

Stereotactic Body Radiation Therapy for Early Stage Non-Small Cell Lung Cancer: an ASTRO Evidence-Based Guideline

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Conflict of Interest Disclosure Statement

Before initiating work on this guideline, all task force members completed disclosure statements and pertinent disclosures are published within this report. Where potential conflicts are detected, remedial measures to address them are taken and noted here.

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Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death for both women and men in the United States, with more than 158,000 estimated deaths attributable to lung cancer expected for 2016.¹ Approximately 16% of lung cancer patients will present with early stage (T1-2 N0) disease,² a percentage that may increase in coming years with implementation of low-dose computed tomography (CT)-screening algorithms.³ Early stage NSCLC in medically fit patients is traditionally managed surgically, with lobectomy and mediastinal lymph node sampling. However, with an average age at diagnosis of 70,¹ many lung cancer patients are considered medically inoperable due to cardiovascular, pulmonary, or other comorbidities that preclude surgical management. Historically, conventionally fractionated radiation therapy with simple beam arrangements was used for patients too frail to tolerate surgery. However, this approach resulted in high rates of local failure because of inability to deliver effective dose and of treatment-related toxicities, particularly of the lung, because of limitations in defining and constraining the treatment volume.⁴⁻⁷

Over the past two decades, technological developments in target delineation, motion management, conformal treatment planning, and image guidance at the time of daily dose delivery have allowed the development and implementation of stereotactic body radiation therapy (SBRT), a strategy that employs very high (i.e., ablative) doses of radiation delivered to the cancer target over 1-5 fractions with highly conformal techniques. This approach is also referred to as stereotactic ablative radiation therapy, or SABR, in some publications but, for the purposes of this guideline, the term SBRT is exclusively used. Publication of the first reports outlining clinical implementation of lung SBRT appeared in the mid-1990s. Early reports, primarily from Japan and Europe, were single institution retrospective analyses of small patient series.^{8,9} Characteristics of these series demonstrated treatment courses that generally ranged from a single fraction to a ten-fraction course, with marked variability between series on how the dose was prescribed, planned, and delivered. For all their differences, the clinical findings seen in these early experiences with lung SBRT were consistently very high rates of local control (LC) ($\geq 85\%$ at three years) and minimal rates of toxicity ($< 4\%$ grade 3 or higher).^{8,9}

Pioneering prospective phase I and phase II lung SBRT studies were performed both at Indiana University (IU) in the United States and by the Nordic study group to understand the efficacy and toxicity of this modality.¹⁰⁻¹² The Indiana phase II study in particular was the first to introduce the concept that location could influence toxicity rates for a given SBRT schedule. It showed that treatment of central and perihilar tumors, where “central” was

defined as a tumor within 2 cm of the proximal tracheobronchial tree, posed a higher risk of severe toxicity than treatment of “peripheral” tumors.¹³ Peripheral tumors included all those that did not meet the “central” definition. In this study, all patients received 60 to 66 Gy in 3 fractions, and those with central tumors had nearly an eleven-fold increase in the rate of severe toxicity at initial publication, with a three-fold increased risk at 4 year follow-up. However, there was no difference in LC or median overall survival (OS) by location.¹³ It is important to note that, prior to this publication, there had been no defined terminology distinguishing “peripheral” from “central” tumors in the non-American literature, since no treatment-related toxicities had been associated with other lung SBRT treatment schedules.

For the purposes of this guideline, this IU categorization of a lung cancer by its location as either central or peripheral has been adopted. Furthermore, SBRT is defined as a course of stereotactic treatment delivered over 1-5 fractions, in accordance with other ASTRO consensus reports and as used by the Current Procedural Terminology (CPT) editorial panel.^{14,15} However, fractionation schedules using 6-10 fractions with a biologically effective dose (BED) of $\geq 100 \text{ Gy}_{10}$ using stereotactic techniques are also similarly used by groups outside the United States and are also discussed as alternatives within the guideline where appropriate. (BED calculations involve the use of an accepted radiobiological equation to compare different fractionations regimens by converting them to comparable values for a given tissue of interest.) Technical aspects of SBRT treatment and delivery, including simulation, motion management, plan optimization, and target localization, are outside the scope of the current guideline, but are addressed in practice papers from the American Association of Physicists in Medicine (AAPM)¹⁶ and ASTRO.¹⁴

The Radiation Therapy Oncology Group (RTOG) conducted the first multicenter, North American cooperative group prospective study of lung SBRT for early stage peripheral NSCLC. RTOG 0236, reported in 2010, was a phase II trial in which treatment consisted of 54 Gy in 3 fractions delivered over 8-14 days.¹⁷ Eligible patients had peripheral (per the IU definition), biopsy-proven tumors with maximum diameter $\leq 5 \text{ cm}$, and they were unable to undergo surgical resection due to concurrent medical comorbidities. Fifty-nine patients were enrolled, of which fifty-five were evaluable. With a median follow-up of 34.4 months, the three-year rate of control at the treated primary site rate was 97.6% and the OS rate was 55.8%. This high rate of primary control was felt to be the contributing factor to the study’s high OS when compared to historic reports of patients treated with conventional techniques. An updated report on RTOG 0236 with a median follow-up of 4.0 years, presented only in abstract form, demonstrated 5-year estimates of primary tumor, in-lobe, and locoregional failure of 7%, 20%, and 38%,

respectively.¹⁸ In aggregate, rates of local control, regional control and overall survival at 3 years of 85-90%, 85-90% and 50-60%, respectively, are expected following SBRT for early stage, peripheral NSCLC when a BED of $\geq 100 \text{ Gy}_{10}$ is delivered to the tumor periphery, with low associated rates (<5%) of grade 3 or higher clinical pneumonitis.¹⁹ For purposes of this guideline, we have adopted the recurrence nomenclature from RTOG 0236 in defining recurrences as local (in-field), in-lobe, regional, or distant. The task force concurred on the importance of studies adopting uniform recurrence definitions and reporting in-lobe, regional, and distant failures in addition to in-field failures, as inconsistent nomenclature has been used in past SBRT literature, particularly in retrospective cohort studies.

An initial concern with delivering higher effective doses to the lung with SBRT was the potential for increasing pulmonary toxicity in patients with limited respiratory reserve. In a medically inoperable population with high rates of underlying lung disease, differentiating radiation-induced decrements in lung function from the natural history of advanced underlying lung disease is also often challenging. Grade 3-4 pulmonary complications occurred in 16% of the patients treated on RTOG 0236.¹⁷ However, as noted by the authors, these findings were primarily related to pre-specified changes in pulmonary function tests (PFTs) rather than patient symptoms. Several subsequent studies have concluded that PFTs change minimally after SBRT for peripheral lesions²⁰⁻²² and that poor baseline PFTs do not correlate with decreased cause-specific survival.²³ Thus, in this very fragile population, poor PFTs should not be used to exclude patients from treatment with lung SBRT.

Treatment of peripheral lesions may result in rare but potentially serious toxicities. Damage to the chest wall may be expressed as skin, soft tissue, bone, and neurologic symptoms. Neuropathic pain and rib fractures may occur with 10-15% of treatments targeting tumors abutting the chest wall, although symptoms are generally modest and they are predicted by chest wall dose volume metrics.²⁴⁻²⁸ Skin ulcers,²⁹ brachial plexopathy,³⁰ and bronchial or esophageal fistulas³¹ have been reported, though these are extremely uncommon, and their risk is modifiable during the planning process when identified.

With the accumulated evidence from retrospective and prospective series, SBRT has thus emerged over the last decade as the standard-of-care for medically inoperable, peripherally located early stage NSCLC.³² While noting the utility of SBRT for medically fragile patients with poor alternative treatment options, questions addressing the appropriateness of SBRT for complex or challenging scenarios have arisen as expertise in this modality increases. These include “centrally” located tumors, large (>5 cm) tumors, multifocal lesions, or recurrent tumors in the setting

of previous surgery or irradiation. Likewise, SBRT for those lacking tissue confirmation also remains controversial, even as supportive data are emerging. Lastly, although the focus of the current guideline is the inoperable patient, the place of SBRT in the approach to the medically operable patient is important to address as it represents an active source of debate and controversy.

The present clinical practice guideline therefore systematically reviews the clinical evidence for SBRT for early stage NSCLC, with specific attention to patient selection for SBRT in challenging or controversial clinical settings, individualization of SBRT in high-risk clinical scenarios, and use of SBRT as a salvage therapy for recurrent disease. The task force used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) criteria to assess the quality of evidence available to address each key clinical question and generate a recommendation statement. Regardless of clinical scenario, the task force uniformly recommends multidisciplinary review of all patients under consideration for SBRT, including input from thoracic surgeons, radiation oncologists, medical oncologists, radiologists, pathologists, and/or pulmonologists, ideally in a multidisciplinary tumor board or clinic, and consideration of enrollment on clinical trials for all eligible patients. Although extending survival and providing optimal LC are often seen as the most important goals of cancer treatment, patients should nonetheless be engaged in the treatment decision-making process to ensure that their treating physician understands each individual's risk tolerance and goals of care. Toxicity, pain, and other side-effects impact quality of life (QOL) differently for each patient. Thus, individual goals and QOL should be considered by all disciplines when making treatment recommendations.

This guideline is endorsed by the European Society for Radiotherapy & Oncology and the Royal Australian and New Zealand College of Radiologists.

Methods and Materials

Process

The ASTRO Board of Directors approved creation of an evidence-based guideline on SBRT for early stage lung cancer in June 2015. A task force of radiation oncologists specializing in lung cancer, along with surgical representatives, was recruited. A patient representative was also included. The members were drawn from academic settings, community practice, and residency.

Through a series of conference calls and emails, the task force and ASTRO staff completed the systematic review, created evidence tables, and formulated the recommendation statements and narratives for the guideline. The task force members were divided into writing groups by key question (KQ) according to their areas of interest and expertise. The initial draft was reviewed by five expert reviewers (see Acknowledgements) and ASTRO legal counsel. A revised draft was placed on the ASTRO website for public comment in November 2016. Following integration of the feedback, the Board of Directors approved the final guideline in March 2017. Going forward, the ASTRO Guidelines Subcommittee will monitor this guideline and assess it for updating annually beginning at two years post-publication.

Literature Review

A systematic literature review formed the basis of the guideline. An analytic framework incorporating the population, interventions, comparators, and outcomes (PICO) was used to develop search strategies in MEDLINE PubMed for each KQ. The searches identified English-language studies between January 1995 and November 2015 that evaluated adults with T1-2 N0 NSCLC receiving primary or salvage SBRT. The search was later extended until August 3, 2016. Both MeSH terms and text words were utilized and terms common to all searches included: *lung cancer; non-small cell lung cancer; lung neoplasms[MeSH]; carcinoma, non-small-cell lung[MeSH]; lung carcinoma; stereotactic body radiation therapy; stereotactic body radiotherapy; stereotactic ablative radiation therapy; stereotactic ablative radiotherapy; SBRT; and SABR*. Additional terms specific to the KQs were also incorporated. The outcomes of interest were OS and disease-free survival (DFS), recurrence rates, acute and late toxicity, and quality of life. The electronic searches were supplemented by hand searches.

