

ORIGINAL ARTICLE

Outcomes and toxicity of stereotactic body radiation therapy for advanced stage ultra-central non-small cell lung cancer

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Keywords

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Abstract

Background: Previous studies have documented a high incidence of toxicity in patients with ultra-central non-small cell lung cancer (UC-NSCLC) treated with stereotactic body radiation therapy (SBRT). However, these studies mainly focused on early stage patients and included small sample populations. We reviewed the outcomes and toxicity of SBRT in patients with advanced stage UC-NSCLC treated at our institution.

Methods: Fifty-one consecutive patients with advanced UC-NSCLC treated with SBRT using a regular regimen of 35 Gy administered in five fractions between December 2014 and August 2017 were reviewed. UC was defined as tumors abutting or overlapping the trachea or the proximal bronchial tree. We included locally advanced patients who were unfit or unwilling to receive conventional chemoradiotherapy and patients with metastatic or postoperative recurrent disease. Clinical outcomes, dosimetric parameters, and SBRT toxicity were analyzed.

Results: The median age was 63 years (range: 35–82), and the median tumor diameter was 6.8 cm (range: 2.1–12.4). The overall median follow-up duration was 17 months (25.5 months for surviving patients). The median local control was 17 months for stage III patients and 11 months for stage IV or recurrent patients. Grade 3 or higher toxicity was observed in 9.8% of patients: G3 radiation pneumonitis (5.9%) and possible treatment-related death (3.9%).

Conclusion: SBRT with a moderate dose in 4–6 fractions is effective and tolerable for patients with advanced stage UC-NSCLC. However, caution should be taken considering possible treatment-related death. Further studies are warranted.

Introduction

Lung cancer has the highest incidence among all cancers and is the highest contributor to cancer-associated mortality, both globally as well as in China. Globally, an estimated 2.1 million new cases of lung cancer and 1.8 million deaths as a result of lung cancer were projected for 2018.^{1,2} Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all patients with lung cancer.³ According to national Chinese cancer statistics, the age-standardized five-year overall survival rate of patients with lung cancer is only

16.1% because most patients are diagnosed at an advanced stage.⁴ Stereotactic body radiotherapy (SBRT) is a radiotherapeutic modality associated with higher precision and less toxicity; it is recommended as an option for medically inoperable patients with early stage peripheral lung cancer.^{5,6}

However, the outcomes and safety of SBRT in patients with central lung cancer is widely contested. The Radiation Therapy Oncology Group (RTOG) 0236 trial first reported the severe pulmonary toxicity and high incidence of treatment-related deaths associated with SBRT among patients with central lung tumors treated with a radiotherapy regimen of

60 Gy administered in three fractions; this regimen has previously been used for peripheral lung tumors.⁷ At that time, central lung cancer was defined as tumor located within 2 cm of the proximal bronchial tree (PBT) in all directions, which was also referred to as the “no fly zone.” Based on the RTOG 0813 results, the definition of central lung cancer was expanded to include tumors abutting the pericardium, mediastinum, or spine, and these cases were treated with a modified SBRT regimen with a 5 fraction schedule of 50–60 Gy, which showed good efficacy and safety despite the occurrence of grade 3 or higher toxicity.⁸

With increasing attention and research on SBRT for central lung cancer, a new subset, “ultra-central” (UC) lung cancer, has been defined and is associated with a higher risk of toxicity. The definition of UC was first introduced by Chaudhuri *et al.*, who described it as gross tumor volume (GTV) abutting the central airways including the trachea and the PBT.⁹ However, varying definitions have been used in several other studies; for example, it has been defined as the planning target volume (PTV) overlapping the trachea or main bronchi;¹⁰ the PTV overlapping the PBT or esophagus¹¹ and the PTV in contact with or overlapping the PBT, trachea, esophagus, and the pulmonary artery or vein.¹² Herein, we defined UC lung cancer as the GTV abutting or overlapping the trachea and the PBT based on our clinical experience.

At our center, the majority of patients present with advanced stage lung cancer. For high-risk patients, those with a poor general condition, those unwilling to undergo standard chemotherapy, or those resistant to systemic therapy, SBRT could be a useful palliative option because of the high dose per fraction, precision irradiation, and short treatment course. In this study, we report our institutional experience of SBRT for advanced stage UC-NSCLC.

