Thermal Ablation of Stage I Non-Small Cell Lung Carcinoma

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Abstract

Keywords

- ablation techniques
- carcinoma
- non-small cell lung
- tomography
- x-ray computed
- positron emission tomography
- radiology
- interventional radiology

Ablation options for the treatment of localized non-small cell lung carcinoma (NSCLC) include radiofrequency ablation, microwave ablation, and cryotherapy. Irreversible electroporation is a novel ablation method with the potential of application to lung tumors in risky locations. This review article describes the established and novel ablation techniques used in the treatment of localized NSCLC, including mechanism of action, indications, potential complications, clinical outcomes, postablation surveillance, and use in combination with other therapies.

Objectives: Upon completion of this article, the reader will be able to describe the role of thermal ablative technologies in the treatment of non-small cell lung cancer.

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Radiofrequency ablation (RFA) was first described in normal liver in 1990 using a modified Bovie knife.^{1,2} Subsequent descriptions of successful thermal liver tumor

ablation in the mid-1990s elicited interest in applying the technique to other organs.^{3,4} In the late 1990s, thermal ablation in the lung was first found to be safe and efficacious in both normal tissue and in VX2 sarcomas in the lungs of rabbits.^{5,6} Its successful use in lung tumors in humans was subsequently described in patients with inoperable non-small cell lung carcinoma (NSCLC) in 2000.⁷ RFA has since been joined by microwave, cryoablation, and recently irreversible electroporation as potential lung tumor ablation techniques.

Mechanism of Action

A detailed description of the mechanism of action of each thermal ablation technology is beyond the scope of this article and can be sought in existing review articles on the topic, as well as the articles by Yu and Burke,⁸ and Zivin and Gaba,⁹ in this issue of *Seminars in Interventional Radiology*.^{10–12}

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In brief, frictional heat is produced during RFA as a result of delivery of an electrical current to tumor cells surrounding the RFA probe tip, creating a rise in tissue temperature, known as the Joule effect.¹⁰ Tissues nearest to the electrode are heated most effectively, while more peripheral tissue is heated by thermal conduction. Common to all thermal ablation modalities, a temperature at the electrode tip above 60°C is needed to achieve cell death.^{13,14} However, particularly in the case of RFA, thermal tissue conductivity is impaired at temperatures above 95°C due to tissue charring, which causes increased tissue impedance and thus a decrease in the effectiveness of RFA.^{15,16}

Microwave ablation (MWA) involves the application of either 915 MHz or 2.45GHz to the target tissue; water molecules in the tissue continuously realign with the applied field leading to an increase in local tissue temperatures known as dielectric hysteresis.¹⁷ Tissue destruction occurs when tissues are heated to lethal temperatures (up to 150°C). Microwave power penetrates tissues of low electric conductivity such as lung and desiccated or charred tissue, as it does not rely on electrical conduction.

Cryoablation involves the rapid cooling of the tissues by means of the Joule–Thompson effect, whereby rapid expansion of a high-pressure gas^{12,18} (typically argon) causes rapid tissue cooling. Sequentially, cooling and warming augments cellular damage.^{12,19} The optimal temperature to ensure tumor death is in the range of – 50°C. Cryoablation confers a benefit over other thermal ablation modalities because the ice ball created during freezing is visible on computed tomography (CT), allowing the operator to monitor the extent of the ablation.²⁰ This is particularly helpful during ablation of soft tissue and bone tumors; however, the advancing edge of ice is less conspicuous in the lung.

Irreversible electroporation is a nonthermal tumor ablation technique that causes irreversible cell damage to the cell membrane by applying pulsed electric fields of up to 3 kV/cm to the ablation target, thereby inducing cell death.^{21,22} Since it is nonthermal, the heat sink phenomenon is not observed; it also respects tissue interfaces, and therefore is felt to spare collagenous tissues, airways, and nerve sheaths.¹⁷ Its potential in preserving airways and mediastinal vessels makes it an attractive future option for the treatment of unresectable lung tumors in anatomically sensitive locations.

