Radiofrequency ablation in primary non-small cell lung cancer: What a radiologist needs to know

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Abstract

Lung cancer continues to be one of the leading causes of death worldwide. In advanced cases of lung cancer, a multimodality approach is often applied, however with poor local control rates. In early non-small cell lung cancer (NSCLC), surgery is the standard of care. Only 15-30% of patients are eligible for surgical resection. Improvements in imaging and treatment delivery systems have provided new tools to better target these tumors. Stereotactic body radiation therapy (SBRT) has evolved as the next best option. The role of radiofrequency ablation (RFA) is also growing. Currently, it is a third-line option in stage 1 NSCLC, when SBRT cannot be performed. More recent studies have demonstrated usefulness in recurrent tumors and some authors have also suggested combination of RFA with other modalities in larger tumors. Following the National Lung Screening Trial (NLST), screening by low-dose computed tomography (CT) has demonstrated high rates of early-stage lung cancer detection in high-risk populations. Hence, even considering the current role of RFA as a third-line option, in view of increasing numbers of occurrences detected, the number of potential RFA candidates may see a steep uptrend. In view of all this, it is imperative that interventional radiologists be familiar with the techniques of lung ablation. The aim of this article is to discuss the procedural technique of RFA in the lung and review the current evidence regarding RFA for NSCLC.

Key words: Non-small cell lung cancer; radiofrequency ablation; stereotactic body radiation therapy

Introduction

Overview of lung cancer

Epidemiology

Lung cancer is the leading cause of cancer deaths worldwide in men and the second most common cancer in women. In the United States, lung cancer occurs in approximately 225,000 patients and causes over 160,000 deaths annually.[1] Worldwide, lung cancer occurred in approximately 1.8 million patients in 2012 and caused an estimated 1.6 million deaths.

Classification and treatment guidelines based on tumor node metastasis

Lung cancer is classified into two major categories: Small cell carcinoma (SLC) and non-small cell carcinoma (NSCLC).[1,2] Knowledge of the current (seventh) edition of the Tumor Node Metastasis (TNM) staging system is crucial for

treatment planning and prognostic purposes in patients with NSCLC.[3] In patients with stage I and II NSCLC and a favorable risk, surgical resection with lobectomy is recommended. However, only 15–30% of patients presenting with localized lung cancer are eligible for surgical resection due to various factors such as advanced age, co-morbidities, and poor cardiopulmonary reserve,[4,5] necessitating the development of alternative treatments. Although standard fractionation radiation therapy is a useful tool,[4,6,7] for patients with a poor pulmonary reserve, stereotactic body radiation therapy (SBRT) is needed. Radiofrequency ablation (RFA) may be considered for peripheral tumors of less than 3 cm in inoperable patients.[8] In more advanced stage III and IV NSCLC, a multimodality therapy, which includes combined chemo-radiotherapy with after-look surgery is suggested.[9]

Role of RFA in lung tumors

RFA and its clinical use
RFA has been widely utilized in the management of tumors in many other solid organs - primarily the liver - for over two decades, with a high safety and efficacy profile.[10] RFA is a thermal ablative modality that causes tissue death by coagulative necrosis.[11] RFA has been shown to be safe and reasonably efficacious in the management of primary and secondary lung neoplasms.[6,7,12-16] Presently, the primary indication for lung RFA in NSCLC is stage Ia tumors less than 3 cm.[17,18]

Rationale for use of RFA in lung tumors
Local efficacy of RFA in destroying lung tumors has been demonstrated in animal lung VX2 tumor models that show the feasibility of complete ablation.[18] More recently, a single session of percutaneous RFA in nine patients was performed before surgical resection of lung metastases. There was histologic proof of complete tumor destruction.[19] The lungs provide a unique environment for RFA under computed tomographic (CT) guidance. First, there is an excellent contrast ratio between the tissue of the targeted tumor, the aerated lung, and the metal of the needle. Second, a given quantity of RF current produces a larger volume of ablation in the lung than in other solid organs like the liver or kidney. This is because the energy deposition is greater in the lung tissue due to heat insulation and low electric conductivity.[20]

The Lung RFA Procedure: A Practical Approach

Pre-procedure evaluation

Patient selection
Pre-procedure workup includes cross-sectional imaging within 4 weeks of the planned ablative therapy. Various parameters are evaluated including the size and location of the tumor (i.e., central vs. peripheral, close to vessels).[11] At present, there are no set lower parameter limits like forced expiratory volume in 1 s (FEV1) to determine candidacy for the ablation procedure. The presence of pulmonary fibrosis serves as a relative contraindication.[21,22]