Methods

Patient characteristics

We performed a retrospective analysis of 51 consecutive adult patients with UC-NSCLC who were treated with SBRT using CyberKnife (Accuray, Sunnyvale, CA, USA) at the Department of Radiation Oncology in our hospital between December 2014 and August 2017. The human research ethics committee of our hospital approved the study protocol and all patients signed informed consent. UC tumors were defined as the GTV abutting or overlapping the trachea or PBT. Patients with tumors that were previously irradiated were excluded from this study. We included patients with biopsy-confirmed primary NSCLC or those clinically diagnosed based on positron emission tomography-computed tomography (PET-CT). The indications for SBRT were: stage III patients who were unwilling

or unfit to receive conventional chemoradiotherapy; stage IV or postoperative recurrent patients with stable systemic disease but a remaining primary lung tumor (palliative intent); or patients whose systemic therapy was limited but improvement of symptoms was required.

Radiotherapy

SBRT was delivered using the Accuray CyberKnife. Patients were immobilized with a vacuum cushion. PHILIPS Brilliance Big Bore CT (Philips Healthcare, Cleveland, OH, USA) was used to simulate a four-dimensional (4D) enhanced chest CT scan with 3 mm slices to provide imaging data for physicians to contour the target and volume of interest using the Multiplan treatment system. The GTV was delineated in the lung window referring to all of the inspiratory and expiratory phases of 4D-CT to include the full movement of the tumor, thus generating the internal target volume (ITV). At our center, the PTV was regularly expanded with a 3 mm margin on the basis of ITV and modified at the discretion of the physician. We defined UC as the trachea and PBT, and introduced the term “TPBT” involving the trachea, left and right main bronchi, left and right superior lobar bronchus, left and right inferior lobar bronchus, intermediate bronchus, and right middle lobar bronchus. The critical structures included the TPBT, esophagus, heart, spinal cord, and the normal lung. Medical physicists prepared the treatment plan as per the dose prescribed by the treating and chief physicians to cover 95% of the PTV with a 68–75% prescription dose curve. The PTV maximum point dose (D_{max}) was calculated as the prescribed dose divided by the percentage of the prescription dose curve. The dosimetric parameters of the plan were assessed to ensure safety. Dose constraints for critical structures were applied according to the experience reported by Timmerman *et al.* in 2011.¹³ The biologic equivalent dose with $\alpha/\beta = 10$ (BED₁₀) of tumors was calculated to compare doses in different fractionations using the formula: $BED = nd[1 + d/(\alpha/\beta)]$ (n = fraction; d = dose per fraction). The dosimetric parameters of TPBT D_{max}; TPBT dose received by 4 cc volume (D_{4cc}); esophagus D_{max}; esophagus D_{5cc}; heart D_{max}; heart D_{15cc}; spinal cord D_{max}; lung D_{max}; mean lung dose (MLD); and lung V5 Gy (V₅), lung V15 Gy (V₁₅), lung V20 Gy (V₂₀, percentage of the volume of the total lung minus PTV receiving ≥ 5 Gy, ≥ 15 Gy, and ≥ 20 Gy, respectively) were calculated using the Accuray Multiplan system.

Follow-up and outcome assessment

All patients were recommended to attend regular follow-up examinations at our center, including routine hematological and blood biochemistry tests, blood tumor biomarkers,

ultrasonography for cervical lymph nodes and abdomen, and chest enhanced CT. Cranial magnetic resonance imaging, isotope bone scan, and PET-CT were performed if necessary. Patients who visited local hospitals for follow-up were contacted and assessed by the treating physicians. The first follow-up was conducted one month after SBRT, followed by examinations every three months for two years, and every six months thereafter. The infield effect was evaluated using chest enhanced CT by the treating and chief physicians according to the Response Evaluation Criteria in Solid Tumors, version 1.1. Treatment-related toxicity was scored by the treating physician and confirmed by an independent group of physicians according to the Common Terminology Criteria for Adverse Events, version 4.0. Possible treatment-related deaths of unknown cause were reviewed by different radiation oncologists and scored as grade 5 toxicity. For each patient, only the highest grade of toxicity was recorded. The follow-up duration was calculated from the first day of SBRT until death or the most recent follow-up. The events of interest for local control (LC), regional and distant progression-free time (RPFT and DPFT, respectively), progression-free survival (PFS), and overall survival (OS) were local recurrence, regional lymph node failure, distant metastasis, disease progression or death, and death, respectively. LC, RPFT, DPFT, PFS, OS, and toxicity were calculated from the first day of SBRT until the occurrence of the event of interest or death/most recent follow-up.

