The HILUS-Trial—a Prospective Nordic Multicenter Phase 2 Study of Ultracentral Lung Tumors Treated With Stereotactic Body Radiotherapy

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ABSTRACT

Introduction: Stereotactic body radiation therapy of thoracic tumors close to the central airways implies risk of severe toxicity. We report a prospective multicenter phase 2 trial for tumors located less than or equal to 1 cm from the proximal bronchial tree with primary end point of local control and secondary end point of toxicity.
Methods: Stereotactic body radiation therapy with 7 Gy × 8 was prescribed to the 67% isodose encompassing the planning target volume. The patients were stratified to group A (tumors ≤ 1 cm from the main bronchi and trachea) or group B (all other tumors). Risk factors for treatment-related death were tested in univariate analysis, and a logistic regression model was developed for fatal bronchopulmonary bleeding versus dose to the main bronchi and trachea.

Results: A total of 65 patients (group A/group B, n = 39/26) were evaluated. The median distance between the tumor and the proximal bronchial tree was 0 mm (0–10 mm). The 2-year local control was 83%. Grade 3 to 5 toxicity was noted in 22 patients, including 10 cases of treatment-related death (bronchopulmonary hemorrhage, n = 8; pneumonitis, n = 1; fistula, n = 1). Dose to the combined structure main bronchi and trachea and tumor distance to the main bronchi were important risk factors. Dose modeling revealed minimum dose to the “hottest” 0.2 cc to the structure main bronchi and trachea as the strongest predictor for lethal bronchopulmonary hemorrhage.

Conclusions: On the basis of the presented data, 7 Gy × 8, prescribed to the planning target volume-encompassing isodose, should not be used for tumors located within 1 cm from the main bronchi and trachea. Group B-type tumors may be considered for the treatment on the basis of an individual risk-benefit assessment and a maximum dose to the main bronchi and trachea in the order of 70 to 80 Gy (equivalent dose in 2 Gy fractions).

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Introduction

Treating peripherally located lung tumors with stereotactic body radiation therapy (SBRT) results in high local tumor control and limited side effects.1,2 To apply the technique for centrally located tumors is, however, debatable because early attempts resulted in an increased rate of high-grade toxic effects.3 Subsequent analyses though have reported an acceptable rate of greater than or equal to grade 3 side effects provided with the use of a modified fraction schedule,4 and results from the prospective RTOG 0813 trial support the use of 12 Gy × 5 for these tumors.5 However, owing to a nonstringent definition of a central location, moderately central tumors have been evaluated together with tumors positioned in an ultracentral location, out of which the latter has been highlighted as a risk factor for high-grade toxic effects.6–10 Hence, the use of SBRT in centrally located lung lesions is still not fully understood. High-quality scientific evidence is needed to understand which tumors may be treated safely and to define maximum tolerated radiation doses to different parts of central thoracic structures.

We here report the outcome of the prospective Nordic HILUS-trial—an open, nonrandomized phase 2 trial in which the patients received risk-adapted SBRT for tumors located within 1 cm of the proximal bronchial tree (PBT).

Materials and Methods

Patient Cohort

The Nordic HILUS-trial included patients at nine centers in Sweden, Denmark, and Norway between July 2011 and March 2016. Primary end point was local control at 6, 12, and 24 months, and secondary end points included toxicity and overall survival (OS). Inclusion criteria consisted of a centrally located inoperable primary lung cancer or a metastasis from any other solid tumor. Central location was defined as a 1-cm zone around the carina, main bronchi, intermedius bronchus, and lobar bronchi (i.e., the PBT) (Fig. 1). Maximum diameter of the central lesion was 5 cm. For primary lung cancer, the target was confirmed either with cytology or radiology with local growth on the basis of two consecutive computed tomography (CT) scans and a positive uptake on positron emission tomography with 18F-fluorodeoxyglucose-postion emission tomography (18F-FDG-PET). For metastases, local progression was required. Further requirements were life expectancy of at least 3 months, age more than 20 years, WHO performance status (PS) of 0 to 2, and signed written informed consent to participate in the trial. Previous and simultaneous radiation therapies to other noncentral tumors were allowed as long as dose constraints to organs at risk (OAR) were not violated, and the planning target volumes (PTVs) did not overlap. Patients with tumors extending through the wall of a main bronchus visible on a CT scan were not included, nor candidates for curative radiochemotherapy or patients with known brain metastases. Concomitant anticancer treatment was not allowed.

