Society of Interventional Radiology Multidisciplinary Position Statement on Percutaneous Ablation of Non-small Cell Lung Cancer and Metastatic Disease to the Lungs

Endorsed by the Canadian Association for Interventional Radiology, the Cardiovascular and Interventional Radiological Society of Europe, and the Society of Interventional Oncology

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ABSTRACT

Purpose: To state the Society of Interventional Radiology's position on the use of image-guided thermal ablation for the treatment of early stage non-small cell lung cancer, recurrent lung cancer, and metastatic disease to the lung.

Materials and Methods: A multidisciplinary writing group, with expertise in treating lung cancer, conducted a comprehensive literature search to identify studies on the topic of interest. Recommendations were drafted and graded according to the updated SIR evidence grading system. A modified Delphi technique was used to achieve consensus agreement on the recommendation statements.

Results: A total of 63 studies, including existing systematic reviews and meta-analysis, retrospective cohort studies, and single-arm trials were identified. The expert writing group developed and agreed on 7 recommendations on the use of image-guided thermal ablation in the lung.

Conclusion: SIR considers image-guided thermal ablation to be an acceptable treatment option for patients with inoperable Stage I NSCLC, those with recurrent NSCLC, as well as patients with metastatic lung disease.

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ABBREVIATIONS

CI = confidence interval, CSS = cancer-specific survival, CA = cryoablation, DLCO = diffusing capacity for carbon monoxide, FEV = forced expiratory volume, FVC = forced vital capacity, HR = hazard ratio, IGTA = image-guided tumor ablation, IQR = interquartile range, MWA = microwave ablation, NCCN = National Comprehensive Cancer Network, NCDB = National Cancer Database, NSCLC = non-small cell lung cancer, OR = odds ratio, OS = overall survival, PFS = progression-free survival, RAPTURE = Radiofrequency Ablation of Pulmonary Tumors Response Evaluation, RFA = radiofrequency ablation, SBRT = stereotactic body radiation therapy

INTRODUCTION

Lung cancer is the second most common cancer type in the United States and remains the leading cause of cancer-related death despite decreasing mortality trends over the past two decades (1). An estimated 228,820 new cases of lung cancer were diagnosed in 2020 in the United States (1). Non-small cell lung cancer (NSCLC) is the most common cancer subtype, making up 80%–85% of cases of primary lung cancer (2). Moreover, the lungs are the second most frequent site of metastatic disease (3). Epithelial carcinomas, such as colorectal carcinoma, renal cell carcinoma, and breast cancer, as well as sarcomas and germ cell tumors (4) are common histologies that metastasize to the lungs. Treatment strategies that can effectively address both primary and metastatic lung tumors are essential. While surgery is the preferred treatment for both early-stage lung cancer and lung metastases amenable to resection, only a minority of patients will meet criteria for surgical resection (5). For surgically inoperable patients, such as those who have poor cardiopulmonary function, multiple medical comorbidities that render them high risk for surgery, or insufficient pulmonary reserve for additional resection or those who refuse surgery, stereotactic body radiation therapy (SBRT) and image-guided tumor ablation (IGTA) are alternative treatment options.

Percutaneous IGTA can be performed using different energy modalities, such as radiofrequency ablation (RFA), cryoablation (CA), or microwave ablation (MWA). IGTA is a management option listed in the multidisciplinary National Comprehensive Cancer Network (NCCN) guidelines as well as several specialty-specific societal guidelines (**Table 1**) (6–9).

In this document, the Society of Interventional Radiology (SIR) states its position on the use of IGTA in the lung for treatment of early-stage NSCLC (stage I), recurrent lung cancer, and metastatic disease to the lungs.

MATERIALS AND METHODS

Panel Formation

Under the direction of SIR, a multidisciplinary group of experts, representing Interventional Radiology, Medical Oncology, Thoracic Surgery, and Radiation Oncology, was convened to review the current literature on the use of IGTA for the management of lung cancer and metastatic disease to the lungs.

Literature Review

A comprehensive literature search was conducted in June 2019 in MEDLINE via PubMed using a combination of the following search terms: “non-small cell lung cancer,” “lung tumors,” “NSCLC,” “metastatic lung cancer,” “oligometastatic,” “biopsy,” “thermal ablation,” "radiofrequency ablation,” “cryoablation,” “cryosurgery,” “microwave ablation,” “ablative therapy,” and “ablation.” The search was limited to 1999 to present, with 1999 representing the publication of the first RFA case series of lung tumors. After removing duplicative cohorts, primary studies included in existing systematic reviews, case reports, technical papers, letters or commentaries, and unrelated papers, a total of 63 studies remained for inclusion in this review. Currently, the evidence base for this topic does not include any randomized controlled trials comparing ablative versus surgical therapies or ablative therapy versus SBRT for lung tumors. The highest quality evidence comes from prospective observational studies. Several systematic reviews of small-cohort studies also make up the evidence base. References are included in a graded evidence table (**Appendix A** [available online on the article’s Supplemental Material page at *www.jvir.org*]).).