Statistical methods

Descriptive statistics were calculated and presented as frequency, percentage, and median values. Survival curves for LC, PFS, OS, and grade ≥ 3 toxicity were generated using the Kaplan–Meier method. Univariate analysis of LC, PFS, and OS were performed using the Kaplan–Meier method and between-group differences were assessed by log-rank test. $P < 0.05$ was considered indicative of statistical significance. The potential predictive factors were gender; age at SBRT; Eastern Cooperative Oncology Group performance status (ECOG PS); symptoms before SBRT; smoking status; tumor histology, stage, maximum diameter, and location; treatment before SBRT (surgery, chemotherapy, targeted therapy, immunotherapy); post-SBRT treatment (chemotherapy, targeted therapy, immunotherapy, local therapy); BED₁₀; lymph nodes irradiated; evaluation after SBRT; GTV; and PTV. For univariate analysis of grade ≥ 3 toxicity, dosimetry factors were also examined, including TPBT Dmax and D4cc; esophagus Dmax and D5cc; heart Dmax and D15cc; spinal cord Dmax; MLD; and lung V5, V15, and V20. Variables that were associated with a P value < 0.10 in the univariate analysis were included in the Cox proportional hazard regression model for multivariate analysis of LC, PFS, OS, and grade ≥ 3 toxicity; significant

predictors were identified as $P < 0.05$. All statistical analyses were performed using SPSS version 20; statistical graphs were generated by GraphPad-Prism software version 7.

Results

Patient and tumor characteristics

A total of 33 male and 18 female adult patients with UC-NSCLC were included in this study. SBRT was used to treat primary lung tumors and mediastinal lymph nodes that were visible on enhanced lung CT. Of the 17 patients whose lymph nodes were treated, 10 patients had two targets including the primary tumor and one lymph node, one patient had three targets including the primary tumor and two lymph nodes, and the remaining six patients had one target including the primary tumor and hilar lymph node. The patient and tumor characteristics are summarized in Table 1. The median age at the start of SBRT was 63 years (range: 35–82). Over 50% of patients in the sample had squamous cell cancer. All tumors invaded the trachea and PBT, with a median diameter of 6.8 cm (range: 2.1–12.4).

Radiotherapy details

Dosimetric details are shown in Table 2. Representations of SBRT for UC tumors are shown in Figure 1. SBRT was delivered every day with a regular prescription dose regimen of 35 Gy/5 fractions, and the median BED₁₀ was 59.5 Gy (Table S1). Approximately 90.2% of patients

Table 1 Patient and tumor characteristics

Characteristic	Patients (%)
Gender	
Male	33 (64.7%)
Female	18 (35.3%)
Age at SBRT (years)	
Median (range)	63 (35–82)
≥ 70	7 (13.7%)
< 70	44 (86.3%)
ECOG PS	
0–1	49 (96.1%)
2	2 (3.9%)
Smoking status	
Never	20 (39.2%)
Past or current	31 (60.8%)
Pre-SBRT symptoms	
None	23 (45.1%)
Cough	21 (41.2%)
Hemoptysis	6 (11.8%)
Chest and back pain	1 (2%)

Table 1 Continued

Characteristic	Patients (%)
Histology	
Squamous carcinoma	29 (56.9%)
Adenocarcinoma	18 (35.3%)
Adenosquamous carcinoma	3 (5.9%)
Unknown†	1 (2%)
Stage	
III	20 (39.2%)
IV	19 (37.3%)
Recurrent	12 (23.5%)
T stage‡	
T1	1 (2%)
T2	6 (11.8%)
T3	16 (31.4%)
T4	18 (54.9%)
N stage‡	
N0	7 (13.7%)
N1	10 (19.6%)
N2	17 (33.3%)
N3	17 (33.3%)
Previous treatment	
None	12 (23.5%)
Surgery	12 (23.5%)
Chemotherapy	31 (60.8%)
Targeted therapy	13 (25.5%)
Immunotherapy	2 (3.9%)
Irradiated site	
Primary tumor	51 (100%)
Lymph node	17 (38.6%)
Tumor diameter	
Primary tumor (cm)	6.8 (2.1–12.4)
≥ 5 cm	44 (86.3%)
≥ 7 cm	24 (47.1%)
Lymph node (cm)	3.7 (2.2–4.9)
GTV location	
Abutting or overlapping TPBT	51 (100%)
PTV location	
Abutting esophagus	19 (37.3%)
Abutting heart	26 (51%)

†One patient was clinically diagnosed via positron emission tomography-computed tomography as he refused to undergo a biopsy.

