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ORIGINAL ARTICLE

Ultra-central lung tumors: safety and efficacy of protracted stereotactic body radiotherapy

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ABSTRACT

Background: For patients with early stage or medically inoperable lung cancer, stereotactic body radiotherapy (SBRT) is a general accepted and effective treatment option. The role of SBRT in ultra-central tumors remains controversial. The aim of this single-center retrospective analysis was to evaluate the safety and efficacy of protracted SBRT with 60 Gy in 12 fractions (with a biological effective dose (BED_{10}) of 90–150 Gy) for patients with ultra-central lung tumors.

Materials and methods: Patients with ultra-central lung tumors treated in our institution with 60 Gy in 12 fractions from January 2012 until April 2020 were included. Ultra-central tumors were defined as planning target volume (PTV) abutting or overlapping the main bronchi and/or trachea and/or esophagus. Data regarding patient-, tumor-, and treatment-related characteristics were evaluated.

Results: A total of 72 patients met the criteria for ultra-central tumor location. The PTV abutted the main bronchus, trachea or esophagus in 79%, 22% and 28% of cases, respectively. At a median follow-up of 19 months, 1- and 2-year local control rates were 98% and 85%, respectively. Overall survival rates at 1 and 2 years were 77% and 52%, respectively. Grade 3 or higher toxicity was observed in 21%, of which 10 patients (14% of total) died of bronchopulmonary hemorrhage. A significant difference between patients with or without grade $\geq$3 toxicity was found for the mean dose (D_{mean}) to the main bronchus ($p = 0.003$), where a D_{mean} BED_3 of $\geq$91 Gy increased the risk of grade $\geq$3 toxicity significantly.

Discussion: A protracted SBRT regimen of 60 Gy in 12 fractions for ultra-central lung tumors leads to high local control rates with toxicity rates similar to previous series, but with substantial risk of fatal bronchopulmonary hemorrhage. Therefore, possible risk factors of bronchopulmonary hemorrhage such as dose to the main bronchus should be taken into account.

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Ultra-central lung tumor; stereotactic body radiotherapy; toxicity

Background

For patients with early stage, inoperable lung cancer, stereotactic body radiotherapy (SBRT) is a recommended alternative to surgery [1,2]. With biological effective doses (BEDs) greater than 100 Gy to the tumor with an α/β ratio of 10 (BED_{10}), excellent local control rates for peripherally located tumors exceeding 90% are achieved without significant (grade $\geq$3) toxicity [3–5]. However, the safety and efficacy of SBRT in central and ultra-central lung tumors remains less well-defined.

In a landmark phase II study patients treated with SBRT to 60–66 Gy in 3 fractions for perihilair or central tumors experienced an 11-fold increase in risk of severe pulmonary toxicity, compared to more peripheral locations [6]. These findings in 2006 led to defining tumors within 2 cm of the proximal bronchial tree (PBT) as 'central tumors' in the so-called 'no-fly zone' where it was recommended to avoid high doses per fraction. In the RTOG 0813 trial, 120 such cases were treated with a SBRT regimen of 50–60 Gy in five fractions, resulting in good local control and acceptable toxicity rates. High grade toxicity including pneumonitis and pulmonary hemorrhage, however, was more frequently observed in tumors near the main bronchi [7–9].

The term 'ultra-central tumors', introduced by Chaudhuri et al. in 2015, refers to tumors directly abutting the central airway (i.e., trachea and PBT) [10]. However, varying definitions have been described in more recent studies. For example by Tekatli *et al.*, as tumors in which the planning target volume (PTV) is overlapping main bronchi or trachea [11] or by Daly *et al.* as PTV overlapping PBT or esophagus [12].

High rates of serious SBRT-induced toxicity are a main concern in treating ultra-central tumors, which had led

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Supplemental data for this article can be accessed here.

investigators to propose increasing the number of fractions and reducing the fractionation dose [13]. Indeed, recent studies have demonstrated that SBRT can still be an effective treatment option with acceptable toxicity in centrally located tumors when using more fractionated regimens [14,15].

Evidence on the safety and efficacy of protracted (i.e., mildly fractionated) SBRT regimens in ultra-central tumors is limited. In addition, the optimal fractionation regimen for ultra-central lung tumors remains unknown. Therefore, the aim of this analysis was to evaluate the safety and efficacy of protracted SBRT in 12 fractions of 5 Gy (BED_{10} 90–150 Gy in the center of the PTV when accepting a maximum dose to the PTV of 145% and BED_3 160–297 Gy) for patients with ultra-central lung tumors.

Materials and methods

Patient selection

This retrospective single-center analysis was approved by the institutional review board (#18-505) and the need for written informed consent for this analysis was waived. All patients treated with 60 Gy in 12 fractions from January 2012 to April 2020 were identified from an institutional database. Exclusion criteria were age <18 years, metastasis of a primary tumor other than lung cancer and location other than ultra-central. An ultra-central tumor location was defined as the PTV abutting or overlapping the main bronchi, trachea and/or esophagus (Figure 1) [11,12]. All patients were staged with ^{18}F-FDG PET/CT.