Diagnostic Work-Up Pre-SBRT and Follow-Up Post-SBRT

Before SBRT, all patients underwent physical examination with grading of baseline symptoms, CT scan of the thorax and upper abdomen, electrocardiography, dynamic pulmonary function test, and if possible an 18F-FDG-PET. After SBRT, the patients were followed up every 3 months during the first 2 years and thereafter.
every 6 months for a further 3 years with clinical examinations and CT scans. Toxicity was graded according to the National Cancer Institute—Common Terminology Criteria for Adverse Events version 4.0. Tumor assessment was scored using the Response Evaluation Criteria in Solid Tumors version 1.1. During follow-up, $^{18}$F-FDG-PET, electrocardiography, and pulmonary function tests were performed regularly. The study was approved by the ethical committee in each country (registration number: 2011/676-31/3), and all patients signed written informed consent.

**Radiation Therapy**

The stereotactic body frame or a vacuum pillow in combination with a wing board was the most common patient fixation method. Four centers used abdominal compression. Tumor movements were evaluated during normal breathing using 4-dimensional CT or fluoroscopy. The treatment-planning CT (with or without contrast) was performed with maximum 3-mm-reconstructed slice thickness within the PTV and the bronchial tree and maximum 5-mm-reconstructed slice thickness outside of these structures. The treatment was delivered during approximately 2 weeks with eight fractions, 1 to 3 days apart, and not exceeding four fractions per week. A cone-beam CT was performed before each fraction for verification and correction of the position on the treatment couch.

The dose ($7 \text{ Gy} \times 8$ to all centrally located targets) was prescribed to approximately the 67% isodose line (in relation to the maximum dose [$D_{\text{max}}$]) as closely as possible encompassing the PTV, resulting in $D_{\text{max}}$ at the center of the target of approximately 50% greater than the prescribed dose. The treatment planning was done using 6 MV photons except for one patient in which the protocol was violated using a combination of 6 and 10 MV photons. The analytical anisotropic algorithm or the collapsed cone algorithm was used for dose calculation. Volumetric-modulated arc therapy, intensity-modulated radiotherapy, and static fields were used (Supplementary Table 1).

**Delineation.** Generally, both the gross tumor volume and the clinical target volume (CTV) comprised the tumor lump. The PTV included the gross tumor volume or CTV with a margin of generally 5 to 10 mm or the internal target volume with a margin of 5 to 10 mm (Supplementary Table 1). The OAR were delineated at each center before treatment and comprised the lungs, esophagus, spinal cord, heart, trachea, and main bronchi. Before opening the trial, a dummy run was performed to verify a consensus in delineation across the centers. Delineation guidelines and dose constraints to OAR are described in Supplementary Table 2.

**Priorities, Dose Guidelines, and Dose Constraints to the OAR.** The protocol was designed on the basis of a hierarchical structure of priorities to optimize the balance between dose coverage of the target and dose constraints to OAR. The highest priority was given to hard dose constraints to the spinal cord, trachea, and contralateral main bronchus followed by dose coverage of the target. Generally, at least 95% of the PTV should be covered by 95% of the prescribed dose, but if an OAR extended inside the PTV, the minimum PTV and CTV doses should be at least 80% and 85% of the prescribed dose, respectively (Supplementary Fig. 1A–C). The third priority consisted of soft dose guidelines to the remaining OAR. However, even if the second and third priorities could not be fulfilled, the patient could remain...
in the trial, provided a clinically approved balance between the violation of dose guidelines and the lack of target coverage.

**Estimated Doses to the Bronchi in the Final Analysis.** Before the analysis, all OAR were redelineated by two members of the study team (CB and VG). Because of the small dimensions, all bronchial structures were defined as high-resolution structures (Eclipse treatment planning system). For a better representation of the absorbed doses to the wall of the trachea and main bronchus, the delineation of the lumen of these structures was expanded by 2 mm. Three new combined structures were then created and used in the final dose analysis, as follows:

1. **Structure 1:** consisting of the lumen of the trachea plus the ipsilateral main bronchus and in some patients also the contralateral main bronchus;
2. **Structure 2:** consisting of structure 1 expanded by a 2-mm margin;
3. **Structure 3:** consisting of structure 1 subtracted from structure 2, representing the wall only.

The absorbed dose to structures 1 to 3 was recalculated in equivalent dose in 2 Gy fractions (EQD2) (using \( \alpha/\beta = 3 \) Gy); \( D_{\text{max}} \), \( D_{0.01cc} \) (the minimum dose to the “hottest” 0.01 cc), \( D_{0.2cc} \) (the minimum dose to the “hottest” 0.2 cc), \( D_{0.5cc} \) (the minimum dose to the “hottest” 0.5 cc), and \( D_{1.0cc} \) (the minimum dose to the “hottest” 1.0 cc) were analyzed.

