

REVIEW ARTICLE

Stereotactic body radiotherapy in ultracentrally located lung tumors

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Abstract

Stereotactic body radiotherapy (SBRT) is a highly conformal radiotherapy technique that delivers high doses of radiation per fraction, typically in 1 – 5 fractions. It is a standard treatment option for patients with early-stage non-small cell lung cancer that is peripherally located, for those who are medically inoperable, or for patients who do not opt for surgery. Similarly, SBRT is considered an effective treatment option for oligometastatic lung tumors. However, in the case of ultracentrally located lung tumors—tumors situated close to the central airway and mediastinal region—there is an increased risk of severe toxicities (grade 4 – 5) due to the dose tolerances of the surrounding organs at risk. The definition of ultracentrally located lung tumors remains unclear. Some studies define an ultracentral lung tumor as one in which the gross tumor volume directly involves the proximal bronchial tree or trachea, while others define it as the planning target volume (PTV) that includes the trachea or main bronchial system. In addition, some studies consider tumors whose PTV touches or overlaps with the central bronchial tree, esophagus, pulmonary vein, or pulmonary artery as ultracentral. In addition, the optimal SBRT regime and organ-at-risk dose limitations for ultracentral tumors have yet to be clearly established. The aim of this review is to explore and discuss the role of SBRT in the treatment of ultracentrally located lung tumors.

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1. Introduction

Stereotactic body radiotherapy (SBRT) is a conformal radiotherapy technique applied in 1 – 5 fractions with high doses per fraction.¹ Although many lung cancer patients are diagnosed at a locally advanced or metastatic stage, the incidence of early-stage lung cancer has recently increased due to more frequent screening.² Lung metastasis from other primary tumors is common; in one study, lung metastases were detected in 50% of the autopsies performed on patients who died from cancer.³ As is well-known, surgery is the preferred treatment for both early-stage lung cancer and oligometastatic disease. However, the majority of these patients are heavy smokers, with compromised lung function and cardiac reserves that often preclude surgery. In addition, some patients refuse surgery due to concerns about surgery-related morbidity and mortality risks. For these reasons, SBRT is considered the preferred

local treatment for patients who are medically inoperable or decline surgery.

Toxicity rates in SBRT vary depending on the tumor's location. Peripheral tumors, being farther from organs at risk, generally exhibit lower toxicity rates. However, the risk of grade 3 or higher toxicity increases in central or ultracentral tumors. Different fractionation regimens are used in SBRT studies, and their oncological outcomes are often compared by calculating BED_{10} values. A previous study has shown that $BED_{10} \geq 100$ is associated with improved oncological outcomes.⁴ In a study of ultracentral early-stage lung cancers, a 15% incidence of grade 5 toxicity was reported, even with hypofractionated regimens.⁵ The therapeutic index in radiotherapy is important; the goal is to determine the most effective dose that improves oncological outcomes while minimizing serious side effects. While dose regimes that achieve good oncological results within acceptable toxicity limits have been established for peripherally or centrally located tumors, there is still no standard SBRT regimen for ultracentral tumors.^{6,7}

In addition, the definition of “ultracentral” is still unclear. Although there is some consistency among studies, no standard definition has been universally accepted. Some studies define an ultracentral tumor as one involving the proximal bronchial system or trachea, while others define it based on the planning target volume (PTV) involving the main bronchial system or trachea. Recently, a relative consensus was reached in the SUNSET study, where an ultracentral tumor was defined as a PTV that contacts or involves the central bronchial system, esophagus, pulmonary artery, or pulmonary vein.^{5,8,9}

Ultracentral tumors are associated with a high risk of serious side effects due to their proximity to organs at risk and the high SBRT dose required for effective treatment. This elevated risk has led clinicians to prefer hypofractionated regimens for treating ultracentral tumors. For these reasons, a standard SBRT regimen for ultra-central tumors remains undefined, and existing studies on this topic are limited and involve small patient cohorts. In this review, the role of SBRT in the treatment of ultracentrally located tumors is discussed in light of the current literature.

2. Literature review method

A comprehensive literature search was conducted using the PubMed database with a wide range of keywords, including “Lung cancer,” “oligometastatic,” “lung tumors,” “SBRT,” “ultracentral,” “toxicity,” “Safety,” “Efficacy,” “survival,” and “local control.”

Studies were included in the review if they provided information on the SBRT dose schedule or BED_{10} value in

the context of ultracentral lung tumors, along with follow-up periods, toxicity rates, and oncological outcomes in patients treated with SBRT for ultracentrally located non-small cell lung cancer (NSCLC) or lung metastases at any stage. Only studies with full texts available were included in the review. Database searches were supplemented by manual searches of manuscript references. The inclusion criteria were as follows: (i) the study focused on ultracentrally located lung tumors (either primary or metastatic), (ii) patients were treated with SBRT, (iii) the study included information on SBRT dosing schedules or BED_{10} values, and (iv) toxicity rates and oncological outcomes were reported.