Treatment planning and delivery

All patients underwent three-dimensional (3D) computed tomography (CT) simulation, as well as a four-dimensional (4D) CT scan to visualize breathing motion. Target volume and organs at risk were delineated. Margin from internal target volume (ITV) to PTV was 3 mm. Organs at risk were delineated in accordance with RTOG 0236/ROSEL [16]. Treatment planning was performed on the average intensity projection of the 4D CT. A radiation plan was made with a prescription dose of 60 Gy delivered in 12 fractions ($EQD2_{10}$ 75 Gy, BED_{10} 90 Gy) at 4 fractions per week. The treatment plan was required to ensure that 95% of the PTV received the nominal fraction dose (PTV $D_{95\%}$ ≥60 Gy), 99% of the PTV received at least 90% of the nominal fraction dose (PTV $D_{99\%}$ ≥54 Gy), and the dose maximum within the PTV was recommended to not exceed 145% (i.e., 87 Gy or BED_{10} 150 Gy) according to the International Commission on Radiation Units and Measurements (ICRU) guidelines [17]. The maximum doses to the organs at risk were kept as low as reasonably achievable with acceptance of PTV underdosage in favor of organ at risk dose at the discretion of the treating radiation oncologist. Guidelines for maximum (max) doses to the organs at risk were as follows: *D*0.5 cc bronchus max 49 Gy, *D*0.5 cc esophagus max 44 Gy, *D*0.5 cc trachea max 49 Gy. Treatment plans were delivered using intensity modulated radiotherapy (IMRT) or coplanar volumetric modulated arc therapy (VMAT) with 6 MV flattening filter free (FFF) beams. Prior to each fraction, a cone-beam CT was used for online setup and position verification.

Data collection and outcome measurement

Data regarding patient-, tumor-, and treatment-related characteristics were extracted from the institutional database and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Tumor stage was determined using the AJCC 7th edition of TNM staging system [18]. Additional dosimetric data were obtained for the PTV and organs at risk. Including near-minimum ($D_{98\%}$) and near-maximum dose ($D_{2\%}$) to the PTV and near-maximum ($D_{2\%}$) and mean dose (D_{mean}) to the trachea, esophagus and bronchus, and the lung volume receiving 20 Gy (V20Gy). Toxicity was assessed during and after treatment using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For each patient, the highest grade of the recorded toxicity and the date of the event were documented. Local control was recorded during follow-up by documenting the time interval between start of SBRT and the date at which local disease progression within the radiation field was established on follow-up imaging. Follow-up imaging using CT scan of the thorax and/or a chest X-ray was performed by and at the discretion of the referring physician at varying time intervals. Clinical follow-up by the radiation oncologist was performed 4 weeks after treatment. Data on overall survival was retrieved from the Municipal Personal Records Database and was calculated from the start date of SBRT. For deceased patients, cause of death was evaluated by requesting medical records from the referring physician and/or general practitioners to establish a potential relation to treatment.

Statistics

Baseline characteristics were provided by depicting continuous data as median with interquartile range (IQR) and categorical data as absolute numbers with percentages. Local control and overall survival rates and 95% confidence intervals (95% CI) were calculated with the Kaplan–Meier method. Mann–Whitney *U* test was used to compare continuous clinical and dosimetric parameters and Fisher's Exact test to compare categorical clinical parameters between patients with or without grade ≥3 toxicity. For the dosimetric parameters that were significantly related to grade ≥ 3 toxicity, receiver operating characteristics (ROC) analysis was performed to identify ideal cutoff values in which equal weight was given to sensitivity and specificity. Logistic regression was performed to identify associations between clinical and dosimetric parameters and to further assess the relation of the dosimetric parameters that were significantly different between patients with and without grade ≥ 3 toxicity. The collected data were analyzed using IBM SPSS statistics, version 25 (IBM Corp., Armonk, NY, USA) and R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria, 2018). In the exploratory analyses on the impact of dosimetry on

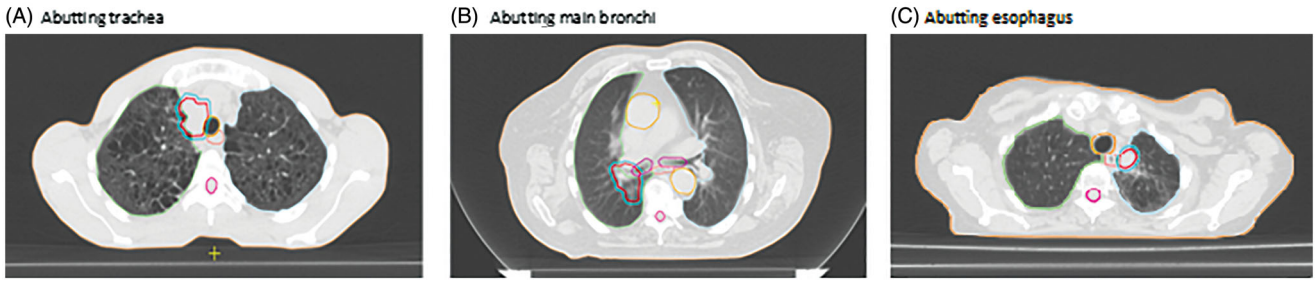

Figure 1. Examples of delineations of ultra-central tumors overlapping the main bronchus (A), the trachea (B) and the esophagus (C). Contoured structures: internal target volume (red), planning target volume (blue), trachea (orange), main bronchi (pink), esophagus (yellow), right lung (light green), left lung (light blue), aorta (dark green), and spinal cord (purple).

toxicity outcomes a p value of <0.01 was considered statistically significant taking into account the issue of multiple testing (i.e., reduce the probability of type I error).