A total of 30 patients received other radiotherapy regimens before, simultaneously, or after the study treatment but outside of the study volumes. The dose contribution to the main bronchi and trachea from nonstudy treatments to structure 1 was less than 2 Gy and considered not relevant for 24 of these patients. For the remaining six patients, a plan sum evaluating the summation dose of both treatments in EQD2 (\( \alpha/\beta = 3 \) Gy) was created, and this summation dose was used in the analysis. To evaluate the summation dose to other thoracic OAR, the same summation procedure was used, however with focus on the relevant OAR.

**Statistics**

The patients were stratified to either group A (≤1 cm from a main bronchus/trachea) or group B (all other patients) (Fig. 1). To evaluate hypotheses of variables in contingency tables, the chi-square test was used or, in the case of small expected frequencies, Fisher’s exact test. Statistical comparisons to test differences between two independent groups were made by the use of the Student’s *t* test for uncorrelated means. Survival rates were estimated by the Kaplan-Meier method and compared by the log-rank test. Logistic regression analyses were performed for time-dependent variables, calculating ORs with 95% confidence intervals (CIs). In addition, descriptive statistics and graphical methods have been used to characterize the data. All analyses were carried out by use of the Statistical Analysis System statistical software (the SAS system for Windows 9.4, SAS Institute Inc., Cary, NC) and GraphPad Prism8 (GraphPad Software, San Diego, California). A *p* value of less than 0.05 was considered significant. Logistic regression was performed to model the risk of fatal bronchopulmonary hemorrhage versus bronchial dose (Interactive statistics web pages).

**Results**

**Patient Cohort Description**

A total of 74 patients were included in the trial; 65 were treated according to protocol and are included in the current analysis. There was an equal distribution between the sexes, the patients were of good PS (83% in PS 0–1), and the predominant primary tumor origin was NSCLC (78%). Baseline patient characteristics of the patients in group A (n = 39 patients) and group B (n = 26 patients) are presented in Table 1. Median follow up was 24 months (3–76 months). Arm A was closed in June 2015 after a preliminary toxicity analysis.

**Hilus Target Description and Doses to OAR**

A total of 68 centrally located tumors were treated according to protocol (target details are presented in Table 1). The tumors in group A had a median (range) distance to a main bronchus of only 5 mm (0–10 mm), whereas in group B, it was 20 mm (12–35 mm). A total of 24 patients had tumors located between 0 and 5 mm from the main bronchus, 15 patients had tumors located 6 to 10 mm from the main bronchus, and 26 patients had tumors located greater than 10 mm from the main bronchus (Fig. 1). The median \( D_{\text{max}} \) minimum dose to the “hottest” 0.01 cc, minimum dose to the “hottest” 0.2 cc, minimum dose to the “hottest” 0.5 cc, and minimum dose to the “hottest” 1.0 cc to structure 1 (i.e., the lumen of trachea plus ipsilateral main bronchus) were 97 Gy (1.9–212 Gy), 85 Gy (1.5–210 Gy), 65 Gy (1.0–207 Gy), 53 Gy (0.8–203 Gy), and 41 Gy (0.6–194 Gy), respectively, in EQD2 (\( \alpha/\beta = 3 \) Gy). Doses to other OAR and structure 2 and structure 3 are presented in Supplementary Table 3.

**Local Control**

A total of 64 patients were evaluated for local control (one patient died within 3 months post-SBRT before radiologic evaluation). Tumor location for tumors with local recurrence is presented in Figure 1 and Kaplan-
### Table 1. Patient Cohort Characteristics, Per Protocol Analysis