A total of 402 abstracts were retrieved and screened by ASTRO staff then by the task force. Subsequently, 230 articles were eliminated based on the inclusion and exclusion criteria. The inclusion criteria were: age ≥ 18 years, early stage lung cancer, treatment with SBRT, and publication date 1995 to 2016. The exclusion criteria were: small cell lung cancer, node positive or metastatic lung cancer, pediatric patients, pre-clinical or non-human studies, dosimetric studies without clinical outcomes, non-English language, and otherwise not relevant to the KQs. Ultimately, 172 articles were included and abstracted into detailed tables to provide supporting evidence for the guideline recommendations. Major studies presented as abstracts but not yet published are discussed in the narrative but were not used to support the recommendations.

Grading of Evidence and Recommendations and Consensus Methodology

Guideline recommendation statements were developed based on the current literature using the GRADE methodology, which is an explicit, systematic approach to defining the recommendation strength and quality of evidence.^{33,34} When available, high-quality data formed the basis of the statements in accordance with Institute of Medicine (IOM) standards.³⁵ When necessary, expert opinion supplemented the evidence.

Recommendations were classified as “strong” or “conditional.” A strong recommendation indicated the task force was confident the benefits of the intervention clearly outweighed the harms, or vice-versa, and “all or almost all informed people would make the recommended choice for or against an intervention.”³⁴ Conditional recommendations were made when the balance between risks and benefits was more even or was uncertain. In these cases, the task force believed “most informed people would choose the recommended course of action, but a substantial number would not” and, therefore, “clinicians and other health care providers need to devote more time to the process of shared decision making by which they ensure that the informed choice reflects individual values and preferences.”³⁴

The quality of evidence underlying each recommendation statement was categorized as either high, moderate, or low. These quality levels indicated:

- “High: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.”³³

Consensus within the task force on the recommendation statements was evaluated through a modified Delphi approach adapted from the American Society of Clinical Oncology (ASCO) process. In an online survey, task force members rated their agreement with each recommendation on a five-point Likert scale, from strongly disagree to strongly agree. The patient representative abstained from rating KQ 3E because she was not comfortable doing so. A pre-specified threshold of $\geq 75\%$ of raters selecting “agree” or “strongly agree” indicated when consensus was achieved.³⁶ If a recommendation statement did not meet this threshold, it was modified and re-surveyed or excluded from the guideline. Recommendation statements achieving consensus that were modified after the first round were also re-surveyed.

Results

Key Question 1: When is stereotactic body radiation therapy appropriate for patients with T1-2, N0 non-small cell lung cancer who are medically operable?

Statement KQ1A: Any patient with operable stage I NSCLC being considered for SBRT should be evaluated by a thoracic surgeon, preferably in a multidisciplinary setting, to reduce specialty bias.

- **Recommendation strength:** Strong
- **Quality of evidence:** Moderate
- **Consensus:** 100%

Statement KQ1B: For patients with “standard operative risk” (i.e., with anticipated operative mortality of <1.5%) and stage I NSCLC, SBRT is not recommended as an alternative to surgery outside of a clinical trial. Discussions about SBRT are appropriate, with the disclosure that long-term outcomes with SBRT >3 years are not well-established. For this population, lobectomy with systematic mediastinal lymph node evaluation remains the recommended treatment, though a sublobar resection may be considered in select clinical scenarios.

- **Recommendation strength:** Strong
- **Quality of evidence:** High
- **Consensus:** 94%

Statement KQ1C: For patients with “high operative risk” (i.e., those who cannot tolerate lobectomy, but are candidates for sublobar resection) stage I NSCLC, discussions about SBRT as a potential alternative to surgery are encouraged. Patients should be informed that while SBRT may have decreased risks from treatment in the short term, the longer-term outcomes >3 years are not well-established.

- **Recommendation strength:** Conditional
- **Quality of evidence:** Moderate
- **Consensus:** 94%

Narrative

The use of SBRT in patients who have adequate cardiopulmonary reserve for lung resection is an area of ongoing controversy. Lobectomy and systematic mediastinal lymph node assessment remains the treatment of choice for stage I NSCLC. This is despite a 20-30% risk of regional and/or distant relapse postoperatively.³⁷ The advantage with this approach is removal of the tumor and more thorough pathologic evaluation including molecular and histologic subclassification information and improved staging of hilar and mediastinal lymph nodes to provide a possible advantage in guiding adjuvant therapy. Occult hilar and mediastinal node involvement is detected in 11-18% of patients undergoing resection for clinical stage I disease staged with positron emission tomography (PET)/CT,^{38,39} and many of these patients are eligible to receive adjuvant chemotherapy and/or radiation therapy.⁴⁰ However, it should be emphasized that a recent meta-analysis demonstrated that the negative predictive value of PET-CT for tumors ≤ 3 cm was 94% compared to 89% for tumors >3 cm.⁴¹ This has led some evidence-based guidelines to endorse the omission of preoperative pathologic lymph node assessments in patients undergoing

resection when all of the following criteria are met: (1) primary tumor located in outer third of lung, (2) largest diameter of tumor is ≤ 3 cm, and (3) absence of suspicious intrathoracic lymph nodes on CT or fluorodeoxyglucose (FDG)-PET/CT.⁴² Nonetheless, given the opportunity to more accurately stage patients who may benefit from adjuvant chemotherapy, all expert panel evidence-based guidelines, including this one, currently recommend surgery as the preferred treatment option for operable patients with stage I NSCLC.^{32,43}

When SBRT is introduced as an alternative to surgery, it is primarily because of a concern for surgical morbidity or mortality, the loss of pulmonary parenchyma, or patient refusal to undergo resection. Postoperative complications and readmissions can occur, and at times are fatal. Outcomes for lobectomy at experienced thoracic surgery centers are excellent, with mortality rates less than 1% in standard risk patients treated at high volume centers.³⁶ Contemporary results from large databases, including the Society of Thoracic Surgeons General Thoracic Surgery Database⁴⁴ and National Cancer Database (NCDB),⁴⁵ all report operative mortality following lobectomy of 1.5-2.0%. In the US, in a series of 22,647 lobectomies (59% of which were open lobectomies versus 41% minimally invasive procedures), the 90-day readmission rate was 20% (open lobectomies 21% versus minimally invasive lobectomies 18%).⁴⁶ From Europe, a cohort of 15,738 surgical patients revealed the 90-day readmission rate was 45%.⁴⁷ Data from large database registries have shown that the 30-day mortality rate after lung cancer surgery is 1.5-2.0%, which increases to 2.5-4.5% when analyzed at 90 days.^{48,49}

Despite the concerns for surgical morbidity and mortality, SBRT is not endorsed in lieu of resection for “standard operative risk” operable patients with stage I NSCLC who have adequate cardiopulmonary reserve to tolerate lobectomy. This is primarily because the long-term survival after SBRT is unknown and these patients typically have a life expectancy of >10 years. Comparative effectiveness research studies have reported the results of numerous comparisons between surgery and SBRT. This includes a meta-analysis of 40 SBRT studies (4850 patients) and 23 surgery studies (7071 patients) that concluded patients treated with SBRT differ substantially from patients treated with surgery in age and operability. After adjustment for these differences, OS and DFS do not differ significantly between SBRT and surgery in patients with operable stage I NSCLC.⁵⁰ However, these studies have been flawed due to their retrospective nature and residual confounding that cannot be adjusted when comparing the survival differences after SBRT to resection, particularly when operable patients are routinely encouraged to undergo surgery by both surgeons and radiation oncologists – as recommended in all evidence-based guidelines – whenever they have a long life-expectancy and are medically fit enough to tolerate a thoracotomy.⁵⁰

Meanwhile, an emerging body of literature has demonstrated OS rates of 76-86% at three years following SBRT in select cohorts of operable patients who have declined surgery (see Table 1).⁵¹⁻⁵⁸ Moreover, a pooled analysis of two prematurely closed phase III trials suggested superior OS at three years with SBRT versus surgery.⁵⁹ While neither of these studies provides the assurance that SBRT offers similar survival to surgery beyond three years, the data suggest some equipoise and support recruitment of patients for enrollment in randomized studies that compare SBRT to surgery. To date, eight randomized clinical trials have been funded in the US, Canada, UK, Netherlands, and China, and currently four are open to provide higher level evidence regarding long-term survival after SBRT [SABR-TOOTH (NCT02629458), RTOG 3502 (NCT01753414), STABLE-MATES (NCT01622621), and VALOR (NCT02984761)]. Enrollments in these trials are closely supervised by human research protection monitoring to reduce the risk of biased recommendations, or misinformation from sensationalized stories about SBRT in the lay media.⁶⁰

Greater clinical equipoise exists regarding SBRT for patients with “high operative risk” and stage I NSCLC who could potentially tolerate a wedge resection, but not lobectomy. The primary reasons for this equipoise are 1) these patients have decreased life expectancy secondary to their co-morbidities,⁶¹ and 2) wedge resections are considered a compromise operation and as such are associated with decreased rates of LC and cancer-specific survival compared to lobectomy.⁶² Unfortunately this “high operative risk” population remains difficult to delineate in precise and reproducible terms. Definitions used for trial purposes include FEV1 < 50% predicted, DLCO <50% predicted, or a combination of advanced age, impaired pulmonary function, pulmonary hypertension, poor left ventricular function.. A thoracic surgeon who specializes in lung resections remains the best person to assess operative risk. This population has also proven to be difficult to study in a prospective randomized fashion. Therefore, SBRT can be considered an acceptable alternative to surgery following multidisciplinary review and shared decision conversations that review the risks and advantages of each treatment approach and minimize specialty bias.

All clinicians involved in the care of patients with stage I NSCLC should be prepared to interact with operable patients who prefer treatment with SBRT over surgery.⁶³ The American College of Surgeons encourages shared decisions during the informed consent process to ensure patient engagement during choices about their care.⁶⁴ Such an approach helps avoid decisional regret, particularly since the outcome after surgery or SBRT cannot be predicted

with certainty. Essential aspects of a shared decision making conversation with operable patients who are considering SBRT include:

- SBRT has never been adequately compared to lobectomy or sublobar resection in a prospectively randomized trial, and similarities or differences in survival >3 years are not well-established.
- The omission of pathologic nodal staging contributes to under-staging in 11-18% of clinical stage IA patients.^{38,39,41} Those operable patients with occult N1 or N2 disease who undergo SBRT would forfeit the benefit of adjuvant therapy that is known to improve OS.
- Interpretation of surveillance imaging following SBRT is challenging and may lead to unnecessary biopsies, salvage surgery, or false reassurance that the tumor has not relapsed.
- Salvage surgery in the setting of post-SBRT progression may be technically challenging and pose increased operative risk compared to up-front surgery in a non-irradiated field, particularly in the case of central tumors.⁶⁵⁻⁶⁸

Preoperative staging with FDG-PET/CT is strongly recommended in all stage I NSCLC patients being considered for SBRT to minimize the risk of under-treating patients with occult stage II or III disease. Preoperative invasive mediastinal staging with mediastinoscopy or EBUS should be considered for operable patients with increased risk for occult mediastinal nodal involvement, including those with tumors > 2 cm, central tumors and tumors with elevated SUV on FDG- PET.⁶⁹ Following SBRT, vigilant surveillance is recommended given the opportunity for salvage resections in a population of patients at risk for second primary lung cancers that occur at a rate that exceeds the risk of local recurrence at three years.⁷⁰ Although limited evidence is available to support a specific surveillance imaging schedule, CT imaging every 3-6 months is recommended for at least two years following SBRT, with FDG-PET/CT scans whenever there is suspicion on the CT images. Evidence-based approaches to evaluating post-SBRT images are advised,⁷¹ with discussions in a multidisciplinary setting that solicits input from a thoracic surgeon when there is concern for relapse. Whenever a salvage resection is considered, a biopsy is recommended to confirm tumor progression as there have been cases reported in which the removed lobe only harbored treatment-related fibrosis.⁷²

Key Question 2: When is stereotactic body radiation therapy appropriate for medically inoperable patients with T1-2, N0 non-small cell lung cancer:

- With centrally located tumors

- **With tumors >5 cm in diameter**
- **Lacking tissue confirmation**
- **With synchronous primary or multifocal tumors**
- **Who underwent pneumonectomy and now have a new primary tumor in their remaining lung?**

For patients with centrally located tumors?