Results

From January 2012 to April 2020, a total of 183 lung cancer patients were treated with SBRT to 60 Gy in 12 fractions. A total of 72 patients (39%) who met the criteria for ultra-central tumor location were included in this analysis. Baseline patient and tumor characteristics are presented in Table 1. Median age was 72 years, (IQR 64–79 years) and 81% had a WHO performance score of 0 or 1 at start of treatment. The majority of patients had an ultra-central primary lung carcinoma (76%), whereas 17 patients (24%) were treated for an ultra-centrally located mediastinal or hilar lymph node metastasis of a primary lung carcinoma. Malignancy was suspected but not pathologically confirmed in 21 (29%) of 72 patients. The PTV abutted the main bronchus in 57 (79%), the trachea in 16 (22%) and the esophagus in 20 (28%) of 72 cases. Median distance between the PTV and the main bronchus was 0.0 mm (range 0.0−61.0 mm). Three patients (4%) had undergone previous radiotherapy for a prior lesion in the same lung as the index lesion, leading to some degree of overlap between the two treatment plans. The interval between the previous radiotherapy and the current SBRT was more than 1 year in all 3 patients. None of these patients experienced grade $\geq$3 toxicity. After the protracted SBRT for the ultra-central lung tumor, 5 patients (7%) received radiotherapy for the same ($n=1$) or for a new lesion ($n=4$) in the same lung with a median time interval of 12 months (range 6−23 months). None of these patients experienced grade $\geq$3 toxicity.

Median follow-up was 19 months in all patients (IQR 10–32 months) and 26 months (IQR 12–41 months) in patients alive at last follow-up. At the time of analysis, 56 patients (78%) were free from local recurrence. Nine patients (13%) had radiologically determined local progression with a median time to local failure of 17 months (IQR 15–39 months). From 7 patients (10%) no follow-up data on local recurrence was available. Median time to local failure from start of treatment was 64 months (95% CI 20–108 months). Local control rates were 98%, 85% and 78% at 1, 2 and 3 years, respectively (Figure 2(A)). Median overall survival from start of treatment was 29 months (95% CI 17–41 months). Overall survival rates were 77%, 52% and 36% at 1, 2 and 3 years, respectively (Figure 2(B)).

Clinical information on toxicity was available for all patients. Table 2 depicts the details of the recorded toxicity.

Table 1. Patient and tumor characteristics.

	No. of patients (%) $N=72$
Male sex	45 (62.5%)
Median age (years)	72 (64−79)
WHO performance score	
0	11 (15.3%)
1	47 (65.3%)
2	14 (19.4%)
Disease stage (TNM 7th)	
T-stage	
Tx	3 (4.2%)
T0	2 (2.8%)
T1	24 (33.3%)
T2	23 (31.9%)
T3	10 (13.9%)
T4	10 (13.9%)
N-stage	
Nx	1 (1.4%)
N0	42 (58.3%)
N1	23 (31.9%)
N2	2 (2.8%)
N3	4 (5.6%)
Overall stage	
Stage I	25 (34.7%)
Stage II	26 (36.1%)
Stage III	12 (16.7%)
Stage IV	9 (12.5%)
PTV location	
Overlap with main bronchus	42 (58.3%)
Overlap with esophagus	7 (9.7%)
Overlap with trachea	4 (5.6%)
Overlap with main bronchus and trachea	6 (8.3%)
Overlap with main bronchus and esophagus	7 (9.7%)
with trachea and esophagus	4 (5.6%)
Overlap with main bronchus, trachea and esophagus	2 (2.8%)
Prior treatment	
None	52 (72.2%)
Surgery	8 (11.1%)
Chemotherapy	7 (9.7%)
Radiotherapy	3 (4.2%)
Immuno- or targeted therapy	2 (2.8%)
Tumor type	
Primary lung tumor	55 (76%)
Lymph node metastasis of a lung tumor	17 (24%)
Tumor histology	
Squamous cell carcinoma	31 (43.1%)
Adenocarcinoma	17 (23.6%)
Large cell carcinoma NOS	2 (2.8%)
No histology	21 (29.2%)
Median PTV (cm^3)	55.6 (30.9–111.0)

Values are *n*(%) or median (interquartile range).