A total of 14 peer-reviewed publications, published from 2017 to 2024, are presented in detail in this review. Of these, 11 studies are retrospective, two studies are prospective, and one is a guideline containing systematic review and meta-analysis results.

3. SBRT regimen used in ultracentral tumors: Oncological results and toxicity

SBRT presents significant challenges for ultracentrally located lung tumors due to their proximity to organs at risk and the associated risk of high-grade side effects. The tolerance of these organs—especially the bronchus, esophagus, pulmonary artery, and vein—to high doses per fraction is not well understood. The experience with ultracentral SBRT is primarily based on a small retrospective study. Despite using regimens with lower BED_{10} values and implementing strategies to protect organs at risk, fatal side effects have been observed in this patient group. The variation in the definition of “ultracentral” across studies creates heterogeneity and complicates the determination of the most appropriate SBRT regimen. Due to concerns about the potential for serious side effects, hypofractionated regimens are often preferred for these patients, and the studies conducted typically involve small patient cohorts. At the same time, the patient groups in these studies are diverse, consisting of individuals with early-stage lung cancer, those receiving salvage treatment for recurrent lung cancer, and patients with oligometastatic and/or polymetastatic disease. The dosage regimens used are heterogeneous, leading to non-standard BED_{10} values. New prospective studies are being added to the body of retrospective research that initially involved a small number of cases. Future phase III randomized multicenter studies, informed by existing research, will help clarify the definition of “ultracentral” and establish standard dose regimens for this patient group.

Early studies of ultracentral SBRT in the literature include its use in salvage treatments for non-metastatic recurrent lung cancer previously treated with conventional

fractionated radiotherapy. In 2017, Repka *et al.*¹⁰ administered a median dose of 35 Gy (range: 25–45 Gy) in five fractions to 20 patients diagnosed with ultracentral recurrence of lung cancer. They reported local control (LC) and overall survival (OS) rates of 66.7% and 77.8%, respectively, at a median follow-up of 12 months. Notably, grade 5 toxicity (hemoptysis) developed in only one patient.

In 2019, the number of SBRT studies on ultracentrally located lung tumors increased, though the studies were quite heterogeneous, including cases of locally advanced lung cancer. One study involving 51 patients diagnosed with locally advanced or metastatic NSCLC applied a total of 35 Gy SBRT in five fractions, considering tumors that touched or overlapped the PTV proximal bronchial system or trachea as ultracentral. The patient population included individuals with short expected survival times, such as those unable to tolerate conventional fractionated chemoradiotherapy, patients with metastatic disease, or those with postoperative recurrence. During a median follow-up period of 17 months, the median LC was 17 months for Stage II patients and 11 months for those with post-operative recurrence or Stage IV disease. Grade 3 and higher toxicity rates have been reported at 9.8%, with Grade 5 toxicity rates at 3.9%.¹¹

In another study, SBRT was applied to 15 of 41 stage III NSCLC patients with ultracentrally located tumors, while the remaining 29 patients received conventional fractionated radiotherapy. At a median follow-up of 16.5 months, 1-year LC and OS were found to be 60.8% versus 37.5% and 17 versus 18 months in the SBRT and conventionally fractionated arms, respectively. The rates of Grade 3 or higher toxicity were reported as 20% in the SBRT and 24.1% in the conventional fractionated arms. No statistically significant difference was found in either oncological outcomes or toxicity rates, indicating that larger prospective studies are needed to draw definitive conclusions.¹² Park *et al.*¹³ applied a regimen of 50 – 60 Gy in 10 fractions to eight NSCLC patients, utilizing a more hypofractionated regimen compared to standard SBRT. This study involved a heterogeneous group, including patients with early-stage lung cancer, local or regional recurrence, and those with metastasis who planned for salvage treatment. The median follow-up period was 8.6 months, during which no Grade 3 or higher toxicity was observed, and a complete response rate of 62.5% was reported.

As the years progressed, more studies began to explore SBRT regimens with higher BED₁₀ values, encompassing more heterogeneous patient groups, including those with early-stage lung cancer.

In a study involving 109 oligometastatic patients, Loi *et al.*¹⁴ included patients with ultracentral PTV overlapping with the central bronchial system, pulmonary artery or vein, or esophagus. The median SBRT BED₁₀ value was 105 Gy (range: 75 – 132 Gy), and the study evaluated both LC and toxicity. At a median follow-up of 17 months, the 2-year LC rate was 87%. The study found that when 95% of the PTV received 85% of the prescribed dose and the GTV volume was <90 cc, the LC rate increased significantly. Toxicity rates were 20%, with Grade 5 toxicity observed in two patients. The study represents a more homogeneous group with a larger patient cohort compared to previous literature, and the median BED₁₀ value is in line with the recommendations in Onishi's study.⁴