Tissue Characteristics

The electrical, thermal, and mechanical properties of the target tissue depend on its water content and cellular makeup. Compared with liver, normal lung tissue has low electrical and thermal conductivity, relative permittivity, and effective conductivity. Low electrical and thermal conductivity limits radiofrequency energy flow.²³ Conversely, lung tumors, with relatively densely packed cells, behave similar to solid organs and therefore have higher conductivity than adjacent lung tissue. The low relative permittivity and effective conductivity of lung is advantageous in the case of MWA, and allows deeper tissue penetration than in solid organs. Cryoablation in lung is limited by its inherently low thermal conductivity;

fortunately, this can be overcome with progressive ice ball formation, which increases the thermal conductivity of the ablation target.²⁴

Heat Sink

Heat loss or “sink” is a process that limits thermal ablation due to convective tissue cooling (or heating in the case of cryoablation). Blood vessels in the target tissue provides a conduit for cooling or heating that can occur in all methods of thermal ablation, but is clinically observed in varying degrees. The presence of vessels > 3 mm in diameter in direct contact with the ablation target is associated with decreased coagulation necrosis in RFA and an increased rate of local recurrence in both liver and lung.^{25,26} MWA is less sensitive to the heat sink effect because it produces heating of greater magnitude and better tissue penetration than RFA.²⁷ Cryoablation has not been clinically demonstrated to suffer from a measurable sink effect in lung or liver.^{28,29}

Indications for Thermal Ablation of Lung Carcinoma

The gold standard of care for stage I NSCLC is surgical resection. Unfortunately, only one-third of patients are eligible for surgical intervention.³⁰ Thermal ablation can be offered to patients with stage I NSCLC who are not candidates for curative surgical resection as a result of cardiorespiratory comorbidity or insufficient vital lung function using criteria of inoperability published by the Society of Interventional Radiologists.³¹ Patients should be assessed by an interdisciplinary team and the maximum tumor diameter should probably not exceed 3 to 3.5 cm.³²

As the duration of clinical experience and the volume of published data on RFA is greater than that of other ablation modalities, RFA is the first ablation modality to receive endorsement by means of clinical guidelines.³³ However, MWA for NSCLC is likely to be increasingly used, given its theoretical advantages over RFA including a less severe heat sink effect and faster, greater heating.³⁴ Cryoablation and irreversible electroporation have not been formally recommended for use in lung tumor ablation, outside of a research setting.²⁰

As well as a therapy for medically inoperable stage I lung carcinoma, RFA has also been proposed as therapy for the following indications: advanced-stage lung tumor treated with definitive radiation and chemotherapy with a persistent, solitary, peripheral nodule; recurrent isolated tumor after previous lung resection³⁵; and salvage therapy of residual or recurrent disease after resection, chemotherapy, and/or radiation.³⁶ Contraindications for treatment include underlying interstitial disease (such as pulmonary fibrosis) due to the risk of severe pulmonary failure and uncorrectable coagulopathy.^{32,37,38}

Complications

Major complications as a result of thermal ablation are rare. The reported major complication rate after lung RFA is 9.8%

and includes aseptic pleuritis, pneumonia, lung abscess, hemorrhage, and pneumothorax requiring pleurodesis.³⁹ Self-limiting pneumothorax after RFA has a reported incidence of 22.4%, while pneumothorax requiring chest tube insertion has an incidence of 22.1% in a large cohort of patients.³⁹ More rare major complications include bronchopleural fistula, tumor seeding, and nerve or diaphragmatic injury. Nerve injury incidence, affecting the phrenic, brachial, left recurrent laryngeal, intercostal nerves, and the stellate ganglion is reported to be 0.3%.⁴⁰ Self-limiting rib fractures have been reported in 13.5% of patients treated with RFA and MWA of lung tumors; tumor location close to the chest wall predisposes patients to this complication.⁴¹ Similar complication rates including self-limiting pneumothorax (27%) and pneumothorax requiring chest tube insertion (12%) are described after MWA.⁴² Skin burns are rare, with an incidence of 0.3%⁴²; one cohort study describes two patients who underwent MWA and experienced skin burns, likely due to shaft heating, one of which required debridement and chest wall reconstruction.⁴²