Recommendation Development and Consensus

The literature for each subtopic was reviewed and is presented in order of increasing level of evidence (ie, single-arm trials to systematic reviews/meta-analysis). Each topic and subtopic had different levels of supporting evidence as several areas lacked appropriate direct comparison data. The best available evidence for each thermal ablation modality in each topic is presented; however, it should be recognized that the evidence levels across each modality are often not similar. If a subtopic does not include a specific level of evidence, this indicates that the literature search returned no results for that evidence level. Where available, the existing clinical practice guidelines on ablation from any specialty are summarized at the end of each section. Recommendations were drafted and graded according to the updated SIR evidence grading system (**Appendix B** [available online at *www.jvir.org*]). A modified Delphi technique was used to achieve consensus agreement on the recommendation statements. Consensus was reached when 80% of the panelists were in agreement with each statement.

Table 1. Current Society Clinical Practice Guidelines on IGTA for NSCLC

American College of Chest Physicians (CHEST), 2013 (30)	RFA may also be considered for peripheral tumors < 3 cm in inoperable patients (Grade 2C)
National Comprehensive Cancer Network (NCCN), 2020 (9)	• For patients with Stage 1A NSCLC (peripheral T1abc, N0), image-guided thermal ablation is an option for selected medically inoperable patients. • In patients with multiple primary lung cancers in which definitive local therapy is possible, image-guided thermal ablation is a treatment option. • In patients with T1-3, N0 tumors for which definitive therapy of thoracic disease is feasible, image-guided thermal ablation is a treatment option for selected patients. • In patients with resectable locoregional recurrent NSCLC, image-guided thermal ablation is a treatment option for selected patients.
Cardiovascular and Interventional Radiology Society of Europe (CIRSE), 2020 (48)	• Lung ablation should be restricted to patients with primary lung cancer not suitable for surgery, or to patients with oligometastatic lung disease (mainly colorectal) with radical intent (Level of Evidence 2). • RFA and MWA present comparable efficacy but MWA is usually considered better tolerated by patients and more suitable for large tumor treatment (Level of Evidence 2). • Better results are achieved when lesion size does not exceed 2 cm; tumor margin recommendation is ≥1 cm (Level of Evidence 2). • For primary NSLC, accurate pre-operative loco-regional staging is crucial and should be performed with contrast-enhanced CT and FDG-PET/CT (Level of Evidence 2). • Pulmonary function tests should be performed in patients with a history of lung surgery or pulmonary disease. There is no lower limit of forced expiratory volume in 1 s or diffusion capacity in candidates for percutaneous thermal ablation, but spirometry should be discussed by the multidisciplinary tumor board (Level of Evidence 2).

General Considerations

Comparison of IGTA Techniques. RFA, MWA, and CA are the current available modalities for image-guided thermal ablation of pulmonary lesions.

Systematic Reviews and Meta-analysis. A systematic review including seven comparative studies of RFA (n = 246) versus MWA (n = 319) for thoracic cancer found no significant difference in overall survival (OS) at 1 (odds ratio [OR], 0.95; 95% confidence interval [CI], 0.63–1.44), 2 (OR, 1.00; 95% CI, 0.70–1.44), and 3 (OR, 0.71; 95% CI, 0.42–1.18) years (10). This systematic review is limited by the retrospective nature of the studies included as well as the small sample sizes in each included study.

A more recent systematic review, including 53 studies, indirectly compared RFA with MWA (11). For patients with primary lung cancer, no significant difference was found in the median OS between the RFA (24.4 months; 95% CI, 16.9–31.8 months) and MWA (28.4 months; 95% CI, 20.9–35.8 months) groups. These results, however, should be interpreted with caution as the analysis indirectly compared the two modalities with marked heterogeneity among studies.

In another meta-analysis including a total of 34 studies (n = 1,840 patients), the efficacy and safety of RFA, CA, and MWA in patients with lung malignancies were compared (12). Local progression after ablation therapy was 19.8% for RFA, 23.7% for CA, and 10.9% for MWA (with follow-up periods of 12–47 months). RFA and MWA were found to be significantly more effective for local control than CA (OR, 0.04; 95% CI, 0.004–0.38; $P = .005$; and OR, 0.02; 95% CI, 0.002–0.24; $P = .001$, respectively). The local progression rate was comparable between RFA and MWA (OR, 0.63; 95% CI, 0.04–10.39; $P = .745$). The 1-, 2-, 3-, 4-, and 5-year weighted average OS rates for RFA were 84.3%, 66.8%, 62.4%, 55.1%, and 43.5%, respectively. The 1-, 2-, and 3-year weighted average OS rates for CA were 86.5%, 73.5%, and 71.2%, respectively. The 1-, 2-, 3-, 4-, and 5-year weighted average OS rates for MWA were 82.5%, 54.6%, 35.7%, 29.6%, and 16.6%, respectively. The pooled network meta-analysis found no difference in safety between CA and RFA ($P = .974$) and MWA and RFA ($P = .979$).

Although there have been no direct comparisons of the different IGTA techniques, based on the current available indirect evidence, all three are valid options for lung ablation, and each modality has advantages and disadvantages that must be considered.

Biopsy. Imaging modalities alone cannot accurately distinguish malignant from benign masses; therefore, percutaneous transthoracic needle biopsy has been used to aid in the diagnosis and management of these lesions, which ultimately reduces overtreatment. Percutaneous biopsy has been proven to be a safe and effective diagnostic modality. A recent systematic review of 22 studies found that the overall sensitivity and specificity of computed tomography-guided percutaneous transthoracic needle biopsy were reported to be 92.52% ± 3.14% and 97.98% ± 3.28%, respectively (13). In several cases, biopsy can be used to establish molecular profiling to help guide therapy and help assess response to targeted treatments (14,15).

