Image-guided Percutaneous Ablation of Lung Malignancies

A Minimally Invasive Alternative for Nonsurgical Patients or Unresectable Tumors

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Summary: **Lung cancer remains the malignancy with the highest mortality and second highest incidence in both men and women within the United States. Image-guided ablative therapies are safe and effective for localized control of unresectable liver, renal, bone, and lung tumors. Local ablative therapies have been shown to slow disease progression and prolong disease-free survival in patients who are not surgical candidates, either due to local extent of disease or medical comorbidities. Commonly encountered complications of percutaneous ablation of lung tumors include pneumothorax, pleural inflammation, pleural effusions, and pneumonia, which are usually easily managed. This review will discuss the merits of image-guided ablation in the treatment of lung tumors and the underlying mechanism, procedural techniques, clinical utility, toxicity, imaging of tumor response, and future developments, with a focus on radiofrequency ablation.**

Key Words: radiofrequency ablation, lung malignancy, non–small cell lung carcinoma, pneumothorax, laser, microwave, cryoablation, irreversible electroporation, impedance, heat sink

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Lung cancer is the leading cause of cancer-related deaths and has the second highest incidence in both men and women within the United States.[1] Treatment options largely depend on the stage or extent of the disease. Surgical excision of the tumor is preferred in the treatment of non–small cell lung cancer (NSCLC) or metastases to the lung if the lesion is amenable to resection and the patient is a surgical candidate.[2,3] Advanced disease (> 50% of cases at initial presentation) is usually treated with chemotherapy and/or radiation therapy, and has significantly lower 5-year relative survival rates.[4] Ablative therapies can be used as alternative modalities for localized control in the management of unresectable lung tumors. Thermal ablative technologies include heat-based modalities such as radiofrequency ablation (RFA), microwave ablation (MWA), and laser-induced interstitial thermotherapy (LITT) as well as the extreme cold-based modality of cryoablation (Table 1). Heat-based modalities cause localized tissue heating which results in irreversible coagulative tumor necrosis and localized tumor control.[5] Cryoablation involves cycles of cellular freezing and dehydration causing cell death. Irreversible electroporation (IRE) is a newer technology that uses electrical pulses to increase permeability of the cell membrane inducing cellular apoptosis. The primary goal of lung tumor ablation is selective tumoricidal effect and localized control in a curative setting, but it can also be utilized as a neoadjuvant or palliative treatment modality. Ablation performed with a percutaneous image-guided approach offers the advantages of decreased morbidity and mortality with relative preservation of pulmonary function.

RFA

RFA involves delivery of high-frequency alternating current (450 to 500 kHz) within the tumor and immediate vicinity resulting in ionic agitation, frictional heat (50 to 105°C), with subsequent denaturation and coagulation necrosis of the tissue. RFA is an effective and established treatment modality, which can be utilized as a primary therapy, neoadjuvant treatment modality, or as a bridge to other therapies. One of the primary advantages of image-guided RFA is the ability to ablate the

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TABLE 1. Comparison of Ablative Therapies Utilized in Local Control of Lung Malignancies[5,6]

Ablation Type	Radiofrequency	Microwave	Laser	Cryotherapy
Mechanism	Resistive heating with alternating current; 450-500 kHz	Electromagnetic waves oscillating the dipole water molecule and increased temperature; 1-2 GHz	Monochromatic laser optical fiber light with direct increased temperature; 1064 nm	Rapid expansion of gas through a low-pressure probe results in freezing temperature
Guidance and monitoring	CT	CT	CT, MRI	CT, MRI
Impedance	Yes	No	No	No
Interelectrodal interference	Possible	No	No	No
Thermometry	No	No	Possible	No
Grounding pads	Yes (not required in bipolar system)	No	No	No
Heat sink effect or convectional cooling[5,7]	Yes	No; paradoxical response[8,9]	No	No
Clinical efficacy	Localized control	Similar (pending further studies)	Similar (pending further studies)	Similar (pending further studies)
Complications	Nontarget heating	Minimal nontarget heating	Increased	Minimal
Relative merits and limitations	Easily available and widely accepted Issues of impedance and nontarget heating	Higher and uniform temperature Increased target volume Decreased treatment times	Real-time MR monitoring Requires utilization of coaxial system for insertion of laser probe Larger size of probe Higher treatment times with increased risk of pneumothorax and bleeding	Relatively more effective in tumors near vital structures and vasculature Less pain complication[10]

CT indicates computed tomography; MRI, magnetic resonance imaging.

tumor and a desired radius of surrounding tissue while sparing the unaffected lung parenchyma. Selective targeting through a minimally invasive approach decreases the toxicity and complications with relative preservation of pulmonary function. RFA is currently utilized for treatment of different tissue malignancies including liver, renal, and bone tumors and has also been shown to be effective and safe for localized control of lung malignancies.[5,6]

Devices

Commercially available RFA devices within the United States include LeVeen (Boston Scientific/RadioTherapeutics, Watertown, MA), RITA (Angiodynamics, Latham, NY), and Cool-tip (Covidien, Boulder, CO). The optimal choice of a particular device depends on tumor location, tumor size, operator experience, and institutional preference.[11] The basic principles guiding the RFA treatment remain the same for all available systems. RFA technology is currently approved by the Food and Drug Administration in the United States for general indications of soft-tissue cutting, coagulation, and ablation by thermal coagulation necrosis but not specifically for the treatment of lung tumors. RFA of lung tumors is considered an off-label use until further evidence of safety and effectiveness is established.