The procedure

Anesthesia versus sedation
Most thermal ablations are performed under general anesthesia. Even in the lung, authors have reported lower feasibility rates and higher peri-procedural pain after conscious sedation compared with general anesthesia.[23,24] The feasibility of the technique under general anesthesia is reported to be as high as 97%.[13] However, most of the patients who present for RFA have medical co-morbidities, which presents a high anesthesiology risk. Hoffmann *et al.* reported similar results in terms of feasibility, complication rate, hospitalization, and local tumor control after general anesthesia or conscious sedation, and concluded that conscious sedation should be preferred, reserving general anesthesia for non-compliant patients.[25]

Imaging guidance
CT is the only accurate image guidance modality for lung RFA. Accurate planning of the needle track is a key factor for technical success. The path should be the shortest possible, and should avoid interlobar fissures and vital structures.

Multiplanar reconstruction and real-time CT with foot-pedal control results in faster and more accurate needle placement.[17] The choice of electrode length, active tip length, and the target ablation zone is determined by the size and location of the tumor.

Protocol
Parameters of temperature and impedance should be adjusted according to manufacturer specifications for the RF device used. Treatments generally range between 5 and 12 min in any given position. Multiple overlapping ablations are performed in larger tumors to ensure adequate coverage and optimal margins.[21,26] RF protocols have to be adapted to the tumor location, which can cause variation in impedance.[17]

Post-procedure follow-up

Protocol
Post-ablation follow-up regimens vary. Most authors suggest performing an immediate post-ablation chest CT, mainly to check for complications and to assess the adequacy of the ablation zone. A new baseline post-contrast CT is performed at 1 month with the next routine follow-up at 4 months.[27] Abtin *et al.* suggest performing bedside chest radiography at 1 and 3 h. Initial CT is performed, usually at 1-2 months after RFA, and is followed by positron emission tomography PET/CT at 3 months, which thereafter is alternated with CT every 6 months for 2 years.[28]

Immediate post-procedure imaging

After the probe removal, a CT is required to exclude immediate complications, such as pneumothorax (PTX), and to estimate the area of ablation. An area of ground-glass opacity around the tumor margins is expected.[29] Most pneumothoraces are small and asymptomatic. For larger ones, a pleural catheter attached to wall suction can be used to treat the air leak. Again, chest radiographs are obtained to ensure resolution of the air leak prior to discharge.

Tumor response

CT and PET/CT have been used to follow-up ablated tumors.

Normal "expected" findings

An immediate post-treatment CT showing a halo of ground-glass opacification (GGO) encompassing the lesion with a satisfactory margin is a good indicator of successful treatment.[24,29-32] At 3 months, the ablated lesion is usually slightly larger than baseline owing to residual edema, but by 6 months, the ablation zone usually starts to decrease in size.[33] Early, uniform, non-nodular arterial enhancement is common early after ablation, reflecting reactive hyperemia in the tissues at the margin of the treatment zone and may persist for up to 6 months [Figure 1].[32]

PET/CT may detect recurrence earlier than does conventional CT, but there is limited evidence to support this.[34,35] In a study of 68 patients, standardized uptake value (SUV) <8 was found to be a predictor of improved disease-free survival [Figure 2].[36]

Signs of relapse/recurrence

CT and PET imaging features suggestive of residual or recurrent disease include:[28]

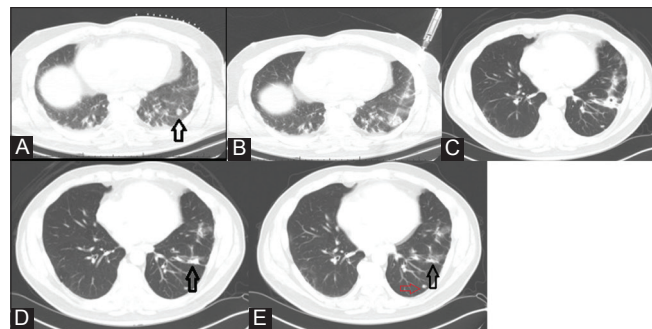- Change of CT morphology from ground-glass opacity to solid opacity

- Growth of the RFA zone after 3 months (when compared to baseline) and definitely after 6 months, especially peripheral nodular growth
- Contrast enhancement in the ablation zone (nodular > 10 mm, central > 15 HU, and enhancement greater than the baseline)
- Regional or distant lymph node enlargement and new intrathoracic or extrathoracic disease
- Increased metabolic activity beyond 2 months, residual activity centrally or at the ablated tumor, and development of nodular activity [Figure 3].

Tumor response after RFA is summarized in Table 1.