Statement KQ2A: SBRT directed towards centrally located lung tumors carries unique and significant risks when compared to treatment directed at peripherally located tumors. The use of 3 fraction regimens should be avoided in this setting.

- **Recommendation strength:** Strong
- **Quality of evidence:** High
- **Consensus:** 94%

Statement KQ2B: SBRT directed at central lung tumors should be delivered in 4 or 5 fractions. Adherence to volumetric and maximum dose constraints may optimize the safety profile of this treatment. For central tumors for which SBRT is deemed too high-risk, hypofractionated radiation therapy utilizing 6-15 fractions can be considered.

- **Recommendation strength:** Conditional
- **Quality of evidence:** Moderate
- **Consensus:** 94%

Narrative

A major principle of SBRT is that rapid dose fall-off is achieved beyond the tumor such that critical normal structures are not exposed to ablative doses of radiation. However, for tumors located centrally within the thorax, the close proximity of the tumor to critical structures including the heart, esophagus, spinal cord, central airways, and great vessels may not allow these normal tissues to be fully spared from high radiation doses.

Severe toxicities to centrally located normal tissues have been observed (Table 2). In the phase II study of 70 patients with medically inoperable NSCLC by Timmerman and colleagues at IU, patients with early-stage (T1-T2, N0) medically inoperable lung tumors were treated with SBRT to a total dose of 60 Gy in 3 fractions (T1 tumors) or 66 Gy in 3 fractions (T2 tumors). After a median follow-up of 17.5 months, 8 patients (11.4%) experienced grade 3 or 4 adverse events, including declines in pulmonary function, pleural effusion, and pneumonia. Six patients (8.6%) may have died (grade 5 toxicity) as a consequence of treatment due to fatal hemoptysis, infectious pneumonia, and pericardial effusion. Importantly, the chief predictor of severe toxicity was central tumor location; freedom from severe toxicity at two years was 54% for patients with central tumors and 83% for peripheral tumors.¹³ Because of the scale of these risks, it is advisable to avoid SBRT for central tumors with the 3 fraction regimens used for peripheral tumors.

Other retrospective studies have also reported severe toxicities and fatal complications following stereotactic or hypofractionated radiation therapy directed at central tumors.⁷³⁻⁷⁹ These are discussed in detail in KQ3

and include potentially devastating toxicities, such as tracheal or great vessel rupture, esophageal ulceration, and spinal cord myelopathy.⁸⁰⁻⁸⁶ In one published case report, fatal airway necrosis was observed approximately 8 months following SBRT directed at a tumor located near to the right mainstem bronchus.⁸⁷ While this brief correspondence in the *New England Journal of Medicine* garnered significant attention, it was incomplete insofar as it did not mention the repeat biopsy as a possible proximate cause of the fatal cascade of events that followed, or at least as a major contributing influence. It should be noted that these studies and case reports are outside of the context of a prospective protocol and are subject to bias and/or the absence of strict quality assurance. Nonetheless, the point that patients with centrally located lesions treated by SBRT are subject to rare but potentially severe adverse events remains an important observation and should prompt providers to use caution when considering SBRT for these tumors. In this setting, adequate informed consent to patients – including a discussion of patient risk tolerance and goals of care – is a necessary part of communication between radiation oncologists and patients.

Because of the adverse events observed above, the landmark RTOG 0236 trial, which sought to validate the use of SBRT in a prospective, multi-institutional setting, specifically excluded patients whose tumors fell inside the 2 cm region around the proximal tracheobronchial tree (also commonly referred to as the “no-fly zone”).¹⁷ However, several institutions have explored SBRT for central lung tumors using modified dose and treatment schedules to mitigate the risk of severe toxicity. Generally, these alternative regimens reduced the BED delivered to critical structures by altering the total prescription dose, fraction size, or both. For instance, investigators at MD Anderson reported on a series of 27 patients with centrally and superiorly located tumors that were treated to 50 Gy in 4 fractions.⁸⁸ The crude LC rate at the site of the primary tumor was 100% after a median follow-up of 17 months. Complication rates were relatively modest compared to the aforementioned studies: four patients (14.8%) developed grade 2 pneumonitis and three patients (11.1%) developed grade 2-3 skin toxicity and/or chest wall pain.

A similar retrospective report by investigators at Yale reviewed 47 patients with either central lung cancers or lung metastases treated with 3 to 5 fractions.⁸⁹ The most commonly utilized regimen was the same as the MD Anderson study: 50 Gy in 4 fractions. With a median follow-up of 11.3 months, 11% of patients experienced grade ≥ 3 toxicity (4 patients experienced grade 3 dyspnea and 1 patient developed fatal hemoptysis). An important observation in this study was that patients whose tumors received a BED₁₀ <100 Gy had a statistically higher rate of lobar failures (80% v. 100%, P=0.02).

In light of these initial experiences, RTOG 0813 was opened to determine a dose-fractionation scheme for central lesions that is biologically potent for tumor eradication while still having an acceptable safety profile. This trial evaluated tiered radiation doses for central lung tumors treated in 5 fractions with SBRT delivered every other day. The starting dose was 50 Gy and the maximum dose was 60 Gy. SBRT plans had to meet defined volumetric and maximum dose constraints for critical normal structures.⁸² Of note, the definition of central tumor location varied from the IU definition in that tumors abutting the mediastinum, pericardium, or spine were also considered “central.”

Initial toxicity results of RTOG 0813 have been presented. Importantly, dose limiting toxicities (DLTs) were defined as grade 3+ adverse events occurring within 12 months following SBRT, although adverse events occurring beyond this time point were also reported. The eight patients treated at the lowest dose level (50 Gy) did not experience any grade ≥ 3 DLTs, whereas those treated at the highest level (60 Gy) had an estimated posterior probability of DLT of 7.2% (95% CI 2.8 -14.4%). Though this rate of toxicity was lower than the predefined threshold of 20%, possibly due to the more generous inclusion criteria and more tumors located further away from the proximal tracheobronchial tree, the severity of toxicities was considerable in some cases. One patient on the 10.5 Gy/fraction arm experienced a fatal DLT, and an additional 3 patients developed grade 5 treatment effects beyond the pre-specified 12 month DLT window, all hemoptysis.^{82,90,91} The oncologic efficacy analysis, which is still pending, will help determine the dose that best balances the twin goals of tumor control and avoidance of severe toxicities. Nonetheless, the toxicity data provide proof of principle that an acceptable safety profile can be achieved with SBRT in central tumors provided a suitable dose-fractionation scheme is selected and that protocol-defined normal tissue dose constraints are met.

Given the potential for severe toxicities following SBRT, patients with medically inoperable central lung tumors should be informed about alternative treatment options including non-SBRT hypofractionated regimens using between 6 and 15 fractions and conventionally fractionated radiation therapy. In the specific setting of centrally located tumors, the likely advantage of SBRT in treatment efficacy needs to be weighed against morbidity/mortality risk from the treatment itself. In cases where the risk of SBRT is deemed too high, such as “ultracentral” tumors directly abutting or invading the esophagus or proximal bronchial tree, several hypofractionated regimens have been described as an alternative to SBRT. One such regimen, reported by Chang and colleagues for centrally located or recurrent tumors, delivered 70 Gy in 10 fractions, which resulted in a 1% rate of grade ≥ 3 toxicities (one case of

grade 3 pneumonitis) and 97% LC rate at three years.⁹² Likewise, Haasbeek and colleagues reported on 63 patients with central tumors treated to 60 Gy in 8 fractions. Four patients developed grade 3 toxicities and no definitive grade 4/5 toxicities were observed. It should be noted that the authors pointed out treatment-related death in 9 patients who died of cardiopulmonary causes. The tumor control rate at three years among the patients with central tumors was 92.6%.⁹³

With regard to conventionally fractionated radiation, historical data have suggested inferior outcomes when compared to SBRT both in terms of LC and OS.^{6,7} However, randomized evidence from the SPACE trial has questioned this conclusion. In this trial, 102 patients with stage I medically inoperable NSCLC were randomized to receive SBRT to 66 Gy in 3 fractions or 3-D conformal treatment using conventional fractionation (70 Gy in 35 fractions).⁹⁴ Participants were followed to assess efficacy, toxicity, and quality of life. There was no statistically significant difference observed for either progression-free or OS, although there was a trend for OS favoring SBRT (HR=0.75, 95% CI 0.43-1.30). Of note, the authors pointed out that efficacy in the SBRT arm was similar to that in the conventional arm despite the fact that the SBRT cohort included more high risk patients (larger tumors, male gender). Furthermore, SBRT was associated with better quality of life and less toxicity. In light of these observations, they concluded that SBRT should be a standard treatment for patients with early-stage inoperable tumors. In the context of central tumors, providers must carefully select between the two options by weighing the controlled risk of exposing central structures to ablative doses of radiation in the case of SBRT against the inconvenience and toxicity of prolonged conventional treatment.

In summary, we conclude that careful consideration should be given to favoring stereotactic treatment. Altering fractionation to 4 or 5 fractions rather than 3 and, when necessary, using highly conformal techniques to avoid critical structures may reduce the risks of SBRT. Finally, adhering to protocol dose constraints such as those used in RTOG 0813⁸² may also reduce the risk of severe toxicity (though it should be noted that these dose constraints represent expert opinion and do not have the same rigorous radiobiological underpinning as dose constraints for conventionally fractionated radiation). A thorough discussion of risks and benefits with each patient with a central tumor is warranted to ensure an informed treatment decision.

For patients with tumors >5 cm in diameter?

Statement KQ2C: SBRT is an appropriate option for tumors >5 cm in diameter with an acceptable therapeutic ratio. Adherence to volumetric and maximum dose constraints may optimize the safety profile of this treatment.