RFA devices have been modified since the introduction of single-needle electrodes to deliver higher energy safely and more effectively with increased size of ablation zones. Multiprobe arrays (Starburst, Angiodynamics; LeVeen, Boston Scientific) have deployable electrodes that result in a larger reproducible area of tumor ablation with a well-defined geometry, obviating

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the need to work with complex configurations which can be required with use of multiple single-probe arrays. Internally cooled tip electrodes (Cool-tip; Covidien) are designed such that cooled saline is perfused within a lumen in the shaft to the needle tip and returned through a different lumen back to the collection unit. By cooling the tip, there is decreased charring of tissue surrounding the electrode which reduces the electrical impedance and allows for more efficient energy deposition. Closely spaced cluster electrodes (Cool-tip; Covidien) are available which create a confluent area of ablation by appropriately spacing 3 single electrodes 5 mm apart. Perfusion electrodes (Starburst, Angiodynamics) can be used to elute normal or hypertonic saline into the target tissues, increasing the electrical conductivity and reducing tissue resistance. Different modes of energy delivery, such as energy pulsing, gradual ramp up, stepped deployment, and electrode switching aim to decrease the tissue impedance and increase conduction surrounding the electrode with a net effect of increased energy delivery to the deeper ablation zone.

TABLE 2. Indications and Contraindications for Lung RFA[12–14]

Indications
Primary nonresectable NSCLC or metastatic predominant lung malignancy
Nonsurgical candidate (poor cardiopulmonary reserve, refusal to surgery, other comorbid conditions)
Primary radiation, chemotherapy, or surgical therapy failure
Residual primary tumor with control of nodal disease
Single nonresponding focus
Persistent satellite nodule
Repeat RFA, after 1 y time interval[15]
Primary < 3 cm (relative: < 5 cm)
≤ 5 metastatic lesions per lung, each < 3 cm (relative: < 5 cm)
Palliative treatment of symptoms
Bridging therapy
Contraindications
Absolute
Uncorrected coagulation profile
Active infection or bacteremia
Lesion near vascular structures due to heat sink effect[7]
Central/hilar lesions or near vital structures < 1 cm (cryoablation can be considered)
Resectable/surgical candidate
Lesion not safely accessible
Relative
Large tumor (> 5 cm, relative contraindication)
Forced expiratory volume in 1 s (FEV_1) < 1 L, relative contraindication[16]
Predominant or active extra pulmonary malignancy
Short life expectancy

NSCLC indicates non–small cell lung cancer; RFA, radiofrequency ablation.

RFA Procedure

The decision to utilize RFA to treat lung tumors usually involves an interdisciplinary team discussion as well as an extensive workup to determine patient eligibility and select optimal tumors for ablative therapy (Table 2). The ideal target lesion for RFA is a small slow growing tumor in the lung periphery, which is easily accessible percutaneously. "Heat sink" refers to convectional heat loss due to blood flow within large vascular structures adjacent to the tumor which prevents achievement of lethal temperatures and results in an incomplete target ablation.[5,7] Ablation of central or hilar tumors carries an increased risk of vascular or bronchus injury. The initial consultation includes review of recent computed tomography (CT), ^{18}F-FDG positron emission tomography (PET), pulmonary function tests, and pathology. Patient history is also reviewed for presence of artificial pacemakers or automatic implantable cardioverter defibrillators, which can be affected by the alternating current of the RFA electrode. Routine preprocedural laboratory values (complete blood count including platelets, and coagulation labs) are obtained. Anticoagulation and antiplatelet agents should be stopped for 5 to 7 days before the procedure.[17] Although evidence is limited, some institutions consider broad-spectrum antibiotic prophylaxis before and after the procedure based on the potential for infection within the necrotic tissues, especially in diabetic patients.[12]

The patient is positioned supine or prone within the CT scanner based on the preferred approach to the lesion. Deep sedation or general anesthesia is recommended for patient comfort, better cough and pain control, and operator convenience.[18,19] Within the RFA circuit, the electrode or probe acts as the cathode and grounding pads placed on the patient's thighs serve as the anode, completing the circuit during the ablation process. The grounding pad temperatures are monitored during the procedure to prevent overheating and skin burns. When positioning the patient and planning the trajectory, care should be taken to assure that the inserted ablation probe will clear the opening of the CT scanner to facilitate intraprocedural imaging. CT-fluoroscopy can provide real-time

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guidance at the expense of increased radiation exposure to the operator. Magnetic resonance imaging (MRI) guidance and monitoring are not compatible with RFA due to the interference from electromagnetic radiation. The needle trajectory is planned using the most direct and safest approach, avoiding passes through bullae, fissures, or large vessels. Appropriate localization also involves placement of the conductive tip centrally within the lesion, and in certain electrode designs, the tines are deployed throughout the tumor (Fig. 1). The ablation process involves delivery of a predefined energy to maintain a target temperature for a certain time period based on the device and institutional experience. Temperatures higher or lower than the recommended range may result in incomplete ablation. "Roll off" is defined as an increased impedance with decreased flow of current seen on the generator instrumentation after an ablation period. Achieving "roll off," while not necessary, may be predictive of an effective ablation. A target of approximately 1 cm margin around the lesion is planned to treat microscopic disease and tumoral extension into surrounding lung tissue. On the postablation CT scan images, ground glass changes seen on imaging are often used as a surrogate for zone of ablation (Fig. 1). These changes, however, may not reliably indicate the true extent of coagulative necrosis.[20] Tract ablation is often performed to cauterize the tract and may decrease the incidence of tumor seeding and bleeding along the needle track.[21,22] This is performed by delivering heat energy as the probe is being removed slowly. After removal of the probe, evaluation for postprocedural pneumothorax should be performed. A pneumothorax, if present, can be aspirated immediately. Follow-up chest radiographs are performed at 1 and 4 hours after the procedure in our institution. Procedural and postprocedural pain control is