Amended RECIST criteria have also been proposed, taking into account not only the lesion size, but also tumor geometry and contrast enhancement. In a large multicenter trial, complete response was defined as a decrease in the longest diameter of at least 30% compared with the diameter measured at the 1-month CT examination, with no evidence of peripheral tumor growth or contrast enhancement.[37]

Literature review of studies on RFA of NSCLC

A review of the English literature was conducted by searching the PubMed database using the keywords "non-small cell lung cancer" and "radiofrequency ablation." We restricted this review solely to the use of RFA for NCSLC in humans and with the number of patients >30. There were some reports of RFA in both NCSLC and metastasis. In some of these, we separated out the data only for NSCLC patients for local efficacy and survival. With regard to complications, the use of RFA in NCSLC as well as metastasis was studied, since in our opinion, the procedural details for both are similar. The search resulted in 10 relevant studies - 3 prospective and 7 retrospective. All relevant articles were subsequently evaluated.
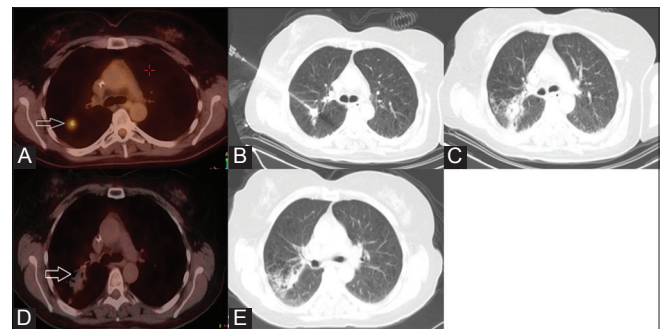

Figure 1 (A-E): A 55-year-old male with NSCLC. (A) CT scan (Siemens Healthcare, Knoxville, Tennessee, USA) of the chest shows a nodule measuring 1.4 × 1.4 cm in the left lower lobe (black arrow) (B) CT-guided RFA performed (Boston Scientific, Natick, MA, USA). A small area of GGO is seen developing around the nodule (C) CT 1 month later shows increase in size of the nodule as compared to pre-RFA, measuring 2.1 × 2.1 cm and showing central cavitation (D) CT 3 months later shows reduction in size of nodule to 1.5 × 1.3 cm (black arrow) (E) CT at 6 months shows further reduction in size (black arrow). Meanwhile, another nodule had developed (red arrow)

Figure 2 (A-E): A 56-year-old male with NSCLC. (A) Pre-RFA PET-CT scan (Siemens Healthcare, Knoxville, Tennessee, USA) shows a lung nodule measuring 1.4 × 1.4 cm in the right lower lobe, SUV 4.9 (white arrow) (B) CT-guided RFA performed using an RF ablation system (Boston Scientific, Natick, MA, USA) (C) A large area of GGO is seen around the nodule immediately after ablation (D) PET-CT performed the next day shows GGO around the nodule. However, there is resolution to background of the fluorodeoxyglucose (FDG) activity (white arrow) (E) CT follow-up at 3 months shows residual GGO, but no obvious increase in the solid aspect of the nodule
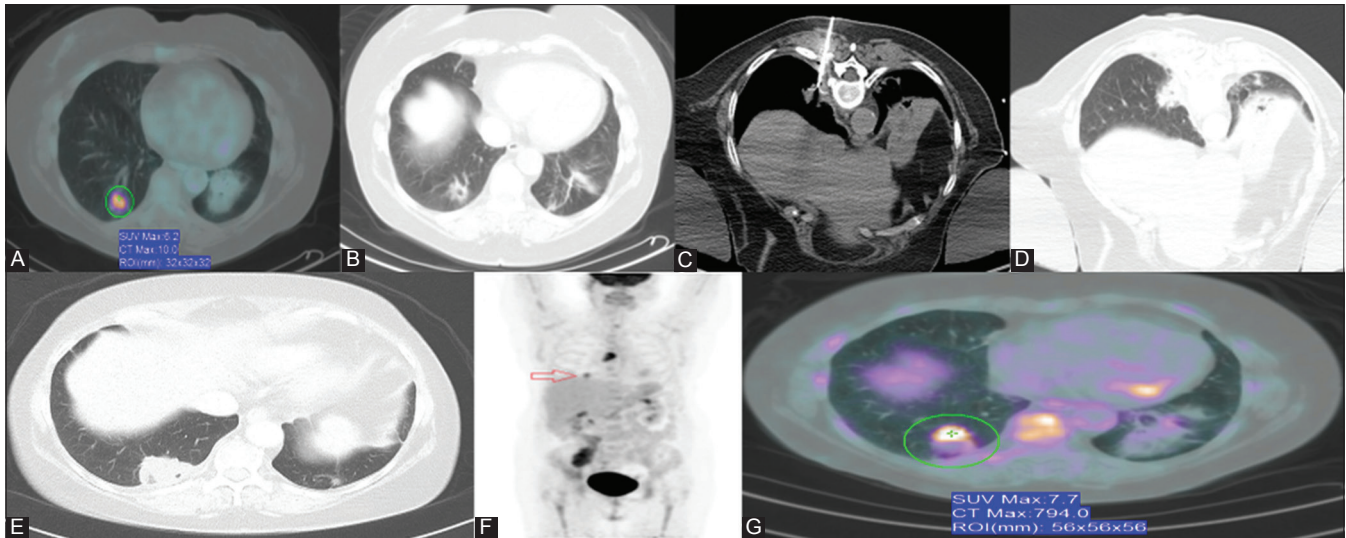
Figure 3 (A-E): A 65-year-old male with NSCLC. Pre-RFA PET-CT (A) and CT (B) Scans show a cavitatory lung nodule 1.6 × 1.5 cm in the right lower lobe, SUV 6.2 (C) CT-guided RFA performed (D) Large area of GGO is seen around the nodule (E) CT at 6 weeks shows a large solid nodular area now measuring 2.9 × 2.6 cm. PET-CT MIP images (F) and axial images (G) at 3 months show FDG uptake in the nodule, SUV 7.7 (red arrow in F) compared to prior SUV 6.2 and measuring 2.9 × 2.6 cm, with photopenia/necrosis in the posterior half of the lesion