Retrospective Studies. Biopsy can be used either before or during ablative therapy to obtain histology. Optimal timing of biopsy has not been widely studied. Only two small retrospective studies have assessed outcomes when biopsy is performed during the ablation procedure (16,17). Liu et al (17) combined coaxial biopsy with MWA on 27 tumors in 23 patients and found the positive rate of biopsy was 81.48% with minimal complications (8.7%). Wang et al (16) assessed 54 patients (with 62 suspicious lesions) and evaluated outcomes among those who synchronously underwent percutaneous core-needle biopsy and MWA to those who sequentially underwent these procedures. The overall technical success rate was 100% across both groups. However, the pneumothorax rates were higher in the group that synchronously underwent biopsy and ablation (29.6% vs 57.1%, $P = .031$). The effective rate (defined as complete and partial response) after 6 months was 100% in both groups, indicating that synchronous biopsy and ablation is technically feasible with minimal associated morbidities and no effect on procedural efficacy.

Current Society Recommendations on Biopsy. The NCCN currently recommends that patients require tissue confirmation of lung cancer before any nonsurgical therapy (9). They also recommend that a multidisciplinary evaluation, including interventional radiology, thoracic surgery, and interventional pulmonology, be conducted to determine the safest and most efficient approach or provide consensus that a biopsy is too risky or difficult (9).

There is a lack of evidence evaluating outcomes for biopsy-proven NSCLC prior or during ablation. A multidisciplinary discussion regarding the safety and feasibility of biopsy prior to therapy may be helpful in informing future prognosis.

Safety. Complications following thermal ablation of lung malignancies have been assessed and synthesized by existing systematic reviews and meta-analyses as well as registry-based studies. Although pneumothorax has been identified in the studies listed in the following as a complication, it is typically an expected event as a result of the ablation procedure. We suggest that future trials should consider reporting pneumothorax as an expected outcome.

Registry-Based Cohort Studies. Using the National (Nationwide) Inpatient Sample, Welch et al (18) evaluated the complications and length of stay for patients undergoing inpatient percutaneous image-guided lung ablation between 2007 and 2011. In-hospital mortality occurred in 1.3% of cases, and the median length of hospital stay was 1 day (interquartile range [IQR], 1–3 days). The most common complication noted was pneumothorax (38.4%).

Systematic Reviews and Meta-analysis. A systematic review, including 34 studies, that assessed the comparative effectiveness and safety of ablation modalities found that the weighted average of major complication rate of thermal ablation was 11.5% (11.6% for RFA, 4.6% for CA, and 22.5% for MWA, specifically) (12). The predominant complication across all studies and all modalities was pneumothorax. Similarly, a systematic review specifically evaluating the safety of RFA found pooled major and minor complication rates of 6% (95% CI, 3%–8%) and 27% (95% CI, 14%–41%), respectively (19).

Overall, complications are acceptably low, indicating that ablation is a safe and effective option.

Preservation of Lung Function. Studies have consistently demonstrated preservation of lung function without permanent decline following treatment with ablation. In 2006, a phase II study of RFA and conventional radiotherapy for patients with unresectable stage I NSCLC demonstrated no worsening of pulmonary function after treatment (20). Similar results were seen in the Radiofrequency Ablation of Pulmonary Tumors Response Evaluation (RAPTURE) trial of 33 patients with stage I NSCLC undergoing RFA, in which pulmonary function tests did not show any significant worsening in forced expiratory volume (FEV), FEV percentage predicted, forced vital capacity (FVC), or FVC percentage predicted, in any follow-up visits compared with baseline values among patients undergoing RFA (21).

Post Hoc Analysis of Clinical Trials. A follow-up study in 2015 examining RFA alone for stage I NSCLC showed a sustained improvement in FVC 2 years after treatment. No changes in FEV1 or diffusing capacity for carbon monoxide (DLCO) were observed at 3 or 24 months (22). In contrast, other forms of local control, specifically surgical resection, have been associated with a measurable decline in pulmonary function. In general, wedge resections (up to 3) can result in a cumulative decline in postoperative FEV1 of 5%; segmentectomy, 3%–11%; and lobectomy, 9%–16% (23–25).

Retrospective Studies. Studies have indirectly compared lung function with ablation to that of SBRT. SBRT is associated with demonstrable decreases in TLC, FEV1, FVC, and DLCO (26–28). Hörner-Rieber et al (26) demonstrated a relative decline of 9.8% (−33.9 to +33.3) occurring approximately 9 months after SBRT. At 12 months following SBRT, Stone et al (28) demonstrated a decline in FEV1 of 4.1%, corrected diffusion capacity for carbon monoxide of 5.2%, FVC of 5.7%, and total lung capacity of 3.6%, and these declines persisted at 24 months.

The ability to preserve lung function benefits patients with comorbid pulmonary insufficiency, those who may require treatment of multiple tumors, due to either multiple synchronous or metachronous primary cancers or limited

metastases. Patients who require multiple procedures to address lung tumors are often good candidates for percutaneous ablation since options for repeated surgical resection or radiation therapy may be limited.

Cost-Effectiveness. Given that IGTA for stage IA NSCLC yields similar survival outcomes to sublobar resection and SBRT, the cost of healthcare delivery for each of these interventions may play a role in selection of therapy.