| Patient and Target Characteristics | Entire Cohort | Group A | Group B |
|-----------------------------------|--------------|---------|---------|
| **Patient characteristics**       | n or Median  | n or Median | n or Median |
| No. of patients, n                | 65           | 39      | 26      |
| Men/women, n                      | 37/28        | 21/18   | 16/10   |
| Age, y median                     | 70           | 69      | 71      |
| ECOG-PS 0-1/2/ND, n               | 54/10/1      | 35/3/1  | 19/7/0  |
| FEV1, liters median               | 1.5 (0.5-4.6)| 1.7 (0.8-4.0)| 1.3 (0.5-4.6)|
| **Primary tumor**                 |              |         |         |
| LC-ADCA, n                        | 17           | 10      | 7       |
| LC-SCC, n                         | 19           | 13      | 6       |
| LC-NS, n                          | 15           | 6       | 9       |
| RCC, n                            | 8            | 6       | 2       |
| CRC, n                            | 4            | 2       | 2       |
| Other, n                          | 2            | 2       | 0       |
| **Hilus target characteristics**  |              |         |         |
| No. of hilus targets, n           | 68           | 42      | 26      |
| Type of hilus target, primary LC/lymph node/metastasis | 36/24/8 | 17/20/5 | 19/4/3 |
| Distance to the PBT (any part), mm median | 0 (0-10) | 0 (0-6) | 6 (0-10) |
| Distance to the main bronchus, mm median | 8 (0-35) | 5 (0-10) | 0 (0-10) |
| Distance to the lobar bronchus, mm median | 1 (0-20) | 0 (0-20) | 6 (0-10) |
| Overlap PTV−main bronchus, n      | 23           | 23      | 0       |
| Overlap PTV−PBT, n                | 49           | 35      | 87      |
| Size, mm median                   | 22           | 9-54    | 9-48    |
| GTV, cc median                    | 7.5          | 6.2     | 8.8     |
| CTV, cc median                    | 10.8         | 9.7     | 11.7    |
| PTBV, cc median                   | 43.1         | 40.3    | 45.5    |
| GTV mean physical dose, Gy median | 79           | 79      | 80      |
| PTBV min physical dose, Gy median | 43           | 41      | 47      |
| Cytologically verified, n         | 42           | 24      | 18      |
| **Nonhilus target characteristics**|            |         |         |
| No. of nonhilus lung targets, n   | 21           | 17      | 4       |
| No. of nonhilus nonlung targets, n| 2            | 1       | 1       |

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Figure 2. Local control for (B) the entire cohort and (A) divided in Grps A and B (p > 0.05). Grp, group.
Meier curves for local control are presented in Figure 2. The local control rate at 6, 12, 24, and 36 months was 95% (95% CI: 85%–98%), 85% (95% CI: 72%–92%), 83% (95% CI: 69%–91%), and 83% (95% CI: 69%–91%), respectively. Local control did not differ between groups A and B ($p > 0.05$) (Fig. 2). Nine patients had local failure, which was diagnosed with CT only (n = 4), PET-CT (n = 2) or CT with a subsequent PET-CT (n = 3).

**Toxicity**

A total of 65 patients were included in the toxicity analysis. The most common baseline symptoms were grades 1 to 2 cough, 1 to 2 dyspnea, and 1 to 2 fatigue (Supplementary Table 4), and the most frequently registered toxic effects were grades 1 to 2 cough, 1 to 2 dyspnea, and 1 to 2 pneumonitis. Grades 3 to 4 toxicity was noted in 14 patients. Toxic symptoms are presented in Table 2, and Supplementary Table 5 provides detailed information on doses to different OAR for patients with grades 3 to 5 toxicities.

There were 10 cases of possible grade 5 toxic effects (hemoptysis n = 8, pneumonitis n = 1, tracheoesophageal fistula n = 1) (tumor location is presented in Fig. 1). Univariate analyses (Supplementary Table 6) revealed that the distance between the tumor and main bronchus and $D_{0.2cc}$, $D_{0.5cc}$ and $D_{1.0cc}$ for structure 1 (i.e. the lumen of the main bronchus plus trachea) were significant for both overall grade 5 toxicity and for fatal bleedings specifically ($p < 0.05$) (results from the UVA for structure 2 and 3 as well as for tumor distance to the lobar bronchi differed between the outcomes and are presented in Supplementary Table 6). The clinical risk factors tested (age, PS, histology, tumor size) were not significant neither for all grade 5 toxicity nor for grade 5 bleeding specifically ($p > 0.05$). Time to grade 5 bleeding is presented in Figure 3. The importance of the proximity of the target to a main bronchus as a risk factor for grade

### Table 2. Maximum Recorded Toxicity Attributed to SBRT

| Toxic Symptoms                  | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---------------------------------|---------|---------|---------|---------|---------|
| Prespecified toxicity           |         |         |         |         |         |
| Atelectasis                     | 20      | 9       | 1       | 1       | 1       |
| Bronchopulmonary hemorrhage     | 1       | 2       | 1       | 1       | 1       |
| Cough                           | 16      | 21      | 7       | 2       | 1       |
| Dyspnea                         | 16      | 15      | 7       | 2       | 1       |
| Fatigue                         | 10      | 8       | 2       | 1       | 1       |
| Fistula                         | 1       | 1       | 1       | 1       | 1       |
| Fever                           | 2       | 1       | 1       | 1       | 1       |
| FEV-decrease$^a$                | 16      | 2       | 1       | 1       | 1       |
| Lung infection                  | 1       | 6       | 1       | 1       | 1       |
| Pain                            | 9       | 5       | 2       | 1       | 1       |
| Pericardial effusion            | 12      |         |         |         |         |
| Pleural effusion                | 20      | 9       | 1       | 1       | 1       |
| Pneumonitis                     | 22      | 3       |         |         |         |
| Pulmonary fibrosis              |         |         |         |         |         |
| Ventricular arrhythmia          |         |         |         |         |         |
| Nonprespecified toxicity        |         |         |         |         |         |
| Atrial fibrillation             |         |         |         |         |         |
| Atroventricular block           |         |         |         |         |         |
| Bronchial obstruction           |         |         |         |         |         |
| Bronchial constriction          |         |         |         |         |         |
| COPD-exacerbation               |         |         |         |         |         |
| Dysphagia                       |         |         |         |         |         |
| Empyema                         |         |         |         |         |         |
| Gastric ulcer                   |         |         |         |         |         |
| Mucous                          | 3       | 1       |         |         |         |
| Pneumothorax                    |         |         |         |         |         |
| Other$^c$                       |         |         |         |         |         |

