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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 years' 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 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 cm, and they were unable to undergo surgical resection due to concurrent medical co-morbidities. 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 ≥100 Gy10 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 lesions[20-22] 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 fistulas[31] 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

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 based on 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. 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.

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 Database[44] and National Cancer Database (NCDB),[45] all report operative mortality following lobectomy of 1.5-2.0 %. In the US, 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, all 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 minimizes 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

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 3D 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 0813[82] 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.

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 Institute[105] 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 SBRT[95] or comparing SBRT to surgical resection[59] 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 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 4 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 are 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 1,294 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 $\geq$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 dispositioned 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 grand 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 Gy_{10} 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 $\geq$100 Gy_{10} 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

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 2 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 were 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 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 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 all 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

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 3D-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 3D-CRT/IMRT UDGLDWLRQ Rf 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 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 five 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, BED_{10} 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 ≥ 30%,[170] FEV1 ≤ 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 variable in the dose delivered, and only 2 patients received both initial and salvage SBRT courses with a BED of >100 Gy_{10}. The follow-up was not reported past 5 months. It is difficult to draw conclusions on a limited study.

The Cleveland Clinic reported on 10 patients who received SBRT for salvage therapy for isolated local failures.[175] In all 10, the repeat SBRT course had a BED of >100 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 ≥100 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 and/or brachytherapy. 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, and provide 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 ≥ 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 =/>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 ≥ 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 cancers[119]

Metachronous	Different histology	
	Same histology if:	Prolonged interval between tumors (typically > 2 years)
		Development from separate area of carcinoma in situ
		Different lobes with: 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: 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 ≥ 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 ≥ 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≥ 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