cooling of a cryoprobe in direct thermal contact with tumor resulting in ice crystal formation and osmotic shock
Energy source	Electric magnetic energy	Electromagnetic energy	Argon gas
Ablation function	Heating	Heating (dielectric hysteresis)	Cooling
Radiofrequency range	375–500 kHz	900–2,450 kHz	–
Temperature	60–100 ℃	Over 100 ℃	Less than −40 ℃
Function	Coagulation necrosis	Coagulation necrosis	Protein denaturation
Ablation lesion	Single lesion	Simultaneous treatment of multiple lesions	Simultaneous treatment of multiple lesions
Procedural time	–	Less than RFA	More than RFA
Ablation volume	–	Larger than RFA	Larger than RFA
Procedural pain	–	Less than RFA	Less than RFA
Grounding pad injury	Potential occur	No need pad	No need pad
Advantage	Experience regarding efficacy and safety (most widely studies and most outcome data available)	More effective ablation of cystic masses; less “heat sink” effect; less tissue charring	Compared to RFA: larger tumor ablation volume
Disadvantage	Not suitable for tumors in mediastinum or lung apex due to non-target injury to neuro-vasculature structures and airways; limited by “heat sink” effect from nearby vessels; limited by tissue charring may prevent tumor ablation at the periphery	Limited safety and efficacy data available	Limited safety and efficacy data available; longer procedural time due to freeze-thaw-freeze cycle; higher hemorrhage risk secondary to lack of tissue cauterization

Modified from Lee *et al.* (2). RFA, radiofrequency ablation; MWA, micro wave ablation.

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ablation or lowering convective cooling close to the bronchi or vessels. MWA uses microwaves to cause friction between water molecules, generating hyperthermia (10). Unlike RFA, during which only one probe is activated at a time, MWA enables simultaneous energy delivery with multiple probes, thus MWA can achieve larger ablation zones more quickly with less heat sink effect. Cryoablation uses compressed argon gas to generate subzero temperatures with the ice-ball formation effect. When temperatures are less than −40 ℃, protein denaturation, cell rupture, and ischemia reactions occur (11). Unlike heat-based ablation, cryoablation does not create GGOs intra-procedurally rather; the ice ball is used to estimate the ablated margin. Most ablation protocols call for three freeze-thaw cycles to achieve tissue necrosis (12). Cryoablation involves inserting the probe into the tumor tissue providing moderate freezing and moving the probe away from accessible adjacent organs as necessary (13). An advantage of having the probe frozen to the tumor is that probe displacement will not occur during treatment as is the case with expandable RFA electrodes, which are very popular for lung ablation. Again, both MWA and cryoablation allow for simultaneous delivery of energy through several probes activated at the same time with a synergistic effect versus subsequent activation of the same probe. Large ablation volume gives improvement of local control of larger tumors and is under evaluation in clinical practice.

Clinical outcome of comparative study

The purpose of this author's review was to demonstrate thermal ablation has shown safety and efficacy in the treatment of both NSCLC and oligometastatic disease in nonsurgical candidates (1). As the author mentioned in this article, one major limitation is that there have been no large randomized studies available to compare surgery with thermal ablation. Therefore, to ensure the availability of thermal ablation content, we investigated and summarized the clinical significance of thermal ablation for early stage NSCLC in *Table 2* (14-20). Based on these studies, thermal ablation could be an alternative therapeutic modality to surgical treatment and stereotactic body radiation therapy (SBRT), specifically in selected patients with lung malignancies who have combined medical illnesses, who have limited lung function, and/or who are elderly. In the absence of randomized prospective trials, population based comparative studies may provide a higher level of evidence to guide clinical management decisions. Kwan *et al.* (17) examined survival in 1,897 patients with early stage NSCLC who underwent surgical resection or thermal ablation using the database from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. They sought to control for selection bias in their retrospective study using population-based data. After propensity score matching analysis was performed to reduce bias, overall survival and cancer specific survival were not significantly different between RFA and surgery. This study suggests that medical providers are appropriately selecting patients for thermal ablation based on factors such as age and presence of comorbid conditions.

