

Stereotactic Body Radiotherapy and Ablative Therapies for Lung Cancer



Ghulam Abbas, MD, MHCM, FACS^{a,*}, Adnan Danish, MD^b,
Mark J. Krasna, MD^c

KEYWORDS

- Stereotactic body radiation therapy (SBRT) • Radiofrequency ablation
- Microwave ablation • Ablative therapies for lung cancer
- Stereotactic ablative therapy (SABR)

KEY POINTS

- The treatment paradigm for early stage lung cancer and oligometastatic disease to the lung is rapidly changing.
- Ablative therapies, especially SABR, are challenging the surgical gold standard and have the potential to be the standard for operable patients with early stage lung cancer who are high risk for morbidities.
- Microwave ablation is another promising novel ablative modality that in the near future would also be available for transbronchial ablation of small lung tumors, especially more central tumors.
- The outcome results of the ablative therapies should be compared with anatomic minimally invasive segmentectomy or lobectomy with lymph node dissection rather than historical surgical data.

Lung cancer remains the leading cause of cancer-related death in men and women in United States.¹ Surgical resection offers the best chance of cure in early stage disease. Surgical resection is also beneficial in a select group of patients with limited pulmonary metastases. Unfortunately, most patients with lung cancer present with advanced-stage disease and are not surgically curable. Among the patients with early stage lung cancer, more than 20% cannot tolerate surgery because of comorbid conditions.² Similarly, some patients with limited pulmonary metastases, who would benefit from metastectomy, are deemed high-risk secondary to poor cardiopulmonary reserves.

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^a Minimally Invasive Thoracic Surgery, Meridian Health, 1 Riverview Plaza, Red Bank, NJ 07701, USA; ^b Radiation Oncology, Meridian Health, 1 Riverview Plaza, Red Bank, NJ 07701, USA;

^c Meridian Cancer Care, Jersey Shore University Medical Center, Ackerman South, Room 553, 1945 Route 33, Neptune, NJ 07753, USA

* Corresponding author. 1 Riverview Plaza, Red Bank, NJ 07733.

E-mail address: gabbas@meridianhealth.com

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External beam radiation therapy may be offered as an alternate to surgery in patients with limited-stage disease who are too high-risk for surgery. However, reported 5-year survival with this modality is only 10% to 30%.^{3,4} The outcome data for stage I non-small cell cancer (NSCLC), treated with radiation therapy alone, from Duke University in 156 patients showed 2- and 5-year survival rates of 39% and 13%, respectively. In a study of 71 node-negative patients who received at least 60 Gy of radiotherapy, 3- and 5-year survivals were 19% and 12%, respectively.⁴ Another concern with external beam radiation is radiation pneumonitis, which is a potentially life threatening complication in these severely impaired patients. Zierhut and colleagues,⁵ in their study of 60 patients with NSCLC, reported an 8.3% incidence of radiation pneumonitis in patients treated with definitive radiotherapy. Several studies have reported a benefit to dose escalation with a dose-response relationship for local control and survival. When dose escalation is attempted using conventional treatment techniques, however, dose-limiting toxicity occurs. Increased doses of radiation result in increased toxicity and damage to surrounding pulmonary parenchyma, which limits safe dose escalation.^{6,7} Dose-volume histogram data show a correlation between risk of pulmonary toxicity and indices of dose to lung parenchyma. The risk of toxicity increases as the area of irradiated adjacent normal lung increases.⁸⁻¹⁰ Radiation fibrosis seems to depend on the volume of the lung that is radiated above a threshold of 20 Gy to 30 Gy and dose escalation is limited primarily by the risk of radiation pneumonitis.

Over the last two decades, ablative alternatives to resection or standard external beam radiation therapy have been introduced into clinical practice for the treatment of limited-stage lung cancer or limited pulmonary metastases. The most common modalities offered by many centers around the world are stereotactic body radiotherapy (SBRT), microwave ablation (MWA), radiofrequency ablation (RFA), cryotherapy, photodynamic therapy, and irreversible electroporation.

STEREOTACTIC BODY RADIOTHERAPY

SBRT, also known as stereotactic ablative therapy (SABR), holds the most potential for curative radiotherapy in patients with early stage lung tumors. Stereotactic targeting uses a variety of systems to decrease the effects of lung motion, which translate into target motion, and improve localization techniques by collection of precise measurements to account for tumor motion during treatment planning and delivery of each fraction. These systems allow dramatic reduction of treatment volume, facilitating hypofractionation with markedly increased daily doses and a significantly reduced overall treatment time and decreased irradiation of normal surrounding tissues with an associated reduction in toxicity. This is possible because radiation can be precisely contoured to the tumor with a very rapid fall-off of radiation in the surrounding lung parenchyma. Treatment is typically delivered in three to five fractions over a 1- to 2-week period, ranging on average from 10 Gy to 20 Gy per fraction. The resulting biologic effective dose (BED) of SBRT is typically in excess of 100 Gy, in contrast to a BED of 79.2 Gy with standard fractionation.^{11,12}

Currently there are a variety of platforms available for SABR. Some of these systems, especially Acuray Cyberknife (Accuray, Sunnyvale, CA), need placement of gold fiducial for image-guided tumor location during treatment. These can either be placed percutaneously using computed tomography (CT) guidance or transbronchially using navigational bronchoscopy (Electromagnetic Navigation Bronchoscopy, Medtronic, Dublin, Ireland). CT-guided fiducial placement is done under local anesthesia and is complicated by pneumothorax in 13% to 47% of cases. Electromagnetic

Navigation Bronchoscopy system is used to place the fiducials around the tumor transbronchially. This technique is associated with less incidence of pneumothorax.