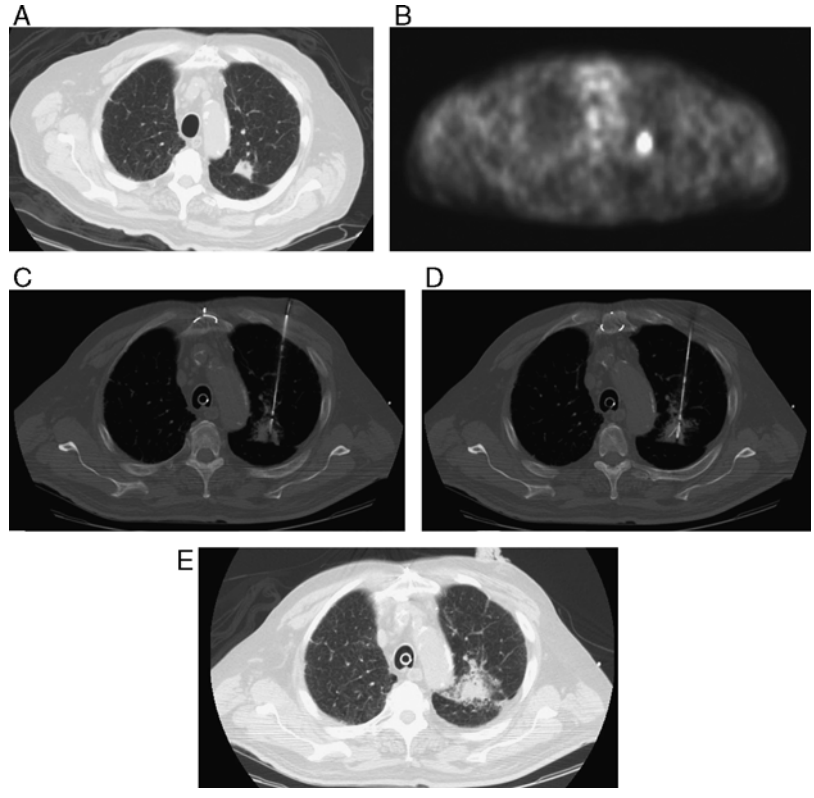

FIGURE 1. RFA technique and expected immediate postprocedural changes. A and B, CT and PET scan images in a 79-year-old male reveals a left upper lobe spiculated nodule with intense uptake consistent with known malignancy. C, The image obtained during the ablation procedure demonstrates insertion of the needle electrode within the central deep portion of the nodule. D, The image demonstrates deployment of the tines throughout the lesion for an effective ablation volume within and surrounding the lesion. E, Postprocedural image shows the expected changes consistent with coagulation and hemorrhage. The target ablation zone extends up to 1 cm surrounding the lesion to account for microscopic tumor involvement within the periphery based on traditional surgical experience. Complete target ablation is an important factor determining decreased local recurrence and improved survival outcomes.

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very important to prevent secondary medical complications. Antiemetic prophylaxis can also be administered. The patient is typically discharged on the next day, however, some centers discharge on the same day of the procedure.

The technical success of the procedure is usually very high.[23,24] The manufacturer's algorithms should be followed for considerations of technique, energy, and ablation time based on the needle and generator combination. Modifications of the technique can be performed for individual cases and lesions to facilitate a safe and effective ablation (Table 3). For example, a larger lesion might be treated with overlapping volumes from multiple probes. Artificial pneumothorax can be created while treating pleural and subpleural lesions to limit pain complications and nontarget injury.

TABLE 3. Practical Considerations and Useful Procedural Tips[6,16,25–28]

Clinical Scenario	Significance or Technical Consideration
Large lesion	Overlapping target volumes achieve larger ablation zone
Pleural based or subpleural lesion	Pneumothorax is created to prevent the ablation zone extending to the ribs/chest wall and pleura, thereby minimizing the complications and pain
	A longer needle track is advisable for ease of procedure
Para-aortic lesions	Intentional pneumothorax as noted in above situation for safe and effective ablation
Beneath the rib	CT fluoroscopic guidance with gantry tilt
Elderly frail patient	Lung biopsy followed by immediate ablation within the same setting to decrease procedure-related complications
Chasing the lesion	Prudent selection of the needle track beforehand avoids injury to vital structures if the nodule is pushed away during the procedure
Diaphragmatic lesions	General anesthesia might facilitate accurate needle placement
Close to vasculature	Temporary occlusion, investigational
Charring and impedance	Pause RFA, retract, rotate, redeploy and ablate
Pacemaker, defibrillator, or metallic implants	Cardiology consult for temporary suspension
	Grounding pads placed as far as possible
Pneumothorax precautions	Similar considerations and technique as for lung biopsy procedures
Decrease the tumor seeding along the tract	Minimize the needle passes
	Tract ablation
Prevention of air embolism	Minimize the manipulation
	CT fluoroscopy decreases chances of traversing the vessels
Pulmonary hemorrhage	Might obscure other adjacent lesions in dependent location
	Limits treatment after biopsy within the same session
	Reschedule treatment if target lesion is obscured

CT indicates computed tomography; RFA, radiofrequency ablation.