- **Recommendation strength:** Conditional
- **Quality of evidence:** Low
- **Consensus:** 89%

Narrative

There is a paucity of data to guide clinical decision making in tumors >5 cm on diagnostic CT that are not suitable for surgical resection (Table 3). The large multi-institutional studies from the RTOG (0236, 0813 and 0915) have only allowed inclusion of tumors ≤ 5 cm in size.^{17,82,95} Because larger tumors have an increased propensity to develop nodal metastases, treatments directed solely at the primary tumor, such as SBRT, may entail a higher risk of locoregional recurrence. However, limited data from prospective registry studies support that SBRT in this setting has an acceptable toxicity profile and provides adequate local tumor control.⁹⁶⁻⁹⁹ As expected, these patients experienced a predominantly distant pattern of failure^{96,97} and their reported survival is lower than patients with smaller tumors.¹⁰⁰⁻¹⁰³

Woody et al. report the largest experience of tumors >5 cm treated with SBRT. They reviewed 40 such patients with a median age of 76 years and median tumor size of 5.6 cm (5.1 – 10.0 cm). They observed an 18 month LC of 91.2%, locoregional control of 64.4% and OS of 59.7%. They also reported modest toxicity with two grade 2 and one grade 4 pneumonitis events; there was no statistically significant decline in pulmonary function following SBRT in these patients.⁹⁷

Allibhai et al. reported a prospective series of 185 SBRT cases whose median tumor diameter was 2.2 cm (range: 0.6-5.7 cm). In larger tumors, there was significantly higher regional ($p=0.04$) and distant ($p<0.01$) failure. Furthermore, they reported grade 2 pneumonitis rates of 17.9% in T2 tumors vs 4.4% in T1 tumors ($p=0.02$).⁹⁶ In a series of 63 patients with tumors >3 cm there was a lower local failure-free survival seen in tumors with planning target volume (PTV) >106 cc.⁹⁸ A meta-analysis of eighty-eight studies (7752 patients) suggested age and tumor size were important risk factors for grade 2 and above pneumonitis.¹⁰⁴

When treating patients with tumors ≥ 5 cm with SBRT, the radiation therapy plans should adhere to established dose constraints for the chosen dose and fractionation regimen for organs at risk and maximum dose levels to optimize the safety profile of treatment.^{17,56,82,95} The understanding of the optimal planning targets for organs-at-risk for the different dose and fractionation regimens continues to improve with new published studies and the literature should be reviewed when establishing treatment protocols. Additionally, though adjuvant

chemotherapy is a standard treatment for T3 tumors following surgical resection, there is currently insufficient data to comment on the role of chemotherapy following SBRT in this setting.

Data is currently lacking to determine if there is an upper limit of tumor size for SBRT and there is very limited information on SBRT outcomes in tumors >7 cm. When SBRT is considered in tumors >7 cm it should be in the context of other treatment options and with consideration of the existing data. There are on-going clinical trials to explore SBRT in large tumors, which include the VOLUMES trial from the Netherlands Cancer Institute¹⁰⁵ and a dose-escalation trial of SBRT for tumors >3 cm and/or N1 nodal involvement followed by chemotherapy led by the Memorial Sloan Kettering Cancer Center (MSKCC).¹⁰⁶

For patients lacking tissue confirmation?

Statement KQ2D: Whenever possible, obtain a biopsy prior to treatment with SBRT to confirm a histologic diagnosis of a malignant lung nodule.

- **Recommendation strength:** Strong
- **Quality of evidence:** High
- **Consensus:** 100%

Statement KQ2E: SBRT can be delivered in patients who refuse a biopsy, have undergone non-diagnostic biopsy, or who are thought to be at prohibitive risk of biopsy. Prior to SBRT in patients lacking tissue confirmation of malignancy, patients are recommended to be discussed in a multidisciplinary manner with a consensus that the lesion is radiographically and clinically consistent with a malignant lung lesion based on tumor, patient, and environmental factors.

- **Recommendation strength:** Strong
- **Quality of evidence:** Moderate
- **Consensus:** 100%

Narrative

While surgery for stage I NSCLC carries risks of morbidity and mortality, a significant proportion of patients who undergo definitive resection do not have preoperative histologic confirmation of malignancy.^{107,108} A similar approach for delivering SBRT in patients who lack tissue confirmation can be considered in select circumstances.

While most prospective trials evaluating SBRT⁹⁵ or comparing SBRT to surgical resection⁵⁹ have required diagnostic biopsy for enrollment, many nonrandomized prospective and retrospective reports of SBRT have included patients with and without tissue confirmation of malignancy (Table 4). In patients with significant comorbidities and limited lung function, bronchoscopic biopsy and peripheral CT-guided biopsy can be associated with significant risks, including pneumothorax and hemoptysis. Thus, radiation oncologists are increasingly asked to

consider SBRT in patients without biopsy-proven confirmation of malignancy due to a perception that SBRT can be associated with less morbidity than the biopsy itself, particularly for peripheral lesions.

In a prospective study that included patients without biopsy-proven malignancy, the Princess Margaret Hospital reported outcomes for 108 patients with medically inoperable stage I NSCLC treated with SBRT, 28 of whom did not have pathologic confirmation of malignancy.¹⁰⁹ In order to be included, these unconfirmed lesions had to be radiographically “suspicious” based on interval progression in size on at least two serial CT imaging studies obtained at a minimum of 1 month apart and/or based on increased FDG uptake on PET imaging and required multidisciplinary tumor board consensus for enrollment in the study. Of the 10 local failures in the study, six occurred in patients with tissue confirmation and four in patients without tissue confirmation, for a 1-year LC of 93% and 87%, respectively ($p=0.41$). Similarly, there was no significant difference in regional or distant control rates or in overall and cause-specific survival between patients with and without a pathologically-confirmed diagnosis of NSCLC.

Retrospective reports have commonly included patients without tissue confirmation. In a post-hoc exploratory analysis of the Japan Clinical Oncology Group (JCOG) 0403 trial, 115 cases lacking a histologic confirmation with SBRT were reviewed.¹¹⁰ These lesions were found to have definitive enlargement of the lesion on sequential CT scans or positive findings on FDG-PET imaging and the radiographic appearance of the lesion was thought to be consistent with a primary lung cancer. Local progression free survival was 96.6% for lesions ≤ 2 cm ($n=58$) and 94.7% for lesions > 2 cm ($n=57$). A number of retrospective studies have compared disease outcomes for biopsied and unbiopsied lung nodules, typically including patients with FDG-avid lesions with enlargement on serial imaging and multidisciplinary consensus. Such studies have consistently identified similar disease control among biopsy-proven patients and patients treated without tissue confirmation of malignancy.¹¹¹⁻¹¹³

In the largest such study, Dutch investigators performed a retrospective analysis of 591 patients comparing outcomes after a pathological diagnosis ($n=209$) or a clinical diagnosis lacking tissue confirmation ($n=382$).¹¹⁴ Patients without a tissue diagnosis were included based on CT appearance of the lesion, PET imaging findings, and multidisciplinary tumor board review. The investigators also calculated the probability of malignancy for each patient using previously validated models.^{115,116} The mean probability of malignancy in the clinically diagnosed cohort was 92.5%, similar to the probability of 94.8% calculated for a validation subset of patients who had histologically confirmed NSCLC. There were no significant differences between patients with or without tissue

diagnoses in median OS (39.2 months vs. 40.2 months, $p=0.999$), LC (3-year 90.4% vs. 91.2%, $p=0.982$), regional control ($p=0.947$), or distant metastasis free survival ($p=0.980$).¹¹⁴

Based on the numerous prospective and retrospective studies of SBRT that have included patients with radiographic evidence of early stage NSCLC but who lack tissue confirmation, there do not appear to be any differences in local, nodal, or distant control rates between patients with or without histologic confirmation of malignancy. As such, it does not appear that LC rates have been artificially upgraded by the inclusion of benign lesions, and the overall outcomes in these studies are unlikely to be biased by inclusion of potentially benign lesions. In summary, provided patients lacking a tissue diagnosis are well selected and are at a low predicted likelihood of having a benign lung nodule, SBRT can be reasonably considered in patients unable or unwilling to undergo biopsy. Any patient being considered for SBRT without tissue diagnosis should be discussed at a tumor board or in a multidisciplinary manner with consensus that the lesion is radiographically consistent with a malignant lung lesion based on factors such as lesion size, growth over time, presence of spiculations or lack of benign-appearing calcifications, PET avidity, and lesion location. Other patient-specific factors, such as smoking history or history of prior lung cancers, should also be considered. Finally, regional environmental factors, such as the incidence of histoplasmosis, may impact the probability that a lesion is a malignant and should also be considered in the calculation of obtaining histological confirmation.

For patients with synchronous primary or multifocal tumors?

Statement KQ2F: Multiple primary lung cancers (MPLC) can be difficult to differentiate from intrathoracic metastatic lung cancer and pose unique issues for parenchymal preservation, therefore it is recommended that they are evaluated by a multidisciplinary team.

- **Recommendation strength:** Strong
- **Quality of evidence:** Moderate
- **Consensus:** 100%

Statement KQ2G: PET/CT and brain MRI are recommended in patients suspected of having MPLC to help differentiate from intrathoracic metastatic lung cancer. Invasive mediastinal staging should be addressed on a case-by-case basis.

- **Recommendation strength:** Strong
- **Quality of evidence:** Moderate
- **Consensus:** 100%

Statement KQ2H: SBRT may be considered as a curative treatment option for patients with synchronous MPLC. SBRT for synchronous MPLC has equivalent rates of local control and toxicity but decreased rates of overall survival compared to those with single tumors.

- **Recommendation strength:** Conditional
- **Quality of evidence:** Low
- **Consensus:** 94%

Statement KQ2I: SBRT is recommended as a curative treatment option for patients with metachronous MPLC. SBRT for metachronous MPLC has equivalent rates of local control and toxicity and overall survival compared to those with single tumors.

- **Recommendation strength:** Strong
- **Quality of evidence:** Moderate
- **Consensus:** 94%

Narrative

The concept of multiple primary lung cancers (MPLCs) was introduced by Beyreuther in 1924,¹¹⁷ but remained a rarity for several decades. It was not until the integration of CT scanning into lung cancer care that the true magnitude of this clinical occurrence was appreciated. Older series noted rates of <5% of all NSCLCs but these are likely an underestimation of the true incidence,¹¹⁸ which is further fueled by the increased detection of ground glass opacities (GGOs), adenocarcinomas with lepidic growth patterns and predilection for indolence and multiplicity. Prognosis for these multifocal adenocarcinomas is different from traditional MPLCs reported in older series. Management for MPLCs follows general principles for other early stage NSCLC with special consideration for preservation of pulmonary function, which may increase indication for SBRT.

Whether synchronous or metachronous, the diagnostic challenge is in differentiating MPLCs from intra-thoracic metastatic disease. There is a paucity of clear criteria differentiating intrapulmonary metastasis from MPLC. The definition from Martini and Melamed is the most widely referenced,¹¹⁹ though it applies most appropriately to metachronous lesions, and relies heavily on cell type (Table 5). In this schema, patients are placed into management categories based on the appearance, location of nodules, and the presence of nodal or extra thoracic metastatic disease. Numerous mutational and molecular techniques for more precise determination of tumor clonality are under investigation, but none are currently clinically available. Diagnosis and management of MPLCs should be based on the judgment of a multidisciplinary team consisting of a thoracic surgeon, radiation oncologist, medical oncologist, pulmonologist, thoracic radiologist, and pathologist. With biopsy providing supplemental information, multidisciplinary clinical expertise can best define care. Invasive mediastinal staging and extra-thoracic imaging with whole-body PET and brain MRI for those patients being considered for curative local therapy are important for characterizing the nature of the disease.