Clinical Results

In one of the earliest studies from Indiana University, Timmerman and colleagues¹³ reported the outcome of a phase I dose escalation toxicity study. In this trial 47 medically inoperable patients with T1 and T2 NSCLC were treated with SBRT. Patients were treated with three fractions administered over a 2-week period using a frame-based radiosurgery system. The doses started at 8 Gy per fraction and were escalated to 20 Gy. At a median follow-up of 15.2 months, no late toxicity attributable to therapy was identified. Complete response was seen in 27% of patients and partial response was seen in 60%. With a 15-month follow-up, more than one-third (13 of 37) of patients showed progression of cancer. Among these 13 patients with cancer progression, six (6 of 13) showed local recurrence. These local recurrences were observed more commonly at lower radiation doses and occurred at a median of 13 months after treatment. A superior response rate of 87% with dose escalation was also noted. No patient treated with greater than 18 Gy per fraction showed progression during short-term follow-up.

A phase II trial from the same institution further evaluated efficacy and safety of SABR in this patient population.¹⁴ Doses established in the phase I trial were used to treat 70 patients with stage I NSCLC. For the initial report, 2-year local control was 95%, with a median follow-up of 17.5 months, and overall survival (OS) was 56% at 2 years. Most of the deaths were related to comorbid illnesses seen in this inoperable population, rather than death associated with lung cancer; however, there were six treatment-related deaths. Severe toxicity (grades 3–5) was seen in a greater proportion of patients with “central” tumors, defined as tumors near the proximal bronchial tree (see section on toxicity). The report was later updated after a median follow-up of 50 months, showing 3-year local control and survival of 88% and 42%, respectively.

In the Radiation Therapy Oncology Group (RTOG) 0236 protocol, 55 patients with peripheral, less than 5 cm (T1-T2, N0) tumors were treated with three fractions of 18 Gy with total dose of 54 Gy.¹⁵ Eleven patients had distant metastasis within 1 year of treatment and 22% had disseminated recurrence at the end of 3 years. Although the local control rates were high, the 3 years disease-free and OS rates were 48% and 56%, respectively.

At the American Society of Radiation Oncology's 56th annual meeting, Timmerman and colleagues¹⁶ presented updated 5-year data from the RTOG 0236 trial. The updated results showed a local recurrence rate of 20%, caused primarily by intralobar recurrence. Additionally, 5-year locoregional and distant recurrence rates were 38% and 31%, respectively. The high incidence of recurrence is probably caused by less optimal staging and use of less than 100 BED doses during RTOG 0236 protocol.

The University of Pittsburgh radiation oncology and thoracic surgery groups have successfully proven a model in which patients for SABR are evaluated by the radiation oncologist and thoracic surgeon. In their early experience, they reported the results of 32 patients treated with CyberKnife stereotactic radiosurgery.¹⁷ They subsequently analyzed 21 medically inoperable patients with stage I NSCLC that were treated with a median dose of 20 Gy in a single fraction using the Cyberknife system.¹⁸ An initial response was observed in 12 patients (12 of 21; 57%), and disease was stable in five (5 of 21; 24%), progressed in three (3 of 21; 14%), and was not evaluable in one (one of 21; 5%). At a mean follow-up of 24 months, the estimated probability of survival at 1-year was 81% (confidence interval [CI], 0.73–0.90). The median survival was

26.4 months (95% CI, 19.6 [not reached]). Local progression occurred in nine patients (42%). The median time to local progression was 12.3 months. This led to the adoption of a more aggressive protocol where all peripheral tumors were treated with 60 Gy in three fractions and more central tumors were treated with 48 Gy in four fractions. Recently they published their outcomes using SABR for recurrent lung neoplasms in 100 patients.¹⁹ The postprocedure 30-day mortality was 0%; median follow-up was 51 months. The median OS for the entire group was 23 months (95% CI, 19–41 months). The probability of 2- and 5-year OS was 49% (95% CI, 40%–60%) and 31% (95% CI, 23%–43%), respectively.

Multiple studies have shown that BED of 100 Gy or more leads to better outcomes with less local recurrence. Onishi and colleagues²⁰ reported on an amalgamation of multi-institutional data from Japan that included 257 patients (164 patients with stage IA disease and 93 with stage IB disease) with a median tumor size of 2.8 cm (range, 0.7–5.8 cm). The median follow-up period for the entire cohort was 38 months. The patients were divided into two groups based on the dose they received, 215 patients received 100 Gy BED and the other 42 patients received less than 100 Gy BED. The overall local control rate for the entire cohort was 86%. The group that received 100 Gy BED had a local control rate of 91.6%, whereas those who received a BED less than 100 Gy had a local control rate of only 57.1% ($P < .001$). The 3- and 5-year OS for the entire cohort was 56.8% and 47.2%, respectively. The 3-year OS rate in medically operable patients was 88.4% for BED greater than 100 Gy compared with 69.4% for less than 100 Gy. The 5-year OS for the BED 100 Gy cohort was 53.9%, compared with only 19.7% for less than 100 Gy ($P < .05$).

In another Japanese trial, Japan Clinical Oncology Group 0403, Nagata and colleagues²¹ initially published the results inoperable patients in 2010,²² in operable in 2012, and follow-up in 2015.²³ The aim of the study was to evaluate the safety and efficacy of SBRT in patients with histologically or cytologically proven NSCLC. Between July 2004 and November 2008, a total of 169 patients from 15 institutions were registered. One hundred inoperable and 64 operable patients (total 164) were eligible. Patient characteristics were 122 male and 47 female; median age, 78 years (range, 50–91 years); and 90 adenocarcinomas, 61 squamous cell carcinomas, and 18 others. Of the 100 inoperable patients, the 3-year OS was 59.9%. Grade 3 and 4 toxicities were observed in 10 and 2 patients, respectively. No grade 5 toxicity was observed. The 3-year OS for operable patients was better and was 76.5%. The progression-free survival was 54.5%. Grade 3 toxicities were observed in five patients. No grade 4 and 5 toxicities were observed.