Clinical Utility

Tumor ablation is an effective treatment modality in the appropriate patient cohort who cannot undergo surgery either due to underlying comorbidities or unresectable disease from local tumor extension. Several retrospective studies have demonstrated the clinical efficacy of RFA for local tumor control in the lung since it was first reported by Dupuy et al[29] in 2000. Although these studies widely differ in design and endpoint evaluation, there is consensus within the reported literature on ablation, suggesting improved local control in small and peripheral unresectable lesions (Table 4). The reported technical success and median rate of complete ablation is very high.[23,24] Successful tumor ablation is inversely related to the size of the target lesion and directly related to the post-treatment ground glass changes within and surrounding the lesion.[50] On a systematic review, the median progression-free interval for RFA-treated lung lesions (mean number of lesions, 1 to 2.8; mean size of lesions, 1.7 to 5.2 cm) was 21 months. Survival rates at 1, 2, and 3 years were 63-85%, 55-65%, and 15-46%, respectively, with a reported median local recurrence of 11.2%.[24]

Patients with stage-I NSCLC who are at high risk for surgery can benefit from sublobar resection or local ablative therapies. Kim et al[51] and Lee et al[52] reported comparable survival rates between RFA and surgery for early-stage elderly NSCLC patients. A study by Zemlyak et al[53] reported comparable survival outcomes at 3 years for sublobar resection, radiofrequency, and cryoablation in stage-I NSCLC patients not fit for lobectomy. MWA and laser ablation offer theoretical advantages in comparison with RFA including increased energy deposition with more

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TABLE 4. Literature Review on Role of RFA in Treatment of Lung Tumors

Population	Results	Complications
NSLC and mets, 30 patients, retrospective[18]	mS: 19.7 mo (complete necrosis) vs. 8.7 mo (partial necrosis); complete necrosis 100% with lesions < 3 cm	10% major complications
CRC mets, 23 patients, retrospective[30]	CR: 42.5%, PR: 12.5%, SD: 10%, PD: 35% at 1 y	26% chest tube placement
NSLC stages I-IV, 18 patients, medD: 2.8 cm, retrospective[31]	Local progression at 14 mo median follow-up: 38%; median PFS time: 18 mo	40% chest tube placement
NSCLC and mets, 54 patients, mD: 2.4 cm, retrospective[32]	Mean (median) OS time: 17.3 (28.9) mo Mean (median) local progression-free interval: 12.9 (24.1) mo	12.7% morbidity
NSCLC and CRC mets, 31 patients, mD: 2.2 cm, prospective[33]	Mean follow-up of 11.4 ± 7.7 mo, overall local recurrence rate 20% for NSCLC and 9.5% for CRC mets	Minimal
CRC mets, 55 patients, mD: 2.1 cm, prospective study[34]	Overall medS time: 33 mo Actuarial 1-, 2-, and 3-y survival of 85%, 64%, and 46%, respectively	18% chest tube placement
NSCLC, 50 patients, retrospective[35]	CR on imaging of 59% at median follow-up of 31 mo; medS: 25 mo	4% chest tube placement
Mets from CRC, 27 patients, mD: 1.5 cm, retrospective[36]	1-, 2-, and 3-y OS of 96%, 54%, 48%, respectively	7% chest tube placement
NSCLC stage I, 20 patients, mD 2.4 cm, retrospective[37]	Median local progression: 35% patients in a median of 9 mo; mS: 42 mo OS: 90%, 84%, 74% and CSS: 100%, 93%, 83% at 1-, 2-, and 3-y, respectively	4% chest tube placement
NSLC stage I, 19 patients, mD: 2.6 cm, retrospective[38]	MTP: 27 mo; 1 y survival: 95%	63% chest tube placement
NSLC and mets, 153 patients, mD: 2.7 cm in local control group and 6.1 cm in symptom palliation group, retrospective[39]	5 y survival: 27% (NSCLC), mets (57%), 47% (< 3 cm), 25% (> 3 cm)	10% chest tube placement; 2.6% procedure-specific 30 d mortality rate
CRC mets, 71 patients, mD: 2.4 cm, retrospective[40]	47% intrapulmonary recurrence; 3 y survival rate: 46%	20% chest tube placement; 1% empyema
NSCLC stage I, 31 patients; mD: 2 cm, retrospective[41]	31.5% local recurrence; 2- and 4-y survivals: 78% and 47%; medS time: 30 mo	8% chest tube placement
NSCLC and mets, 106 patients, mD < 1.7 cm, prospective single-arm multicenter clinical trial[23]	OS: NSCLC (1 y: 70%, 2 y: 48%), mets (1 y: 89%, 2 y: 66%) CSS: NSCLC (1 y: 92%, 2 y: 73%), mets (1 y: 91%, 2 y: 58%)	23% chest tube placement
Metastases from musculoskeletal sarcomas, 20 patients, mD 1.4 cm, retrospective[42]	1- and 3-y survival rates: 58%, 29% medS time: 12.9 mo	38% chest tube placement
CRC mets, 78 patients, mD: 2 cm, retrospective[43]	1-, 3-, and 5-y local tumor progression rates: 10.1%, 20.6%, and 20.6%; 1-, 3-, and 5-y survival rates: 83.9%, 56.1%, and 34.9%; medS time: 38 mo	14.2% chest tube placement
Mets, 148 patients, mD: 4 cm, prospective[44]	Median PFS: 11 mo median OS: 51 mo 3- and 5-y survivals: 60% and 45%	30% chest tube placement
Lung primary and mets, 105 patients, mD: 1.3 cm, retrospective[45]	Overall local control rates at 6 mo: 97%, 12 mo: 86%, 18 mo: 81%, and 24 mo: 76%	Not reported
Lung primary and mets, 72 patients, mD: 2.1 cm, retrospective[46]	Local progression at 14 mo: 32% 1-, 2-, 3-, and 5-y overall local control rates were 61%, 57%, 57%, and 38%, respectively	14% major complications; 2% chest tube placement
NSCLC stage I, 57 patients, mD: 2.6 cm, prospective[47]	Median OS and CSS: 33.4 and 41.4 mo, respectively Cancer-specific actuarial survival: 89% at 1 y, 59% at 3 y, and 40% at 5 y	7% chest tube placement
Resected colorectal liver metastases with concomitant or recurrent pulmonary metastases, 64 patients, mD: 3.9 cm, retrospective[48]	Sequential treatment group: medS of 31 mo and DFS of 9 mo Salvage treatment group: medS of 59 mo and DFS of 16 mo	16% chest tube placement