In another study of 74 patients, which included both localized recurrence and metastatic disease, the definition of “ultracentral” was slightly different. Cases in which the PTV overlapped the trachea, left or right main bronchus, intermediate bronchus, lobe bronchi, heart, or esophagus were considered ultracentral, while mediastinal main vessels were not included in this definition. The radiotherapy dose was heterogeneous, with hypofractionated regimens ranging from 4.5 to 10 Gy per fraction administered in 5 – 10 fractions. The median BED₁₀ value is 82 Gy (range: 28 – 105 Gy). The 1- and 2-year LC rates are 96.7% and 87.6%, respectively. Median progression-free survival (PFS) was 12 months, while the median OS was 31 months. No toxicity was observed in 59.5% of the patients, while grade 3 toxicity occurred in 2.7%. No Grade 4 or 5 toxicity was reported.¹⁵ The absence of grade 4 – 5 toxicity may be due to the relatively low BED₁₀ values used in the SBRT regimens. Although the 2-year LC rates are similar to those in Loi *et al.*'s study, the study also included early-stage lung cancer cases, where better oncological results are expected compared to oligometastatic disease.

In the study of Lodeweges *et al.*,¹⁶ involving a heterogeneous group of 72 patients, the definition of “ultracentral” was based on PTV touching or involving the main bronchus, trachea, or esophagus. A dose of 60 Gy in 12 fractions was administered, with a BED₁₀ value of 90 Gy. At a median follow-up of 19 months, the 1- and 2-year LC rates were 98% and 85%, respectively, while the 1- and 2-year OS rates were 77% and 52%. Grade 3 and higher toxicity rates were 21%, and Grade 5 toxicity (bronchopulmonary hemorrhage) was observed in 14% of the patients. The study determined that a mean dose of BED₃ <91 Gy received by the main bronchus significantly reduced the rate of grade 3 and higher toxicity. Salvestrini *et al.*¹⁷ evaluated 126 ultracentral tumors, including T1-4N0M0 NSCLC and oligometastatic disease. They defined an ultracentral tumor as one where the PTV touched or involved the trachea, main bronchial

system, intermediate, upper, middle and lower lobe bronchi, or esophagus. The SBRT dose ranged from 45 to 60 Gy in 5 – 7 fractions, with a median BED₁₀ value of 92 Gy (range: 83 – 132 Gy). At a median follow-up of 23 months, the 1- and 2-year LC rates were 86% and 78%, respectively. The median PFS was 29.3 months, and the median OS was 16 months. While acute Grade 4 and 5 toxicity was not observed, acute Grade 3 toxicity was reported in one patient, and chronic Grade 3 toxicity was observed in four patients. In the study by Lodeweges *et al.*, the median BED₁₀ was 90 Gy, with Grade 5 toxicity observed in 14% of patients. In contrast, in the study by Salvestrini *et al.*, the median BED₁₀ value was 92 Gy, and no Grade 4 or 5 toxicity was observed. These findings suggest that SBRT regimens are crucial for assessing toxicity, and that various factors beyond BED₁₀ values may affect toxicity. Both patient-related clinical characteristics (such as age, performance status, and comorbidities) and dosimetric characteristics (such as the maximum dose received by organs at risk or the dose received by a certain volume) may increase the risk of developing toxicity.

Wang *et al.*¹⁸ conducted a study involving 58 patients diagnosed with T1-3N0 lung cancer, defining “ultracentral” as tumors that touch or involve the proximal bronchial system, trachea, esophagus, heart, pulmonary artery, or vein, and are within 2 cm of the bronchial tree. The SBRT dose was 56 Gy in 6 – 8 fractions, with a median BED₁₀ value of 100.8 Gy (range: 95.2 – 111.5 Gy). The follow-up period in the study was considerably longer compared to other studies, with a median of 57 months. The 1-year, 2-year, and 5-year OS rates were 94.7%, 75%, and 45%, respectively. The study found a statistically significant relationship between PTV volume and OS, with PTVs below 53 cc associated with longer OS. The incidence of Grade 3 and higher toxicity was 3.5%, with one patient dying from unexplained sudden and severe hemoptysis.

In another study, toxicity was retrospectively evaluated in detail in 88 patients who underwent SBRT for tumors located in the proximal airway or where the PTV overlapped with the esophagus. The SBRT dose was heterogeneous, with regimens applied in 5 – 15 fractions, and a BED₁₀ value of ≥84 Gy. The median follow-up period was 19.5 months, and Grade 3 or higher toxicity was observed in 22% of the patients. Six patients developed Grade 3 radiation pneumonitis, four patients developed Grade 3 esophagitis, and two patients developed tracheoesophageal fistula. Mean lung dose and esophageal maximum dose (D_{max}) were found to be statistically significantly associated with the development of toxicity.¹⁹

In more recent studies, the study by Rim *et al.*,²⁰ published in 2024, evaluated 20 primary lung cancers and

lung cancer recurrences. The definition of “ultracentral” was based on the PTV touching or including the proximal bronchial tree. The SBRT dose was planned at 45 – 60 Gy in 10 fractions, with a median BED₁₀ value of 82.5 Gy. At a median follow-up of 15.8 months, the 1- and 2-year OS rates were 79.4% and 62.4%, respectively. The LC rates were 87.1% and 76.2% at 1 and 2 years, respectively. Grade 2 toxicity was observed in four patients, and one patient died due to Grade 5 massive hemoptysis. No grade 3 or 4 toxicity was observed.