$^a$Grade 1: 90% to 75% of baseline value; grade 2: 75% to 50% of baseline value.

$^b$In addition, have grade 5 hemoptysis.

$^c$Other includes dry skin grade 1 (n = 1), esophagitis grade 1 (n = 1), rib fracture grade 1 (n = 1), nausea grade 1 (n = 1), radiologic CT changes grade 1 (n = 1), rash grade 1 (n = 1) and grade 2 (n = 1), recurrence paresis grade 1 (n = 1), stridor grade 2 (n = 1), swallowing difficulties grade 1 (n = 1), and vertebral compression fracture grade 2 (n = 1).

COPD, chronic obstructive pulmonary disease; CT, computed tomography; FEV, forced expiratory volume.
5 bleeding was further highlighted by the significant difference in risk of grade 5 bleeding between tumors located 0 to 5 mm from a main bronchus in comparison to tumors located greater than 10 mm from a main bronchus \((p < 0.05)\) (Fig. 3C).

Fatal bronchopulmonary hemorrhage presented between 2 and 22 months post-SBRT (median = 15 months); the affected patients had few other lower-grade side effects. Clinical details, dose volume histograms (DVHs), and dose plans for the patients with grade 5 toxicities are presented in ES (Supplementary Table 7 and Supplementary Figs. 2 and 3). One of these patients had a regional recurrence and received additional radiotherapy to central parts of the lungs. One patient was not evaluated for local control. The patient presenting with a tracheoesophageal fistula at 9 months

![Figure 3](image3.png)

**Figure 3.** Time to grade 5 bleeding for (A) the entire cohort treated per protocol, (B) divided in Grps A and B \((p < 0.05)\), and (C) divided dependent on distance between the tumor and the main bronchus \((p < 0.05)\). Grp, group.

![Figure 4](image4.png)

**Figure 4.** Estimated probability of bronchopulmonary hemorrhage versus bronchial dose to the main bronchus plus trachea (lumen) in EQD2 for (A) different dose measures \(D_{\text{max}}, D_{0.01cc}, D_{0.2cc}, D_{0.5cc}, D_{1.0cc}\) with the corresponding \(p\) values of 0.12, 0.087, 0.049, 0.054, and 0.069, respectively. (B) reveals the specific estimate for \(D_{0.2cc}\) and (C) the specific estimate for \(D_{\text{max}}\), both with 95% confidence interval and patient-specific data. One patient received doses of greater than 200 Gy \(D_{\text{max}}\ and \(D_{0.2cc}\) and no grade 5 events. The data points generated from this patient represent extreme values and are not found in B and C. CI, confidence interval; \(D_{0.01cc}\), minimum dose to the “hottest” 0.01 cc; \(D_{0.2cc}\), minimum dose to the “hottest” 0.2 cc; \(D_{0.5cc}\), minimum dose to the “hottest” 0.5 cc; \(D_{1.0cc}\), minimum dose to the “hottest” 1.0 cc; \(D_{\text{max}}\), maximum dose; EQD2, equivalent dose in 2 Gy fractions.
also suffered from several other ≥grade 3 side effects during the entire follow-up period, such as lung infection, fever, and pain grade 4, and dyspnea grade 3) died nearly 2 years poststudy treatment in conjunction with surgical intervention of the fistula. At the central review, it was discovered that the esophagus unintentionally had extended into the PTV and had received a maximum physical dose of 80 Gy, greatly exceeding the guidelines of the protocol.

Modeling of fatal bronchopulmonary hemorrhage versus bronchial dose. Doses to structure 1, that is, lumen of the trachea plus the main bronchi, were the best predictors for bronchopulmonary hemorrhage. The dose-response models for this structure are found in Figure 4A to C.

Survival

The 1-, 2-, and 3-year OS rates were 81% (70%–89%), 58% (44%–69%), and 50% (37%–62%), respectively, for the entire cohort. Group A had inferior OS as compared with group B (p < 0.05, Supplementary Fig. 4A–C). The patients in group A as compared with group B were more often treated owing to metastatic disease (38% versus 19%) and less often treated to a primary node-negative NSCLC with curative intent (33% versus 62%).