‡T and N stage were assessed by the patients' status at the time of stereotactic body radiation therapy (SBRT) according to the 8th edition National Comprehensive Cancer Network guidelines. ECOG PS, Eastern Cooperative Oncology Group performance status; GTV, gross tumor volume; PTV planning target volume; TPBT, trachea and proximal bronchial tree.

exceeded the dose constraints for TPBT (29.4% for esophagus, 15.7% for heart, and 5.9% for spinal cord).

Clinical outcomes

The outcomes and details of post-SBRT treatment are shown in Table S2. The Kaplan–Meier curves for LC, PFS, and OS of patients with stage III and IV or recurrent

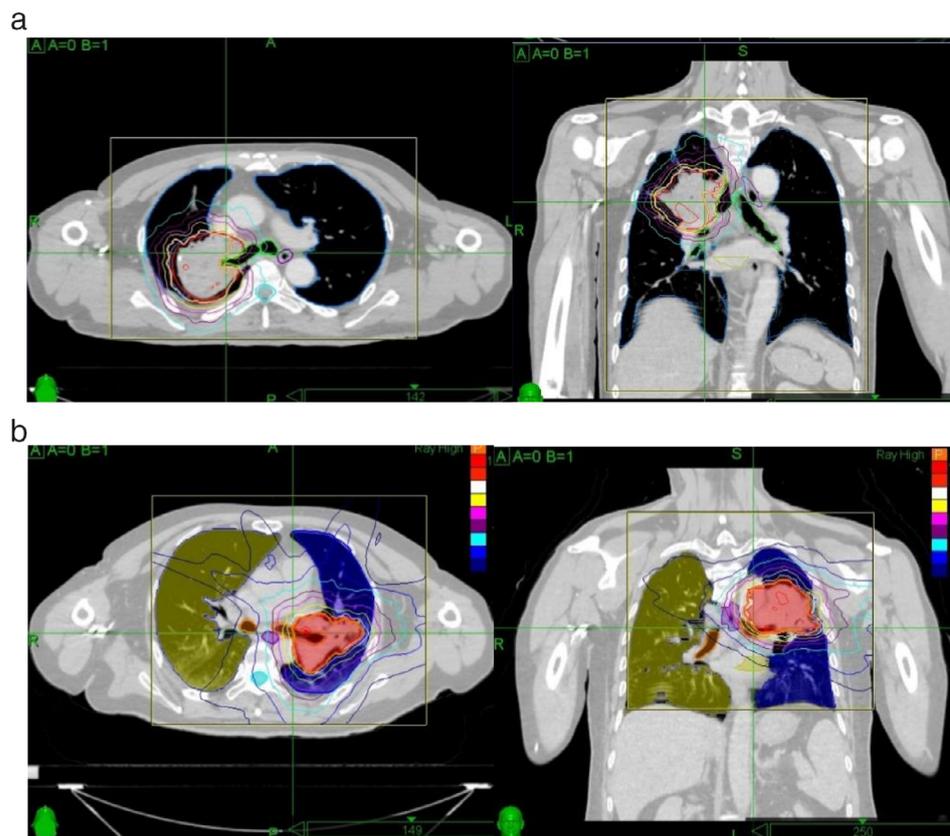
Table 2 Dosimetric details

Radiotherapy parameters	Median (range) (n = 51)
Prescribed dose‡	35 Gy/5f (30–37.5Gy/4–6f)
BED ₁₀ (Gy)†	59.5 (48–65.6)
GTV diameter (cm)	6.8 (2.1–12.4)
GTV (cc)	88.4 (4.1–569.7)
GTVn (cc)	13.7 (4.3–24.2)
PTV (cc)	111.3 (9.8–688.9)
PTV Dmax (Gy)	48.9 (41.1–58.1)
TPBT Dmax (Gy)	38.4 (27.6–50.6)
TPBT D4cc (Gy)	28.2 (9.3–37.5)
Esophagus Dmax (Gy)	23.9 (7.9–43.5)
Esophagus D5cc (Gy)	13.3 (4.4–27.0)
Heart Dmax (Gy)	28.8 (9.4–48.7)
Heart D15cc (Gy)	14.9 (4.1–31.4)
Spinal cord Dmax (Gy)	14.1 (2.8–35.4)
Lung Dmax (Gy)	38.7 (10.9–58.7)
Lung MLD (Gy)	4.4 (1.0–11.0)
Lung V5 Gy (%)	42.5 (11.4–83.4)
Lung V15 Gy (%)	9.4 (0–30.0)
Lung V20 Gy (%)	5.1 (0–20.4)