RTOG protocol 0618²⁴ was a phase II trial using SBRT to treat early stage NSCLC in operable patients (deemed surgically resectable). Patients with biopsy-proven peripheral T1 to T3 tumors were treated with 18 Gy in three fractions delivered in 2 weeks. The study opened December 2007 and closed May 2010 after accruing a total of 33 patients. Of 26 evaluable patients, 23 had T1 and three had T2 tumors. Median age was 72 years. Four patients (16%) had SBRT-related grade 3 toxicity, whereas none had grade 4 to 5 adverse events. Median follow-up was 25 months. Two-year estimates of local failure, regional failure, and distant failure were 19.2%, 11.7%, and 15.4%, respectively. Two-year estimates of progression-free survival and OS are 65.4% and 84.4%, respectively.

The results of RTOG 0915 trial were recently published.²⁵ This was a randomized phase II study comparing two SBRT schedules for medically inoperable patients with stage I peripheral NSCLC. The aim of the study was to compare two SBRT schedules for medically inoperable early stage lung cancer to determine which produces the lowest rate of grade 3 and higher protocol-specified adverse events at 1 year. Patients

with biopsy-proven peripheral T1 or T2 were randomized either to receive 34 Gy in one fraction (arm 1) or 48 Gy in four consecutive daily fractions (arm 2). Ninety-four patients were accrued between September 2009 and March 2011. The median follow-up time was 30.2 months. Of 84 analyzable patients, 39 were in arm 1 and 45 in arm 2. Four (10.3%) patients on arm 1 and six (13.3%) patients on arm 2 experienced adverse events. The 2-year OS and disease-free survival rate was 61.3% and 56.4% for arm 1 and 77.7% and 71% for arm 2. The short follow-up is the major limitation of this study because the adverse events, such as pneumonitis, rib fracture, and nerve injury, can happen beyond 1 year posttreatment. The survival seems to be better with multi-fraction rather than single fraction arm 2. Until further comparison is performed patients should be treated in three to five fractions.

COMPARING STEREOTACTIC ABLATIVE THERAPY WITH SURGERY

The encouraging results with good outcome in medically inoperable patients led to the enthusiasm of using SBRT for medically operable patients and also comparing this modality with surgical resection, which is the gold standard for the treatment of early stage lung cancer.

In an earlier retrospective comparison of 464 patients who underwent surgery and 76 who underwent SABR for clinical stage I NSCLC, local control at 3 years was improved with surgery for stage IA patients (96% vs 89%; $P = .04$) but no different for stage IB patients ($P = .89$).²⁶ Although no difference in disease-specific survival was seen, surgery was associated with improved OS ($P < .001$). In their updated T-stage matched analysis of patients treated with lobar resection ($N = 260$) or SBRT ($N = 78$), there was no significant difference in patterns of failure or cause-specific survival, whereas OS favored surgery.²⁷

Multiple studies from the Netherlands have compared surgery with SABR. In a propensity score-matched analysis based on stage, age, gender, comorbidity score, lung function, and performance status, locoregional control rates were higher in patients receiving SABR ($N = 64$) than those receiving video-assisted thoracoscopic surgery (VATS) ($N = 64$) (86.9% vs 82.6%; $P = .04$), whereas there was no difference in distant recurrence rate or OS.²⁸ The less than desired outcome in the VATS group may be caused by the institution's early experience with VATS (adopted VATS in 2007) and less aggressive lymph node dissection with only 70% having more than five lymph nodes harvested. In an updated propensity score-matched analysis ($N = 73$ for each modality), survival was similar ($P = .089$) at 12 months (95% vs 94%) and 60 months (80% vs 53%) for patients undergoing surgery and SABR, with a trend toward improved survival with surgery at longer follow-up identified.²⁹ Another recent publication from the Netherlands evaluated the outcome of patients with stage I (T1 and T2) NSCLC treated with surgery ($N = 143$) or SABR ($N = 197$); survival was similar across modalities when controlling for prognostic covariables ($P = .73$). When examining recurrences, local and distant control were similar but locoregional recurrences occurred more following SABR ($P = .028$), suggesting a need to improve staging in SABR.³⁰

In the United States, Surveillance, Epidemiology, and End Results (SEER) studies have also compared surgery with SABR. Among 10,923 patients aged greater than or equal to 66 years with stage I NSCLC treated from 2001 to 2007, most (59%) were treated with lobectomy, whereas only 1.1% were treated with SABR. SABR was associated with a lower risk of death at 6 months, whereas lobectomy had better long-term survival.³⁰ On propensity score-matched analysis, SABR and lobectomy had similar survivals. Similarly, a SEER study of 9093 patients with stage I NSCLC

treated from 2003 to 2009 with lobectomy (79.3%), sublobar resection (16.5%), or SABR (4.2%) reported unadjusted 90-day mortality to be highest with lobectomy and lowest with SABR (4.0% vs 1.3%; $P = .008$). However, at 3 years, unadjusted mortality was lowest with surgery (25.0% vs 45.1%; $P < .001$), showing better long-term survival with surgery.³¹

Based on the highly promising outcome of SBRT in medically inoperable patients, three randomized trials comparing SBRT with lobectomy (ROSEL, STAR) or sublobar resection (American College of Surgery Oncology Group [ACOSOG] Z4099/RTOG 1021) have been started but all three studies closed very early because of poor accrual: less than 5% of the planned patients were enrolled.