Synchronous Primary Lung Cancers

The lack of uniformity for the definitions for synchronous primary NSCLC has resulted in a paucity of large series of homogeneously treated patients. According to the current American Joint Commission on Cancer (AJCC) staging system for lung cancer, multiple nodules in the same lobe and lung represent T3 and T4 disease, respectively, but bilateral nodules are considered stage IV.¹²⁰ This may “over stage” a significant number of patients with synchronous primary early stage tumors, therefore the next iteration of the guidelines are expected to specifically address this scenario.¹²¹ Recent trials support an aggressive approach to the treatment of patients with more than one nodule suspicious for early stage NSCLC with the understanding that these may represent MPLC. For patients seeking aggressive local therapy for multiple lung cancer nodules, thorough pre-treatment assessment is essential to rule out metastatic disease and careful planning is needed to preserve normal pulmonary parenchyma.

The majority of published series of synchronous MPLCs involve patients who underwent resection.¹²² Five-year survivals for resected patients range from 16-76% but are improved in more recent series and those with a predominance of multifocal adenocarcinoma.^{123,124} A 2013 meta-analysis looked at prognostic factors and outcomes of resections for synchronous MPLCs.¹²⁵ Risk factors for poor outcome included male gender, advanced age, nodal involvement and unilateral tumors, with N2 involvement being the strongest predictor of poor outcome.

Multiple single institution retrospective series report on toxicity and efficacy of SBRT in the setting of synchronous MPLC. Most patients in these series are treated with resection of one lesion and SBRT of the other, but several have reported SBRT for both foci (Table 6).¹²⁶⁻¹³⁰ Toxicity and LC are equivalent to what is reported for single lung cancers. The largest series to date of SBRT for synchronous MPLCs is from the Netherlands, where 62 patients with synchronous tumors were treated.¹²⁶ Fifty-six had SBRT to both lesions and 6 underwent resection for one tumor and SBRT for the other. There were no grade 4 or 5 toxicities; primary tumor control was 84% at two years and actuarial two-year OS was 56%.¹²⁶ An exploratory analysis between patients with unilateral and bilateral tumors noted no differences in toxicity. Importantly, those with unilateral MPLCs had significantly worse local and regional control, suggesting that bilateral synchronous tumors are more likely to represent separate primaries.

Metachronous Primary Lung Cancers

Similar to synchronous MPLCs, the definition for metachronous tumors remains somewhat ambiguous. Recent increases in the incidence of metachronous MPLC are attributed to: 1) more patients presenting with early

stage disease, 2) more patients surviving treatment for early stage NSCLC, and 3) increased use of CT scans in routine NSCLC follow-up care.¹³¹ Series of resected NSCLC patients prior to the year 2000 typically reported rates of metachronous MPLC at 0.5-3.2% in resected patients.¹³²⁻¹³⁵ A 2013 report of 1294 patients from MSKCC found a 7% rate of second primary lung cancers.¹³⁶ This was higher than previous series, but lower than the rate of recurrence within the same population (20%). In this series, the rate of recurrence after resection began to decrease after four years, while the incidence of a MPLC increased steadily over time, going from an initial rate of 3/100 person-years to 6/100 person-years at five years following resection. The majority of second primary NSCLCs (93%) in the MSKCC series were detected by scheduled surveillance CT scan. A 2010 analysis of the Surveillance Epidemiology and End Result (SEER) database found only 1.5% incidence for development of second primary NSCLC, but there was less utilization of post-operative CT surveillance in the SEER population.¹³⁷ Similar to synchronous tumors, approximately two-thirds of metachronous MPLCs reported in large series are of the same histology,^{135,138} with adenocarcinoma reported more frequently in modern series.¹³⁶ This shift in histology may impact prognosis, as multifocal adenocarcinomas are thought to have a more indolent course and excellent survival following retreatment.¹³⁹

Patients suspected of having metachronous MPLCs require careful evaluation to rule out the possibility of recurrent disease. Whole body PET and brain MRI are recommended for restaging, but the role for invasive mediastinal staging is less clear and should be addressed on an individual basis. Most (75-90%) metachronous MPLCs are detected at an early stage and, therefore, local therapy is used in most cases, with the majority undergoing sublobar resections. Survival following resection is approximately 40% at five years, which is lower than for early stage tumors but better expected for recurrent disease.^{138,140} Stage of the subsequent tumor is the most consistent predictor of survival.

SBRT is a particularly attractive modality in this setting because these tumors are typically diagnosed at an early stage and the need to preserve pulmonary parenchyma is heightened due to prior treatment. Multiple small single institution retrospective series have reported on the use of SBRT for metachronous MPLC with LC and OS at two years, which are comparable to surgery (Table 7).^{127,141,142} Similar to synchronous MPLC, increased toxicity does not appear to be increased in this setting compared to single tumors. In a retrospective series of 48 metachronous MPLCs treated at Washington University in St. Louis, two-year OS was 68%.¹²⁷ No grade ≥ 3 toxicities were reported. The largest reported series of SBRT for metachronous MPLC is from the Netherlands,

where Griffioen reported on 107 patients treated from 2003 to 2013.¹⁴² The majority had an anatomic resection for their first NSCLC and median interval between tumors was 48 months (range 6-349). At two years, LC was 89% and OS was 60%, which is comparable to single primary NSCLC.¹⁴²

In summary, the evaluation and treatment of patients with MPLCs poses a challenge to the thoracic oncologic community. Treatment approach should be guided by multidisciplinary discussion, careful evaluation of diagnostic and histological data, and patient goals-of-care. For patients disposed to aggressive treatment, SBRT may be beneficial for preserving pulmonary parenchyma while still delivering ablative therapy to the target lesion(s).

For patients who underwent pneumonectomy and now have a new primary tumor in their remaining lung?

Statement KQ2J: SBRT may be considered a curative treatment option for patients with metachronous MPLC in a post-pneumonectomy setting. While SBRT for metachronous MPLC appears to have equivalent rates of local control and acceptable toxicity compared to single tumors, SBRT in the post-pneumonectomy setting might have a higher rate of toxicity than in patients with higher baseline lung capacity.

- **Recommendation strength:** Conditional
- **Quality of evidence:** Low
- **Consensus:** 94%

Narrative

Patients who develop a metachronous MPLC following pneumonectomy present a unique treatment challenge. Pathologic confirmation of disease is challenging in this population due to fear of pneumothorax with a single lung and therefore is more frequently deferred. Surgical resection is possible with >100 post-pneumonectomy NSCLC resections reported in the literature, but the great majority of these are sublobar resections and have decreased survival compared to *de novo* resections.¹⁴³ A growing body of evidence suggests that SBRT is an effective treatment option with an acceptable safety profile in selected patients with metachronous MPLC after pneumonectomy (Table 8).¹⁴⁴⁻¹⁴⁷ Testolin et al. reported a series of 12 patients treated for MPLC after pneumonectomy for NSCLC. All patients completed the planned treatment with 2-year DFS and OS of 36.1% and 80%, respectively.¹⁴⁷ The lower DFS rates may be explained by the relatively low radiation doses in this series. Haasbeek reported on SBRT delivered to doses of a BED of >100 Gy₁₀ in 15 post-pneumonectomy patients, with a DFS and OS of 91% and 80.8%.¹⁴⁶ Two-year LC in this series was 100%. No acute grade 3 toxicity, but 13% late pulmonary grade 3 toxicity was seen. An updated experience by this group including 27 patients, 20 of them treated

with SBRT, shows 3-year local, regional, and distant recurrence rates of 8%, 10%, and 9%.¹⁴⁸ Grade 3 radiation pneumonitis occurred in 2 patients (10%) who received SBRT and 1 patient (5%) developed grade 5 radiation pneumonitis.

While most studies on SBRT adhere to standard lung dose constraints, these constraints were derived in patients with two lungs, and it is unclear what the appropriate constraints should be in patients with a single lung. Generally, great caution should be taken to minimize the dose to the single lung, as high grade radiation pneumonitis in a single lung may be a serious and potentially life-threatening toxicity.

Key Question 3: For medically inoperable early stage lung cancer patients, how can SBRT techniques be individually tailored to provide an adequate dose for tumor eradication with minimal risk to normal structures in “high-risk” clinical scenarios, including:

- Tumors with intimal proximity/involvement of mediastinal structures (bronchial tree, esophagus, heart, etc.)
- Tumors abutting or invading the chest wall?

For tumors with intimal proximity/involvement of mediastinal structures (bronchial tree, esophagus, heart, etc.)?

Statement KQ3A: For tumors in close proximity to the proximal bronchial tree, SBRT should be delivered in 4-5 fractions. Physicians should endeavor to meet the constraints that have been utilized in prospective studies given the severe toxicities that have been reported.

- **Recommendation strength:** Strong
- **Quality of evidence:** Low
- **Consensus:** 83%

Narrative

Reports of SBRT to tumors abutting the proximal bronchial tree are limited and retrospective in nature, though most reports are of treatments with 4 or more stereotactic fractions. Comparisons between these tumors and peripheral tumors suggest similar high rates of LC, provided ablative doses with a cumulative BED ≥ 100 Gy₁₀ are used. There is also a suggestion of similar OS rates between patients with tumors abutting the bronchial tree and patients with more peripheral tumors in retrospective institutional series.¹⁴⁹ However, the use of SBRT to treat tumors directly abutting the proximal bronchial tree has been associated with death due to treatment complications including obstructive pneumonia, respiratory failure, and pulmonary hemorrhage in rates ranging from 0% to as high as 22%. Fatal hemorrhages were associated with exposure to the anti-angiogenic agent bevacizumab in one series, though this was limited to two patients.⁸⁰ Fatal hemoptysis and grade 3 obstructive pneumonia were also reported when the proximal bronchus exceeded 40 Gy in 5 fractions at rates of 7% each in another series.⁸¹ Due to these

severe toxicities, other alternative hypofractionated schedules are being explored. One such series of patients whose planning target volumes overlapped the main airways received 12 fractions of 5 Gy and had a rate of possible treatment-related death of 21%.¹⁵⁰

Despite these reports, SBRT to tumors near the proximal bronchi should still be utilized, as two-year OS rates are high and have not yet been proven to be significantly different than the OS rates after SBRT to tumors in more peripheral locations. Until more robust measures are reported, dose limits from RTOG 0813 should be used.⁸² To minimize the chance of airway stenosis and fistula formation, the maximum point dose to the proximal bronchi should not exceed 105% of the PTV prescription dose. The volume of the proximal bronchi receiving more than 18 Gy should also be limited to less than 4 cc.⁸² Highly conformal techniques can be used to attempt to meet these constraints and to attempt sparing of the contralateral walls of the bronchi involved. Even with these constraints and techniques, patients with tumors abutting the proximal airways should still be counseled about the potentially fatal treatment complications.

Statement KQ3B: For tumors in close proximity to the esophagus, physicians should endeavor to meet the constraints that have been utilized in prospective studies or otherwise reported in the literature given the severe esophageal toxicities that have been reported.