†The regular prescription dose at our center was 35 Gy/5f with a biologic equivalent dose with $\alpha/\beta = 10$ (BED₁₀) of 59.5Gy. Doses to targets and critical structures were calculated in the MultiPlan system and shown although three cases were not in 5 fractions. cc, cubic centimeter; D4cc, D5cc, D15cc, dose received 4cc, 5cc, 15cc volume of organ at risk, respectively; Dmax, maximum point dose; GTV, gross tumor volume; GTVn, GTV of lymph node; MLD, mean lung dose; PTV, planning target volume; PTVn, PTV of lymph node; V5 Gy, V15 Gy, V20 Gy, percentage of the volume of total lung minus PTV receiving 5 Gy, 15 Gy, 20 Gy or more, respectively.

disease are shown in Figure 2a,b,c, and that for toxicity is shown in Figure 2d. Twenty-eight patients (54.9%) suffered from symptoms before SBRT, including cough (41.2%), hemoptysis (11.8%), and chest and back pain (2%), while 24 patients (88.7%) experienced symptom relief post-SBRT. At the most recent follow-up conducted in September 2018, approximately 64.7% of the patients had died. The median follow-up duration was 17 months (range: 3–39) for all patients and 25.5 months (range: 13–39) for the surviving patients. Approximately 47.1% of patients developed local recurrence, of whom 37.5% had stage III disease. Of the 24 patients who developed local recurrence, 19 were treated: 16 patients received systemic therapy including chemotherapy, targeted therapy, and immunotherapy; one patient received chemotherapy, radioactive seed implantation, and intensity modulated radiotherapy (IMRT); one patient received targeted therapy and radiofrequency therapy; and one patient received interventional therapy. The median LC was 16 months (17 months for stage III and 11 months for patients with stage IV or recurrent disease, $P = 0.59$). The one-year LC rate was 54.4% for all patients (61.2% for stage III and 49.1% for patients with stage IV or recurrent disease).

Figure 1 Representations of stereotactic body radiation therapy for ultra-central tumors. Axial and coronal computed tomography of a patient with an ultra-central tumor abutting or overlapping (a) the right mainstem bronchus and upper lobe bronchus, and (b) the left upper lobe bronchus.



Approximately 74.5% of patients developed disease progression, of whom 28.9% had stage III disease. On analysis of the pattern of initial disease progression, local, regional, and distant failure occurred in 54.5%, 36.4%, and 27.3% patients with stage III disease, and in 48.1%, 18.5%, and 51.9% patients with stage IV disease or recurrence, respectively. The overall median PFS was 7 months (95% confidence interval [CI] 4.21–9.80 months; 8 months for patients with stage III and 7 months for patients with stage IV or recurrent disease; $P = 0.48$). The one, two, and three-year PFS rates were 27.5, 15.7, and 6.5%, respectively. Thirty-three patients (64.7%) died, 31 of which were considered non-treatment related, including: recurrence or lung metastases (20 patients); distant metastases including brain or meningeal metastases and bone (5 patients); chemotherapy-induced granulocytopenic infection (2 patients); hemoptysis following IMRT (1 patient); infection with respiratory failure (1 patient); and pleural and pericardial effusion, respectively (2 patients). Two deaths were possibly treatment-related, including heart failure and myocardial infarction, respectively. The median OS was 18 months (95% CI 12.56–23.44; 17 months for patients with stage III and 21 months for patients with stage IV or recurrent

disease; $P = 0.38$). The one, two, and three-year OS rates were 76.5, 38.9, and 20.6%, respectively. No significant predictors of longer LC or PFS were identified in univariate and multivariate analyses. In univariate analysis, the following four factors showed a significant association with longer OS: gender (female > male, $P = 0.047$), tumor maximum diameter < 7 cm ($P = 0.004$), GTV < 100 cc ($P = 0.004$), and PTV < 150 cc ($P = 0.000$). However, none of these factors showed a significant association with OS in multivariate analysis.

Stereotactic body radiotherapy toxicity

Grade 3 or higher toxicity was observed in five (9.8%) patients: G3 radiation pneumonitis (5.9%, 3 patients) and possible treatment-related death (3.9%, 2 patients) (Table 3). Two patients had a cardiac cause of death at 4 and 11 months post-SBRT; both had heart disease before SBRT. The Dmax of the heart was 39.2 and 19.0 Gy, respectively, while the D15cc of the heart was 14.9 and 13.1 Gy, respectively. The overall median of Dmax and D15cc for the heart were 28.8 and 14.9 Gy, respectively. The actuarial incidence of the first occurrence of grade 3 or higher toxicity was 11.0% at 12 months (Fig 2d).