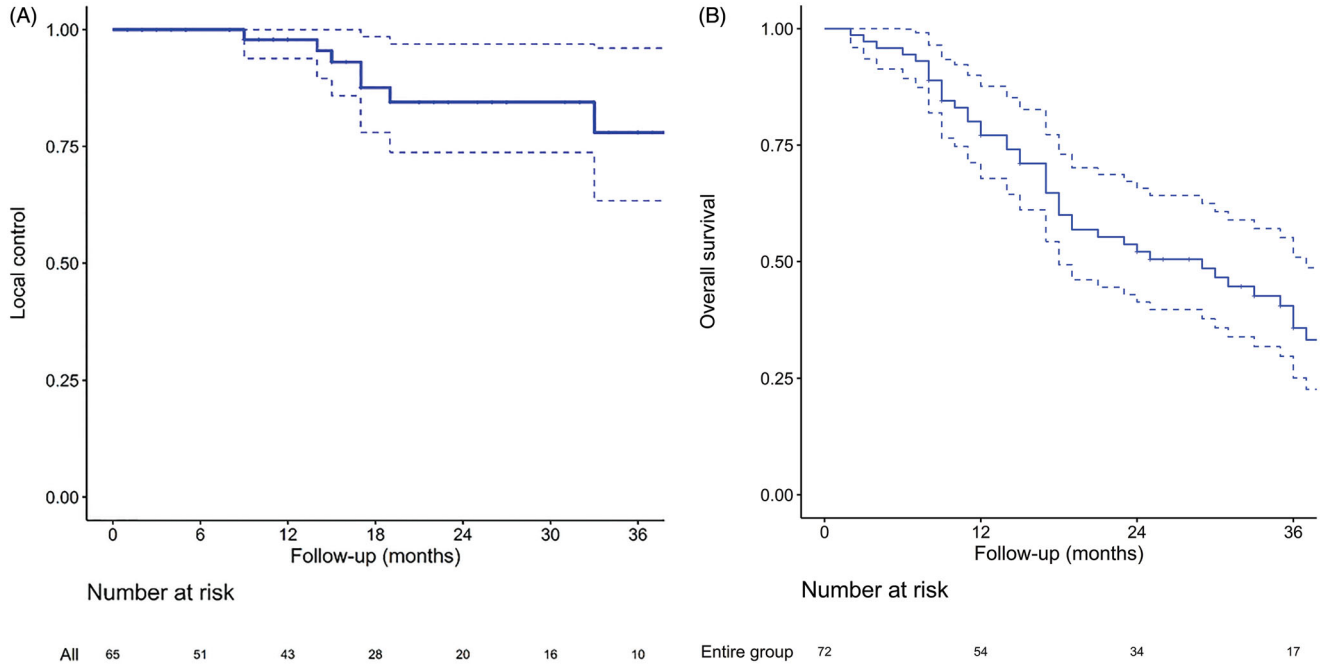

Figure 2. Kaplan–Meier curves for local control (A) and overall survival (B). In both graphs, dashed lines represent the 95% confidence intervals.

Table 2. Treatment related toxicities.

		Treatment toxicity ($n = 72$)	
Adverse events	At baseline ($n = 72$)	Occurred during treatment (≤3 weeks after start SBRT)	Occurred after treatment (>3 weeks after start SBRT)
Bronchial fistula			
None	72 (100.0%)	72 (100.0%)	–
Grade 5	–	–	2 (2.8%)
Coughing			
None	49 (68.1%)	29 (40.3%)	–
Grade 1	23 (31.9%)	27 (37.5%)	7 (9.7%)
Grade 2	–	5 (6.9%)	3 (4.2%)
Grade 3	–	–	1 (1.4%)
Dysphagia			
None	72 (100.0%)	58 (80.6%)	–
Grade 1	–	5 (6.9%)	–
Grade 2	–	8 (11.1%)	1 (1.4%)
Dyspnea			
None	46 (63.9%)	38 (52.8%)	–
Grade 1	22 (30.6%)	15 (20.8%)	6 (8.3%)
Grade 2	4 (5.6%)	7 (9.7%)	3 (4.2%)
Grade 3	–	1 (1.4%)	2 (2.8%)
Fatigue			
None	46 (63.9%)	14 (19.4%)	–
Grade 1	17 (23.6%)	31 (43.1%)	8 (11.1%)
Grade 2	8 (11.1%)	10 (13.9%)	5 (6.9%)
Grade 3	1 (1.4%)	2 (2.8%)	2 (2.8%)
Bronchopulmonary hemorrhage			
None	63 (87.5%)	58 (80.6%)	–
Grade 1	9 (12.5%)	2 (2.8%)	2 (2.8%)
Grade 5	–	–	10 (13.9%)
Pneumonitis	–		
None	72 (100.0%)	57 (79.2%)	–
Grade 1	–	–	2 (2.8%)
Grade 2	–	–	11 (15.3%)
Grade 3	–	–	2 (2.8%)

Values are *n* (%).

Forty-seven patients (65%) already had symptoms of fatigue, dyspnea, coughing and/or hemoptysis before start of treatment. All but 2 (3%) of 72 patients reported one or more adverse event(s) during or after treatment with SBRT. Fifty-seven patients (79%) had a mild adverse event only (CTCAE grade <3) during or after treatment. The median time to the highest experienced toxicity was 19 days after start of treatment (IQR 12–108 days). Of all 15 patients (21%) with grade

Table 3. Association between dosimetric details and toxicity outcomes.