- **Recommendation strength:** Strong
- **Quality of evidence:** Low
- **Consensus:** 94%

Narrative

The esophagus is of particular concern when SBRT is utilized for intrathoracic tumors. It is a serially functioning organ and thus, the maximum dose delivered at any point to the organ, as well as dose to small volumes, is relevant when assessing an SBRT plan's safety profile. In that regard, designing a planning organ-at-risk volume should be considered when tumors are in close proximity to the esophagus. Furthermore, one must bear in mind that the esophagus is not fixed in the chest and organ motion for this structure has been quantified.⁷⁹ Rates of esophageal toxicity are low with SBRT, ranging from 6-14%, typically manifesting as self-limiting odynophagia and/or dysphagia. Predictably, toxicity is related to proximity of the primary tumor to the esophagus and dose delivered to the structure itself.^{77,78,83} More severe, potentially fatal toxicities have also been reported, including ulceration,^{84,85} hemorrhage,^{77,78} perforation,⁸⁶ stricture,⁸⁴ and tracheoesophageal fistula.^{31,77,78,84,86} These unusual complications are often associated with other contributing factors such as prior external-beam radiation therapy, concurrent or sequential chemotherapy, or adjuvant vascular endothelial growth factor modulating agents.^{84,86}

There are limited data on esophageal tolerance in the setting of SBRT without uniform endpoints. Further, studies have utilized different fractionation regimens with necessary conversions into BEDs. The most common metrics are consistent with a serially organized organ-maximum dose and dose to small volumes. Using a 5 fraction regimen, D1.5cc >16 Gy and D5cc > 19 Gy have been associated with grade ≥ 2 acute esophageal toxicity.^{77,83} In terms of late toxicity, no significant complications were observed in a review of 52 patients with PTV located within 2 cm of the esophagus with Dmax < 50 Gy and D1cc < 45 Gy using a 5 fraction regimen.³¹

In summary, severe, life-threatening esophageal toxicity is possible after SBRT. Despite limited data to support firm recommendations, dose to the esophagus should be carefully assessed and minimized. Highly conformal techniques can be used to facilitate esophageal avoidance with central tumors. The risks and benefits of combining SBRT with other modalities should be carefully considered when esophageal toxicity is a concern.

Statement KQ3C: For tumors in close proximity to the heart and pericardium, SBRT should be delivered in 4-5 fractions with low incidence of serious toxicities to the heart, pericardium and large vessels observed. Adherence to volumetric and maximum dose constraints utilized in prospective trials or reported in the literature may optimize the safety profile of this treatment.

- **Recommendation strength:** Strong
- **Quality of evidence:** Low
- **Consensus:** 83%

Narrative

Serious toxicities to the heart, pericardium and large vessels have rarely been observed after SBRT for centrally located NSCLC in a clinical trial setting. In the IU phase I trial of SBRT for medically inoperable early stage NSCLC using a 3-fraction regimen, pericardial effusions were observed in patients with centrally located tumors.¹¹ In the updated report of their phase II trial of SBRT for NSCLC using a 3-fraction regimen (60-66 Gy in 3 fractions), there were no toxicities of heart, pericardium and large vessels reported.¹² When a 4-fraction regimen (48 Gy in 4 fractions) was used in the JCOG 0403 phase II trial, which also included patients with T1N0M0 centrally located NSCLC, serious toxicities to heart, pericardium and large vessels were not observed.⁵⁶ In a recent report combining the results of two randomized trials compared surgery and SBRT for stage I operable NSCLC, 5 patients with non-peripheral NSCLC treated with a regimen of 50 Gy in 4 fractions did not experience any toxicities in the heart, pericardium and large vessels.⁵⁵ Using a risk-adaptive approach, Bral et al. demonstrated that 60 Gy in 4 fractions had an acceptable safety profile for centrally located NSCLC without causing cardiac toxicities in a phase II trial.⁷⁴

A systematic review on SBRT for centrally located lung tumors, including early primary NSCLC, using a wide variety of regimens, including 50 Gy in 10 fractions, 48-60 Gy in 8 fractions, 35-60 Gy in 5 fractions, 48-50 Gy in 4 fractions, and 60 Gy in 3 fractions, demonstrated that the incidence of toxicities of the heart, pericardium and large vessels is very low.⁷⁴ Park et al. from Yale University treated 111 centrally-located lung tumors (NSCLC and lung metastases) with SBRT to a dose of 50 Gy in 4-5 fractions and did not observe toxicities to the heart, pericardium and large vessels.¹⁵¹ In a recent retrospective series of SBRT for centrally located lung tumors, including both primary NSCLC and lung oligometastases, two (2%) patients with lung oligometastases died of pulmonary hemorrhage after SBRT (45-50 Gy in 5 fractions) for tumors very close to large vessels. Of note, those 2 patients also received anti-vascular endothelial growth factor therapy before and after SBRT.⁸⁰ In another retrospective study of SBRT for centrally located lung tumors, mostly NSCLC, using mostly 45 Gy in 5 fractions, three out of 125 patients developed cardiac toxicities.⁷⁸

In summary, SBRT to 45-50 Gy in 4-5 fractions can be delivered to centrally located lung tumors with an acceptable safety profile and low incidence of serious toxicities to the heart, pericardium, and large vessels. Efforts should be made to minimize the doses to these structures. None of the studies reporting specifically heart, pericardial, or vascular toxicities had dosimetric correlations to anatomy. This, coupled with small numbers, makes it difficult to accurately determine tolerance of those structures. The risk of pulmonary hemorrhage may increase with the use of anti-vascular endothelial growth factor therapy.⁸⁰

For tumors abutting or invading the chest wall?

Statement KQ3D: SBRT is an appropriate option for treatment and should be offered for T1-2 tumors that abut the chest wall. Grade 1 and 2 chest wall toxicity is a common occurrence post SBRT that usually resolves with conservative management. Patients with peripheral tumors approximating the chest wall should be counseled on the possibility of this common toxicity.

- **Recommendation strength:** Strong
- **Quality of evidence:** High
- **Consensus:** 94%

Statement KQ3E: SBRT may be utilized in patients with cT3 disease due to chest wall invasion without clear evidence of reduced efficacy or increased toxicity compared to tumors abutting the chest wall.

- **Recommendation strength:** Conditional
- **Quality of evidence:** Low
- **Consensus:** 88%

Narrative

It is common for early stage cT1-2 N0 NSCLC to abut the chest wall. Chest wall toxicity, usually manifesting as pain or rib fracture, has been reported widely within both prospective trials and retrospective series, with typical incidence ranging widely from 5%-45%.^{17,27,95} The mechanism of chest wall pain is thought to be multifactorial and can include direct rib fracture from compromise of the cortical bone strength, as well as irritation of the intercostal nerves. These two mechanisms appear to be independent entities, and thus chest wall pain can occur in the absence of rib fracture. Chest wall pain and rib fracture manifested within prospective series has been limited to grade 1 and 2 toxicity which can be effectively managed with NSAIDs or short acting narcotic pain medications.^{17,95} Grade 3 pain that severely affects activities of daily living or requires treatment with long acting narcotics has been seen in retrospective series.¹⁵² Based on the conservative management for treatment of this toxicity, SBRT continues to be an effective treatment option with an acceptable safety profile for tumors in close proximity to the chest wall.

Multiple retrospective series have evaluated predictors of chest wall toxicity. Clinical factors may include patient obesity.¹⁵³ Dosimetric factors that have been evaluated include fractionation scheme and volumetric dose to the chest wall and ribs. In two retrospective series looking specifically at patients who developed chest wall toxicity, there was significant increase in toxicity for patients receiving 30 Gy to a large volume of chest wall (typically >30 cc).^{25-27,152} In one of the studies, >3 cc of chest wall volume getting 60 Gy was also a predictor of toxicity.²⁷ In retrospective studies comparing different dose regimens for peripheral tumors, the incidence of chest wall toxicity was less when 5 or more fractions were used.^{154,155} Other strategies to reduce volume of chest wall may include highly conformal techniques as discussed above to spare other critical structures, however, utilization of these techniques to spare the chest wall may actually increase dose to the ipsilateral lung.¹⁵⁶ Given the low likelihood of high grade toxicity and that chest wall toxicity is typically manageable for patients, compromising coverage of the PTV or PTV trimming away from the chest wall are not favored as a techniques to meet chest wall constraints.

Treatment of peripheral early stage NSCLC where tumors are invading the chest wall has been sparsely described in the literature. While prospective trials have allowed enrollment of cT3 tumors <5 cm with chest wall invasion, very few patients with T3 disease have been enrolled.^{11,12,17,157,158} Other retrospective series have included patients with cT3 disease with chest wall invasion, but overall the absolute number of patients with outcomes data for this clinical scenario remains low.^{98,99,159-161} Nevertheless, there does not appear to be decreased efficacy or increased toxicity for cT3 tumors with chest wall invasion. In the largest series that included cT3 tumors, LC and OS

at three years was reported to be 93% and 64%, respectively.⁹⁹ In an additional series specifically looking at cT3 tumors, but that included some patients with recurrent disease, 1-year LC was reported at 89%, and improvement in chest wall pain was seen in 78% of patients that reported it prior to SBRT.¹⁵⁸

Key Question 4: In medically inoperable patients, what is the role of SBRT as salvage therapy for early stage lung cancer that recurs:

- **After conventionally fractionated radiation therapy,**
- **After SBRT,**
- **After sublobar resection?**

After conventionally fractionated radiation therapy?

Statement KQ4A: The use of salvage SBRT after primary conventionally fractionated radiation may be offered to selected patients due to reported favorable local control and survival.

- **Recommendation strength:** Conditional
- **Quality of evidence:** Low
- **Consensus:** 100%

Statement KQ4B: Patients treated with salvage SBRT after primary conventionally fractionated radiation should be informed of significant (including fatal) toxicities.

- **Recommendation strength:** Strong
- **Quality of evidence:** Low
- **Consensus:** 100%

Statement KQ4C: Patient selection for salvage SBRT after primary conventionally fractionated radiation is a highly individualized process. Radiation oncologists should assess evidence-based patient, tumor, and treatment factors prior to treatment initiation.

- **Recommendation strength:** Strong
- **Quality of evidence:** Low
- **Consensus:** 94%

Narrative

Conventionally fractionated radiation therapy, usually combined with either concurrent or sequential chemotherapy, is the standard treatment approach for locally advanced NSCLC in patients where surgical resection is either not appropriate or not selected.^{162,163} The risk of new primary tumors or local/regional relapse of the original lung cancer has been increasing given improvements in patient prognosis and systemic therapy.^{164,165} Such thoracic relapses can be treated with various options such as surgery, conventionally fractionated reirradiation, SBRT, chemotherapy, and targeted therapy.

Given the development of SBRT techniques for the treatment of thoracic malignancies, a growing collection of reports related to salvage SBRT after primary radiation therapy is available.^{166,167} Successful implementation of retreatment in this salvage patient population is complicated by potential acute and late normal tissue effects, which include effects against the lung (e.g. pneumonitis/fibrosis, hemoptysis, and fistula), other thoracic organs (e.g. heart, esophagus), as well as other tissue types (e.g. blood vessels, bone/cartilage etc.). Approaches for the prediction and mitigation of such effects are not understood, and no agreed upon international standards for the dosimetric planning of such cases currently exist.¹⁶⁷

In a review by De Bari in 2015, 12 retrospective studies assessing the use of SBRT as salvage therapy after primary conventionally fractionated radiation therapy were assessed. They reported on various aggregate clinical outcomes such as one-year OS (59-90%), two-year OS (29-74%), one-year LC (59-95%) and two-year LC (50-92%).¹⁶⁷ In terms of significant treatment toxicity, the most frequently reported toxicity was grade 3 or greater pulmonary toxicity in 3-28% of patients, depending on the report assessed. Fatal radiation-induced toxicities were reported in 4/12 studies, for a total crude rate of 7/177 (4%) cases. DeRuysscher also conducted a similar review in 2014 including not only SBRT salvage post-radical radiation therapy, but also salvage with high dose three-dimensional conformal radiation therapy (3-D CRT) and proton therapy as well.¹⁶⁶ In this broader review, a total of 14 studies (including a small prospective study) with 408 patients were evaluated. Reirradiation was initiated after a median of 12 months and mean of 23 months after primary radiation therapy. The authors reported a median OS of 17 months and progression-free survival of 10 months with retreatment. In this high dose salvage treatment cohort, grade 3-4 lung toxicity was observed in 10% of patients. Grade 5 fatal bleeding was seen in 3% of patients, particularly in central tumors, and grade 5 lung toxicities were seen in 0.5% of cases.