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TABLE 4. (*continued*)

Population	Results	Complications
Recurrent NSCLC after surgery, 44 patients, mD:1.7 cm, retrospective[49]	1-, 3-, and 5-y OS: 97.7%, 72.9%, and 55.7%, respectively; 1- and 3-y recurrence-free survival rates: 76.7% and 41.1%	5.5% major pneumothorax

CR indicates complete response; CRC, colorectal; CSS, cancer-specific survival; DFS, disease-free survival; mD, mean diameter; medD, median diameter; medS, median survival; mets, metastasis; mS, mean survival; MTP, median time to progression; NSCLC, non–small cell lung cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

selective and uniform heating of a larger tumor volume (Table 1). The clinical efficacy, however, described in the current literature does not demonstrate significant differences among the different ablative therapies. Prospective randomized studies with large populations are needed to define the exact role of RFA in relation to other localized forms of therapies. RFA can be performed after failure of other treatment modalities and can also be repeated after a time period of 1 year.[15] Utilization of RFA in conjunction with other modalities of treatment such as radiation and chemotherapy is an area of active research with encouraging results and prospective randomized large population would extend the arena of ablative therapies in future.[52,54–56]

Toxicity Profile

RFA is an established, well tolerated, and a safe procedure, which is able to ablate tumoral tissue while preserving lung function.[57] The procedure-related mortality and morbidity rates are low compared with surgical resection.[58] Zhu et al[24] conducted a systematic review of the available RFA data and reported a procedural mortality of 0-5.6% and morbidity of 15.2-55.6%. Most complication rates are related to electrode placement and nontarget tissue heating. Complication rates are increased in patients with prior lung surgery.[59] Pneumothorax is one of the most common complications reported in up to 4.5-61.1% of cases, with approximately 11% of these patients requiring treatment with a pleural chest drain.[12,24] Similar to any percutaneous lung procedure or biopsy, the risk for pneumothorax is dependent on multiple factors, including emphysematous lungs, the location of the target lesions, and number of needle passes.[60] Visualization of a pneumothorax during the procedure can be immediately addressed by evacuation of the air with a needle. A larger or symptomatic pneumothorax may need to be managed with the insertion of a pleural drainage catheter (Fig. 2). Chest radiograph monitoring is usually performed to document stability and interval resolution of a previously noted pneumothorax and for the rare complication of a delayed pneumothorax. Other common postprocedural complications including fever, pain, pleuritis, pleural effusions (0-4% requiring drainage), parenchymal hemorrhage (1-10%), and pneumonia (0-22%) are usually self-limited and easily managed. More severe complications include lung abscess (0-6%), hemoptysis (0-12%), hemothorax (0-2%), COPD exacerbation (0-6%), bronchopleural fistula (0.6%), pulmonary artery aneurysms, phrenic nerve injury (0-1%), brachial plexus injuries from positioning, and skin burns.[11]

Posttreatment Changes and Follow-up

Familiarity of expected postablation changes on imaging is important to distinguish them from residual tumor. Close follow-up with contrast-enhanced CT and ^{18}F-FDG PET scan is important to differentiate the postablative inflammatory changes from residual or recurrent neoplasm.[61] Routine follow-up imaging includes noncontrast-enhanced and contrast-enhanced chest CT scans at 1, 3, 6, and 12 months, and thereafter, annually to demonstrate the effectiveness of therapy. Currently available imaging criteria may be utilized to evaluate tumor response; however, there are no established or evidence-based guidelines specific to the assessment of ablated lung tumors. A recent article by Abtin et al[62] describes the early, intermediate, and late imaging features in detail within the postablation zone. Expected changes include, an increase in the mean diameter of the lesion with surrounding peripheral ground glass opacification for up to 3 months, followed by a decrease in size and subsequent cavitation. Progressive increase in size or contrast enhancement of a