STEREOTACTIC RADIOTHERAPY VS SURGERY AND RADIOSURGERY OR SURGERY FOR OPERABLE EARLY STAGE NON-SMALL CELL LUNG CANCER TRIALS

STARS (StereoTactic Radiotherapy vs. Surgery) is an international randomized phase III trial comparing CyberKnife SABR with surgical resection. ROSEL (Radiosurgery Or Surgery for operable Early stage non-small cell Lung cancer) is a randomized phase III trial by VU Medical Centre Amsterdam and the Dutch Lung Cancer Research Group comparing SABR with surgery.

In the STARS trial, patients with tumors smaller than 4 cm and operable clinical stage I NSCLC received either surgical resection and mediastinal lymph node dissection or SABR to 54 Gy in three fractions for peripheral tumors or 50 Gy in four fractions for central tumors.

In the ROSEL trial, patients with tumors less than 3 cm with operable clinical stage IA NSCLC received either surgical resection (lobectomy was preferred but limited resection was acceptable) or SABR to 54 Gy in three fractions for peripheral tumors or 60 Gy in five fractions for central tumors. Histologic confirmation of an NSCLC diagnosis was required in the STARS trial but not the ROSEL trial, although lesions had to be new or growing and radiographically consistent with NSCLC and avidity on PET/CT.

Although the STARS and ROSEL trials closed early because of poor accrual, a pooled analysis of the two trials was conducted by Chang and colleagues³² with a primary outcome of OS. Fifty-eight patients were enrolled and randomized to SABR ($N = 31$) or surgery ($N = 27$, 5 VATS and 22 thoracotomy), with no differences in patient or tumor characteristics found between arms. OS was found to be significantly higher among patients randomized to SABR with 3-year survival of 95% versus 79% for surgical patients. This survival difference was significant in the STARS trial alone ($P = .0067$) but not the ROSEL trial ($P = .78$). At 3 years, there was no difference in local control (SABR 96% vs surgery 100%; $P = .44$), regional nodal control (90% vs 96%; $P = .32$), metastatic-free survival (97% vs 91%; $P = .42$), and recurrence-free survival (86% vs 80%; $P = .54$). These results should be interpreted with caution because the STARS trial only enrolled 36 of its intended 1030 patients and the ROSEL trial only enrolled 22 of its intended 960 patients. Also 5 of 27 patients had VATS and the rest had thoracotomy probably associated with higher morbidity and poorer outcome.

A SURGEON'S VIEW

Several well-designed prospective studies have clearly proven that SABR is safe and effective for medically inoperable and operable patients with NSCLC. However, the results of these studies should be interpreted with caution. The results of SABR outcomes are usually compared with the historical surgical outcomes rather than

contemporary outcomes of minimally invasive surgery. In these series, preoperative staging was less accurate because of nonexistent modern imaging technology. Also morbidity and mortality was higher because minimally invasive surgery for lung cancer has only matured recently. In the United States almost half of the lung cancer resections are performed by surgeons who are not trained in thoracic oncology, leading to less optimal decision-making and oncologic resection. The less aggressive lymph node dissection may lead to higher recurrence and decreased survival.

Multiple studies have shown that 20% to 30% of stage I lung cancers are upgraded during surgery because of occult N1 or N2 disease.^{33–35} These patients are at a disadvantage if treated with SABR because their nodal status is unknown and are at higher risk for recurrence without adjuvant systematic treatment.

A retrospective analysis using SEER data suggests SABR is superior to sublobar resection.³¹ There are excellent outcome studies from Japan and the United States showing anatomic segmentectomy for stage 1A lung cancer has the same recurrence and survival rates as lobectomy with less morbidity, especially in older patients.³³ It is misleading to compare the well-organized prospective SABR data with historical surgical outcomes or SEER data.

Similarly, how recurrence is defined is different in SABR data versus surgical literature. SABR literature refers to local recurrence as recurrence at the primary tumor site. However, local failure in surgical series has generally included recurrence within the same lobe away from the primary site (regarded as distant failure in many SABR experiences), and may include recurrence within an ipsilateral nonprimary lobe, usually hilar lymph nodes.

Another factor that must be considered is how local failure is identified. After SABR, residual scarring may remain in the lung, and the challenge is differentiating this from viable tumor. Biopsy may be difficult, and so serial imaging provides the best estimation of potential recurrence. However, in a high-risk group of patients, death may occur from another cause, before growth is appreciated in a region of viable tumor, therefore underestimating the incidence of recurrent disease (ask affect overall but not recurrence-free survival).

Another concern is the selection of patients deemed medically inoperable or high-risk operable. An analysis comparing the patient populations from three cooperative group studies included patients from Z4032, a study of high-risk operable patients treated with sublobar resection; Z4033, a study of medically inoperable patients treated with RFA; and RTOG 0236, a study of medically inoperable patients treated with SABR.³⁶ The Z4032 and Z4033 studies had similar inclusion criteria, except that an ACOSOG-approved surgeon had to declare the patient medically inoperable to enter Z4033. The Z4033 patients were significantly older and had the worst predicted carbon monoxide diffusion capacity compared with the other groups. The best pulmonary function was reported in the RTOG 0236 patients showing challenges in comparing these different modalities for the treatment of early stage lung cancer.