Parameter	Grade < 3 toxicity ($n = 57$)	Grade ≥ 3 toxicity ($n = 15$)	p value	Grade < 5 toxicity ($n = 62$)	Grade 5 toxicity ($n = 10$)	p value
Distance PTV bronchus, mm	0.0 (0.0–1.5)	0.0 (0.0–0.0)	0.175	0.0 (0.0–0.8)	0.0 (0.0–0.0)	0.085
PTV volume, cm^3	52.1 (28.4–113.6)	58.3 (38.1–108.6)	0.708	53.3 (28.8–112.7)	64.6 (39.8–109.7)	0.504
PTV $D_{2\%}$, Gy	81.4 (77.5–84.0)	81.6 (79.9–84.3)	0.356	82.0 (77.7–84.1)	81.0 (79.5–84.1)	1.000
PTV $D_{98\%}$, Gy	58.2 (57.2–59.1)	58.5 (57.4–59.5)	0.442	58.2 (57.1–59.1)	58.5 (57.9–59.5)	0.275
Bronchus, $D_{2\%}$, Gy	58.9 (36.1–68.6)	69.6 (41.5–77.3)	0.075	58.9 (37.0–69.1)	71.1 (59.2–75.2)	0.034
Bronchus, D_{mean}, Gy	25.6 (13.9–34.6)	48.1 (27.7–51.6)	**0.003**	26.4 (14.0–34.9)	49.3 (30.8–51.7)	**0.001**
Esophagus, $D_{2\%}$, Gy	30.5 (19.2–43.0)	30.8 (23.4–38.8)	0.894	29.8 (19.8–41.2)	31.6 (22.4–39.9)	0.785
Esophagus, D_{mean}, Gy	6.3 (4.3–9.4)	5.1 (3.9–8.3)	0.805	6.3 (4.2–9.8)	6.4 (4.0–9.1)	0.928
Trachea, $D_{2\%}$, Gy	19.7 (4.9–48.3)	18.9 (8.0–29.7)	0.598	19.3 (6.0–47.9)	17.7 (6.3–25.7)	0.459
Trachea, D_{mean}, Gy	4.3 (1.0–14.2)	3.0 (1.4–5.2)	0.366	4.2 (1.1–14.1)	2.0 (1.0–3.5)	0.076
Total lung, V20Gy, %	7.4 (4.5–12.0)	9.3 (6.9–13.8)	0.172	7.4 (4.6–11.8)	10.2 (7.7–15.5)	0.024

Values are median (interquartile range). *P* values marked with bold indicate statistically significant p values.

≥ 3 toxicity, the majority (73%) experienced toxicity within 12 months after start of treatment with a median time to toxicity of 9 months (IQR 2–17 months). Fatigue, coughing and dyspnea were the most common adverse events, occurring in 81%, 60% and 47% of patients, respectively.

At the time of analysis, 45 patients (63%) had died. No information on the cause of death was available in 7 patients (10%) who survived 8–41 months. Of the latter, only one patient had manifested grade 3 toxicity. Seventeen patients (24%) died of the consequences of lung cancer and 11 patients (15%) as a result of causes unrelated to lung cancer. Possible treatment-related death was seen in 10 patients (14%) who all died of bronchopulmonary hemorrhage. This was observed at a median time after start of treatment of 11 months (range 8–21 months). All 10 patients had a PTV overlapping the main bronchus. Autopsy performed in 2 cases revealed a bronchial fistula between the main bronchus of the right lower lobe and the bronchial artery in one patient and a fistula between the main bronchus and the pulmonary artery in the other patient. These fistulas were both located in the high dose radiation area and due to ulceration and necrosis of the bronchus. One of 10 patients started with bevacizumab 2 months after SBRT for the lung because of synchronous diagnosed rectal cancer and developed fatal bronchopulmonary hemorrhage 6 months later. Among the patients with fatal bronchopulmonary hemorrhage, 6 patients (60%) used anticoagulant or antiplatelet drugs during SBRT, compared to 31 (50%) of 62 patients who did not die of bronchopulmonary hemorrhage ($p = 0.736$). Tumor histology was not significant associated with fatal bronchopulmonary hemorrhage ($p = 0.094$).

Dosimetric details are shown and related to toxicity in Table 3. Median PTV $D_{2\%}$ was 136% of the prescription dose (IQR 130–140%) in all patients, meaning a median PTV $D_{2\%}$ of 81.5 Gy with a BED_{10} of 137 Gy. Sufficient coverage with a PTV $D_{95\%}$ of more than 60 Gy and a PTV $D_{99\%}$ of more than 54 Gy was achieved in 42 (58%) and 61 (85%) patients respectively, with a median PTV $D_{95\%}$ of 60.1 Gy (59.3–60.9 Gy) and a median PTV $D_{99\%}$ of 56.9 (55.4−58.1 Gy). A significant difference between patients with or without grade ≥3 toxicity was found for the D_{mean} to the main bronchus (median 48.1 Gy vs 25.6 Gy, $p = 0.003$). The mean dose to the main bronchus above which the risk of grade ≥3 toxicity increased significantly was determined at 41.0 Gy in 12 fractions with a BED_3 of 91 Gy. Patients with a mean dose more than versus less than this threshold experienced grade ≥3 toxicity in 56% versus 11% of cases, respectively. For the D_{mean} to the main bronchus, the odds ratio (OR) was 1.065 (95%CI 1.019–1.113), indicating an increase in the odds of grade ≥3 toxicity of 6.5% per Gy mean dose increase. Adjusted for age, the D_{mean} to the main bronchus remained significant and age appeared redundant. A significant difference between patients with or without grade 5 toxicity was found for the D_{mean} to the main bronchus (median 49.3 vs 26.4 Gy, $p = 0.001$). A trend toward significance was seen for the $D_{2\%}$ to the main bronchus and the V20Gy for the lung. There was no significant association between the distance from PTV to main bronchus and the risk of grade ≥ 3 or grade 5 toxicity.