Discussion

In this prospective phase 2 trial of ultracentrally located lung lesions, we have found that SBRT using 7 Gy × 8 (prescribed to the 67% isodose line encompassing the PTV) offers high local tumor control. At the same time, patients with tumors less than or equal to 1 cm from the main bronchi and trachea presented high risk of lethal toxic effects and survival was compromised.

Our reported local control of 83% at 2 years, with no difference between group A and group B, reflects an effective local treatment, especially considering the limited treatment options for this patient cohort. It also compares well to reported outcomes of SBRT from both primary tumors from NSCLC and metastases from other solid tumors, and despite including four cases of metastases from colorectal cancer, which is known to have a higher radioresistance to SBRT, all failures but one originated from NSCLC.

A total of 34% of the patients experienced grades 3 to 5 toxicity. The most frequently encountered grade 3 side effect in the current study was dyspnea, but given that most of the patients had NSCLC with reduced pulmonary capacity, this was not entirely unexpected and we cannot exclude that at least part of this was due to the disease itself or COPD. The other grades 3 to 4 side effects were of various types (Table 2) with different OAR of primary concern, which makes it difficult to certainly point out one specific OAR in common for these patients. In line with our experience, treating ultracentral lung lesions carries a risk of greater than or equal to grade 3 toxicity, reported to occur in 0% to 56% of treated patients, in which the broad range of incidence may be explained by the variety in tumor location and differences in treatment technique and applied dose restrictions to OAR.

Our major concern is the high rate of, as we suspect, fatal toxic effects, dominated by eight cases of grade 5 hemoptysis. As revealed in our and other reports, fatal hemoptysis was the most common form of grade 5 toxicity and may present more than one year postradiotherapy. A challenge here is to understand the underlying biological mechanism of this sudden bleeding and whether it was a result of a too high dose to normal tissue or if the bleeding was a consequence of local tumor growth or tumor necrosis. However, none of the patients with grade 5 bleeding had radiological signs of local recurrence before the bleeding and even though patients, categorized as group A rather than group B, were more likely to develop fatal hemoptysis (Fig. 3B), local control did not differ between these groups (Fig. 2B). The postmortem of two of these patients did neither reveal signs of local tumor growth nor verify the bleeding source, although a necrotic main bronchus was described in one of the patients.

No consensus exists on the definition of the ultracentral location, and dependent on the used definition, both the PBT, and other central thoracic structures may be the OAR of primary concern at treatment. Results from the current study, in which the main risk organ was the PBT, indicate that injury to the main bronchi or trachea results in increased risk for high-grade toxic effects. With a location similar to our group A patients, three other studies specifically investigated SBRT of tumors located close to the main bronchus. First, Tekatli et al. evaluated 47 patients treated with 5 Gy × 12, in which the PTV overlapped the trachea/main bronchus and reported a 21% occurrence of possible treatment-related death and no local recurrences. The tumor location and outcome are similar to the patients in group A in the current study (23% toxic death in group A and 2-y local control rate of 82%). A subsequent analysis from the same group on dose-response modeling with pooled data with another center, considering clinical and radiological toxicities of a less than or equal to 12-fraction course for centrally located lung tumors, revealed that a PTV overlapping with the main bronchi and trachea, COPD, and bronchial...
The dose were correlated to high-grade toxic effects.\textsuperscript{9} Secondly, Lischalk et al.\textsuperscript{17} also had a similar definition to ours of the ultracentral location and treated patients with 35 to 40 Gy in five fractions with no reported lethal toxicity but with inferior local control.\textsuperscript{17} Modified fraction schedules of 50 Gy in four fractions,\textsuperscript{25} 60 Gy in eight fractions,\textsuperscript{12,15,20} and 70 Gy in 10 fractions\textsuperscript{25} have reported less toxicity as compared with the current study. Unfortunately, these reports did not stipulate whether the tumors were close to a main or a lobar bronchus which is of interest because the latter situation seems to have a lower risk for high-grade side effects according to our results.

Reported clinical risk factors for lethal hemoptysis of SBRT of ultracentral lung tumors include endobronchial tumor growth,\textsuperscript{6,7} squamous histology,\textsuperscript{6,7,19} and the use of antiplatelet/anticoagulant medications.\textsuperscript{6,7} The current analysis could not confirm squamous histology as a risk factor. We did not evaluate the presence of endobronchial tumor growth before SBRT, and the use of bevacizumab post-SBRT was prohibited according to protocol and could thus not be tested. The interpretation of the use of anticoagulants is unreliable because it was only noted at the time of inclusion, and the bleedings developed at later times. For one patient, the possible impact of medical treatment with everolimus which has known bleeding side effect could however not be ruled out as a contributing factor to the fatal event.