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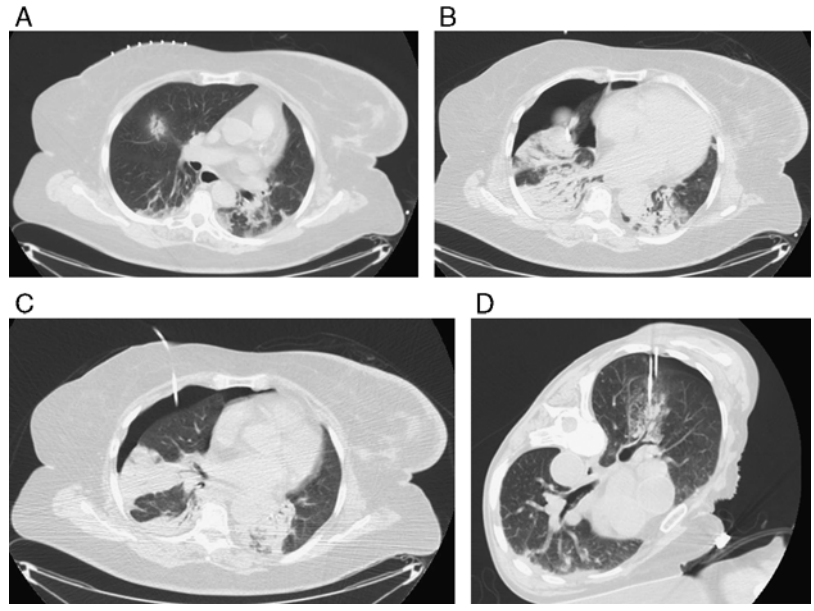

FIGURE 2. Complication of a large, worsening or symptomatic pneumothorax. A, The image demonstrates a 1 cm spiculated right middle lobe nodular malignancy on the preprocedural images. B, The image obtained during the ablation procedure demonstrates procedural changes and a small pneumothorax. The pneumothorax was subsequently found to be worsening and the patient became symptomatic. The RFA procedure was stopped, and a small pleural chest tube was inserted percutaneously (C). Pneumothorax is one of the common complications, and the rate of occurrence is similar to lung biopsy procedures. Prompt recognition of pneumothorax during and immediately after the procedure is crucial. Management of a large, worsening or symptomatic pneumothorax is performed with immediate needle evacuation or pleural chest drain. D, The image in a different patient demonstrates a small pneumothorax during the ablation procedure that was evacuated with a Yueh needle.

treated lesion is worrisome and may represent residual tumor tissue or recurrence. ^{18}F-FDG PET imaging is recommended a few months after treatment to allow for resolution of post-treatment inflammation that might result in false-positive uptake if performed without adequate interval.[63–65] Singnurkar et al[66] reported utility of PET scans before and after RFA to predict local recurrence. Failure of treatment usually occurs within the periphery of the lesion (the temperature achieved around the probe is inversely proportional to the square of the radius) and particular attention should be directed to this region on follow-up imaging (Fig. 3). A suspicious or nondiagnostic lesion at follow-up might require tissue sampling. There is a need for further research to standardize the timing and criteria for postablation assessment of tumoral response.

Recurrence, Prognosis, and Survival

The greatest benefit from RFA is seen with small peripheral lesions where high energy can be deposited safely. The median local recurrence rate for small lesions was 11.2% on a reported systematic review.[24] The rate of recurrence is increased for larger lesions due to a higher likelihood of incomplete ablation. Central lung lesions located near large vessels or heart (Fig. 4) may demonstrate increased rates of recurrence due to incomplete ablation from heat sink effect.[67,68] Other factors such as age above 70 years, male sex, and inability to achieve "roll off" were also predictors for local recurrence.[46] Predictors of survival and prognosis include lesion size, location, proximity to vasculature, completeness of ablation, concomitant or adjuvant therapies, tumor histology (eg, more favorable for solitary, metachronous colorectal metastasis), and status of extrapulmonary disease (Table 5). Best survival outcomes have been reported with ablation of a small single peripheral metastatic deposit or a small primary lesion < 3 cm.[13,34,39,46]

Other Ablative Treatment Modalities

MWA

MWA utilizes electromagnetic waves (1 to 2 GHz) to oscillate the dipole water molecule resulting in increased temperature and cell death. CT guidance is utilized for placement of the microwave antenna and the technical details are similar to RFA procedure. MWA effectively

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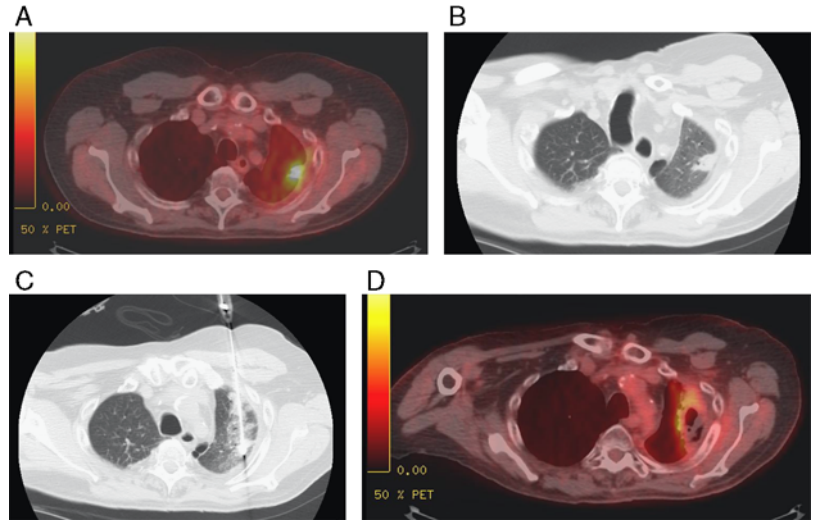