Future Trials

The ACOSOG Z4099/RTOG 1021 randomized phase III trial of sublobar resection with or without brachytherapy versus SABR in high-risk patients with stage I NSCLC, the only other phase III randomized trial conducted to date other than the STARS and ROSEL trials, is unlikely to provide any significant additional insight in the debate of SABR versus surgery given that it closed early in 2013 because of lack of accrual and is without publication. However, additional insight from two upcoming randomized trials may be forthcoming. The VALOR trial (Veterans Affairs Lung cancer surgery Or stereotactic Radiotherapy) is scheduled to open in the United States within the

year, and the SABRTooth trial (a multicenter pilot and feasibility study that will compare SABR and surgery for peripheral stage I NSCLC in patients thought to be at higher risk of surgical complications) is also planned to open in the United Kingdom.

Toxicity of Treatment

Although SABR is safe and usually without any short-term adverse effects, it may lead to significant delayed morbidity or even death. A study by Timmerman and colleagues¹⁴ reported the outcome of 70 patients with T1 or T2 less than 7-cm tumors, treated with high-dose stereotactic radiosurgery. T1 tumors were treated with 60 Gy in three fractions and T2 tumors were treated with 66 Gy in three fractions. Fifty-eight of 70 patients had grade 1 to 2 toxicity consisting mostly of fatigue, musculoskeletal discomfort, and radiation pneumonitis, which was sometimes treated with oral corticosteroids. Most grade 1 to 2 toxicities occurred within 1 to 2 months of treatment and resolved by 3 to 4 months posttreatment. Eight patients had grade 3 to 4 toxicity as evidenced by decrease in pulmonary function tests, pneumonias, pleural effusions, apnea, and skin reactions. The time from treatment to toxicity for these more severe toxicities was a median of 7.6 months. Four of the six deaths were seen in patients with central or perihilar tumors. Central and perihilar tumors had an 11 times increased risk of toxicity. Size of the gross tumor volume was also a significant predictor of grade 3 to 5 toxicity. Tumors with gross tumor volumes greater than 10 mL had an eight times increased risk of high-grade toxicity versus smaller tumors. Survival was worse in patients with T2 tumors, worse in patients with cardiac comorbidities compared with pulmonary comorbidities, and worse in patients with a forced expiratory volume in 1 second less than 40%. The authors concluded that treatment with 60 Gy in three fractions to central tumors may be too toxic.

MICROWAVE ABLATION

MWA is a relatively recent development in the approach to tumor ablation. The mechanism of MWA is dielectric heating (frictional heating of water molecules in tissue). As microwave radiation interacts with water molecules, the polarity of these molecules changes resulting in heating and eventually leading to cell death.

MWA is slowly replacing RFA for thermal ablation of lung tumors. In comparison with RFA, MWA leads to enhanced thermocoagulation of tumor cells as a result of improved energy deposition in the lung, higher temperatures within the tumor in a shorter amount of time, and a larger ablative area. MWA may allow for improved treatment of central lesions compared with RFA because of minimal heat sink effect associated with surrounding vasculature. The most common complications of MWA are similar to those of RFA, including risk of pneumothorax, postprocedure pain, and hemoptysis.

Clinical experience with MWA for lung tumors is limited at this time. Feng and colleagues³⁷ reported on MWA of 28 tumors in 20 patients. A response of 50% ablation or more was noted in 13 (46.4%) nodules and a complete response in three (10.7%). No significant complications were noted. An ablate and resect study was performed by Simon and colleagues.³⁸ Patients undergoing elective lung resection underwent MWA before their resection. The mean tumor diameter was 3 cm (range, 2–5.5 cm) with an average tumor volume of 7.1 cm³. The mean maximum ablation achieved was 4 cm (range, 3–5 cm), with an average tumor volume of 23.4 cm³. Wolf and colleagues³⁹ reported their results of MWA in 82 lung tumors of 50 patients. At a mean follow-up of 10 months, 26% of the patients had residual disease at the ablation site and another 22% had recurrent disease distant from the ablation site.

Local control at 1 year was seen in 67%. Kaplan-Meier analysis yielded an actuarial survival of 55% at 2 years postablation and 45% at 3 years postablation.

RADIOFREQUENCY ABLATION

During RFA, a high-frequency electrical current heats and coagulates tissue. This alternating current moves from an active electrode placed within the tumor to dispersive electrodes (Bovie pads) placed on the patient. RFA systems, therefore, have three components: (1) a generator, (2) an active electrode, and (3) a dispersive electrode. As the radiofrequency energy moves from the active electrode to the dispersive electrode and then back to the active electrode, ions within the tissue oscillate to follow the changing direction of the alternating current. This results in frictional heating of the tissue; as the temperature within the tissue rises to greater than 60°C, instantaneous cell death begins because of protein denaturation and coagulation necrosis. Typically, when RFA is performed, the local temperature in the ablated tumor will be 60°C and above.

Like MWA, it is performed under CT guidance using local anesthesia. It leads to necrosis of tumor without significantly affecting the surrounding parenchyma. The so-called “heat-sink” phenomenon is a major limitation. Vessels larger than 3 mm in diameter reduce the amount of energy delivered to the target as a result of the loss of heat through convection within the circulatory system.⁴⁰ Other limitations are the size and site of the tumor. Tumors larger than 3 cm usually have a less than 50% necrosis.⁴¹ Also, RFA is prohibitory for central tumors because of the risk of injuries to bronchus, major vessels, and esophagus.