Table 1: Tumor response after RFA

Characteristics	Response	Early (<1 wk.)	Intermediate (>1 wk. to 2 mo.)	Late (3 mo.)	Later 6 mo.
CT morphology	E	GGO, complete encasement Intralesional bubbles	GGO denser with bizarre central cavity (resembles abscess)	GGO continues becoming dense	Gradual retraction End appearance: Rounded area of dense scarring
	R	Incomplete encasement	Solid opacity	Solid opacity, nodules along electrode track	No retraction
Size	E	Larger than preablation	Larger than preablation, smaller than early phase	same size or larger than preablation	same or smaller than preablation
	R	Smaller than preablation	Larger than early phase	Growth after 3 mo	larger than preablation
Enhancement	E	Mild enhancement possible	Mild enhancement possible	Mild enhancement possible	No enhancement
	R	Enhancement >preablation Central/nodular enhancement >10 mm or >15 HU	Enhancement >preablation Central/nodular enhancement >10 mm or >15 HU	Enhancement >preablation Central/nodular enhancement >10 mm or >15 HU	Enhancement >preablation Central/nodular enhancement >10 mm or >15 HU
PET uptake	E	-	-	No uptake	
	R	-	-	Uptake centrally or at ablated tumor	

In green is the expected response and red is features of recurrence/relapse. Mo: Months, Wk: Week, E: Expected, R: Recurrence/residual, RFA: Role of radiofrequency ablation, GGO: Ground-glass opacification

Local efficacy
Review of recent literature of lung RFA for both primary and secondary lung tumors showed a median complete ablation rate of 90% (range 38-97%).[38] In their review of 14 studies limited to NCSLC that was conducted in 2014, Hiraki *et al.* reported a rate of about 31-42%.[39] In the 10 series reviewed, we too found the same number (13-41%). Table 2 summarizes a review of 10 series of RFA ablation of lung tumors.

Three factors have been described that appear to be predictive of complete ablation:
- Size of the tumor: Tumor size is the single most important factor associated with local recurrence. According to several reports with prolonged imaging follow-up, tumors less than 2 cm in size can be successfully ablated in 78-96% of cases. A statistically significant lower success rate of ablation is reported for tumors greater than 2-3 cm[12,40-44]
- Ablation margins: Unlike most classical hepatocellular carcinomas, lung tumors are not usually encapsulated; hence, it is necessary to obtain an adequate ablative margin.[45,46] Beland *et al.*[47] suggest an ablation zone "that includes the primary tumor plus at least an additional 8–10 mm of ablation beyond the visible tumor margin in all directions" as ideal. Newer studies have shown that RFA with overlapping ablations may prove useful[44] and is not followed by many complications[40,48]
- Location of the tumor: Proximity of the target lesion to major vasculature has been shown to increase the risk of incomplete ablation due to the "heat sink phenomenon," explained by the fact that flowing