Retrospective Studies. In a propensity score-matched cohort of 128 Medicare patients with stage IA/IB NSCLC treated with either sublobar resection or IGTA, Kwan et al (23) found that patients who underwent ablation had significantly lower treatment-related costs than those who underwent sublobar resection ($P < .001$). The difference in median treatment-related cost was $16,105. A major driver of cost savings was ablations that could be performed on an outpatient basis, although the cost of care for patients who were hospitalized following IGTA was also lower in comparison to that following sublobar resection. A similar cost savings was found in a smaller single-center retrospective study comparing Medicare costs for patients who underwent RFA (n = 56) and those who underwent sublobar resection (n = 28) (29). The median cost per month lived was $620.74 (IQR, $166.71–$1,301.93) for a patient treated with RFA, compared with $1,195.92 (IQR, $993.24–$1,957.28) for a patient treated surgically, and this difference was found to be statistically significant ($P < .01$).

The current available evidence does indicate that the overall cost of care is significantly lower for patients treated with IGTA in comparison to competing modes of therapy. However, the evidence base on cost-effectiveness focuses on early-stage NSCLC; therefore, these results are not generalizable to later stages or metastatic disease to the lungs.

Management of stage IA NSCLC

For patients with stage I or II NSCLC, surgical resection provides the best curative option, with 5-year survival rates of 60%–80% for stage I and 30%–50% for stage II (30). However, only one-third of patients meet the criteria for lobar or sublobar resection (31).

While there have been no randomized trials comparing percutaneous IGTA with surgery or SBRT, multiple non-randomized studies have evaluated IGTA in comparison to these treatment options and provide some insight as to their comparative clinical efficacy. Several population-based registry studies using the Surveillance, Epidemiology and End Results Medicare Database and National Cancer Database (NCDB) have been published comparing ablation with surgical resection and SBRT. While drawing from large patient cohorts, these studies are all inherently limited by their retrospective design as well as by the limited and inconsistent reporting of data in the registry databases from which patient information was drawn. It is also significant to note when interpreting results that patients who underwent ablation often did not have similar characteristics to patients who were treated with either sublobar resection or SBRT, indicating underlying selection bias across multiple studies. For example, in the RAPTURE study, all patients had contraindications to chemotherapy and radiation and were not eligible for surgery (32). Furthermore, in the ACOSOG Z4033 trial, patients treated with RFA were older and had decreased DLCO compared with patients undergoing sublobar resection (22). Similarly, patients who received SBRT in the RTOG 0236 trial were younger and had better pulmonary function than the IGTA patient cohort described in ACOSOG Z4033 (27). Therefore, the results in these trials are from patients with poorer lung function and baseline characteristics that may not fully represent the true patient population that could benefit from ablation.

Single-Arm Trials. The early prospective single-arm RAPTURE trial established IGTA as an effective and safe procedure for early-stage NSCLC. The 2-year OS and cancer-free survival rates were found to be 75% and 92%, respectively (21). Ambrogi et al (24) reported 5-year data following RFA of 59 tumors in 57 medically inoperable patients with stage I disease (IA, 44; IB, 15). The combined 1-, 3-, and 5-year survival rates were 83%, 40%, and 25%, respectively. The 1-, 3-, and 5-year cancer-specific survival (CSS) of 95%, 71%, and 52% in patients with clinical stage IA disease notably improved compared with those in patients with stage Ib disease. Palussiere et al (25) reported a 5-year OS rate of 58% in their series of 87 patients undergoing RFA for NSCLC. Long-term survival data reported by Huang et al (33), who studied 50 patients with stage IA NSCLC, with 73 treated lesions found that the 1-, 2-, 3-, 5-, and 10-year OS were 96.0%, 86.5%, 67.1%, 36.3%, and 1%, respectively.

More recent studies of RFA for the treatment of stage IA NSCLC have found OS to be between 86.3% and 91.6% at 1 year, 69.8% at 2 years, and 58% at 3 years (22,34).

MWA for stage I NSCLC has also been studied in small single-arm series. Yang et al (35) reported 1-, 2-, 3-, and 5-year survival of 89%, 63%, 43%, and 16%, respectively, in patients with stage I NSCLC (35). More recently, Han et al (36) reported 1-, 2-, 3-, 4-, and 5-year survival of 92.6%, 63.4%, 54.4%, and 32.6% in 63 patients aged ≥80 years undergoing MWA for stage IA NSCLC.

CA has also been studied in a single-arm prospective trial. Moore et al (37) reported 5-year data following percutaneous CA of stage I NSCLC in 45 patients with 47 biopsy-proven tumors. The OS rates at 1, 3, and 5 years were 89.4%, 78.1%, and 67.8%, respectively. The 5-year progression-free survival (PFS) and CSS were 87.9% and 56.6%, respectively (37).

Comparative trials with various levels of evidence have assessed IGTA compared with surgical resection or SBRT. The evidence on these comparisons is provided in the following section.

IGTA versus Surgical Resection

Registry-Based Cohort Studies. Using the Surveillance, Epidemiology and End Results Medicare linked database, Kwan et al (38) evaluated the survival outcomes of sublobar resection and thermal ablation in 1,897 patients with stage IA and IB NSCLC aged ≥65 years. The propensity score-matched cohort (n = 69) showed no statistically significant differences in OS between sublobar resection and ablation ($P = .695$) or lung CSS ($P = .819$).