The dose constraint to the contralateral main bronchus (6.1 Gy × 8) was chosen on the basis of previous work evaluating radiation-induced bronchial damage in which no atelectases were noted below a corresponding dose of 6.5 Gy × 8.\textsuperscript{26} The result of the modeling of fatal bronchopulmonary hemorrhage versus bronchial dose revealed a significant correlation to the dose to structure 1. However, the few fatal events from a statistical point of view, the large confidence intervals of the modeling (Fig. 4B and C), and the uncertainty of the cause of the fatal bleedings make it difficult to draw definitive conclusions on the radiosensitivity of the large bronchi. In comparison to the planned dose, when the daily anatomy is not known, the accumulation of the dose from each treatment fraction would probably be closer to the actually absorbed dose, and thus give a better estimate of the tolerance of the bronchi. However, a dose constraint obtained from the accumulated delivered dose would be difficult to use at conventional dose planning in which a PTV is used as a measurement of geometric uncertainty.

A direct comparison between ours and other reports of the absorbed doses (on the basis of the planned dose) is difficult to make because these reports either do not have the same outcome definition\textsuperscript{18,27} or report doses to the PBT rather than doses to the trachea/main bronchi.\textsuperscript{18,12,14,16} However, data presented in the current study reveal that all patients with lethal hemoptysis except one had a D\textsubscript{max} to the main bronchus or trachea of greater than 100 Gy (EQD\textsubscript{2}) and only one patient with grade 5 hemoptysis had received a D\textsubscript{max} of less than 70 Gy (EQD\textsubscript{2}) (Fig. 4C). This in combination with the finding that fatal hemoptysis was only recognized in one patient (4%) in group B compared with seven patients (18%) in group A supports the hypothesis that group B patients probably could be treated safely provided a D\textsubscript{max} of less than 70 to 80 Gy to the main bronchi/trachea. However, given the high-toxicity profile in group A, this treatment regimen carries too high a risk for serious side effects to be recommended for these patients. Treatment for them would require a balance between keeping the dose to the OAR below tolerance levels and maintaining an adequate dose coverage of the target. However, the current study cannot provide such a dose constraint for tumors less than or equal to 1 cm of the main bronchi and trachea and preliminary dose modeling of local control was inconclusive (data not found). Hence, extended and expanded data are needed, and it is hoped that the ongoing dose-escalation SUNSET-trial for ultracentral tumors can give further guidance on dose constraints to central thoracic structures.\textsuperscript{28}

OS differed between groups A and B in our analysis. This could not be entirely explained by the grade 5 toxic effects because death owing to other causes also was more common in group A (data not found) and might instead reflect more advanced tumor stages treated in group A as compared with group B. In contrast to our findings, Stam et al.\textsuperscript{27} could not confirm this difference statistically in their analysis of noncancer death in patients with tumors located according to the group A and B definitions, but the cohorts were limited.

There are several strengths of the study including its prospective design, the detailed treatment protocol, the tight definition of centrality, and the central redelineation of all OAR. Toxicity was consistently evaluated with prespecified toxic effects being graded at each visit to ascertain a thorough review. Limitations of the study include the relatively small patient material and limited number of events and the uncertainty regarding the cause of the fatal bleedings. We also allowed primary tumors and lymph nodes and distant metastases to be treated within the study, which limits the interpretation of survival. The study included medically frail patients who therefore had a limited follow-up.

In conclusion, treating tumors within 1 cm from the main bronchi and trachea with 56 Gy in eight fractions with inhomogeneous dose distribution implicates high risk for high-grade toxic effects, and this treatment regimen should therefore not be used for these tumors.
However, on the basis of the presented data, treating group B tumors (i.e., tumors ≤1 cm of the PBT but >1 cm from the main bronchi and trachea) with the evaluated regimen while observing a D$_{\text{max}}$ of 70 to 80 Gy EQD$_2$ ($\alpha/\beta = 3$) to the main bronchi and trachea would probably carry an acceptable risk of toxic effects and good local control of the treated lesion.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the Journal of Thoracic Oncology at www.jto.org and at https://doi.org/10.1016/j.jtho.2020.03.019.

References

1. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol. 2009;27:3290-3296.

2. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys. 2009;75:677-682.

3. 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;24:4833-4839.

4. Senthi S, Haasbeek CJ, Slotman BJ, Senan S. Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. Radiother Oncol. 2013;106:276-282.