Prospective data related to salvage SBRT in previously irradiated lung cancer patients are extremely limited, as discussed in the above two studies.^{166,167} However, one small prospective clinical trial has been reported in the literature by Seung and Solhjem.¹⁶⁸ In this prospective clinical trial, eight patients with locally recurrent disease at least six months after primary radical radiation therapy (50-68 Gy in 1.8-2.5 Gy/fraction) were treated with various SBRT fractionation schedules including 12 Gy x 4 fractions, 10 Gy x 5 fractions, 8 Gy x 5 fractions, or 20 Gy x 3 fractions. Crude locoregional control post-treatment was 86% and the median survival for the cohort was 18 months. No high grade late toxicities were identified, but all patients reported grade 2 dyspnea related to protocol treatment. The authors concluded that salvage SBRT may be given with an acceptable safety profile, but

that further clinical information and follow-up would be required to demonstrate the long-term efficacy and toxicity of this approach.

Several retrospective studies have evaluated salvage SBRT after thoracic radiation in relatively small patient cohorts. Two related papers have reported on the MD Anderson experience using salvage SBRT treatment after initial thoracic radiation in 36 patients.^{169,170} Initial treatment was definitive in 67% of cases and was given with 3-D CRT in 69% and IMRT in 31%.¹⁶⁹ Salvage SBRT was given with 50 Gy in 4 fractions in 72%, 40 Gy in 4 fractions in 17%, and other fractionation schedules in 11%. Two-year overall and progression-free survival were 59% and 26%, respectively. LC was 92%, with a 96% rate for patients with optimal dosimetry without PTV compromise. No grade 4 or 5 toxicities were reported; however, one-third of patients had at least one grade 3 toxicity event. The authors conclude that salvage SBRT is associated with good LC and an acceptable toxicity profile, but that intrathoracic failure is still a significant issue. As such, better patient selection may be needed. Similar outcomes from MSKCC and the Mayo Clinic have also been reported, without grade 5 toxicity, and with relatively good LC but an excess of regional and distant recurrences.^{171,172}

For centrally located salvage SBRT after an in-field recurrence, Trovo et al. published a report on 17 patients treated with 30 Gy in 5-6 fractions after primary 3-D CRT/IMRT radiation therapy of 50-60 Gy in 20-30 fractions).¹⁷³ One-year LC and OS were 86% and 59%, respectively. In this high-risk central retreatment patient population, severe toxicities were more common than in some other retrospective reports and included a 23% grade 3 pneumonitis risk, 6% grade 5 pneumonitis risk, and 6% grade 5 hemoptysis risk. The authors conclude that LC can be achieved but that the high-risk nature of these central in-field recurrences warrants caution due to significant risk of grade 5 fatal events.

Review of the collective literature in this patient population demonstrates that positive prognostic factors for successful salvage with SBRT after radical conventionally fractionated radiation therapy include having an out-of-field salvage target, BED₁₀ for salvage treatment of ≥ 100 Gy, and ideally a longer retreatment interval. Predictors of toxicity for SBRT salvage include central tumor location, in-field recurrence, larger treatment volumes, bilateral mediastinal primary PTV targets, composite lung V20 $\geq 30\%$,¹⁷⁰ FEV1 $\leq 65\%$,¹⁷⁰ and poor baseline performance status. The utilization of salvage SBRT is a highly individualized treatment decision based on the potential benefits and risks previously outlined in the context of patient goals of care and risk tolerance. Salvage SBRT treatment plans should ideally be reviewed with medical physics and other radiation oncologists (in a peer review quality

assurance setting) to ensure high quality results to optimize patient selection, maximize LC and survival, and minimize treatment toxicities.

After SBRT?

Statement KQ4D: Patient selection for salvage SBRT after previous SBRT is a highly individualized process. Radiation oncologists should assess evidence-based patient, tumor, and treatment factors prior to treatment initiation.

- **Recommendation strength:** Strong
- **Quality of evidence:** Low
- **Consensus:** 100%

Narrative

Local recurrence occurs in approximately 5-20% of patients after primary SBRT treatment, depending on the series. The management options for local recurrences is already limited by pre-selection. Many of the patients receiving SBRT already have limited pulmonary reserve, thus surgical salvage is not an option in medically inoperable patients.

The literature on both initial SBRT *and* salvage SBRT is limited to two retrospective studies. Peulen et al. reported on 29 medically inoperable patients were re-irradiated for local failure.¹⁷⁴ In all cases, SBRT was used for both initial and salvage treatment. Unfortunately, there was great variability in the dose delivered, and only 2 patients received both initial and salvage SBRT courses with a BED of $>100 \text{ Gy}_{10}$. The follow-up was not reported past 5 months. It is difficult to draw conclusions on this limited study.

The Cleveland Clinic reported on 10 patients who received SBRT for salvage therapy for isolated local failures.¹⁷⁵ In all patients, the repeat SBRT course had a BED of $>100 \text{ Gy}_{10}$. Median tumor size was 3.4 cm (range 1.7- 4.8 cm). Two of the 10 lesions were “central” by proximity to the mediastinum, but they were outside the zone of the proximal bronchial tree. The median length of follow-up was 13.8 months from salvage SBRT (range 5.3-43.5 months). Following salvage SBRT, 3 patients were alive and without evidence of disease. A fourth patient died of medical comorbidities without recurrence 13.0 months after salvage SBRT. Two patients developed distant disease only. Four patients (40%) had local failure. Toxicity included grade 1-2 fatigue (3 patients) and grade 1-2 chest wall pain (5 patients). There was no grade 3-5 toxicity.

In summary, repeat SBRT with BED $\geq 100 \text{ Gy}_{10}$ is feasible and appeared well tolerated in a highly selected population. Physician who utilize salvage SBRT after previous SBRT should realize that limited data exist for this

treatment paradigm/approach. Therefore, the treating physician needs to understand that the potential exists for increased toxicity and/or worse overall outcomes. SBRT in this setting is a highly individualized treatment decision based on the potential benefits and risks previously outlined in the context of patient goals of care and tolerance for risk. LC can be achieved with salvage SBRT in many patients, although the local failure rates are likely higher than for initial SBRT courses for *de novo* lesions. Studies defining the dose constraints to be used in this setting are needed.

After sublobar resection?

Statement KQ4E: Patient selection for salvage SBRT after prior sublobar resection is a highly individualized process. Radiation oncologists should assess evidence-based patient, tumor, and treatment factors prior to treatment initiation.

- **Recommendation strength:** Strong
- **Quality of evidence:** Low
- **Consensus:** 94%

Narrative

In the setting of locally recurrent parenchymal lung cancer where surgical salvage is not feasible, there are limited data regarding the role of salvage SBRT for locally recurrent NSCLC after surgery. However, it appears to result in high LC rates and low toxicity, similar to SBRT for primary NSCLC. Gill et al. recently reported on 13 consecutive patients initially treated with sublobar resection and I-125 vicryl mesh brachytherapy who later developed locally recurrent NSCLC along the suture line. These patients received salvage SBRT to a median prescription dose of 48 Gy in 4 fractions. With a median follow-up of 2.1 years, the two-year LC rate in these 13 patients was 84% (95% CI, 64-100%). The two-year DFS and OS estimates were 39% (95% CI, 0- 65%) and 66% (95% CI, 38-93%), respectively. One patient (8%) developed a grade ≥ 3 toxicity, which involved a grade 3 esophageal stricture for a centrally located recurrence (previously treated with radiofrequency ablation).¹⁷⁶ This limited retrospective experience suggests that even in the setting of prior surgery and high local radiation doses delivered via prior I-125 brachytherapy, salvage radiation therapy with SBRT for locally recurrent NSCLC after surgery can result in promising LC with limited morbidity. This experience, taken together with the prior data of excellent LC in the setting of patients treated with definitive SBRT who have not had prior surgery or radiation, suggests that patients who recur locally after surgery alone could be considered candidates for salvage SBRT. Further studies are required in this setting.

Conclusion

This evidence-based clinical practice guideline has been generated to address the use of SBRT for early stage NSCLC. A distinction was made between lung tumors defined as either “peripheral” or “central” based on their relationship to the tracheobronchial tree or other mediastinal structures. For comparison purposes, the principles and practice of SBRT for peripheral tumors, along with expected outcomes and associated toxicities, were briefly presented as a standard-risk medically inoperable clinical scenario. Consensus statements in this guideline then provide recommendations for the use of SBRT in challenging clinical scenarios, including centrally located, large, multi-focal, medically operable, unbiopsied, and recurrent tumors, as well as guidance on the individualization of SBRT for high-risk tumors abutting critical structures. Strong consensus was also achieved on the importance of multidisciplinary review of all patients, and thorough patient consent and counselling on risks, benefits, and alternatives to SBRT. Specific guideline statements were graded by evidence quality and required greater than 75% agreement of all task force members for adoption.

Although few randomized trials have been completed for this relatively young technology, strong consensus recommendations based on extensive, consistent publications were generated for several KQs. In particular, evidence supporting increased risks for centrally located tumors was felt to justify a recommendation for protracted SBRT regimens of 4-5 fractions for central tumors. Strong consensus also supported a recommendation that in the absence of completed, prospective randomized trials, surgery remains the standard-of-care for standard-risk medically operable patients with early stage NSCLC.

However, low-quality evidence was available for a several other KQs, leading to conditional recommendations on important topics, including the use of SBRT for tumors >5 cm, in patients with prior pneumonectomy, for T3 tumors with chest wall invasion, for synchronous MPLC, and as a salvage therapy after prior radiation therapy. These conditional recommendations highlight areas lacking in prospective or large, well designed retrospective clinical studies. In particular, this was reflected in the conditional recommendation on the appropriateness of discussing lung SBRT as an alternative to sub-lobar resection for high-risk medically operable patients. Considerable discussion was also generated on the use of alternative hypofractionated regimens of 6-15 sessions for select high-risk central tumors in the absence of any prospective comparisons to SBRT. These areas of moderate and

low quality evidence highlight the importance of clinical trial enrollment, particularly in ongoing randomized comparisons between surgery and SBRT, as well as the role of prospective data registries.

Shared decision making with patients should be performed in all cases to ensure the patient understands the risks related to SBRT treatment, the side effects, and the alternative treatments available. When assessing treatment strategies, it is also important to understand the patient's goals (e.g., long term survival at any cost, pain free survival, survival with no reduction in pulmonary function) and discuss them as part of the multidisciplinary review. The task force uniformly recommends consideration of enrollment on prospective clinical trials for all eligible patients.