Another retrospective study published in 2024, which included the largest number of patients to date, evaluated 154 patients with 162 ultracentral tumors. The patient cohort included both curative and palliative cases. Cases where the PTV overlapped the central bronchial tree and/or esophagus were considered ultracentral. The most commonly used SBRT regimen was 50 Gy in five fractions, though doses varied between 30 and 55 Gy in five fractions, with a median BED₁₀ value of 85.5 Gy. The median follow-up period was 21.5 months, with the primary endpoint of the study being toxicity. The 3-year rate of serious (≥ grade 3) toxicity was 9.4%, and one patient died from pneumonia potentially related to treatment. Factors affecting the development of serious toxicity included the size of the PTV, increased PTV V95%, and lung V5 and V20. Median OS and PFS are 44 and 8.8 months, respectively, and the 3-year local failure rate is 14%.²¹

The SUNSET study is a multicenter prospective study involving ultracentral SBRT, including 30 cases of T1-3N0 lung cancer from five centers. PTV was considered ultracentral if it touched or included the proximal bronchial tree, esophagus, pulmonary artery, or vein. The SBRT dose was standardized among patients, set at 60 Gy in eight fractions. During a median follow-up of 37 months, Grade 3 or higher toxicity was observed in two patients, and one patient with an interstitial lung disease pattern on computed tomography died from grade 5 pneumonia. The 3-year results showed distant control at 85.9%, regional control at 96.4%, and LC at 89.6%. The 3-year OS and PFS were 72.5% and 66.1%, respectively. The maximum allowable hotspots in the SUNSET study were 120% of the prescribed dose. According to the study, favorable oncological outcomes with acceptable toxicity can be achieved by adhering to the maximum allowed hot spots and using a 60Gy/8 fractions dose regimen.²²

In the multicenter prospective study conducted by Lindberg *et al.*,²³ “ultracentral” was defined as a tumor located ≤1 cm of the proximal bronchial tree. The SBRT dose used was 7 Gy/8 fractions, and a total of 65 patients were included in the study. The patient cohort consisted of individuals with primary lung cancer and metastatic

disease. The patients were divided into two arms: Arm A included 39 patients who met the definition of ultracentral, and arm B included 26 patients with centrally located tumors that did not meet the ultracentral criteria). At a median follow-up of 24 months, the 2-year OS rate was 83%. Grade 3 – 5 toxicity was observed in 22 patients, and 10 patients died due to treatment-related toxicity. The study highlighted that minimizing the maximum dose received by 0.2 cc of the main bronchus and trachea could reduce the risk of Grade 5 bronchopulmonary hemorrhage.

A summary of the above-mentioned studies is available in [Table 1](#).

In 2023, the International Stereotactic Radiosurgery Society (ISRS) published a guideline based on a systematic review and meta-analysis of 27 studies. In all studies, PTV involvement in the proximal bronchial tree was considered indicative of an ultracentral tumor. The most commonly used SBRT dose regimens were 60 Gy/12 fractions, 60 Gy/8 fractions, and 50 Gy/5 fractions. BED₁₀ value was identified as the most important parameter affecting the 1-year LC rate, with 1- and 2-year LC rates of 92% and 89%, respectively. Across all studies, the Grade 3 – 4 toxicity rate was 6%, primarily manifesting as pneumonitis, while the Grade 5 toxicity rate was 4%, with hemoptysis being the most common cause. ISRS identified several risk factors for fatal toxicity, including concurrent targeted therapy, use of anticoagulants, interstitial lung disease, and the presence of an endobronchial tumor. Based on their findings, the ISRS made the following recommendations:

- SBRT regimens of 60 Gy/8 fractions or 60 Gy/15 fractions are recommended
- Hot spots should not be located on critical organs, and even within PTV, D_{max} should be <150%.
- Breath monitoring systems should be used to minimize the internal target volume.
- The D_{max} for the proximal bronchial tree should be kept <133 – 150 Gy (BED₃ or EQD2₃ < 80 – 90 Gy).
- If endobronchial involvement is present, non-ablative doses should be used.
- If possible, anti-platelets or anticoagulants should be discontinued during SBRT. If discontinuation is risky, the D_{max} dose of the proximal bronchial tree should be reduced, or non-SBRT regimens should be chosen.
- SBRT should not be administered simultaneously with targeted therapies or immunotherapies. Immunotherapy should be discontinued 2 – 3 days before SBRT, and vascular endothelial growth factor inhibitors should be discontinued 3 – 4 weeks before treatment.
- For endobronchial tumors, non-SBRT regimens such as 60 Gy/15 fractions should be used, and the proximal

bronchial tree D_{max} should be kept <100 Gy (BED₃ or EQD2₃ <60 Gy).