Complications from cryotherapy of lung tumors follow trends similar to previously described ablation modalities. There is a theoretically greater risk of hemorrhage with cryotherapy due to the lack of a cautery effect observed with heat-based ablation. Two studies of cryoablation-related complications describe a hemoptysis rate of 36.8 to 55.4% and a massive hemoptysis rate of 0 to 0.6%.^{43,44} Pneumothorax and pleural effusion are the most common reported complications with incidences of 61.7 and 70.5%, respectively. Less common complications include phrenic nerve palsy (0.5%), frostbite (0.5%), empyema (0.5%), and tumor seeding (0.2%).

The reported mortality rate after lung tumor RFA is 0.4%. Intraprocedural or periprocedural death has not been described after cryoablation or MWA. One death as a result of a

delayed infective complication at 6 months after MWA and two deaths as a result of exacerbation of idiopathic pulmonary fibrosis after cryoablation have been described.^{45,46}

Careful patient selection may minimize the risk of complications. For example, in the largest case series reporting complications after RFA, previous systemic chemotherapy was a significant risk factor for aseptic pleuritis, while prior external beam radiotherapy and advanced age were significant risk factors for pneumonia. Patients with emphysema have a greater predilection for lung abscess and pneumothorax requiring pleurodesis. Serum platelet count ($\leq 180,000$ cells/ μ L) and tumor size (> 3 cm) are significant predictors for hemorrhage.³⁹

Reported Outcomes

The literature analyzing outcomes after RFA as a therapy for stage I primary NSCLC is limited by study size and population heterogeneity, and in terms of concomitant treatments such as chemotherapy and in-field radiation.^{47,48} When interpreting long-term survival data, it is important to bear in mind the influence of this patient population's substantial medical comorbidities. For example, the all-cause mortality rate for inoperable patients with early-stage lung carcinoma has been reported to be as high as 19.1% in the short to medium term, significantly higher than that of operable patients (3.4%).⁴⁹ Allowing for these limitations, nine studies report recurrence rates after RFA of stage I NSCLC; the aggregate rate of local progression is 29% (75/260 patients)^{48,50–56} and metastasis at any site is 31% (42/137) (►Table 1).^{48,50,52,54,55} Reported 3- and 5-year survival rates range from 36 to 88%^{48,53,55–57} and 19 to 27%, respectively.^{48,50,57} Estimated 3-year cancer-specific survival rates range from 59 to 90%.^{48,50,53,56} Outcomes may differ based on tumor cell type. Lanuti et al

Table 1 Patient outcomes after thermal ablation of stage 1 primary lung carcinoma as a primary therapy