FIGURE 3. Local recurrence after RFA treatment. A, The fused PET-CT demonstrates intense uptake within the recently biopsied left upper lobe adenocarcinoma. B, Preablation CT demonstrates the target left upper lobe nodule. C, The accurate placement of an 18 G microwave probe within the center of the lesion, and subsequently the ablation was performed. D, Posttreatment PET-CT fused images performed 3 months after the treatment demonstrate residual uptake within the rim of the posttreatment cavity concerning for recurrence that was pathologically confirmed. Close imaging follow-up and knowledge of expected changes are integral to the patient care after ablation procedures.

delivers heat energy over a larger tumor volume within a shorter time.[70] As opposed to RFA, there are no limitations regarding interelectrode interference and multiple probes can be used at once for a synergistic effect. In addition, issues related to electrode impedance and complications from use of electric current are not seen with MWA. There is less concern for perfusion-mediated heat loss or heating sink effect due to a larger zone of microwave-related active heating as opposed to the passive thermal conduction seen in RFA. MRI monitoring is not possible due to the interference from electromagnetic radiation. In a retrospective analysis of 82 lung parenchymal lesions, MWA resulted in a 1-year local control rate of 67% with mean time to recurrence of 16.2 months. The survival rates were 83%, 73%, 61% at 1, 2, and 3 years, respectively.[71] Another prospective study reported MWA of 130 lung metastatic lesions with 73.1% complete ablation and minimal procedural complications. The 1- and 2-year survival rates were 91.3% and 75%, respectively.[72] MWA is gaining wide recognition, and is currently the procedure of choice at some institutions. Predominant advantages include a

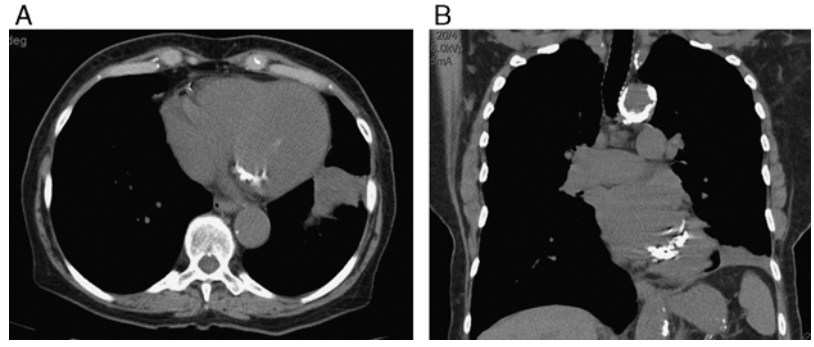

FIGURE 4. Central lesion. A and B, Axial and coronal CT chest images demonstrate a 3 cm lingular mass with a portion of it abutting the cardiac apex in a patient referred for RFA. The proximity of the mass to the cardiac apex would prevent effective energy deposition due to heat sink affect. In addition, there is increased risk of complications from nontarget ablation. The procedure was not performed and the patient referred for other treatment modalities. Similarly, lesions located centrally or within close proximity to the vascular structures would result in incomplete heat deposition and are contraindications for radiofrequency ablation treatment.

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TABLE 5. Factors Associated With Adverse Prognosis and Poor Survival

Primary[18,39,49,54]	Metastatic Disease[34,36,39,40,42–44,55,69]
Size > 3 cm	Largest size
Male gender	Central location
Incomplete ablation or necrosis	Repeat ablation
Standalone (compared with combined therapies)	Post-RFA CEA level in CRC
	Proximity to major pulmonary vessels
	Extrapulmonary metastasis
	Incomplete ablation of lesion
	Less disease-free interval
	No response to other treatments
	Standalone (compared with combined therapies)

CEA indicates carcinoembryonic antigen; CRC, colorectal carcinoma; RFA, radiofrequency ablation.

more effective ablation, shorter treatment times, and better safety profile from relative sparing of nontarget tissues.

LITT

In LITT, the monochromatic optical fibers deliver laser light that interacts with the tissues resulting in heating and coagulative necrosis.[11] The resulting cell death and histologic changes are similar to that of other hyperthermal ablations.[73] LITT is MRI compatible, which provides excellent anatomic detail and topographical accuracy. Another theoretical possibility with MRI monitoring is utilization of thermal-susceptible MRI sequences to monitor real-time temperature changes. MRI thermometry is noninvasive and provides real-time temperature changes throughout the area of interest compared with embedded temperature sensors, which are limited by positioning and provide data only at discrete points. Larger caliber devices and longer treatment times may increase complication rates and may limit its role in the treatment of lung malignancies. A prospective study by Rosenberg et al[74] reported 1-, 2-, 3-, 4-, and 5-year survival rates of 81%, 59%, 44%, 44%, and 27%, respectively, with a median progression-free interval of 7.4 months after laser ablation of lung lesions. The clinical use of laser ablation is not yet widespread in the current practice.