Table 2: Review of 10 series of RFA ablation of lung tumors

Author	Type of study	No of patients/ tumors	Size (mean-cm)	Follow up time (mo)	Local progression (%)	Overall survival (OS) Cancer free survival (CS) 1 year	3 years	5 years	Median OS (mo)
Ambrogi *et al.*, 2011[46]	Prospective	57 (59)	2.6	47	41	83 89	40 59	25 40	33 41
Lencioni *et al.*, 2008[37]	Prospective multicenter (rapture)	33 (38)	2.2	na	13	70 92	48 73	na	na
Lanuti *et al.*, 2012[55]	Prospective Observational	45 (55)	2.0	32	33	na	67	31	44
Huang *et al.*, 2011[56]	Retrospective	237	na	na	na	80	46	24	na
Simon *et al.*, 2012[57]	Retrospective	82	na	na	na	77	51	21	37
Simon *et al.*, 2007[43]	Retrospective	75 (80)	3	20.5	na	78	36	27	29
Hiraki *et al.*, 2011[53]	Retrospective	50 (52)	2.1	37	31	94 100	74 80	61 74	67
Lee *et al.*, 2012[58]	Retrospective	40	3.8	na	40	100	77 33	19	38
Lanuti *et al.*,2009[16]	Retrospective	31 (34)	2.0	17	32	85	47 39	Na	30 26
Palussiere *et al.*, 2015[44]	Retrospective	87	2.1	30.5	18	na	na	58	na

Mo: Months, na: Not applicable. Data for lung RFA in NSCLC and metastasis, RFA: Role of radiofrequency ablation

blood carries heat away from adjacent tissues, thereby cooling and protecting these tissues from lethal thermal injury. The presence of an adjacent large vessel within 3 mm of the lesion has been reported by several authors as a negative predictor for complete tumor ablation.[49-51] Percutaneous balloon occlusion of the involved pulmonary artery branch during lung RFA has been reported in animal studies to improve the shape and volume of ablation.[52]

Overall and cancer-specific survival
Survival data for RFA of NSCLC are scarce due to the relative recent application of this ablative modality in lungs with the first report published in 2000.[7]

The RAPTURE trial (a prospective multicenter trial) reported overall survival (OS) of 70% and 48% at 1 and 2 years, respectively, and cancer-specific survival (CS) of 92% and 73% at 1 and 2 years, respectively.[37] Co-morbidities explained the gap between OS and CS.

In their review of 14 studies limited to NCSLC that was conducted in 2014, Hiraki *et al.* reported the 1-, 2-, 3-, and 5-year OS rates after RFA of stage I NSCLC to be 78-100%, 53-86%, 36-88%, and 25-61%, respectively. The median survival time ranged from 29 to 67 months. The 1-, 2-, and 3-year CS rates after RFA of stage I NSCLC were 89–100%, 92–93%, and 59–88%, respectively.[39]

In our review of 10 studies, the 1-, 3-, and 5-year OS rates were 70-100%, 36-77%, and 19-61%, respectively. The 1-, 3-, and 5-year CS rates were 78-100%, 33-73%, and 40-74%, respectively. Median OS was between 29 and 67 months.[16,37,43,53-58]

There appear to be two factors that predict OS, which are as follows:

• Size of tumor: Size as a prognostic factor of survival was explained by Kodama *et al*. In their study, they found 1-, 3-, and 5-year OS rates of 100%, 79.8%, and 60.5%, respectively, in patients with tumors measuring <3.0 cm, compared with 1-year and 3-year OS rates of 83.3% and 31.3%, respectively, in patients with tumors measuring 3.1-4.0 cm.[59] Again Palussiere *et al*. reported better survival in tumors ≤3 cm, with a survival rate close to 50% at 5 years in 135 patients. However, results were in the same range with the 1-, 3-, and 4-year OS rates[43]

• Co-morbidities: Indeed, lung RFA for NSCLC is usually performed in non-surgical patients with severe co-morbidities. It is important to note that deaths reported in the literature are not typically related to cancer progression, but to co-morbidities. Both Simon *et al*. in 2012[57] and Lencioni *et al*.[37] reported that co-morbidities explain the gap between OS and CS.

Simon *et al.* retrospectively reviewed 82 patients treated with RFA using the Charlson Co-morbidity Index (CCI) as the survival predictor. They explained that CCI appeared to be a strong predictor of OS in patients treated with RFA for NSCLC. A CCI score ≥5 (OS: 10.43 months; 95% CI: 7.61-19.85) was associated with significantly increased mortality compared to patients who had a CCI grade of 1-2 (OS: 55.5 months; 95% CI: 39.46–64.02) or 3-4 (OS: 36.62 months; 95% CI: 25.54-58.29). No statistically significant difference was observed between CCI grades 1-2 and 3-4.[40,57,60]

Tolerance and Complications

Tolerance
Studies have shown no changes in post-ablation pulmonary function tests when evaluated prospectively at 1 and 12 months. There have been no reports of patients requiring long-term or permanent oxygen therapy as a result of RFA.[13,37]