- In patients with interstitial lung disease, the risk of pneumonia is significantly increased, and V20 should be kept <10%.²⁴

Although there is still no universally accepted definition for ultracentral tumors, the definition in the SUNSET study is widely regarded as acceptable, given that it is based on a prospective, multicenter study. The literature indicates that SBRT can achieve good oncological outcomes in ultracentral tumors, whether in early-stage cases, salvage treatments for recurrence, or oligometastatic disease. However, due to the proximity of these tumors to the organs at risk, SBRT regimens with acceptable toxicity rates should be preferred. The most common Grade 3 and higher toxicities include pneumonia and hemoptysis, so careful attention should be paid to doses received by the proximal bronchial tree and lung. At the same time, it is crucial to be aware of the patient's medications and comorbidities to minimize the risk of Grade 5 toxicity.

4. Recommendations for a standard treatment regimen

Studies on ultracentral lung tumors are limited, and due to their location, comparisons of different treatment modalities are insufficient. Consequently, the standard treatment for ultracentral tumors remains unclear. The treatment and follow-up of these patients should be managed in a multidisciplinary setting. It is important for radiation oncologists, pulmonologists, thoracic surgeons, radiologists, nuclear medicine specialists, and medical oncologists to collaboratively determine the most appropriate, personalized treatment plan for each patient. Accurate clinical staging is vital for making informed treatment decisions. This requires the expertise of a competent radiologist and nuclear medicine specialist to determine the clinical stage of the tumor, its proximity to organs at risk, the degree of invasion, and the lymph node status. Thoracic surgeons should determine resectability, perform surgical staging, and manage pulmonary resection. An experienced pulmonologist should evaluate the patient's respiratory functions. The medical oncologist should decide on systemic treatment options (chemotherapy, immunotherapy or targeted therapies) for early-stage, recurrent, or metastatic disease. For patients who are not suitable candidates for surgery, evaluation for SBRT by a radiation oncologist is necessary, with careful selection of the appropriate SBRT regimen.

When examining studies comparing conventional fractionation versus SBRT and hypofractionation versus SBRT in early-stage lung cancer, there is evidence suggesting

Table 1. Summary of the studies included in the literature review

Study	Number of patients	Diagnosis/stage	Median SBRT dose (Gy)	Median BED ₁₀ (Gy)	Ultracentral definition	Follow-up time (month)	Oncological results (%/median)	Toxicity
Repka <i>et al.</i> ¹⁰	20	Locally advanced NSCLC	35 Gy	NA	PTV directly adjacent to the trachea, main bronchus, or esophagus	12	LC: 66.7%; OS: 77.8%	Grade 5 hemoptysis: 1 patient
Cong <i>et al.</i> ¹¹	51	Stage III/IV NSCLC	35 Gy/5 fr	59.5	GTV abutting or overlapping the trachea and PBT	17	LC: 17 months (stage II), 11 months (postoperative recurrence or stage IV)	≥Grade 3: 9.8%; grade 5: 3.9%
Park <i>et al.</i> ¹³	8	NSCLC (early stage/ recurrence/stage IV)	50 – 60 Gy/10 fr	75 – 96	Tumors abutting or invading the PBT	8.6	CR: 62.5%	No grade 3 or higher toxicity
Loi <i>et al.</i> ¹⁴	109	Oligometastatic	NA	105	PTV overlapped with the central bronchial system, pulmonary artery or vein, or esophagus	17	2-year LC: 87%	Toxicity rate: 20%; grade 5: 2 patients
Guillaume <i>et al.</i> ¹⁵	84	NSCLC (recurrence/ stage IV), stage IV (lung metastases)	4.5 – 10 Gy/5–10 fr	82	PTV overlapped the trachea, left or right main bronchus, intermediate bronchus, lobe bronchi, heart or esophagus	25	1- and 2-year LC: 96.7% and 87.6%; PFS: 12 months; OS: 31 months	Grade 3: 2.7%; no grade 4 – 5 toxicity
Lodeweges <i>et al.</i> ¹⁶	72	NSCLC (stage I–IV)	60 Gy/12 fr	90	PTV abutting or overlapping the main bronchi, trachea and/ or esophagus	19	1- and 2-year LC: 98% and 85%; 1-and 2- year OS: 77% and 52%	≥Grade 3: 21%; grade 5: 14%
Salvestrini <i>et al.</i> ¹⁷	126	T1-4N0M0 NSCLC and oligometastatic	45 – 60 Gy/5–7 fr	92	PTV touching or involving the trachea, main bronchial system, intermediate, upper, middle and lower lobe bronchi or esophagus	23	1- and 2-year LC: 86% and 78%; PFS and OS: 29.3 and 16 months	Acute grade 3: 1 patient; chronic grade 3: 4 patients
Wang <i>et al.</i> ¹⁸	58	T1-3N0 lung cancer	56 Gy/6 – 8 fr	100.8	Tumors that touch or include the proximal bronchial system, trachea, esophagus, heart, pulmonary artery or vein, and are within 2 cm of the bronchial tree	57	1-, 2-, and 5-year OS: 94.7%, 75%, and 45%	≥Grade 3: 3.5%
Wang <i>et al.</i> ¹⁹	88	NSCLC (early stage, recurrence), stage IV (lung metastases)	NA	≥100	GTV abutted proximal airways, or PTV overlapped esophagus	19.5	1- and 2-year rates of local failure: 12.2% and 19.0%; OS: 38.6 months; 1-, 2-, and 3-year OS: 78.6%, 64.5%, and 53.1%	≥Grade 3: 22%