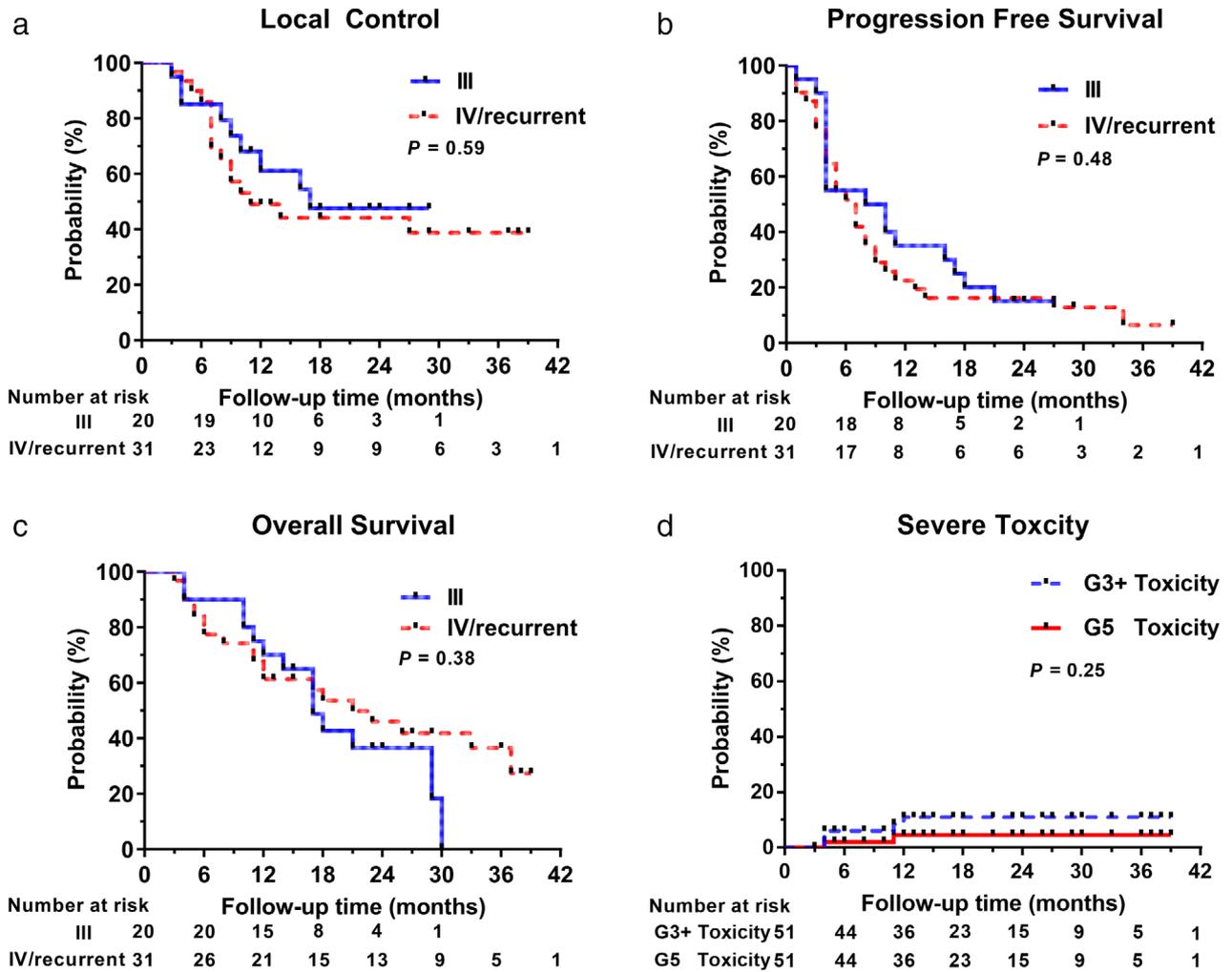


Figure 2 Outcomes of stereotactic body radiation therapy for ultra-central non-small cell lung cancer. Kaplan–Meier curves for stage III and IV or recurrent patients: (a) local control, (b) progression-free survival, (c) overall survival for all patients, and (d) grade 3 or higher and grade 5 toxicity.