Cryoablation

Cryoablation is performed as a freeze-thaw cycle and delivers freezing temperatures (−20 to −40°C) with crystallization and cellular dehydration resulting in mechanical and vascular injury. It is performed under CT or MRI guidance, and the technical details are similar to other ablative procedures. The ability to monitor treatment changes in real time and visualize the ice ball provides the opportunity to treat lesions selectively and accurately, such as lesions near vital structures. Cryotherapy is less susceptible to heat sink effect and lesions near vascular structures can be effectively treated. Recent initial studies on the role of cryoablation of inoperable lung tumors seem to be promising.[75–77] Niu et al[78] reported 1-, 2-, and 3-year survival rates of 64%, 45%, and 32%, respectively, for cryoablation in NSCLC. Cryoablation has a relatively similar toxicity profile but less pain complications compared with other ablative therapies.[10]

Stereotactic Ablative Radiotherapy

Stereotactic ablative radiotherapy involves precise delivery of high-dose radiation therapy to the tumor fractionated over a few sessions. Poststereotactic radiation tumor response is encouraging and a retrospective exploratory analysis in select populations demonstrated outcomes similar to surgery.[79] Complications include pneumonitis, chest wall pain, and rib fractures. Stereotactic radiation is advantageous in treating lesions not accessible from a percutaneous approach. A prospective comparison clinical trial using stereotactic body radiotherapy, sublobar resection, and RFA in high risk and inoperable patients with stage-I lung cancer demonstrated no difference in early morbidity and mortality.[80] Two recent meta-analysis studies reported better 5-year local control rate, improved overall and cancer-specific survival rates, and decreased postprocedural morbidity after stereotactic radiation compared with other nonsurgical treatment modalities.[81,82] However, the authors state that the published evidence is limited and further blind, prospective randomized controlled studies are needed. Currently, the treatment needs to be tailored to individual patients based on local availability, institutional expertise, and risk factors.

IRE

IRE is a new minimally invasive treatment modality wherein probes positioned surrounding the tumor delivers brief and controlled electrical pulses resulting in increased cellular permeability, apoptosis, and cell death. The

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mechanism of action differs from other ablative therapies as it is not associated with either hyperthermal or cryothermal damage. Noncellular tissue elements such as collagen and elastin fibers, basal membranes, and interstitial matrix are preserved with IRE. Relative preservation of the anatomic "scaffolding" allows for reepithelialization of the vascular and bronchial structures after ablation and recovery of function. Nerve fibers also demonstrate relative preservation. Heat sink effect is not associated with IRE and tumors adjacent to large blood vessels can be effectively treated. ECG gating is necessary to ensure that the electrical pulses are delivered during the refractory period of the cardiac cycle, reducing the risk of cardiac arrhythmias. In addition, these patients are required to be paralyzed and under general anesthesia during the procedure to prevent severe muscular contractions. IRE probes must be placed in a parallel alignment and can often be technically challenging in certain locations, particularly in the thorax when one must work around the ribs. Low density of the lung tissues and surrounding air limit homogenous and efficient energy deposition, which may increase the risk of incomplete ablation and treatment failure with IRE. Extended procedural time, limited expertise and availability, and lack of efficacy studies are current drawbacks for adoption of this procedure. The safety and feasibility are established in the initial studies and efficacy studies are pending.[83,84] IRE is a promising novel technology, although evidence from current literature is limited for treatment of lung tumors.[85]

Alternative Approaches for Ablation

CT-guided percutaneous approach is the current preferred method for ablation therapy due to ease of accessing the target lesion and placement of required applicators, in addition to the procedural imaging guidance and widespread availability. Other ablative approaches that have been described include intraoperative RFA and bronchoscopic-guided ablation treatments.[78,86] Linden et al[87] reported use of intraoperative RFA approach for lesions near vital structures that are difficult to access percutaneously, in situations when ablation needs to be performed in conjunction with limited resection, or if resectability can be determined only at the time of surgery.

Percutaneous ablation procedures have complications similar to those that occur after percutaneous needle biopsies, as described. Ablations performed through a bronchoscope may theoretically have fewer procedure-related complications as the pleura are not transgressed.[86] The electrode is placed into the lesion from an endobronchial approach and CT imaging is then performed to confirm adequate position of the probe within the target lesion. Tsushima et al[88] reported initial use of an internally cooled electrode introduced through the fiberoptic bronchoscope for ablation of sheep lung tissue. Virtual and electromagnetic navigation techniques facilitate access of difficult lung lesions compared to conventional bronchoscopy and aid in administration of thermal ablative therapies.[89,90] Technical developments in improved designs of ablation probes are ongoing to facilitate easier endoscopic placement. Although therapeutic bronchoscopic-guided thermal ablation is a promising and novel therapeutic tool, there is need for further studies to establish the extent of ablation, clinical efficacy, and selection of optimal lesions for this treatment modality.

CONCLUSIONS

Surgical resection is the standard of care for early-stage lung cancer. Image-guided percutaneous ablative therapies are utilized as alternative treatments for patients with unresectable malignancy or nonsurgical candidates with improved overall survival rates and prolonged time to disease progression. These procedures are available, technically feasible, and effective for localized tumor control in carefully selected populations with NSCLC or metastatic disease. RFA is an established modality for treatment of smaller and peripheral lung tumors located distant from vital structures or large vessels. The safety profile for ablation therapy has been well established with easily manageable common complications including pneumothorax, pleural effusions, and pneumonia. Close imaging follow-up is mandatory after ablation therapy to confirm expected treatment changes and monitor for subsequent response or recurrence. The comparative role of percutaneous or endobronchial ablative therapies, stereotactic radiation, IRE, limited surgical resection, and combined modality treatments warrants further larger and randomized studies.

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