5. Bezjak A, Paulus R, Gaspar LE, et al. Safety and efficacy of a five-fraction stereotactic body radiotherapy schedule for centrally located non-small-cell lung cancer: NRG oncology/RTOG 0813 trial. J Clin Oncol. 2019;37:1316-1325.

6. Rim CH, Kim Y, Kim CY, Yoon WS, Yang DS. Is stereotactic body radiotherapy for ultra-central lung tumor a feasible option? A systematic review and meta-analysis. Int J Radiat Biol. 2019;95:329-337.

7. Chen H, Laba JM, Zayed S, Boldt RG, Palma DA, Louie AV. Safety and effectiveness of stereotactic ablative radiotherapy for ultra-central lung lesions: a systematic review. J Thorac Oncol. 2019;14:1332-1342.

8. Tekatli H, Haasbeek H, 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;11:1081-1089.

9. Tekatli H, Duijm M, Oomen-de Hoop E, et al. Normal tissue complication probability modeling of pulmonary toxicity after stereotactic and hypofractionated radiation therapy for central lung tumors. Int J Radiat Oncol Biol Phys. 2018;100:738-747.

10. 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:e27-e33.

11. Horne ZD, Richman AH, Dohopolski MJ, Clump DA, Burton SA, Heron DE. Stereotactic body radiation therapy for isolated hilar and mediastinal non-small cell lung cancers. Lung Cancer. 2018;115:1-4.

12. Yang D, Cui J, Zhao J, et al. Stereotactic ablative radiotherapy of 60 Gy in eight fractions is safe for ultracentral non-small cell lung cancer. Thorac Cancer. 2020;11:754-761.

13. Lenglet A, Campeau MP, Mathieu D, et al. Risk-adapted stereotactic ablative radiotherapy for central and ultracentral lung tumours. Radiother Oncol. 2019;134:178-184.

14. Chang JH, Poon I, Erler D, Zhang L, Cheung P. The safety and effectiveness of stereotactic body radiotherapy for central versus ultracentral lung tumors. Radiother Oncol. 2018;129:277-283.

15. Raman S, Yau V, Pineda S, et al. Ultracentral tumors treated with stereotactic body radiotherapy: single-institution experience. Clin Lung Cancer. 2018;19:e803-e810.

16. Nguyen KNB, Hause DJ, Novak J, Monjazeb AM, Daly ME. Tumor control and toxicity after SBRT for ultracentral, central, and paramediastinal lung tumors. Pract Radiat Oncol. 2019;9:e196-e202.

17. Lischalk JW, Malik RM, Collins SP, Collins BT, Matus IA, Anderson ED. Stereotactic body radiotherapy (SBRT) for high-risk central pulmonary metastases. Radiat Oncol. 2016;11:28.

18. Jingu K, Matsushita H, Yamamoto T, et al. Stereotactic radiotherapy for pulmonary oligometastases from colorectal cancer: a systematic review and meta-analysis. Technol Cancer Res Treat. 2018;17:1533033818794936.

19. Wang C, Rimner A, Gelblum DY, et al. Analysis of toxic effects with antiangiogenic agents plus stereotactic body radiation in ultracentral lung tumors. JAMA Oncol. 2019;5:737-739.

20. Zhao Y, Khawandanh E, Thomas S, et al. Outcomes of stereotactic body radiotherapy 60 Gy in 8 fractions when prioritizing organs at risk for central and ultracentral lung tumors. Radiat Oncol. 2020;15:61.

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

22. Meng MB, 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;110:3553-3564.

23. Park S, Kim Y, Yoon WS, Rim CH. A preliminary experience of moderate-intensity stereotactic body radiation therapy for ultra-central lung tumor. Int J Radiat Biol. 2019;95:1287-1294.
24. Korzets Ceder Y, Fenig E, Popvtzer A, et al. Stereotactic body radiotherapy for central lung tumors, yes we can!. Radiat Oncol. 2018;13:77.

25. Chang JY, Li QQ, Xu QY, et al. Stereotactic ablative radiation therapy for centrally located early stage or isolated parenchymal recurrences of non-small cell lung cancer: how to fly in a “no fly zone” Int J Radiat Oncol Biol Phys. 2014;88:1120-1128.

26. Karlsson K, Nyman J, Baumann P, et al. Retrospective cohort study of bronchial doses and radiation-induced atelectasis after stereotactic body radiation therapy of lung tumors located close to the bronchial tree. Int J Radiat Oncol Biol Phys. 2013;87:590-595.

27. Stam B, Kwint M, Guckenberger M, et al. Subgroup survival analysis in stage I-II NSCLC patients with a central tumor partly treated with risk-adapted SBRT. Int J Radiat Oncol Biol Phys. 2019;103:132-141.

28. 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:e529-e532.