Complications
The largest assessment of serious complications comes from a retrospective single institution series of 420 patients with 1403 lung tumors who underwent 1000 RFA sessions. There were four deaths related to the RFA procedure (0.4%). The major complication rate was 9.8%, the most frequent of which were aseptic pleuritis, pneumonia, lung abscess, bleeding requiring transfusion, and PTX requiring pleural sclerosis.[61]

In a review of 14 series conducted in 2014, Hiraki *et al*. concluded that although mortality after RFA was quite rare, it occurred in isolated cases due to acute respiratory distress or pulmonary embolus. PTX was frequently associated with a maximum of 63% of the cases, 2-13% of which needed a chest tube. Other complications were less frequent.[39]

We reviewed our series of 10 studies for complications [Table 3]. There is no uniform standard for reporting complications. We labeled PTX and PTX requiring drainage as the major complications. Minor complications in our review included pleural effusions/hemothorax, parenchyma hemorrhage and hemoptysis, neuropathy, bronchopleural fistula, and needle track seeding. In our review, we found that the overall major and minor complication rates associated with lung RFA have been reported as: PTX 11-50%, PTX needing drainage 5-20%, and minor complications 4.2-20%.

The common complications and their management are subsequently discussed.

Peri-procedural complications
- PTX (11-63%): Risk factors associated with PTX include: Male gender, multiple tumor ablations, tumors at the bases of the lungs, long intrapulmonary course of the electrode, pulmonary emphysema, advanced age, small tumors, and traversal of the major fissure by the electrode.[62-67] In 2-29% of PTX cases, chest tube placement for drainage may be required. In 10% of cases, PTX can also present after a delay following RFA. Rarely, RFA is complicated by formation of a bronchopleural fistula that results in intractable PTX. The mechanism

Table 3: Review of complications in 10 series of RFA ablation of lung tumors

Author	Tolerance and complications* Mortality	Major (pneumothorax)	Minor/other
Ambrogi *et al*., 2011[46]	No mortality	Overall 11% Requiring drainage 5%	Overall: 20% Pain 6%, Tiny pleural effusion 4% Minor hemoptysis 3% Chest wall hematoma 1%
Lencioni *et al*., 2008[37]	No mortality	Overall 40% Requiring drainage: 19%	Pleural effusion 10% Hemorrhage 2%
Lanuti *et al*., 2012[55]	No mortality	Overall 18% Requiring drainage 2%	na
Huang *et al*., 2011[56]	One death (0.9% pericardial tamponade)	Overall 19.1%	Overall 4.2% Hemothorax 3%, Pneumonia 4.5% Needle-track implantation 1.8%
Simon *et al*., 2012[57]	No mortality	na	na
Simon *et al*., 2007[43]	Mortality (exacerbation of pulmonary fibrosis)	na	na
Hiraki *et al*., 2011[53]	No mortality	Overall 42%	Overall 6% Pleural effusion 2% Bronchopleural fistula, empyema 2%
Lee *et al*., 2012[58]	No mortality	Overall 8%, pneumomediastinum 3%	Hemothorax 3% Hemoptysis 3%
Lanuti *et al*., 2009[16]	No mortality,	Overall 13%, needing drainage 8%	minor hemoptysis 16% hemothorax 5%, Pneumonia 16% Effusion 21% Neuropathy: 3% Bronchopleural fistula: 8%
Palussiere *et al*., 2015[44]	Two (2.2%) deaths (cardiac and respiratory failure)	Overall 50% Needing drainage 20%	Brachial plexus neuropathy: 2.2%

Mo: Months, na: Not applicable. Data for lung RFA in NSCLC and metastasis. RFA: Role of radiofrequency ablation

is thought to be RFA-induced necrosis of the lung tissue between the pleural space and the bronchus. This is managed by pleurodesis, endobronchial repair, or surgical repair[68]

- Pleural effusion (6-19%): Pleural effusion is thought to result from pleuritis caused by thermal injury and is almost always treated conservatively. Associated risk factors include the use of a cluster electrode and a short distance from the lesion to the pleura[62,66,69]
- Parenchyma hemorrhage and hemoptysis (6-18% and 3-9% of ablations, respectively):[66,67,70] Hemoptysis, in most cases, is self-limiting. More severe hemorrhage can occur in tumors in contact with the hilum. Delayed major hemorrhage due to development of false aneurysms of the pulmonary artery may need coil embolization[71]
- Needle track seeding: This rarely occurs. Risk factors include the use of an internally cooled electrode, an electrode tip temperature of less than 60°C immediately after RFA, lack of tract ablation, biopsy prior to RFA, and poor differentiation of cancers[72]
- Thermal neuropathy: Although rare, injury to nerves such as the brachial plexus, phrenic nerve, and the intercostal nerves has been reported from treatment of nearby tumors[73,74]
- Rare adverse effects include interstitial pneumonitis, bronchiolitis obliterans organizing pneumonia, and air embolism.[69,72,75] Asymptomatic microbubble embolism depicted by duplex ultrasound has been reported during lung RFA in humans.[76] Non-fatal major air embolism has been reported as a consequence of RF probe placement in two case reports.[75,77] Only one case of cerebral infarction after lung RFA was found.[23]

Post-procedural complications

The expected post-ablation course includes mild-to-moderate pain, fever, and mild dyspnea during the first week. These can be managed with oral analgesics and nasal or mask administration of oxygen. Most patients can be discharged the next day.[40] Post-procedural hemoptysis is usually minor, consists of brownish blood, and lasts from 2 to 7 days without requiring treatment.