Univariate analysis showed that GTV ≥ 100 cc ($P = 0.04$) and PTV ≥ 150 cc ($P = 0.02$) were significantly correlated with a higher incidence of grade ≥ 3 toxicity; however, neither of these factors showed statistical significance in multivariate analysis.

Table 3 SBRT severe toxicity (grade 3 or higher toxicity)

Toxicity†	Adverse event	Patients (%)	Months post-SBRT
Grade ≥ 3	All	5 (9.8%)	1.5–11
Grade 3	Radiation pneumonitis	3 (5.9%)	1.5–3
Grade 5		2 (3.9%)	4–11
Possibly treatment related	Heart failure	1 (1.96%)	4
	Myocardial infarction	1 (1.96%)	11

†Toxicity was assessed based on the Common Terminology Criteria for Adverse Events version 4.0. SBRT, stereotactic body radiation therapy.

Discussion

SBRT for UC-NSCLC has evoked considerable attention because of the higher risk of toxicity compared to central tumors.^{11,14} To date, the efficacy and safety profile of SBRT for UC-NSCLC has not been well characterized; in addition, clinical experience in China is particularly limited. As the majority of patients at our department are diagnosed with stage III, IV, or recurrent NSCLC and some are unfit for conventional chemoradiotherapy, we conducted a prospective study to compare SBRT versus IMRT for high-risk central NSCLC between 2015 and 2018. Considering the promising outcomes of using a moderate dose of SBRT reported by Unger and Duncker, and the constraints for organs at risk reported by Timmerman *et al.*, we tried to maintain a balance between safety and efficacy with the use of a moderate dose 4–6 fraction regimen.^{13,15,16}

Table 4 Published reports of the use of SBRT for UC lung tumors

Study year (reference)	UC definition	Patient and tumor characteristics	Regular radiotherapy scheme	BED $\alpha/\beta = 10$ (Gy)	Local control rate	Grade 3–5 SBRT-related toxicity
Chaudhuri <i>et al.</i> ⁹	GTV abutting the PBT or trachea	6 early stage UC-NSCLC patients with a median GTV of 34.5 cm ³	50 Gy/4-5f	100/112.5	100% at 2 years	None
Haseltine <i>et al.</i> ¹⁴	GTV abutting the PBT	18 UC lung tumors	45 Gy/5f	85.5	UA	SBRT-related death in 4 patients,
Tekatli <i>et al.</i> ¹⁰	PTV overlapping the trachea or main bronchi	47 UC- NSCLC patients of whom 38% were stage IIIA, 17% recurrent; median tumor diameter 5.6 cm	60 Gy/12f	90	No local recurrence	G3 or higher toxicity rate 38%, including 21% likely or possibly SBRT-related death
Lischalk <i>et al.</i> ¹⁷	GTV abutting or invading the main bronchus	20 patients with UC pulmonary metastases	35-40 Gy/5f	59.5–72	70% at 1 year	G3 pneumonitis 1 patient and the G4 atelectasis in 1 patient;
Daly <i>et al.</i> ¹¹	PTV overlapping the PBT or esophagus	9 UC lung tumors	50 Gy/5f	100	UA	G3 or higher toxicity rate 22.2%
Raman <i>et al.</i> ¹²	PTV contacting or overlapping the PBT, trachea, esophagus, pulmonary artery, or vein	26 UC lung tumors with a median PTV of 58.2 cm ³	60 Gy/8f 48 Gy/4f	105 105.6	100% at 2 years	No grade 4 or 5 toxicity
Chang <i>et al.</i> ¹⁸	ITV abutting the PBT	46 UC primary or metastatic lung tumors	30–49 Gy/5f or ≥ 50 Gy/5f	48–97 or 100	95.7% at 2 years	G3 or higher toxicity rate 8.7%
Nguyen <i>et al.</i> ¹⁹	PTV overlapping the PBT or esophagus	14 UC tumors including 13 early NSCLC and 1 metastatic disease	50 Gy/5f or 56 Gy/8f	100 or 95.2	89%	G3 or higher toxicity rate 14.3%; G5: 7.1%

G3, grade 3; GTV, gross tumor volume; Gy/5f, Gy in five fractions; ITV, internal target volume; NSCLC, non-small cell lung cancer; PBT, proximal bronchial tree; PTV, planning target volume; UA, unavailable; UC, ultra-central.