Authors	Modality	Median tumor size (range) mm	2-year survival (%)	3-year survival (%)	5-year survival (%)	3-year CSS (%)	Local progression N (%)	Any metastasis N (%)
Pennathur et al ⁵²	RFA	26 ^a (16–38)	68	NR	NR	NR	3/19 (16)	NR
Hiraki et al ⁵³	RFA	20 (13–60)	84	83	NR	83	7/20 (35)	4/20 (20)
Simon et al ⁵⁷	RFA	30 ^a (10–75)	57	36	27	NR	NR	NR
Hsie et al ⁵⁴	RFA	NR	NR	NR	NR	NR	1/12 (8)	4/12 (33)
Lanuti et al ⁵⁵	RFA	20 ^a (8–44)	78	47	NR	NR	12/34 (35.2)	15/34 (44)
Zemlyak et al ⁴⁸	RFA	NR	NR	87.5	19	87.5	4/12 (33)	3/12 (25)
Hiraki et al ⁵⁶	RFA	21 ^a (7–60)	86	74	NR	80	16/52 (31)	NR
Ambrogi et al ⁵⁰	RFA	26 (11–50)	NR	NR	25	59	13/59 (22)	16/59 (27)
Dupuy et al ⁵¹	RFA	NR	70	NR	NR	NR	19/52 (37)	NR
Liu and Steinke ⁵⁸	MWA	24 (8–40)	NR	NR	NR	NR	5/15 (33)	NR
Zemlyak et al ⁴⁸	Cryoablation	NR	NR	77	77	90.2	3/27 (11)	2 (7.4)
Yamauchi et al ⁴⁶	Cryoablation	14 (5–30)	88	88	NR	NR	1/34 (3)	6/34 (18)

Abbreviations: CSS, cancer-specific survival; MWA, microwave ablation; NR, not reported; RFA, radiofrequency ablation.

^aMean.

describe a 90% local control rate of adenocarcinoma in situ or minimally invasive adenocarcinoma after RFA, compared with 68.5% for all cell types.⁵⁵

In the microwave and cryoablation literature, the outcomes of patients with early-stage lung carcinoma are often not reported separate to those with metastatic lesions; therefore, specific long-term survival data for stage I NSCLC treated with microwave and cryoablation are needed. One initial report on the outcomes of patients with stage I lung carcinoma treated with MWA describes a local recurrence rate of 26% at a median follow-up of 12 months.⁵⁸ Two studies reporting outcomes of patients with stage I lung carcinoma treated with cryoablation describe a local recurrence rate of 3 and 11%, overall 3-year survival rates of 77 and 88%,^{46,48} and a 3-year cancer-specific survival rate of 90.2%.⁴⁸

Imaging Surveillance

In clinical practice, positron emission tomography (PET)-CT and/or CT are typically performed within 2 months of thermal ablation, to establish a new baseline for surveillance. The patient then undergoes imaging every 3 months for a year, and annual surveillance thereafter. An initial perilesional ground glass halo with or without an increase in lesion size on CT during the first 2 months is likely due to inflammation and is expected to decrease in size over time. The expected CT appearances after 6 months include¹: a residual nodule that is stable or decreasing in size²; an elongated linear nodule due to fibrosis³; atelectasis; or⁴

cavitation (►Fig. 1). Complete disappearance of the initial nodule is rarely observed.⁵⁹

PET-CT at 24 hours and at 1 month after ablation can exhibit tracer activity at the ablation site despite adequate treatment; this finding is likely due to inflammation, and is expected to resolve by 3 months postablation.⁶⁰ The absence of tracer activity at the site of ablation on PET-CT at 6-month postablation has been shown to correlate best with clinical outcome at 1 year.⁶¹ The expected early PET-CT appearance is that of a relatively uniform ring of low level FDG activity (about the same as mediastinal blood pool activity) and central photopenia, a finding that may persist until 6 months and should resolve by 12 months (►Fig. 2).⁶²

Residual disease or recurrence of disease may be present if there is contrast enhancement in the ablation zone, peripheral nodular growth, a change within the ablation zone from ground glass to solid opacity, regional or distant lymph node enlargement, new sites of intrathoracic disease, or new extrathoracic disease. Increased metabolic activity centrally or in a nodular pattern at the ablation site on PET-CT more than 3 months after ablation also likely indicates residual or recurrent disease (►Fig. 3).⁶³

Identifying the Ideal Ablation Candidate

Ablation of stage I primary NSCLC can be considered for patients who are not candidates for curative surgical resection as a result of cardiorespiratory comorbidity or poor vital lung function. Patients being considered for ablation should

Figure 1 Expected CT appearances after thermal ablation. A left lower lobe adenocarcinoma exhibits homogenous ground glass opacity (arrow) before ablation (A). The lesion is treated with a single probe RFA (B), and CT immediately after treatment exhibits new consolidation and minor perilesional ground glass opacity, likely due to hemorrhage (C). CT 2 weeks later exhibits a perilesional ring of increasing opacity, known as the cockade phenomenon (D). At 3 months after radiofrequency ablation, cavitation has developed (arrow) (E), followed by fibrosis at 12 months after RFA, which has an elongated linear appearance (F). CT, computed tomography; RFA, radiofrequency ablation.