Advantages and drawbacks of RFA in the lung: A synopsis

A summary of the advantages and disadvantages of RFA for NSCLC is presented in Table 4.

Table 4: Summary of advantage and disadvantages of RFA for NSCLC

Minimally invasive	Local recurrence
Can be repeated multiple times	High rate of complications
Insignificant impact on pulmonary function	
Applied regardless of any previous treatments (Salvage option)	
Costs less than surgery and SBRT	

RFA: Role of radiofrequency ablation, NSCLC: Non-small cell lung cancer, SBRT: Stereotactic body radiation therapy

Comparison to other available modalities

Sublobar resection

Zemlyak *et al.*, in their study comparing RFA and surgery, reported a longer cancer-free survival in the surgical group and a higher recurrence in the RFA group.[78] Kwan *et al.*[79] used the National Cancer Institute Surveillance, Epidemiology, and End Results Medicare-linked data to examine the survival of patients with early-stage NSCLC after RFA and sublobar resection. They suggested that although local recurrence after RFA presents a major problem, it does not have a significant impact on OS or CS, explained by the fact that patients who underwent RFA were older and tended to have substantial co-morbidities, so they tended to die due to causes other than cancer recurrence.[79]

Stereotactic body radiation therapy

SBRT is associated with favorable local control and survival rates in patients with stage I NSCLC. Hiraki *et al.* analyzed about 14 studies of SBRT for stage I NSCLC. In most studies, no mortality was found. Grade 5 toxicities were found in 7–9% of patients, and Grade 3 toxicities were found in less than 5% of patients. Local recurrence was reported in up to 20% of patients. The 1-, 3-, and 5-year OS rates were 80-95%, 43-85%, and 25-70%, respectively. The median OS was 32-62 months. The 3- and 5-year CS survival rates were 67-88% and 41-76%, respectively.[39]

Whether RFA offers better results than SBRT in patients with NSCLC who are unfit for surgery has been evaluated in two studies where a "best evidence topic" was constructed according to a structured protocol. These studies are summarized in Table 5. In 2013, Renaud *et al.* opined that the current evidence shows that SBRT is a safe and effective procedure and should be proposed first to patients suffering from primary NSCLC who are unfit for surgery as it offers lower complications, better control rates, and OS as well as CS.[80] Bilal *et al.* opined that in the choice between SBRT and RFA, treatment for early-stage inoperable NSCLC should be tailored to individual patients, and under certain circumstances, a combined approach may be beneficial. They reported that both treatments have a similar incidence of complications, and OS at 1 year was similar. However, the local progression was lower and the 5-year survival was higher with SBRT.[81]

Thus, SBRT appears to have evolved as the next best option for early NSCLC in inoperable patients, with the main advantage being superior local control of the tumor. However, some of the drawbacks of SBRT include patients who have tumors in central locations (near hilum, mediastinum, and vertebral body) or in the lower lobe in patients with considerable respiratory motion. Also, SBRT involves multiple fractionated doses. SBRT is a relative contraindication in severe pulmonary dysfunction and is not useful for re-treatment in recurrence

Table 5: Summary of studies comparing RFA and SBRT

Author	Number of papers/best evidence	Local efficacy/ period	Overall survival (OS) Cancer free survival (CS)	1 year	2/3 years	5 years	Tolerance and complications Mortality	Major complications	'The verdict'	Authors comments
Renaud *et al.*[80]	RFA- 90/5 papers	58-68%, at 18 m	OS CS	na	47-74%	na	Null	Pneumothorax 33-100%	'Current evidence shows SBRT should be proposed first, prior to RFA in primary NSCLC unfit for surgery'	Limited evidence due to few studies Need for prospective randomized comparison trials
	SBRT-112/10	83-89.5%, 5 years	OS CS	na	38-84.7% 64-88%	na	One case (5.5%), null in the other papers	radiation pneumonitis 3-38% rib fracture1-4%		
Bilal *et al.*[81]	RFA	47-76.3%	OS	68.2-95%	36-87.5%	20.1-27%	na	Pneumothorax 19-63%	'Treatment should be tailored to individual patients. Combined approach may be beneficial'	RFA better for ≤3 cm, performed in single session RFA v/s SBRT depends on location of tumor
	SBRT	85.5-96.5%	OS	81-857%	42-56%	47%	na	Fatigue 31-32% pneumonitis 2-12% chest wall pain 3-12%		