The details of recent published reports on the outcomes and toxicity of SBRT for UC lung cancer are listed in Table 4.^{9,10,12,14,17–19} Most of the studies showed that SBRT achieved an excellent LC rate (95.7–100%) in patients with UC lung tumors, while Lischalk *et al.* reported a one-year LC rate of only 70%. The difference is likely attributable to the fact that all patients in the study by Lischalk had advanced stage disease with metastases, and the prescribed dose (35–40 Gy administered in 5 fractions with a BED of 59.5–72 Gy) was lower than that in the other studies (BED ≥ 100 Gy). Our study population was quite different from those in the previous studies and included patients with larger tumors, advanced stage disease, and limited systemic therapy. The LC rate in our study was much lower than in the aforementioned studies, which may be because patients with advanced stage disease had more aggressive tumors and had a higher risk of recurrence and metastasis compared to early stage patients. The lower median BED (59.5 Gy) employed in our study may also have prevented the achievement of longer LC. However, the larger tumor size and PTV would probably result in a greater dose to the critical structures, which may lead to a higher risk of

toxicity. Moreover, the initial disease failure pattern also suggests that attention should be paid to systemic disease in advanced patients, and a high dose to local tumors might not be administered in the first place, especially considering the potential risk of treatment-related toxicity, as well as pulmonary symptoms before SBRT. The median OS from the commencement of SBRT was 18 months, which is similar to that of patients treated with conventional chemoradiotherapy at our center. Ironically, although the difference was not statistically significant, the OS of stage III patients was shorter than that of patients with stage IV or recurrent NSCLC (17 vs. 21 months) (Fig 2c). Further analysis revealed that this might be because a greater proportion of stage III patients had squamous carcinoma and these patients received limited targeted therapy.

The incidence of grade 3 or higher pulmonary or esophageal toxicity with SBRT was lower than that with IMRT, while we found that even with moderate doses, doses to the TPBT, esophagus, and heart may exceed the normal constraints. An increase to the low dose region of the lung was observed, potentially because of the centrally located

larger tumors, therefore it was necessary to optimize the Cyberknife treatment planning system. Although the low dose region of lung V5 was higher, the dose regions of V15 and V20 in SBRT-treated patients seemed much smaller than in patients treated with IMRT in our department. Of note, no hemorrhage or bronchial toxicity was observed in our study, which was quite unpredictable in such a patient group with tumors invading the trachea and PBT.¹⁰ This may be a result of the moderate radiation dose scheme we applied; however, the potential for severe toxicity should not be neglected. We reported two possible treatment-related deaths with cardiac causes, as it is difficult to identify toxicity attributable to SBRT. Although a moderate dose might not cause acute severe toxicity, caution should be taken when treating these high-risk patients with SBRT, in whom severe toxicity could manifest > 12 months post-treatment.

The main strength of our study is that it is the largest single institutional study to examine the outcomes and toxicity of SBRT for advanced stage UC-NSCLC. SBRT is a short-course and patient-friendly treatment modality that yields a minimal break in systemic therapy. Moreover, our study shows that a moderate dose regimen of SBRT appears to offer tolerable toxicity and could be a potential palliative option for these patients. Despite the probability of decreasing toxicity to critical structures with more fractions, the cost-effectiveness of SBRT should also be considered in clinical work. Finally, SBRT is a promising radiotherapy modality that may induce an immune enhanced effect, especially when combined with immunotherapy.

Some limitations of our study need to be acknowledged. Firstly, this was a retrospective study and the patients presented with more complicated conditions, which inevitably increased the heterogeneity of our sample. Toxicity scoring is also quite difficult in a retrospective study. Secondly, as patients with advanced stage usually have a poor prognosis, SBRT-related toxicity may not have occurred before the patients died. Thirdly, most patients were treated in an era when immunotherapy was not widely used in China. Currently, SBRT in combination with immunotherapy may offer benefits to some patients with NSCLC.

A moderate dose of SBRT in 4–6 fractions is an effective and tolerable palliative radiotherapeutic modality for advanced stage UC-NSCLC patients, especially for those who are unfit or unwilling to receive conventional chemoradiotherapy. Although this study indicates that the toxicity might be tolerable, caution should be taken when treating these high-risk patients considering the possibility of treatment-related death. Further study is required to identify the optimal radiotherapy scheme and factors associated with SBRT-related toxicity for advanced stage UC-NSCLC.

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Disclosure

No authors report any conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Stereotactic body radiation therapy (SBRT) schemes
Table S2 Clinical outcomes and post-stereotactic body radiation therapy (SBRT) treatment details