Figure 2 Expected PET-CT appearances after thermal ablation. Unenhanced CT (A), fused PET-CT (B), and PET (C) images of a left lower lobe adenocarcinoma 2 months after radiofrequency ablation exhibits a residual lung nodule with a halo of peripheral activity in the ablation zone with central photopenia (B and C). CT, computed tomography; PET, positron emission tomography.

have an Eastern Cooperative Oncology Group performance status of < 3 and a life expectancy of more than 1 year.^{64,65} Lesions larger than 3 cm have a higher incidence of tumor recurrence.⁶⁶ Lesions within 1 cm of sensitive structures such as the trachea, main bronchi, esophagus, and central vessels are at higher risk of complications and may often be incompletely ablated due to heat sink effect.³⁰

Thermal Ablation in Combination with Adjunctive Therapies

Combined therapy using thermal ablation and radiation therapy may synergistically result in an improved survival compared with either modality alone. Thermal ablation followed by external beam radiation therapy for inoperable stages I and II NSCLC resulted in a local recurrence rate of 11.8% for tumors smaller than 3 cm and 33.3% for larger tumors, with a low complication rate in a report of 41 patients.⁶⁷ A smaller series of 24 patients treated with a combination of RFA and adjuvant external beam radiation therapy resulted in a local recurrence rate of 9%.⁶⁸ However, the use of external beam radiotherapy with RFA increases the potential for toxicity to normal lung tissue. A potential solution to this problem may be the use of brachytherapy to optimize local control while sparing normal lung tissue. RFA followed by high dose rate brachytherapy, delivered via a catheter, has been shown to yield good local control in 82% of studied patients while lowering the incidence of pulmonary toxicity.⁶⁹ The synergistic effect is thought to be due to the fact that thermal ablation is most effective in the central portion of the tumor, while brachytherapy can better treat the tumor margin. In addition, neovascularity created by thermal ablation produces superoxide anions and free radicals that results in DNA damage. This damage is hypothesized to enhance the effect of radiation therapy.⁶⁵

Figure 3 PET-CT appearance of local recurrence after thermal ablation. This patient with left upper lobe squamous cell carcinoma after a right pneumonectomy underwent radiofrequency ablation. Residual tumor is demonstrated in the medial aspect of the lesion where peripheral nodular opacity (arrow) (A) and increased metabolic activity (B) are shown. CT, computed tomography; PET, positron emission tomography.

Conclusion

Thermal ablation is an effective therapy in the treatment of localized NSCLC that limits damage to the adjacent normal lung. Thermal ablation technologies used in the treatment of localized NSCLC include RFA, MWA, and cryotherapy. Patient selection is based on patient and lesion characteristics, and influences clinical outcome in terms of local recurrence, survival, and complication rates. The ideal candidate for thermal ablation has a lung tumor size of less than 3 to 3.5 cm in a location that avoids sensitive structures and minimizes heat sink effect. Clinical outcomes after RFA of stage 1 NSCLC are good in terms of local recurrence rate and cancer-specific survival. Comprehensive outcome data after MWA and cryotherapy of primary lung tumors are awaited. Thermal ablation offers a therapeutic alternative to patients ineligible for surgical intervention. Imaging surveillance after lung tumor ablation comprises both anatomic and metabolic imaging. Future directions for lung tumor ablation include a combined approach using thermal ablation and other therapies, which may synergistically result in an improved clinical outcome.

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