SBRT is an effective noninvasive interventional therapy with a good safety profile and remains the preferred treatment modality for patients who are unsuitable for surgery (21). Nevertheless, the disadvantage of SBRT includes the risk of radiation pneumonitis and fibrosis, especially in medically inoperable patients affiliated with interstitial lung disease or other reasons for borderline lung function. In addition, SBRT can cause bronchial stenosis if used to treat tumors in central lesions. SBRT is also limited by the fact that it generally requires five daily treatments, which is much more distressing to patients and their families than a single ablation procedure. Moreover, SBRT is expensive, with an average of $40,000 for the serial-treatment cost, including physician fees (18,21). When comparing the clinical outcomes of RFA with those of SBRT in patients with lung malignancies, RFA provided acceptable local tumor control and survival that were similar to using SBRT (19,20). By contrast, percutaneous thermal ablation therapies for peripheral lung cancers are associated with unacceptably high complication rates, primarily pneumothorax which make these techniques difficult to pursue as an alternative to SBRT. Another downfall of the percutaneous approach is that it is more painful and requires local anesthesia and/or sedation or general anesthesia, unlike SBRT. Therefore, the transthoracic thermal ablation techniques are relatively invasive and must compete with SBRT for effectiveness and safety to justify a place in the management algorithm for peripheral lung cancers. It should be clear and requires further investigation before being proven effective and safe for clinical applications.

Future direction of thermal ablation therapy

As previously discussed in this article, the most common technique for thermal ablation of pulmonary malignancies remains the percutaneous approach. In some patients

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Table 2 Comparative studies of thermal ablation

Authors [years]	Setting/premise	Type of tumor	Survival	Conclusions
Kim *et al.* [2012] (14)	RFA (n=8) *vs.* surgery (n=14)	Stage I NSCLC	Mean survival duration (month): 33.28±7.90 *vs.* 45.49±7.21 (P=0.297); OS (1, 3-, 5-year): 88%, 50%, 25% *vs.* 93%, 77%, 67% (P=0.054)	The local recurrence rate was higher in the patients treated with RFA, OS was similar for the two groups
Lee *et al.* [2012] (15)	RFA (n=16) *vs.* surgery (n=13)	Stage I, II NSCLC	Median survival (month): 33.8 *vs.* 28.2 (P=0.426); OS (1, 2-year, 5-year): 100%, 76.9%, 18.7% *vs.* 85.7%, 70.1%, 0% (P=0.426); CSS (3-year): 33.3% *vs.* 33.5% (P=0.844)	No significant difference in OS, although the RFA group were significantly older than the surgery group
Zemlyak *et al.* [2010] (16)	RFA (n=12) *vs.* sublobar resection (n=25) *vs.* cryoablation (n=27)	Stage I NSCLC	OS (3-year): 87.5% *vs.* 87.1% *vs.* 77% (P>0.05); CCS (3-year): 87.5% *vs.* 90.6% *vs.* 90.2% (P>0.05); PFS (3-year): 60.8% *vs.* 50% *vs.* 45.6% (P>0.05)	No significant difference in 3-year OS or in 3-year CSS; length of hospital stay was shorter than SLR group (P<0.05)
Kwan *et al.* [2014] (17)	Propensity score matched group; RFA (n=69) *vs.* sublobar resection (n=69)	Stage I NSCLC (n=1,897: SEER database)	OS (3-month, 1, 2-year): 98.5%, 85.3%, 61.8% *vs.* 95.5%, 82.9%, 66.1% (P=0.695); CCS (3-month, 1, 2-year): 98.6%, 88.7%, 66.1% *vs.* 100%, 88.3%, 75.8% (P=0.819)	After controlling for selection bias, this study found no difference in OS and CSS
Alexander *et al.* [2013] (18)	RFA (n=56) *vs.* sublobar resection (n=28)	Stage I NSCLC	OS (1, 2-, 3-year): 91%, 73%, 55% *vs.* 100%, 95%, 83% (P=0.046)	Patient treated with surgery showed a significant increase in survival; however, those treated with RF ablation were significantly older
Ochiai *et al.* [2015] (19)	RFA (n=48) *vs.* SBRT (n=47)	Solitary tumors less than 5 cm	Local tumor progression rate (3-year): 9.6% *vs.* 7.0% (P=0.746); OS (3-year): 86.4% *vs.* 79.6% (P<0.05)	No significant difference in 3-year OS
Bilal *et al.* [2012] (20)	RFA (n=328) *vs.* SBRT (n=2,767)	Early stage NSCLC	OS (1, 3-year): 68.2–95%, 36–87.5% *vs.* 81–85.7%, 42.7–56%; OS (5-year): 20.1–27% *vs.* 47%	SBRT showed lower local progression rates than RFA (3.5–14.5% *vs.* 23.7–43%). OS rates were similar between the two treatments, but 5-year OS rates favored SBRT over RFA

RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; NSCLC, non-small cell lung cancer; OS, overall survival; CSS, cancer specific survival; PFS, progression free survival.