(Contd...)

Table 1. (Continued)

Study	Number of patients	Diagnosis/stage	Median SBRT dose (Gy)	Median BED ₁₀ (Gy)	Ultracentral definition	Follow-up time (month)	Oncological results (%/median)	Toxicity
Rim <i>et al.</i> ²⁰	20	Primary lung cancers and lung cancer recurrences	45 – 60 Gy /10 fr	82.5	PTV touches or includes the proximal bronchial tree	15.8	1- and 2-year OS: 79.4% and 62.4%; 1- and 2-year LC: 87.1% and 76.2%	Grade 2: 4 patients; grade 5: 1 patient
Li <i>et al.</i> ²¹	154	NCSLC (stage I–IV), stage IV (lung metastases)	30 – 55 Gy/5 fr	85.5	PTV overlapping the central bronchial tree and/or esophagus	21.5	3-year local failure: 14%; OS: 44 months; PFS: 8.8 months	≥Grade 3: 9.4%; grade 5: 1 patient
Giuliani <i>et al.</i> ²²	30	T1-3N0 lung cancer	60 Gy/8 fr	105	PTV touched or included the proximal bronchial tree, esophagus, pulmonary artery, or vein	37	3-year distant, regional, local control: 85.9%, 96.4%, 89.6%; 3-year OS: 72.5%; 3-year PFS: 66.1%	≥Grade 3: 2 patients; grade 5: 1 patient
Lindberg <i>et al.</i> ²³	65	Primary lung cancer and lung metastasis	7 Gy/8 fr	95.2	Tumor being ≤1 cm away from the proximal bronchial tree	24	2-year OS: 83%	Grade 3 – 5: 22 patients (grade 5: 10 patients)

Abbreviations: CR: Complete response; fr: Fraction; GTV: Gross tumor volume; LC: Local control; NA: Not available; NCSLC: Non-small cell lung cancer; OS: Overall survival, PBT: Proximal bronchial tree; PFS: Progression-free survival; PTV: Planning target volume; SBRT: Stereotactic body radiation therapy.

that SBRT contributes to both LC and OS.^{25–27} However, information regarding treatment options for ultracentral lung tumors is very limited. Until randomized studies specifically addressing ultracentral tumors are conducted, findings from studies on peripherally or centrally located tumors can provide some guidance. Prospective randomized studies are needed to identify regimens with the most appropriate therapeutic index for ultracentral tumors.

To establish a standardized SBRT regimen, the definition of “ultracentral” must first be clarified. The definition used in the SUNSET study could serve as a basis because it is derived from a prospective, multicenter study. However, experts in the field (such as radiation oncologists, pulmonologists, radiologists, and thoracic surgeons) should collaborate to develop a universally accepted standard definition.

Once a standard definition is established, the effectiveness and safety of treatment should be demonstrated through multicenter phase I, phase II, and phase III prospective randomized studies, informed by existing retrospective studies. Sharing the SBRT experiences of various centers, even with small patient numbers, could be valuable for dose escalation studies.

It is important to recognize that even if the total SBRT dose is the same, the radiobiological effect will differ depending on the number of fractions and the dose per fraction. For example, the radiobiological effects of 50 Gy/5

fractions versus 50 Gy/10 fractions are not equivalent. Although the total dose in different studies might be similar, varying BED₁₀ values contribute to increased heterogeneity in outcomes. Accounting for BED₁₀ values in studies with different dosing schedules will help reduce this heterogeneity.

In all studies, especially those evaluating survival, early-stage lung cancer and oligometastatic lung tumors must be assessed separately. Unfortunately, due to the low number of ultracentrally located cases treated with SBRT, most of the studies have combined early-stage lung cancer, recurrent lung cancer, and oligometastatic lung tumors in their analyses. Multicenter studies can help address this issue. By pooling cases from multiple centers, early-stage lung cancer, recurrent lung cancer, and metastatic cases can be evaluated separately. As prospective studies on this topic become more widespread, the standardization of SBRT dosing schedules may reduce the heterogeneity between patient groups.