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Table 1: Series reporting results for SBRT for operable patients

Author	N	Dose	Median F/U (mos)	OS
Uematsu, 2001 ⁵¹	29	Most commonly 50-60 Gy in 5-10 fx	36	86% (3-year)
Onishi, 2011 ⁵⁴	87	45-72.5 Gy in 3-10 fx	55	72% (IA), 63.2% (IB) (5-year)
Lagerwaard, 2012 ¹⁷⁷	177	60 Gy in 3-8 fx	31.5	84.7% (3-year)
Timmerman, 2013 ⁵³	26	54 Gy in 3 fx	25.4	84.4% (2-year)
Chang, 2015 ⁵⁵	31	50-60 Gy in 3-5 fx	40.2	95% (3-year)
Nagata, 2015 ⁵⁶	64	48 Gy in 4 fx	67	76.5% (3-year)
Shibamoto, 2015 ⁵⁷	60	44-52 Gy in 4 fx	52.5	74% (5-year)
Komiyama, 2015 ⁵⁸	661	32-79 Gy in 4-15 fx	35	79% (3-year)

AE, adverse event; F/U, follow-up; N/R, not reported; OS, overall survival; SBRT, stereotactic body radiation therapy

Table 2: Series reporting results for SBRT for centrally located tumors

Author	N	Central tumors	Dose	Median F/U (mos)	AE \geq Gr 3	LC	OS
Onimaru, 2003 ⁸⁵	45	20%	48 Gy in 8 fx (central tumors)	18	N/R	55.1% (3-year, NSCLC only)	41.5% (2-year, stage I only)
Timmerman, 2006 ¹³	70	100%	60 Gy in 3 fx for T1, 66 Gy in 3 fx for T2	17.5	11%	95% (2-year)	54.7% (2-year)
Chang, 2008 ⁸⁸	27 (13 stage I)	N/R (All central or superior)	Initially 40 Gy in 4 fx, later increased to 50 Gy in 4 fx	17	N/R	89% (at follow-up)	N/R
Milano, 2009 ⁷⁵	53 (11 stage I or II)	100%	30-63 Gy in 4-18 fx	10	8%	73% (2-year)	72% (2-year, stage I only)
Song, 2009 ⁷⁶	32	28%	40-60 Gy in 3-4 fx	26.5	33% (pulmonary toxicity, central tumors only)	88.9% (2-year, central tumors only)	50% (2-year, central tumors only)
Oshiro, 2010 ⁷³	21	100%	25 to 60 Gy in 1-13 fx	20	14.3%	59.6% (2-year)	62.2% (2-year)
Bral, 2011 ⁷⁴	40	43%	60 Gy in 4 fx (central tumors)	16	20%	94.1% (at follow-up, central tumors only)	52% (2-year)
Rowe, 2012 ⁸⁹	47 (30 primary tumors)	100%	Most commonly 50 Gy in 4 fx	11.3	11%	94% (2-year)	N/R
Modh, 2014 ⁷⁸	125 (91 primary tumors)	100%	Most commonly 45 Gy in 5 fx	17.4	8%	79% (2-year, pts with BED10 \geq 80 Gy only)	64% (2-year, primary and recurrent tumors only)
Nishimura, 2014 ⁸¹	133 (120 primary tumors)	100%	40-60 Gy in 5 fx	33	3.8%	78% (3-year)	54.1% (3-year)

Author	N	Central tumors	Dose	Median F/U (mos)	AE \geq Gr 3	LC	OS
Wu, 2014 ⁷⁷	125 (91 primary tumors)	100%	Most commonly 45 Gy in 5 fx	14.3	1.6% (esophageal toxicity)	N/R	N/R
Harder, 2015 ⁸³	157 (133 primary tumors)	100%	30-60 Gy in 3-8 fx	28.3	0.6% (esophageal toxicity)	N/R	N/R
Haseltine, 2016 ⁸⁰	108 (101 primary tumors)	100%	36-60 Gy in 2-5 fx	22.7	12%	77.4% (2-year)	63.9% (2-year)

AE, adverse event; F/U, follow-up; LC, local control; N/R, not reported; OS, overall survival; pts, patients; SBRT, stereotactic body radiation therapy

Table 3: Series reporting results for SBRT for patients with tumors >5 cm in diameter

Author	N	Median diameter (cm)	Dose	Median F/U (mos)	LC	OS
Baumann, 2006 ¹⁰³	138 (85 T2 tumors)	2.7	30-48 Gy in 2-4 fx	33	87% (T2 tumors, at follow-up)	52% (3-year)
Beitler, 2006 ¹⁰²	75 (29 with GTV >65 cm ³)	N/R	30-90 Gy in 5-40 fx (conventional RT before SBRT in 8 pts)	17	N/R	23% (GTV >65 cm ³ , 2-year)
Xia, 2006 ⁹⁹	43 (4 tumors >5 cm)	N/R	50 Gy in 10 fx	27	95% (3-year)	78% (3-year)
Dunlap, 2010 ¹⁰¹	40 (13 T2 tumors)	2.3	42-60 Gy in 3-5 fx	11.2 (T2 tumors)	70% (T2 tumors, 2-year)	35% (T2 tumors, 2-year)
Allibhai, 2013 ⁹⁶	185 (52 T2 tumors)	2.2	48 Gy in 4 fx (≤ 3 cm), 54-60 Gy in 3 fx (> 3 cm), 50-60 Gy in 8-10 fx (< 2 cm from mediastinal structures)	15.2	Not statistically associated with tumor size.	Poorer OS statistically associated with tumor size (p=0.001)
Cuaron, 2013 ⁹⁸	63 (all >3 cm)	3.9	40-60 Gy in 3-5 fx	16.9	N/R	57.6% (2-year)
Davis, 2015 ¹⁰⁰	723 (224 T2 tumors)	2.4	10-80 Gy in 1-5 fx	12	85% (T2 tumors, 1-year)	52% (T2 tumors, 2-year)
Woody, 2015 ⁹⁷	40 (all >5 cm)	5.6	Most commonly 50 Gy in 5 fx	10.8	91.2% (18-month)	59.7% (18-month)

AE, adverse event; F/U, follow-up; LC, local control; N/R, not reported; OS, overall survival; pts, patients; RT, radiation therapy; SBRT, stereotactic body radiation therapy

Table 4: Series reporting results for SBRT for patients without tissue confirmation

Author	N	Dose	Median F/U (mos)	LC	OS
Inoue, 2009 ¹¹⁰	115	30-70 Gy in 2-10 fx (median BED 106 Gy [range 56-141 Gy])	14	96.6% (≤ 2.0 cm), 94.7% (> 2.0 cm) (at median follow-up of 14 months)	89.8% (≤ 2.0 cm), 60.7% (> 2.0 cm) (3-year)
Verstegen, 2011 ^{113,114}	382	60 Gy in 3-8 fx	31	91.2% (3-year)	55.4% (3-year)
Takeda, 2012 ³	58	50 Gy in 5 fx (peripheral), 40 Gy in 5 fx (central)	20.2	80% (3-year)	54% (3-year)
Taremi, 2012 ¹⁰⁹	28	48 Gy in 4 fx or 54-60 Gy in 3 fx (peripheral), 50 Gy in 10 fx or 60 Gy in 8 fx (central)	19.1	87% (1-year)	84% (for the entire 108-pt cohort, no difference between pts with and w/o tissue confirmation, 1-year)
Fischer-Valuck, 2015 ¹¹¹	23	48-60 Gy in 4-5 fx	29	94.1% (3-year)	58.9% (3-year)

AE, adverse event; F/U, follow-up; LC, local control; N/R, not reported; OS, overall survival; pts, patients; w/o, without; SBRT, stereotactic body radiation therapy

Table 5: Criteria from Martini and Melamed for multiple primary lung cancers¹¹⁹

Metachronous	Different histology	
	Same histology if:	Prolonged interval between tumors (typically > 2 years)
		Development from separate area of carcinoma in situ
		Different lobes with: <ol style="list-style-type: none"> 1. No shared lymph node basins 2. No extra-thoracic metastasis
Synchronous	Different histology	
	Same histology if:	Development from separate area of carcinoma in situ
		Different lobes with: <ol style="list-style-type: none"> 1. No cancer in shared lymph node basins 2. No extra-thoracic metastasis

Table 6: Series reporting results for SBRT for synchronous MPLC

Author	N	Treatment	Dose	Median F/U (mos)	AE \geq Gr 3	LC (SBRT)	OS
Sinha, 2006 ¹²⁹	8	N/R	48-66 Gy in 3-4 fx	18.5	0%	93% (1.5-year)	100% (1.5-year)
Creach, 2012 ¹²⁷	15	3 surgery + SBRT 12 SBRT x 2	40-54 Gy in 3-5 fx	24	0%	90% (at follow-up)	27.5% (2-year)
Griffioen, 2014 ¹²⁶	62	56 surgery + SBRT 6 SBRT x 2	54-60 Gy in 3-8 fx	44	4.8%	84% (2-year)	56% (2-year)
Kumar, 2014 ¹³⁰	26	SBRT x 2	30-60 Gy in 1-8 fx	12	4%	96% (at follow-up)	N/R
Shintani, 2014 ¹²⁸	18	3 surgery + SBRT 15 SBRT x 2	48-60 Gy in 4-10 fx	34.3	11%	78% (3-year)	69% (3-year)

AE, adverse event; F/U, follow-up; LC, local control; MPLC, multiple primary lung cancer; N/R, not reported; OS, overall survival; SBRT, stereotactic body radiation therapy

Table 7: Series reporting results for SBRT for metachronous MPLC

Author	N	Median interval (months)	Treatment	Dose	Median F/U (mos)	AE \geq Gr 3	LC (SBRT)	OS
Creach, 2012 ¹²⁷	48	N/R	46 surgery + SBRT 2 SBRT x 2	40-54 Gy in 3-5 fx	24	0%	92% (at follow-up)	68% (2-year)
Griffioen, 2014 ¹⁴²	107	48	98 surgery + SBRT 9 CRT + SBRT	54-60 Gy in 3-8 fx	46	3.7%	89% (3-year)	60% (3-year)
Hayes, 2015 ¹⁴¹	17	115	17 surgery + SBRT	48-60 Gy in 3-8 fx	18.3	N/R	93% (2-year)	88% (2-year)

AE, adverse event; F/U, follow-up; fx, fraction; LC, local control; MPLC, multiple primary lung cancer; N/R, not reported; OS, overall survival; SBRT, stereotactic body radiation therapy

Table 8: Series reporting on SBRT for metachronous second primary lung cancer arising after pneumonectomy

Author	N	Pathologic confirmation	Dose	Median F/U (mos)	AE \geq Gr 3	LC (SBRT)	OS
Haasbeek, 2009 ¹⁴⁶	15	20%	54-60 Gy in 3-8 fx	16.5	13%	100% (2-year)	91% (2-year)
Simpson, 2014 ¹⁴⁵	2	50%	48 Gy in 4 fx, 50 Gy in 5 fx	N/R	50%	100%	50%
Thompson, 2014 ¹⁴⁴	13	21%	48 Gy in 4 fx	24	15%	100%	61% (2-year)
Testolin, 2015 ¹⁴⁷	12	0%	25-48 Gy in 1-4 fx	28	0%	64% (2-year)	80% (2-year)

AE, adverse event; F/U, follow-up; LC, local control; N/R, not reported; OS, overall survival; SBRT, stereotactic body radiation therapy