Discussion

For patients with early stage or medically inoperable lung cancer, SBRT has become the first-line therapy [19]. Peripherally located tumors can be treated safely and effectively with SBRT [19–21]. However, treatment of ultra-central tumors remains challenging, because of the proximity of critical mediastinal structures, which led investigators to propose different protracted SBRT regimens [11,13,22]. This retrospective single-center analysis demonstrates the safety and efficacy of a protracted SBRT regimen of 60 Gy in 12 fractions for ultra-central lung tumors in 72 patients. Grade 3 or higher toxicity developed in 21% of patients with grade 5 toxicity in 14%, all related to bronchopulmonary hemorrhage. According to the results of this analysis, limiting the mean dose to the bronchus to 42.0 Gy in 12 fractions could decrease the risk of grade ≥3 toxicity to 11% in this setting. At a median follow-up of 19 months, 1- and 2-year local control rates were 98% and 85%, respectively. Overall survival rates at 1 and 2 years were 77% and 52%, respectively.

A recent large meta-analysis on 9 studies reported on the toxicity of SBRT for ultra-central lung tumors [21]. In line with the present analysis, they found a pooled grade ≥3 toxicity rate of 23.3%, however with a wide range (0−55%) and significant heterogeneity over all studies. Grade 5 toxicity rates ranged from 0 to 22% with lung hemorrhage as the main cause of death (68%) [19]. Explanations for this notable variation include the use of different fractionation regimens,

heterogeneity in the definition of an ultra-central tumor and differences in patient selection. To our knowledge, only 1 study previously reported outcomes of the 60 Gy in 12 fractions regimen for ultra-central lung tumors [11]. Their used definition of ultra-central tumors aligns with the current analysis, with the exception of tumors abutting the esophagus. Their reported toxicity profile compares unfavorably to the current series with 38% of patients experiencing grade $\geq$3 toxicity and 21% scored as having a possible or likely treatment-related death [11]. This might be explained by the high number of patients having tumor sizes $>$5 cm (60%) and even $>$7 cm (32%), which are much larger than those of tumors generally indicated for SBRT [11,23]. As a result, their median PTV volume of 104.5 cm^3 is much larger compared to the median PTV volume of 55.6 cm^3 in the current analysis [11].

Tekatli et al. suggested squamous cell histology, endobronchial involvement and anticoagulant use during radiotherapy as possible risk factors. Also, PTV D_{max} above 123% of the prescription dose in all treatment plans was considered as possible contribution to the observed toxicity, leading to a modification of the institutional protocol with a permitted D_{max} of 110% of the prescription dose instead of 140% [11]. The same risk factors for fatal hemorrhage were proposed by other previous studies, with the addition of the use of anti-vascular endothelial growth factor therapy (anti-VEGF) around the SBRT treatment [24,25]. In our series, 60% of patients with fatal bronchopulmonary hemorrhage used anticoagulant or antiplatelet drugs during SBRT, compared to 50% of patients who did not die of fatal hemorrhage. Also, two patients received the anti-VEGF therapy bevacizumab during and 2 months after SBRT of the lung, respectively. The latter patient died of bronchopulmonary hemorrhage, 6 months after initiation bevacizumab. In addition, Chaudhuri et al. reported that biopsy and bronchoscopy of the radiated main bronchus could increase the risk of lung hemorrhage [10]. This was the case in one of our patients who died of bronchopulmonary hemorrhage one month after she have had a biopsy of a necrotic patch in the irradiated bronchus.

A recent systemic review on ultra-central SBRT found that a D_{max} BED_3 of more than 180 Gy to the PBT was associated with higher rates of excessive toxicity and mortality, whereas no high-grade toxicity was observed for a D_{max} BED_3 below 140 Gy [26]. Although we did not find a significant correlation between the $D_{2\%}$ to the main bronchus and grade $\geq$ 3 toxicity, there was a trend showing higher rates of grade $\geq$3 toxicity with higher maximum doses to the main bronchus. Median $D_{2\%}$ for the main bronchus for patients with grade $\geq$ 3 toxicity was 69.6 Gy in our report, which is equal to 204 Gy BED_3 and thus much higher than the proposed cutoff of 180 Gy BED_3. In addition, median PTV $D_{2\%}$ was 137%, which could, according to Tekatli *et al.* [11] and together with the high median $D_{2\%}$ to bronchus, have contributed to the grade $\geq$ 3 toxicity rate of 21%.

When looking at the previous described risk factors for fatal bronchopulmonary hemorrhage, these could partly explain the observed rate of grade 5 toxicity of 14% in our analysis. On the other hand, a more aggressive behavior of ultra-central tumors with contact or direct invasion of critical mediastinal structures cannot be ruled out. An autopsy study reported fatal hemorrhage as an immediate cause of death due to any lung cancer in 12% of patients [27]. Also, the incidence of fatal hemoptysis in patients with central lung tumors after conventional fractionated radiotherapy in previous studies were 3–8% [28,29], indicating that the rate of fatal hemoptysis after SBRT for ultra-central lung tumors is higher, but not exceptionally high. Besides, the updated meta-analysis of Rim *et al.* (2020) demonstrated a pooled grade $\geq$3 toxicity rate of 10.4%, much lower than revealed in their previous meta-analysis in 2019. This is mainly due to inclusion of more recent trials which found lower rates of grade $\geq$3 toxicity (0−8%) [30–33], potentially because of avoidance of such risk factors as described in the previous studies and improved radiotherapy techniques [34].