A more recent study assessing the survival outcomes for patients with clinical stage I NSCLC using data from the NCDB found conflicting results (39). The 1-, 2-, 3-, and 5-year relative survival rates were 96%, 90%, 84%, and 71% for sublobar resection (n = 30,451) and 90%, 73%, 58%, and 37% for ablation (n = 1388), respectively. In the matched cohort, ablation was found to be associated with shorter OS compared with sublobar resection (hazard ratio [HR], 1.90; 95% CI, 1.73–2.10).

Retrospective Studies. Several studies have retrospectively compared ablation to lobectomy. In a study of 131 patients with stage I NSCLC, Wang et al (40) assessed the effectiveness of MWA (n = 46) versus thoracoscopic lobectomy (n = 85). No significant differences were found in either the OS or disease-free survival rates at 1 and 2 years. The 1- and 2-year OS rates were 97.82% and 91.30% versus 97.65% and 90.59% in the MWA and lobectomy groups, respectively, and the 2-year disease-free survival rates were 95.65% and 76.09% versus 95.29% and 75.29%, respectively. Similar results were found in a propensity score-matched retrospective study comparing 54 patients treated with MWA and 108 patients treated with surgical lobectomy, including patients with stage IA, Ib, and IIa diseases (41). No significant difference was found in the 1-, 3-, and 5-year OS (100%, 92.6%, and 50% for MWA and 100%, 90.7%, and 46.3% for lobectomy; $P = .608$). This relationship was maintained when comparing the treatment of both Ia and combined Ib/IIa diseases. These results indicate that ablation has similar efficacy to lobectomy as a treatment option for patients with early-stage NSCLC.

There have also been several studies comparing ablation with sublobar resection. A retrospective three-arm study by Zemlyak et al (42) compared outcomes in patients with stage I NSCLC undergoing sublobar resection (n = 25), RFA (n = 12), and percutaneous CA (n = 27). They found no significant difference in OS at 3 years (87.1%, 87.5%, and 77%, respectively; $P > .05$) among these three groups (42). Similar results were found in earlier studies. Safi et al (43) evaluated the recurrence and survival rates among patients treated with RFA (n = 25) and sublobar resection (n = 42). After adjusting for age and tumor size, no differences were found in OS or PFS between the two groups (HR, 2.72; 95% CI, 0.77–9.59; $P = .121$; and HR, 1.79; 95% CI, 0.82–3.92; $P = .143$, respectively). A more recent larger study by Iguchi et al (30) retrospectively compared the outcomes of RFA and sublobar resection in patients with stage I NSCLC and found similar results. A total of 38 patients underwent RFA, and 193 were treated with sublobar resection. The 5-year OS and PFS rates were 59.7% and 35.9% for RFA and 71.0% and 61.9% for sublobar resection, respectively; however, following propensity score matching, the OS and PFS were not found to be significantly different between the ablation and sublobar resection groups (HR, 0.56; 95% CI, 0.28–1.10; $P = .090$).

Systematic Reviews and Meta-analyses. No systematic reviews and/or meta-analyses were found that compared IGTA to surgical resection in patients with stage IA NSCLC.

IGTA versus SBRT

Registry-Based Cohort Studies. Uhlig et al (44) used the NCDB to compare thermal ablation with SBRT in patients with stage I NSCLC. Among the propensity score-matched cohort (n = 2,140), there was no difference in OS rates at 1, 2, 3 and 5 years ($P = .694$). Similar results were found in a study conducted by Lam et al (45) among patients with stage IA and Ib NSCLC treated with primary RFA or SBRT. In the propensity score-matched cohort (n = 312 in each group), the estimated 1-, 3-, and 5-year OS rates for patients treated with SBRT were 85.5%, 54.3%, and 31.9%, and the estimated 1-, 3-, and 5-year OS rates for patients treated with RFA were 89.3%, 52.7%, and 27.1%, respectively; these differences were not found to be statistically significant ($P = .835$). In both studies, increased unplanned readmission rates within 30 days were noted in the IGTA group, largely from pneumothoraces.

Retrospective Studies. There are limited data comparing ablation with SBRT in the treatment of NSCLC. Ochiai et al (46) retrospectively compared the clinical outcomes after RFA (n = 48) and SBRT (n = 47) in patients with solitary lung tumors less than 5 cm. The RFA and SBRT groups showed similar 3-year local tumor progression rates (9.6% vs 7.0%, respectively; $P = .746$) and OS rates (86.4% vs 79.6%, respectively; $P = .738$).

More recently, Iguchi et al (30) compared RFA with SBRT in a small retrospective series of patients with stage I NSCLC. A total of 38 patients underwent RFA, and 58 were treated with SBRT. In the propensity score-matched analysis, they found no significant difference in the 5-year OS and PFS rates between the two groups (63.7% and 55.7% for SBRT and 59.7% and 35.9% for RFA, respectively; $P > .05$). Death from any cause (HR, 0.80; 95% CI, 0.35–1.83; $P = .605$) and disease progression (HR, 0.56; 95% CI, 0.28–1.14; $P = .108$) were also not found to be significantly

different between the RFA and SBRT groups, indicating that RFA has similar efficacy for treatment in selected patients with early-stage NSCLC.