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with peripheral lung cancers and advanced underlying lung disease along with low pulmonary function, the risks of percutaneous RFA may be more acceptable than surgical resection. However, the risk of pneumothorax was not lower than SBRT as we mentioned before (1). Furthermore, percutaneous and transthoracic techniques have limitations in their approach for more centrally located tumors. The transbronchial approach can be more readily used to treat tumors located in the central portion of the lung, where the percutaneous approach may result in an unacceptably higher rate of pneumothorax and hemoptysis. If the incidence of complications could be reduced, more patients may benefit from thermal ablation therapy. The transbronchial approach for thermal ablation may potentially develop into a minimally invasive therapy with a low frequency of pneumothorax that can be used to treat patients with inoperable lung tumors located within either the central or peripheral areas of the lung. Hence, we have considered developing a new device for transbronchial thermal ablation. Coupled with advances in therapies, many of which can be delivered through the bronchoscope, we are entering a new era in which bronchoscopy may be used not only to diagnose lung malignancies but also to potentially treat lung malignancies. In fact, various transbronchial techniques have been used to treat central type endobronchial tumors. These techniques include heat modalities (argon plasma coagulation, electrocautery, laser phototherapy, photodynamic therapy), cold modalities (cryotherapy), or a direct injection of chemotherapeutic agents. In our laboratory, several new modalities are being investigated through *ex vivo* and *in vivo* animal experiments, with promising results (22,23). These thermal and non-thermal interventional therapies, and variations of these transbronchial techniques, are now being evaluated for the treatment of peripherally located lung tumors using the advanced diagnostic techniques already described. Given the illustrated antitumor effects of percutaneous thermal ablation of peripheral lung tumors and the hypothesis that transbronchial approaches have lower pneumothorax rates than transthoracic techniques, there have been concerted efforts to develop ablation technologies that can be delivered through the working channel of a flexible bronchoscope and endobronchial ultrasound (EBUS) system.

There have been only a few studies to develop bronchoscopy-guided RFA. Ten patients with stage IA lung cancer were treated using bronchoscopy-guided internally cooled RFA probes inserted within the tumors using CT imaging guidance in advance of planned surgical resection (24). The coagulation necrosis area increased with larger tips and longer ablation times, but the resected tissue contained residual tumor cells in all patients. Remarkably, except for two patients with mild chest pain, there were no complications such as bleeding or pneumothorax. In addition, they treated 23 peripheral lung lesions in 20 patients with early stage NSCLC using CT-guided bronchoscopic cooled RFA in their most recent paper (25). Local disease control was achieved successfully in most patients and there were no serious major complications reported.

A disadvantage of the transbronchial approach is that it can be difficult to reach and treat small, peripherally located tumors due to the lack of resources. As well as, transbronchial treatment may require intubation and anesthesia for patients. Given these recent efforts, it is credible that radial probe-EBUS using a guide sheath or electromagnetic navigational system may have a potential role in guiding thermal ablation for peripheral lung malignancies in patients who are not surgical candidates. The transbronchial techniques used to treat peripheral lung cancer may have significantly lower rates of complication, most notably a decreased incidence of pneumothorax, and would be favored over percutaneous interventional technologies. We believe that the optimal outline for successful bronchoscopic treatment of peripheral lung cancers would be to perform the diagnostic, staging, and therapeutic procedures in the same setting. This requires successful navigation to the targeted cancer with certainty of malignant diagnosis via rapid on site evaluation or frozen section to prevent the unnecessary treatment of non-malignant lesions it is also required for analysis of nodal sampling to exclude treatment of regionally advanced tumors. Emerging techniques such as intratumoral chemotherapy, target therapy, immunotherapy, and combinations of both with local ablative technologies, need to be investigated further in early-phase clinical trials to ensure safety and to confirm findings from preclinical studies of antitumor efficacy and synergy effects of combination therapy. Advanced therapies, such as local irradiation, heat and cold therapies, and gene based technologies, have brought the capability of potentially curing malignant disease without surgery when combined with the tools used in bronchoscopy to localize the tumor. These endoscopic techniques may provide fewer complications than transthoracic approaches when the same treatment modalities are applied.

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Conclusions

In the past decade, there have been significant advances in technology that are facilitating the investigation of the therapeutic role of thermal ablation. In the future, it is likely that lung surgery for small-size oligometastatic lung disease will be replaced by minimally invasive techniques. The ideal therapy will have to demonstrate efficacy, tolerance, and cost effectiveness by prospective randomized control studies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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