In an earlier report from University of Pittsburgh, Herrera and colleagues⁴¹ reported the results in 18 patients (5 NSCLC and 13 metastasis) treated with RFA. Response, assessed by the modified RECIST criteria, was complete in 6% and partial in 44% of patients. Fernando and colleagues⁴² reported the results in 18 patients with NSCLC, of which nine patients were stage I patients. The median follow-up was 14 months and local progression occurred in 38% of nodules. The mean and median progression-free intervals were 16.8 and 17.6 months, respectively. For stage I NSCLC, the mean progression-free interval was 17.6 months and the median progression-free interval was not reached. Subsequently, Pennathur and colleagues⁴³ reported the results of 19 patients with stage I NSCLC treated with RFA. The mean follow-up was 29 months. Local progression occurred in 42% of patients and the median time to progression was 27 months. The estimated OS at 1 year was 95%.

Gadaleta and colleagues⁴⁴ described their preliminary experience in 18 patients (4 NSCLC and 14 metastases). The median follow-up was 8 months and 94% of patients did not have any local progression. Similarly, Yasui and colleagues⁴⁵ reported the early results of RFA (median follow-up, 7 months posttreatment) in 99 tumors and saw local progression in only nine tumors. Yan and colleagues⁴⁶ reported the results of 55 medically inoperable patients with pulmonary metastases from colorectal neoplasms who were treated with RFA. They reported a median OS of 33 months, and estimated 1-, 2-, and 3-year survivals of 85%, 64%, and 46%, respectively. A local recurrence rate of 38% was reported for these patients.

Ambrogio and colleagues⁴⁷ reported the results of RFA in 54 patients with 64 lung lesions (40 NSCLC and 24 metastases). The authors used contrast enhancement on CT scans to assess initial response and used modified RECIST criteria after 6 months to assess the progression of the lesion. They reported a complete response rate of 62%. Mean follow-up was 23.7 months with an OS of 28.9 months. The median progression-free interval was 24.1 months. Another interesting study by Hiraki and

colleagues⁴⁸ evaluated the risk factors for local progression after RFA in a series of 128 patients with 342 tumors. There were 317 metastatic lesions and 25 primary lung neoplasms; the Boston Scientific (Marlborough, MA) expandable probe was used in 142 lesions and Valley Lab (Medtronic, Dublin, Ireland) cluster probe was used in 200 lesions. The mean follow-up was 12 months and local progression was seen in 94 lesions (27%). Comparing the multitined probe with cooled-tip probe showed that the use of cooled-tip probe was an independent risk factor for local progression.

Lee and colleagues⁴⁹ reported their experience in 10 patients with stage I NSCLC. Mean survival was 21 months with 80% of patients being alive at the end of 14.8 months of follow-up. Most recently Lencioni and colleagues⁵⁰ reported the results of a prospective, intention-to-treat, single-arm, multicenter clinical trial from seven centers in Europe, the United States, and Australia (RAPTURE TRIAL). RFA was performed in 183 tumors of 106 patients. Malignancy was confirmed by biopsy in all patients. Diagnoses included NSCLC in 33 patients, metastasis from colorectal carcinoma in 53 patients, and metastasis from other primary malignancies in 20 patients. In patients with NSCLC, OS was 70% (95% CI, 51%–83%) at 1 year and 48% (95% CI, 30%–65%) at 2 years. Patients with stage I NSCLC (N = 13) had a 2-year OS of 75% (45%–92%) and a 2-year cancer-specific survival of 92% (66%–99%). In patients with colorectal metastases, OS was 89% (95% CI, 76%–95%) at 1 year and 66% (95% CI, 53%–79%). For patients with other metastases, OS was 92% (95% CI, 65%–99%) at 1 year and 64% (95% CI, 43%–82%) at 2 years.

Results of the ACOSOG Z4033 were recently published.⁵¹ In this randomized multicenter US trial 54 patients with medically inoperable, biopsy proven, stage IA NSCLC were treated with percutaneous CT-guided RFA. The OS rate was 86.3% at 1 year and 69.8% at 2 years. The local tumor recurrence-free rate was 68.9% at 1 year and 59.8% at 2 years and was worse for tumors greater than 2 cm. Nineteen patients had recurrence. There were 21 grade 3 adverse events, two grade 4 adverse events, and one grade 5 adverse event in 12 patients within the first 90 days after RFA. None of the grade 4 or 5 adverse events were attributable to RFA. A tumor size less than 2.0 cm and a performance status of 0 or 1 were associated with statistically significant improved survival of 83% and 78%, respectively, at 2 years.

PATIENT SELECTION

Patients with limited-stage lung cancer and metastatic disease to the lung, who otherwise would have been candidates for surgery but deemed inoperable because of their comorbidities or who choose ablative therapies because of personal preference, are usually candidates for ablative therapies. For NSCLC, ablative therapies can be used for stage I patients who are believed to be at increased risk for any kind of pulmonary resection or who refuse surgery. Occasionally, ablative therapies are a reasonable therapy option for a patient with more advanced cancer. Such patients include those with a second nodule within the same tumor lobe or a satellite nodule within another lobe. This subgroup of advanced-stage tumors may be more appropriately treated with resection, as long as the cancer is localized to the lung. However, in those patients who are believed to be at increased operative risk, ablative therapies are good alternatives. Other patients who may be considered for treatment with these modalities include those with advanced-stage disease who have responded to definitive radiation therapy and chemotherapy but have a persistent, solitary lesion and those who have a recurrent isolated cancer after previous lung resection.

Ablative therapies are also a suitable option for some patients with limited peripheral pulmonary metastases. As with resection, this treatment should be reserved for those patients with a limited number of metastases, disease localized to the chest, and with their primary cancer either controlled or controllable. Situations may also occur where complete resection of all pulmonary metastases is not possible. In these situations, ablation of some nodules may be an alternative intraoperatively or postoperatively.