RFA: Role of radiofrequency ablation, NSCLC: Non-small cell lung cancer, SBRT: Stereotactic body radiation therapy

following primary SBRT treatments, due to high rates of toxicity. It is in this specific subset of patients that RFA has the potential to replace SBRT. With new developments in RFA technique, interventional radiologists have started treating more centrally occurring tumors. Important advantages are its minimally invasive nature, insignificant impact on pulmonary function,[37,46] ability to be performed regardless of any previous treatments (even in the event of SBRT failure), and multiplicity.[39] Also, another distinct advantage is the cost-effectiveness of RFA. Sher *et al.* showed a significantly higher cost of SBRT (about 4.5 times higher) in comparison to RFA.[82]

Current role of RFA in the management of NSCLC

In patients with no high risks, RFA falls significantly behind surgery as well as SBRT, primarily due to the higher rate of local failure, especially for larger tumors. It is, however, debatable how much of this increased local failure impacts survival outcomes in old and high-risk patients.[83] A recently completed National Cancer Institute NCI-funded multicenter pilot trial (ACOSOG Z4033) compared the selection criteria and short-term outcomes of RFA to sublobar resection and SBRT from other completed multicenter trials - SBRT (RTOG trial 0236), sublobar resection (ACOSOG trial Z4032). Despite the RFA cohorts being older and sicker, their survival was similar. The overall 90-day mortality for SBRT, surgery, and RFA was 0%, 2.4%, and 2.0%, respectively ($P = 0.5$).[84] Although a fallback option in medically inoperable patients who cannot receive SBRT, RFA is beginning to play an increasingly important role in this subset of patients.[8,83]

Various other roles of RFA are being described as an alternative/adjunctive. Schoellnast *et al.*[85] and

Kodama *et al.*[59] suggest that RFA may be a good treatment option for patients with metachronous lung cancer or residual/recurrent disease after surgery, chemotherapy, and/or radiation. Although RFA is mostly used as a stand-alone technique, use of combination therapies with radiation therapy or systemic therapies has already been demonstrated in animal studies.[40] Bilal *et al.* highlighted the advantages and drawbacks of RFA and SBRT and suggested that a combined approach may be beneficial.[81] According to Dupuy *et al.*, this may help overcome the limited local efficacy of RFA.[86] The current role of RFA in the management of NSCLC has been summarized in Figure 4.

Conclusion

Following the National Lung Screening Trial (NLST), screening by low-dose CT has demonstrated high rates of early-stage lung cancer detection in high-risk populations.[87] Although the current role of RFA is limited, in view of increasing numbers of occurrences detected, a fifth of which are inoperable, the number of "potential" RFA candidates may see a steep uptrend.[88] In this age of declining health care reimbursement, the significantly lower cost of RFA compared to that of other modalities[82] may help push RFA to the frontline. In view of all this, it is imperative that radiologists, with the strong support of the bigger societies, aggressively push for funding and development of research protocols to prospectively evaluate the efficacy of RFA and provide comparisons to other modalities like SBRT. We need to step up our game in order to move this attractive treatment option from a "defender position" to "center forward" in the management of lung cancer.[89]
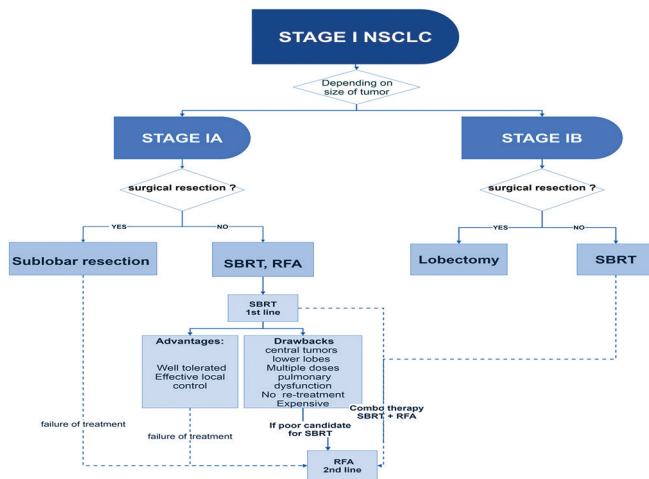
Figure 4: A clinical practice algorithm in the "triage" of patient with stage 1 NSCLC. Solid lines indicate current role, dotted line indicates emerging/potential roles

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