Proton therapy offers several dosimetric advantages over photon therapy. These advantages include a dosimetric profile characterized by a low integral dose, maximum dose accumulation in the tumor through the Bragg peaks, and a negligible exit dose. These properties of proton therapy can reduce the dose to organs at risk near the target volume, thereby potentially lowering the risk of serious toxicity. Proton SBRT is recommended for dose

escalation in early-stage lung cancer, particularly in cases with node-negative NSCLC and tumors ≥ 5 cm, central and ultracentral tumors, relapsed or new primary early-stage lung cancer, cases with a history of radiotherapy in relapse/persistent or oligoprogressive/oligometastatic locally advanced lung cancer, and in patients with interstitial lung disease/idiopathic pulmonary fibrosis, as well as those receiving simultaneous immunotherapy with SBRT.²⁸ A study included 27 patients and 29 lung tumors treated with stereotactic body proton therapy (SBPT), involving early-stage lung cancer, recurrent lung cancer, and metastatic lung cancer. The indications for SBPT included a central/ultracentral location in 69% of patients, severe chronic obstructive pulmonary disease in 48.1%, re-radiotherapy in 44.4%, pulmonary fibrosis in 22.2%, and large tumor size in 18.5%. The SBRT regimen selected involved doses of 5 Gy or more per fraction, with the total number of fractions being eight or fewer. Two patients (7.4%) with interstitial lung disease who were receiving oxygen therapy developed $>$ Grade 2 pulmonary toxicity (one Grade 3, one Grade 5). No acute or late \geq Grade 2 toxicities were associated with esophagitis, cardiac injury, airway injury, pulmonary fibrosis, bronchopulmonary hemorrhage, or brachial plexopathy.

The 3-year actuarial rates of LC were 89% for early-stage NSCLC, 100% for locally recurrent NSCLC, and 43% for metastatic patients. The 3-year actuarial rates of regional control were 89%, 67%, and 86%,²⁹ respectively. According to the study, SBPT has a favorable toxicity profile and appears to be an effective approach for treating most high-risk tumors without requiring dose reduction. However, due to the scarcity of proton centers, its widespread use is currently unlikely.

Four-dimensional computed tomography simulation should be performed to narrow the integral target volume and protect organs at risk by reducing the PTV margin. If possible, techniques such as phase gating or breath-hold should be used. In ultracentral tumors located close to organs at risk, these techniques can help reduce the incidence of serious toxicity.

Due to the location of ultracentral tumors, the application of SBRT is rare, with clinicians often preferring hypofractionated or conventionally fractionated regimens due to concerns about toxicity. The lack of phase III randomized studies and dose escalation studies regarding the definition of ultracentral and SBRT dose schedules in ultracentral tumors has led to a lack of standardization. At present, there is only one guideline on this subject, based on a systematic review and meta-analysis, along with a limited number of retrospective studies with small patient cohorts and even fewer prospective studies. The purpose

of this review is to summarize the existing information and highlight the need for further prospective studies. The limitations of this review include the absence of a meta-analysis and the fact that only systematically screened studies were summarized and interpreted.

5. Stereotactic body radiation therapy from the patient's perspective

Patients make treatment decisions based on their personal circumstances and their doctor's recommendations. For lung cancer, treatment options often include a combination of surgery, chemotherapy, and radiotherapy. The risks or benefits of each treatment vary, and the choice of treatment is typically guided by the stage and location of the tumor, as well as the patient's overall health and comorbid conditions. However, these treatments can significantly affect the patient's quality of life during follow-up. In a survey of 225 participants, participants preferred minimally invasive surgery followed by SBRT for hypothetical lung cancer treatments, with thoracotomy being the least favored treatment method. The type of treatment and the risk of disease recurrence were identified as the most important factors influencing their decisions. In addition, major complications and the distance to the treatment center were significant factors affecting the treatment choice.³⁰ According to this survey, patients prefer the most effective treatment for their cancer, with the lowest complication rate and the least possible invasive approach, ideally at a health-care facility close to their home.