Systematic Reviews and Meta-analyses. In a recent systematic review, Bi et al (47) compared the clinical outcomes of SBRT and RFA. A total of 31 studies on SBRT (n = 2,767 patients) and 13 studies on RFA (n = 328 patients) met the inclusion criteria for their review. The adjusted pooled analysis (adjusting for age and percent of stage IA) demonstrated that the OS following RFA or SBRT was comparable at 1, 2, 3, and 5 years: 85% (80%–89%), 67% (61%–74%), 53% (45%–61%), and 32% (22%–43%) for RFA and 85% (84%–87%), 68% (66%–70%), 56% (53%–59%), and 40% (36%–45%) for SBRT, despite better rates of local control for SBRT. Several of the studies in these reviews include single-arm retrospective studies at high risk of bias (due to patient selection, uncontrolled confounding, etc), ultimately limiting the overall quality of the body of evidence.

Based on the available evidence, ablation has similar survival outcomes as surgical resection and SBRT, indicating that it is a valid treatment option for patients with stage IA NSCLC.

Current Society Recommendations on the Management of Stage IA NSCLC. The current society recommendations (**Table 1**) on the management of early-stage NSCLC suggest the use of thermal ablation in select patient groups (28,48).

Management of Recurrent Lung Cancer

While surgical resection is the gold-standard treatment for early-stage lung cancer, tumor recurrence occurs in 34%–45% of patients who undergo surgery (49,50). An advantage of IGTA therapy is the ability to re-treat lungs that have previously undergone resection. This includes the treatment of areas of local recurrence, including within surgical, radiation, and ablation beds, as well as metachronous NSCLC. The 5-year survival rate for patients undergoing second surgery following a primary resection is fairly poor, 24% at 5 years (51). As opposed to surgical repeat resection, the formation of scar tissue within the chest does not significantly impede the ability to place ablation probes for a completion treatment.

Retrospective Studies. Kodama et al (52) evaluated 44 patients with 51 recurrent NSCLC who had undergone prior surgery, treated with RFA in 55 sessions. After a mean follow-up of 28.6 months, the local tumor progression rate was 11.4% at 2.8 years. The 1-, 3-, and 5-year OS rates were 97.7%, 72.9%, and 55.7%, respectively. The 1- and 3-year recurrence-free survival rates were 76.7% (95% CI, 63.2–90.1) and 41.1% (95% CI, 22.0–60.3), respectively. Additional studies have similarly demonstrated the utility of IGTA as salvage therapy following primary failure of other therapies, including surgery, chemotherapy, and external beam radiation therapy (53,54).

Interestingly, a single-center phase II study of combined SBRT and heat-based thermal ablation for central tumors (primary and metastatic) demonstrated local control rates of 93% and 81% at 1 and 2 years, respectively, with limited toxicity, indicating that a combined modality approach may also have a role in the management of some patients (55).

Current Society Recommendations on the Management of Recurrent Lung Cancer. The NCCN guidelines have specific recommendations for ablation in patients with locoregional recurrent lung cancer (**Table 1**), recommending that image-guided thermal ablation is a treatment option for select patients (9).

Unlike surgical resection or SBRT, ablation can be repeated with limited changes to pulmonary function, and this is particularly significant in the setting of recurrent disease. The available evidence indicates that ablation is a valid treatment option in these patients.

Management of Metastatic Disease to the Lungs

Much like surgical resection, thermal ablation can play a role in the management of metastatic disease in selected patients with limited disease burden that can be ablated with margins (56). Ablation for pulmonary metastases has been widely reported in the literature. The largest study assessing the utility of ablation for pulmonary metastases is that of de Baère et al (57), which included 566 patients with 1,037 metastatic lesions, including 52% with primary tumors of the colon or rectum, kidney, soft tissue, and bone tumors and tumors with a median diameter of 15 mm (range, 4–70) mm). The 4-year local efficacy with ablation was 89%. The OS rates at 1, 2, 3, 4, and 5 years were 92.4%, 79.4%, 67.7%, 58.9%, and 51.5%, respectively (57). The local control rate at the ablation site was 89%, and the overall control of disease in the lungs was 44% at 4 years. Additional studies have also shown the benefit of ablation in the treatment of metastatic disease. A systematic review and meta-analysis including 12 studies (n = 985 patients; 1,336 lung nodules) found that local recurrence after MWA ranged from 9% to 37%, with 1-year local recurrence rates from 18% to 40% and 2-year rates between 12% and 34% (58). More recently, the Multicenter Study of Metastatic Lung Tumors Targeted by Interventional Cryoablation Evaluation (SOLSTICE) trial results found 12- and 24-month OS rates among 128 patients with 244 lung metastases treated with CA to be 97.6% (95% CI, 92.6–99.2) and 86.6% (95% CI, 78.7–91.7), respectively (59). The same trial demonstrated that the local control rate (local tumor efficacy) of the treated

tumor was 172 of 202 (85.1%) at 12 months and 139 of 180 (77.2%) at 24 months after the initial treatment. After a second CA treatment for recurrent tumor, the secondary local recurrence-free response (local tumor efficacy) was 184 of 202 (91.1%) at 12 months and 152 of 180 (84.4%) at 24 months.

The role of ablation in specific cohorts of patients with colorectal cancer, sarcoma, and renal cell carcinoma is described in the following. For each section, the OS rates of ablation are indirectly compared with those from surgical intervention.