Combination of Ablative Therapies

A recent study from University of Pittsburgh reported use of SABR for recurrent tumors, including recurrence after MWA and RFA.⁵² Similarly, recurrent tumors or local failures after SABR can be treated with either surgery or MWA. Also patients with larger (>4 cm) tumors can be treated with a combination of SABR and MWA for a better complete ablation. This approach can be a basis of a future trial.

SUMMARY

The treatment paradigm for early stage lung cancer and oligometastatic disease to the lung is rapidly changing. Ablative therapies, especially SABR, are challenging the surgical gold standard and have the potential to be the standard for operable patients with early stage lung cancer who are high risk for morbidities. MWA is another promising novel ablative modality that in the near future would also be available for transbronchial ablation of small lung tumors, especially more central tumors. The Z4033 trial shows a 2-year overall survival rate with RFA comparable with SABR. The outcome results of the ablative therapies should be compared with anatomic minimally invasive segmentectomy or lobectomy with lymph node dissection rather than historical surgical data.

REFERENCES

1. Stewart BW, Wild C, editors. World cancer report, 2014. Lyon (France): International Agency for Research on Cancer; World Health Organization; 2014.
2. Bach PB, Cramer LD, Warren JL, et al. Racial differences in the treatment of early stage non-small cell lung cancer. *N Engl J Med* 1999;341:1198–205.
3. Sibley G, Jamieson T, Marks L, et al. Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: the Duke experience. *Int J Radiat Oncol Biol Phys* 1998;40:149–54.
4. Kupelian PA, Komaki R, Allen P. Prognostic factors in the treatment of node-negative non-small cell lung carcinoma with radiation alone. *Int J Radiat Oncol Biol Phys* 1996;36:607–13.
5. Zierhut D, Bettscheider C, Schubert K, et al. Radiation therapy of stage I and II non-small cell lung cancer. *Lung Cancer* 2001;34:S39–43.
6. Abratt RP, Morgan GW. Lung toxicity following chest irradiation in patients with lung cancer. *Lung Cancer* 2002;35:103–9.
7. Byhardt RW, Martin L, Pajak TF, et al. The influence of field size and other treatment factors on pulmonary toxicity following hyperfractionated irradiation for inoperable non-small cell lung cancer (NSCLC): analysis of a Radiation Therapy Oncology Group (RTOG) protocol. *Int J Radiat Oncol Biol Phys* 1993;27:537–44.
8. Bradley J, Graham MV, Winter K, et al. Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. *Int J Radiat Oncol Biol Phys* 2005;61:318–28.

9. Kong FM, Hayman JA, Griffith KA, et al. Final toxicity results of a radiation-dose escalation study in patients with non-small-cell lung cancer (NSCLC): predictors for radiation pneumonitis and fibrosis. *Int J Radiat Oncol Biol Phys* 2006;65(4): 1075–86.
10. Fernando HC, Abbas G. Alternatives to surgical resection for non-small cell lung cancer. In: Pearson FG, Patterson GA, editors. *Pearson's thoracic & esophageal surgery*. Philadelphia: Churchill Livingstone/Elsevier; 2008. p. 796–803.
11. Douglas BG, Fowler JF. The effect of multiple small doses of x rays on skin reactions in the mouse and a basic interpretation. *Radiat Res* 1976;66:401–26.
12. Fowler JF, Tome WA, Fenwick JD, et al. A challenge to traditional radiation oncology. *Int J Radiat Oncol Biol Phys* 2004;60:1241–56.
13. McGarry RC, Papiez L, Williams M, et al. Stereotactic body radiation therapy of early-stage non small-cell lung carcinoma: phase I study. *Int J Radiat Oncol Biol Phys* 2005;63:1010–5.
14. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006;24:4833–9.
15. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010;303:1070–6.
16. Timmerman RD, Hu C, Michalski J, et al. Long-term results of RTOG 0236: a phase II trial of stereotactic body radiation therapy (SBRT) in the treatment of patients with medically inoperable stage I non small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2014;90(Suppl):S30.
17. Pennathur A, Luketich JD, Heron DE, et al. Stereotactic radiosurgery for the treatment of lung neoplasm: experience in 100 consecutive patients. *Ann Thorac Surg* 2009;88(5):1594–600.
18. Pennathur A, Luketich JD, Heron DE, et al. Stereotactic radiosurgery for the treatment of stage I non small cell lung cancer in high risk patients. *J Thorac Cardiovasc Surg* 2009;137(3):597–604.
19. Pennathur A, Luketich JD, Heron DE, et al. Stereotactic radiotherapy/stereotactic body radiotherapy for recurrent lung neoplasm: an analysis of outcome in 100 patients. *Ann Thorac Surg* 2015;100(6):2019–24.
20. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* 2007;2(7 Suppl 3): S94–100.
21. Nagata Y, Takayama K, Matsuo Y, et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2005;63:1427–31.
22. Nagata Y, Hiraoka M, Shibata T, et al. A phase II trial of stereotactic body radiation therapy for operable T1N0M0 non-small cell lung cancer: Japan Clinical Oncology Group (JCOG0403). *Int J Radiat Oncol Biol Phys* 2010;78(Suppl): S27–8.
23. Nagata Y, Hiraoka M, Shibata T, et al. Prospective trial of stereotactic body radiation therapy for both operable and in-operable T1N0M0 non small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2015;93(5):989–96.
24. Timmerman RD, Paulus R, Pass HI, et al. RTOG 0618: Stereotactic body radiation therapy (SBRT) to treat operable early-stage lung cancer patients. *J Clin Oncol* 2013;31:abstr 7523.
25. Videtic GM, Hu C, Singh AK, et al. A randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with