Although there is increasing interest in SBRT, particularly as recent data support similar LC and OS outcomes to surgery in medically operable patients, lobectomy remains the standard treatment in those who are operable. For inoperable patients, SBRT offers a more comfortable, less invasive, and less morbid treatment. SBRT offers inoperable patients the potential for better disease control and life expectancy compared to no treatment, and it may also improve patient-reported physical symptoms and quality of life.³¹

In one study, patients undergoing SBRT were asked about their knowledge of the treatment and how the SBRT process compared to their expectations. Patients who had previously undergone surgery for Stage I NSCLC were also asked to compare their experiences with SBRT versus surgery. Before their radiation oncology consultation, 56% of patients were unaware of SBRT. After consultation, 98.9% believed that SBRT was at least as effective as surgery. In addition, 92.3% of patients reported experiencing fewer side effects than they had expected, 59.3% felt that SBRT was more beneficial, and 87.9% reported that SBRT caused less anxiety. All patients who had undergone

previous lung surgery reported easier recovery and less treatment-related stress with SBRT compared to surgery. Overall, 79.5% of patients expressed greater satisfaction with SBRT than with surgery, and 89.7% indicated that they would prefer SBRT over surgery for any future lung cancer treatment.³²

In another study comparing SBRT and surgery in patients diagnosed with Stage 1 NSCLC, 265 patients underwent SBRT, and 41 patients underwent surgery. Quality of life was evaluated at the beginning of treatment and at 3-, 6-, and 12-month post-treatment. The study, which compared a matched cohort, found no clinically meaningful differences in quality of life for patients following SBRT or surgery. These results suggest that surgery and SBRT are comparable treatments in terms of quality-of-life outcomes.³³

Another study further evaluated the quality of life and indirect costs of patient-reported outcomes in the ROSEL randomized control trial, which compared SBRT with surgical resection for medically operable Stage IA NSCLC. Among the 22 patients evaluated, it was found that SBRT offered significant advantages in terms of quality of life and was also less costly than surgery.³⁴

Comparing ultracentral lung SBRT with other treatment methods in terms of patient quality of life is challenging due to the small number of patients. However, studies generally show that patients tend to choose treatments that are both effective and associated with the fewest complications/side effects. In addition, for clinics without inpatient services, the distance between the health-care facility and the patient's home often influences the choice of treatment.

6. Follow-up after SBRT

The bronchial tolerance dose to high-dose radiation per fraction is not well understood, and most available data on SBRT come from small retrospective studies. Although current evidence suggests that multiple fractionation regimens may reduce the risk of serious toxicity, retrospective studies on ultracentral tumors indicate that even these regimens, with multiple fractionation and reduced BED₁₀ values, can still lead to fatal complications. However, dose measurements and constraints in treatment models are typically based on the dose calculated in the treatment planning computed tomography. Set-up uncertainties and tumor movement can cause the actual dose delivered to the bronchi to differ from the planned dose.^{35,36} High doses can result in bronchial strictures. To avoid this, dose distribution should be evaluated using state-of-the-art image guidance according to daily anatomy before each treatment fraction, preventing the formation of hot spots in critical organs at risk.

Due to the proximity of ultracentral lung tumors to organs at risk, complications such as pulmonary hemorrhage, radiation pneumonitis, esophagitis, and tracheoesophageal fistulas may develop. Lung-related side effects may be more common and severe in patients with interstitial lung disease and chronic obstructive pulmonary disease, so these patients should be followed more closely for toxicity after SBRT than other cases. Extreme caution is also warranted when treating tumors located near the esophagus, as the risk of tracheoesophageal fistula is significant. For tumors located close to the esophagus, patients should be regularly questioned about their eating habits and any swallowing difficulties during follow-up visits.

Dose limits for cardiac toxicity are primarily based on patients treated with conventional fractionation, in which large volumes of the heart are exposed to extremely low radiation doses. However, data on cardiac toxicity in small-volume, high-dose-per-fraction SBRT applications are limited, especially for ultracentrally located lung tumors where small cardiac sub-volumes are expected to receive high doses. One study suggests a relationship between the radiation dose administered to the pulmonary artery and superior vena cava in the upper heart region and an increased risk of non-cancer-related death.³⁷ Reducing the dose or protecting the pulmonary artery/superior vena cava may help decrease the risk of radiation-induced heart disease and non-cancer-related mortality. For tumors located extremely close to the heart, a cardiology consultation may be required to assess the patient's symptoms. Patients should be educated about the potential cardiac side effects, be able to recognize related symptoms, and understand the importance of seeking cardiological evaluation if symptoms arise.

After the completion of SBRT, patients should be followed up not only for their oncological responses but also for potential toxicities. Regular questioning of symptoms and detailed physical examinations are essential. Consultations with specialists, such as cardiologists or pulmonologists, should be arranged as needed based on the preliminary diagnosis of possible toxicity.

7. Conclusion

SBRT has shown promising oncological results in ultracentral lung tumors, early-stage lung cancer that is medically inoperable or for patients who decline surgery, salvage treatments for recurrent lung cancer, and in cases of oligometastatic disease. However, the therapeutic index is crucial in radiotherapy, and SBRT should be administered with an emphasis on maintaining acceptable toxicity levels. Both retrospective and prospective studies have

paved the way for the development of a standard treatment regimen. The ISRS guide serves as a valuable resource for clinicians until a standard regimen is established. To solidify standard, safe therapeutic index SBRT protocols, multicenter, prospective randomized studies with large patient cohorts are essential.

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