Colorectal Cancer. The lung is one of the main sites of colorectal tumor metastases. Approximately 10%–20% of patients will develop lung metastases (60). The use of ablation in the treatment of unresectable colorectal pulmonary metastases has been widely studied.

Retrospective Single-Arm Trials. An early study by Simon et al (61) evaluating the use of RFA in patients with unresectable colorectal pulmonary metastases found that the overall 1-, 3-, and 5-year survival rates were 87%, 57%, and 57%, respectively. Kurilova et al (62) evaluated the efficacy of MWA therapy in 50 patients with 90 unresectable pulmonary metastases. They found that the 1-, 2- and 3-year local tumor PFS rates were 93%, 86%, and 86%, respectively, and the 1-, 2- and 3-year OS and CSS were 94% and 98%, 82% and 90%, and 61% and 70%, respectively. The efficacy of CA for metastatic lung tumors from colorectal cancer has also been studied (63). Yamauchi et al (63) performed CA on 24 patients with 55 metastatic tumors and found that the rates of 1- and 3-year local progression-free interval were 90.8% and 59%, respectively. The 1- and 3-year OS rates were found to be 91% and 59.6%, respectively. A more recent large study by Fonck et al (64) including 209 patients with 630 lung metastases found that the OS rates at 1, 2, and 5 years were 95% (95% CI, 90.9–97.3), 85.5% (95% CI, 79.6–89.9), and 54.7% (95% CI, 45.4–63.1), respectively (64). Patients in this study were also treated with chemotherapy, with a median chemotherapy-free survival (defined as the time interval between IGTA and resuming chemotherapy or death without resuming chemotherapy) rate of 12.2 months (95% CI, 10.3–17.7), indicating that ablation can be used in multimodal therapy with improved survival outcomes.

Retrospective Database Studies. Using the prospective database of two French cancer centers, de Baère et al (57) evaluated the results of RFA of pulmonary metastases in 191 patients with colorectal cancer. The 1-, 3- and 5-year survival rates were found to be 92.9%, 76.1% and 56%, respectively. The PFS rates at 1, 3, and 5 years were reported to be 37.6%, 17% and 14.8%, respectively.

Systematic Reviews and Meta-analyses. A recent systematic review assessed the effectiveness and safety of ablative techniques in the management of colorectal pulmonary metastases (65). Eight studies (n = 903 patients) were included, all of which used RFA for ablation. The 1-, 3- and 5-year OS ranges were reported to be 84%–95%, 35%–72%, and 20%–54%, respectively. The local progression rate following ablation ranged from 9% to 21%.

The reported 5-year OS after complete surgical resection of lung metastases from colorectal cancers range from 27% to 68%, which is similar to the reported survival rates of ablation in this patient population (66).

Sarcoma

Retrospective Single-Arm Trials. Koelblinger et al (67) reported on 21 patients with 55 lung metastases from medically inoperable sarcoma who underwent RFA. The 2- and 3-year survival rates were 94% and 85%, respectively, with a mean OS of 51 months. Similarly, Palussiere et al (68) conducted RFA in 29 patients with lung metastases from sarcoma. The 1- and 3-year survival rates were 92% and 63%, respectively. Nakamura et al (69) performed RFA in 20 patients with lung metastases from osteosarcoma. The 1- and 3-year survival rates were 88.9% and 59%, respectively.

Retrospective Database Studies. de Baère et al (57) also assessed the results of RFA of pulmonary metastases in 51 patients with sarcoma. The 1-, 3-, and 5-year survival rates were found to be 94.1%, 58%, and 41.5%, respectively. The PFS rates at 1, 3, and 5 years were reported to be 43%, 26.5%, and 15.9%, respectively.

Evidence from the surgical literature shows poorer survival outcomes with 3-year OS rates after surgical resection for pulmonary metastases from sarcoma ranging from 33% to 65% (67).

Renal Cell Carcinoma

Retrospective Single-Arm Trials. Recently, ablation therapy has been attempted as a method to treat lung metastases from renal cancer. Soga et al (70) used RFA to treat 39 patients with lung metastases from renal cancer. The OS rates at 1, 3, and 5 years for the palliative group were 90%, 52%, and 52%, respectively. A more recent study found similar rates. Gonnet et al (71) assessed 53 patients undergoing RFA for 100 pulmonary metastases. The 1-, 3-, and 5-year OS rates were 94%, 74.5%, and 62%, which are comparable to the surgical literature. Local control was achieved in 91% of patients.

Retrospective Database Studies. In de Baère et al (57)'s large database study, 68 included patients presented with pulmonary metastases from renal cell carcinoma. After treatment with RFA, the 1-, 3-, and 5-year survival rates were found to be 95.9%, 73.5%, and 53.8%, respectively. The PFS rates at 1, 3, and 5 years were reported to be 39.7%, 13.8%, and 9.2%, respectively.

The OS rates for surgical resection of pulmonary metastases from renal cell carcinoma are comparable to those of ablation with 5-year OS ranging from 33% to 45% (72–75).

Other. The lungs are also a common site of metastases for other cancers, both common, such as breast, and rare, such as thyroid or head/neck cancers. Ablation can play a role in the treatment of these metastases as well. In this large series by de Baère et al (57), 154 metastases with breast, thyroid, and miscellaneous other origins were effectively treated with RFA. The OS rates at 1, 3, and 5 years were reported to be 89%, 59.1%, and 49.4%, respectively, with the PFS rates at 1, 3, and 5 years of 49%, 17.6%, and 7.6%.