- stage I peripheral non small cell lung cancer: NRG Oncology RTOG 0915. *Int J Radiat Oncol Biol Phys* 2015;93(4):757–64.
26. Crabtree TD, Denlinger CE, Meyers BF, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2010;140:377–86.
 27. Verstegen NE, Oosterhuis JW, Palma DA, et al. Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. *Ann Oncol* 2013;24:1543–8.
 28. Mokhles S, Verstegen N, Maat AP, et al. Comparison of clinical outcome of stage I non-small cell lung cancer treated surgically or with stereotactic radiotherapy: results from propensity score analysis. *Lung Cancer* 2015;87:283–9.
 29. Van den Berg LL, Klinkenberg TJ, Groen HJ, et al. Patterns of recurrence and survival after surgery or stereotactic radiotherapy for early stage NSCLC. *J Thorac Oncol* 2015;10:826–31.
 30. Shirvani SM, Jiang J, Chang JY, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. *Int J Radiat Oncol Biol Phys* 2012;84:1060–70.
 31. Shirvani SM, Jiang J, Chang JY, et al. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. *JAMA Surg* 2014;149:1244–53.
 32. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015;16:630–7.
 33. Okada M, Yoshikawa K, Hatta T, et al. Is segmentectomy with lymph node assessment an alternative to lobectomy for non small cell lung cancer of 2 cm or smaller? *Ann Thorac Surg* 2001;71:956–60.
 34. Schuchert MJ, Abbas G, Awais O, et al. Anatomic segmentectomy for the solitary pulmonary nodule and early-stage lung cancer. *Ann Thorac Surg* 2012;93(6):1780–5 [discussion: 1786–7].
 35. Landreneau RJ, Normolle DP, Christie NA, et al. Recurrence and survival outcomes after anatomic segmentectomy versus lobectomy for clinical stage I non-small-cell lung cancer: a propensity-matched analysis. *J Clin Oncol* 2014;32(23):2449–55.
 36. Crabtree T, Puri V, Timmerman R, et al. Treatment of stage I lung cancer in high-risk and inoperable patients: comparison of prospective clinical trials using stereotactic body radiotherapy (RTOG 0236), sublobar resection (ACOSOG Z4032), and radiofrequency ablation (ACOSOG Z4033). *J Thorac Cardiovasc Surg* 2013;145(3):692–9.
 37. Feng W, Liu W, Liu C, et al. Percutaneous microwave coagulation therapy for lung cancer. *Zhonghua Zhong Liu Za Zhi* 2002;24:388–90.
 38. Simon CS, Dupuy DE, Mayo-Smith WW. Microwave ablation: principles and applications. *Radiographics* 2005;25:S69–83.
 39. Wolf FJ, Grand DJ, Machan JT, et al. Microwave ablation of lung malignancies: effectiveness, CT findings, and safety in 50 patients. *Radiology* 2008;247(3):871–9.
 40. Lencioni R, Crocetti L, Cioni R, et al. Radiofrequency ablation of lung malignancies: where do we stand? *Cardiovasc Intervent Radiol* 2004;27:581–90.
 41. Herrera LJ, Fernando HC, Perry Y, et al. Radiofrequency ablation of pulmonary malignant tumors in nonsurgical candidates. *J Thorac Cardiovasc Surg* 2003;125(4):929–37.

42. Fernando HC, De Hoyos A, Landreneau RJ, et al. Radiofrequency ablation for the treatment of non-small cell lung cancer in marginal surgical candidates. *J Thorac Cardiovasc Surg* 2005;129:261–7.
43. Pennathur A, Luketich JD, Abbas G, et al. Radiofrequency ablation of stage I non-small cell lung neoplasm. *J Thorac Cardiovasc Surg* 2007;134:857–64.
44. Gadaleta C, Mattioli V, Colucci G, et al. Radiofrequency ablation of 40 lung neoplasms preliminary results. *Am J Roentgenol* 2004;183:361–9.
45. Yasui K, Kanazawa S, Sano Y, et al. Thoracic tumors treated with CT-guided radiofrequency ablation: initial experience. *Radiology* 2004;231(3):850–7.
46. Yan TD, King J, Sjarif A, et al. Percutaneous radiofrequency ablation of pulmonary metastases from colorectal carcinoma: prognostic determinants for survival. *Ann Surg Oncol* 2006;13(11):1529–37.
47. Ambroggi MC, Lucchi M, Dini P, et al. Percutaneous radiofrequency ablation of lung tumors: results in mid term. *Eur J Cardiothorac Surg* 2006;30(1):177–83.
48. Hiraki T, Sakuraj J, Tsuda T, et al. Risk factors for local progression after percutaneous radiofrequency ablation of lung tumors: evaluation based on a preliminary review of 342 patients. *Cancer* 2006;107(12):2873–80.
49. Lee JM, Jin GY, Goldber SN, et al. Percutaneous radiofrequency ablation of lung neoplasms: initial therapeutic response. *Radiology* 2004;230:125–34.
50. Lencioni R, Crocetti L, Cioni R, et al. Response to radiofrequency ablation of pulmonary tumors: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). *Lancet Oncol* 2008;9(7):621–8.
51. Dupuy DE, Fernando HC, Hillman S, et al. Radiofrequency ablation of stage IA non-small cell lung cancer in medically inoperable patients: results from the American College of Surgeons Oncology Group Z4033 (Alliance) trial. *Cancer* 2015;121(19):3491–8.
52. Pennathur A, Luketich JD, Heron DE, et al. Stereotactic radiosurgery/stereotactic body radiotherapy for recurrent lung neoplasm: an analysis of outcomes in 100 patients. *Ann Thorac Surg* 2015;100(6):2019–24.