The most recent meta-analysis of 72 studies of Rim *et al.* demonstrated pooled 1- and 2-year local control rates of 93.3% (95% CI 95.6–8.9%) and 90.4% (95% CI 77.8–96.2%) after SBRT for ultra-central lung tumors, respectively. The corresponding pooled 1- and 2-year overall survival rates were 82.2% (95% CI 71.7–89.7%) and 66.4% (95% CI 51.4–78.7%), respectively [34]. These numbers are in line with our results. When comparing the local control and overall survival rates with the rates for central tumors, to which higher fractionation doses are described in most studies, no differences were found [34]. So, despite the knowledge that a BED_{10} of $\geq$100 Gy leads to a low local failure rate of 8% compared to a local failure rate of 26% for a BED_{10} of $<$100 Gy [4], our protracted SBRT regimen with a BED_{10} of 90–150 Gy leads to somewhat limited, but very decent local tumor control, comparable with that for central tumors. These favorable local control rates might be the result of the higher accepted PTV max doses up to a median of 147 Gy BED_{10}. However, it was also stated that with a threshold of BED_{10} 60 Gy for lymph node metastases and 85 Gy for primary tumors, a favorable 1-year regional control rate of 92% and a pooled 1-year local control rate of 94.3% with low heterogeneity was found respectively, suggesting that BED_{10} over 100 Gy is not always necessary and should be carefully administered, taking the risk factors for fatal hemorrhage into account [34,35]. In addition, we found a lower overall survival rate (36% at 3 years) in our cohort, compared to that for peripheral tumors (about 56% at 3 years [4]). This could be explained by the higher rates of toxicity and mortality and the lower dose that can be given in the treatment of ultra-central tumors, leading to higher rates of local progression and worse overall survival compared to peripheral tumors. Some limitations apply to this analysis. Due to the retrospective design, there was no standardized follow-up regimen for all patients. Second, although the sample size provided reasonable estimates of studied safety and efficacy outcomes, no sufficient power for correlative research and subgroup analyses could be provided. Strengths of this analysis include the consecutive real-world series of patients who were homogeneously treated and that this analysis to our knowledge is the largest single-center analysis examining the safety and efficacy of SBRT for ultra-central lung tumors. To further strengthen the body of

evidence for protracted SBRT the results of the SUNSET study are eagerly awaited, which is a multicenter phase 1 dose–escalation study determining the maximum tolerated dose for ultra-central non-small cell lung cancer [36]. Furthermore, promising results were published on magnetic resonance-guided SBRT with daily online plan adaption [37], offering improved organ at risk sparing and providing opportunities to further escalate the dose to the PTV. Until then, potential risks of toxicity and treatment failure of SBRT for ultra-central lung tumors should be considered and discussed with the patient in the context of shared decision-making.

In conclusion, a protracted SBRT regimen of 60 Gy in 12 fractions for ultra-central lung tumors leads to high local control rates in patients who are not suitable for surgery. The rate of grade $\geq$3 toxicity is similar to previous published results, however with substantial risk of fatal bronchopulmonary hemorrhage. Possible risk factors of bronchopulmonary hemorrhage such as dose to the main bronchus or proximal bronchial tree, peri- or endobronchial tumor location and anti-VEGF or antithrombotic therapy should be taken into account when applying this protracted SBRT regimen. Our analysis suggests to limit the D_{mean} BED_3 to the main bronchus below 91 Gy.

Disclosure statement

The authors report no conflicts of interest.

References

[1] Videtic GMM, Donington J, Giuliani M, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: executive summary of an ASTRO evidence-based guideline. Pract Radiat Oncol. 2017;7(5):295–301.

[2] Guckenberger M, Andratschke N, Dieckmann K, et al. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. Radiother Oncol. 2017;124(1):11–17.

[3] Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer. 2004;101(7):1623–1631.

[4] Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. J Am Med Assoc. 2010;303(11):1070–1076.

[5] Tateishi Y, Takeda A, Horita N, et al. Stereotactic body radiotherapy with a high maximum dose improves local control, cancer-specific death and overall survival in peripheral early-stage non-small cell lung cancer. Int J Radiat Oncol [Internet]. 2021, Apr 21 [cited 2021 May 15]. https://linkinghub.elsevier.com/retrieve/pii/S0360301621003758.

[6] Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol. 2006;24(30):4833–4839.

[7] Bezjak A, Paulus R, Gaspar LE, et al. Efficacy and toxicity analysis of NRG oncology/RTOG 0813 trial of stereotactic body radiation therapy (SBRT) for centrally located non-small cell lung cancer (NSCLC). Int J Radiat Oncol. 2016;96(2):S8.

[8] Lindberg K, Bergström P, Brustugun OT, et al. OA24.05 The nordic HILUS-trial-first report of a phase II trial of SBRT of centrally located lung tumors. J Thorac Oncol. 2017;12(1):S340.

[9] Roesch J, Panje C, Sterzing F, et al. SBRT for centrally localized NSCLC: what is too central? Radiat Oncol. 2016;11(1):157.

[10] Chaudhuri AA, Tang C, Binkley MS, et al. Stereotactic ablative radiotherapy (SABR) for treatment of central and ultra-central lung tumors. Lung Cancer. 2015;89(1):50–56.

[11] Tekatli H, Haasbeek N, Dahele M, et al. Outcomes of hypofractionated high-dose radiotherapy in poor-risk patients with 'ultracentral' non-small cell lung cancer. J Thorac Oncol. 2016;11(7):1081–1089.

[12] Daly M, Novak J, Monjazeb A. P2.05-056 safety of stereotactic body radiotherapy for central, ultracentral, and paramediastinal lung tumors. J Thorac Oncol. 2017;12(1):S1066.