Metastatic disease from other primary tumors often affects the lung. Although there have not been large studies investigating the efficacy of ablation in these groups, ablation may still be a viable treatment option.

Based on the evidence, for patients with metastatic disease in whom local therapy such as surgery or radiation is being considered, ablation may also be a viable treatment option. However, when considering ablation, patient selection is significant. de Baère et al (57) found that tumors < 2 cm were associated with improved local efficacy compared with those larger than 2 cm (HR, 3.59; 95% CI, 1.76–7.32; $P = .0004$). Numerous studies have shown that a tumor size of <3 cm has been identified as an independent prognostic factor of improved survival outcomes after ablation, regardless of modality used (76–80). Tumors <3 cm have also shown improved local tumor progression outcomes (14% vs 69% for tumors > 3 cm) (81).

Several studies have also identified the lack of extrapulmonary involvement (in addition to control of the initial tumor site) as a significant factor in which patients are appropriate for ablation. Yamakado et al (77) found 1-, 3- and 5-year survival rates of 97.7%, 82.5%, and 57.0% in patients without extrapulmonary metastasis at the time of the ablation, but the survival rates for patients who had extrapulmonary metastases were only 53.3%, 6.0%, and 0%. Similar results were found in earlier studies (76,77). Lung metastasis location (unilateral vs bilateral) has also been identified as an independent predictor of local efficacy (HR, 2.10; 95% CI, 1.33–3.33; $P = .0015$) (57).

Current Society Recommendations on the Management of Metastatic Cancer. The Cardiovascular and Interventional Radiological Society of Europe makes specific recommendations for ablation in patients with oligometastatic lung disease (**Table 1**). Additionally, the NCCN recommends that local techniques, such as image-guided ablation, can be considered for oligometastases for colon cancer, renal cell carcinoma, and sarcoma (6–8).

DISCUSSION

Thermal ablation has shown efficacy in the treatment of both primary and secondary lung malignancies. The outcomes from ablation have been established despite inequality in patient cohorts in comparative studies of surgical resection and SBRT, with ablation patients being relatively sicker and older. Thermal ablation has been successfully accomplished in these high-risk patients with stage I NSCLC, objectively defined with a single major (FEV1 or DLCO of $\leq$50%) and/or two or more minor criteria (a less depressed FEV1 or DLCO between 51% and 60%, advanced age $\geq$ 75 years, pulmonary hypertension, left ventricular ejection fraction $\leq$ 40%, resting or exercise PaO2 $<$ 55 mmHg, and pCO2 $>$ 45 mmHg) (22).

Based on the evidence, all ablation modalities are effective in the lung when used appropriately. Across ablation modalities, lesion characteristics and risk mitigation should be the main determinants of energy modality use (56). Local expertise, operator familiarity, comfort with each device, ease of use, preferences of referring physicians, and cost should also be considered when making this decision. In the setting of stage IA NSCLC, thermal ablation has shown comparable efficacy with regard to survival outcomes as sublobar resection and SBRT across all levels of evidence, indicating that ablation is a reasonable treatment option for these patients. Percutaneous thermal ablation also plays a role in patients who present with recurrent lung cancer, offering improved outcomes with limited change to pulmonary function. There is an emerging role for the use of thermal ablation in the setting of metastatic disease. The current evidence, with the best data available from the colorectal cancer population, indicates that ablation is comparable to sublobar resection for these patients.

CONCLUSION

SIR considers IGTA to be an acceptable treatment option for patients with inoperable stage I NSCLC, those with recurrent NSCLC, as well as those with metastatic lung disease. Future comparative effectiveness research into this area is warranted to evaluate if the recommendations can be strengthened.

RECOMMENDATIONS

1. In patients with stage IA NSCLC, image-guided thermal ablation is a safe and effective treatment with minimal complications and acceptable long-term oncological and survival outcomes that are comparable to SBRT and sublobar resection. (Level of Evidence, C; Strength of Recommendation, Moderate)
2. Image-guided thermal ablation is a safe and effective treatment option for patients with recurrent NSCLC. (Level of Evidence, C; Strength of Recommendation, Moderate)
3. Thermal ablation should be considered alongside surgical resection and SBRT in patients who require preservation

of lung parenchyma function. (Level of Evidence, C; Strength of Recommendation, Moderate)

4. Image-guided thermal ablation of metastatic disease to the lungs may be appropriate in some patients, including those with a limited number of small ($\leq$3 cm) lung metastases. (Level of Evidence, C; Strength of Recommendation, Weak)
5. RFA, CA, and MWA are all appropriate modalities for image-guided thermal ablation of primary or secondary lung tumors. The method of ablation should be determined by lesion characteristics and risk mitigation and should be left to the discretion of the operating physician. (Level of Evidence, C; Strength of Recommendation, Weak)
6. Biopsy of lung tumors is recommended before or during thermal ablation, when safe and possible. (Level of Evidence, D; Strength of Recommendation, Weak)
7. Future research in the form of comparative studies (either randomized controlled trials or well-conducted cohort studies) is required to strengthen the evidence base for image-guided thermal ablation in patients with inoperable stage I NSCLC, recurrent NSCLC, and metastatic lung disease. (Level of Evidence, E; Strength of Recommendation, Moderate)

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