[13] Bongers E, Dahele MR, Haasbeek CJ, et al. Hypofractionated stereotactic radiation therapy for large and central lung tumors. Int J Radiat Oncol. 2012;84(3):S549–S50.

[14] Song SY, Choi W, Shin SS, et al. Fractionated stereotactic body radiation therapy for medically inoperable stage I lung cancer adjacent to central large bronchus. Lung Cancer. 2009;66(1):89–93.

[15] Senthi S, Haasbeek CJA, Slotman BJ, et al. Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. Radiother Oncol. 2013;106(3):276–282.

[16] Stanic S, Paulus R, Timmerman RD, et al. No clinically significant changes in pulmonary function following stereotactic body radiation therapy for early-stage peripheral non-small cell lung cancer: an analysis of RTOG 0236. Int J Radiat Oncol Biol Phys. 2014;88(5):1092–1099.

[17] Wilke L, Andratschke N, Blanck O, et al. ICRU report 91 on prescribing, recording, and reporting of stereotactic treatments with small photon beams: statement from the DEGRO/DGMP working group stereotactic radiotherapy and radiosurgery. Strahlenther Onkol. 2019;195(3):193–198.

[18] Edge SB, Byrd DR, Compton CC, et al. 7th ed 2010 AJCC Cancer Staging Manual Seventh Edition. AJCC Cancer Staging Manual Seventh Edition. Ann Surg Oncol. 2010;17(6):1471–1474.

[19] Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol. 2015;16(9):e427.

[20] Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable Stage i non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys. 2011;81(5):1352–1358.

[21] Rim CH, Kim Y, Kim CY, et al. Is stereotactic body radiotherapy for ultra-central lung tumor a feasible option? A systemic review and meta-analysis. Int J Radiat Biol. 2019;95(3):329–337.

[22] Regnery S, Eichkorn T, Weykamp F, et al. Safety and efficacy of stereotactic body radiotherapy in ultracentral lung tumors using a risk-optimized fractionation scheme. Clin Lung Cancer. 2020;S1525–7304(20):30336–30333.

[23] Tekatli H, van 't Hof S, Nossent EJ, et al. Use of stereotactic ablative radiotherapy (SABR) in non-small cell lung cancer measuring more than 5 cm. J Thorac Oncol. 2017;12(6):974–982.

[24] Goto K, Endo M, Kusumoto M, et al. Bevacizumab for non-small-cell lung cancer: a nested case control study of risk factors for hemoptysis. Cancer Sci. 2016;107(12):1837–1842.

[25] Haseltine JM, Rimner A, Gelblum DY, et al. Fatal complications after stereotactic body radiation therapy for central lung tumors abutting the proximal bronchial tree. Pract Radiat Oncol. 2016;6(2):e27–e33.

[26] Chen H, Laba JM, Zayed S, et al. Safety and effectiveness of stereotactic ablative radiotherapy for ultra-central lung lesions: a systematic review. J Thorac Oncol. 2019;14(8):1332–1342.

[27] Nichols L, Saunders R, Knollmann FD. Causes of death of patients with lung cancer. Arch Pathol Lab Med. 2012;136(12):1552–1557.

[28] Topkan E, Selek U, Ozdemir Y, et al. Risk factors for fatal pulmonary hemorrhage following concurrent chemoradiotherapy in stage 3B/C squamous-cell lung carcinoma patients. J Oncol. 2018;2018:1–9.

[29] Kim Y-H, Kim E-Y, Ban H-J, et al. Risk factors for fatal hemoptysis after concurrent chemoradiation therapy in patients with non-small cell lung carcinoma. Chonnam Med J. 2010;60(2):234–241.
[30] Lenglet A, Campeau MP, Mathieu D, et al. Risk-adapted stereotactic ablative radiotherapy for central and ultra-central lung tumours. Radiother Oncol. 2019;134:178–184.
[31] Raman S, Yau V, Pineda S, et al. Ultracentral tumors treated with stereotactic body radiotherapy: single-institution experience. Clin Lung Cancer. 2018;19(5):e803–e810.
[32] Chang JH, Poon I, Erler D, et al. The safety and effectiveness of stereotactic body radiotherapy for central versus ultracentral lung tumors. Radiother Oncol. 2018;129(2):277–283.
[33] Bin MM, Wang HH, Zaorsky NG, et al. Risk-adapted stereotactic body radiation therapy for central and ultra-central early-stage inoperable non-small cell lung cancer. Cancer Sci. 2019;110(11):3553–3564.
[34] Rim CH, Shin IS, Yoon WS, et al. Dose–response relationship of stereotactic body radiotherapy for ultracentral tumor and comparison of efficacy with central tumor: a meta-analysis. Transl Lung Cancer Res. 2020;9(4):1268–1284.
[35] van Diessen JNA, Kwint M, Sonke JJ, et al. Safety and efficacy of reduced dose and margins to involved lymph node metastases in locally advanced NSCLC patients. Radiother Oncol. 2020;143:66–72.
[36] Giuliani M, Mathew AS, Bahig H, et al. SUNSET: Stereotactic radiation for ultracentral non-small-cell lung cancer: a safety and efficacy trial. Clin Lung Cancer. 2018;19(4):e529–e532.
[37] Henke LE, Contreras JA, Green OL, et al. Magnetic resonance image-guided radiotherapy (MRIgRT): A 4.5-year clinical experience. Clin Oncol (R Coll Radiol). 2018;30(11):720–727.