



Dose and Volume of the Irradiated Main Bronchi and Related Side Effects in the Treatment of Central Lung Tumors With Stereotactic Radiotherapy

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High radiation dose to the main bronchi can result in stenosis, occlusion or fistula formation, and death. Only 8 articles have reported side effects to the main bronchi from stereotactic body radiation therapy (SBRT), mostly with only one symptomatic complication per article. Therefore, we calculated the dose to the bronchial structures, such as trachea; mainstem bronchi; intermediate bronchus; upper-, middle-, and lower-lobe bronchus; and the segmental bronchi in 134 patients with central tumors and calculated the normal tissue complication probability (NTCP) for each of these structures, with toxicity determination based upon computed tomography imaging. No side effects were found in the trachea, and only stenosis occurred in the main bronchus and bronchus intermedius. Higher grades of side effects, such as occlusion and atelectasis, were only seen in the upper-, middle-, and lower bronchi and the segmental bronchi. When 0.5 cc of a segmental bronchi was irradiated to 50 Gy in 5 fractions, it was about 50% likely to be occluded radiographically. For grade 1 radiographically evident side effects, the 50% risk level for a 5-fraction $D_{\max}$ was 55 Gy for mid-bronchi and 65 Gy for mainstem bronchi. To assure the relationship between clinical toxicity and side effects to the bronchi, further investigation is needed.

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For several years, stereotactic body radiotherapy (SBRT) has been used for the treatment of stage I inoperable non-small-cell lung cancer and solitary lung metastases. This resulted in promising results for survival and local control.¹⁻³ However, when treating central lung tumors,⁴⁻⁶ these results are sometimes combined with high toxicity. Central lung tumors are defined as those tumors being located less than 2 cm from the trachea, mainstem bronchus, main bronchi, or esophagus; less than 6 mm from the heart or tumors located in the mediastinum (Fig. 1). High radiation dose to the main bronchi can result in stenosis, occlusion or fistula formation,

and death.^{5,7,8} Not only SBRT causes radiation-induced side effects of the lung and bronchus but also by other modalities. Gollins et al⁹ reported 38% and 58% bronchial stenosis after intraluminal brachytherapy (ILT) with a single dose of 15 and 20 Gy at 1 cm, respectively. Fibrotic reactions were seen 10-13 months after ILT.¹⁰

Bronchial stenosis has also been reported after high-dose external beam radiotherapy. Miller et al¹¹ used computed tomography (CT) scans to assess the incidence of bronchial stenosis after radiation treatment twice daily with high external beam radiotherapy. They reported a 1-year and 4-year actuarial rate of stenosis of 7% and 38%, respectively, with a median overall survival of 2.5 years. A suggestion of a dose-response effect was also found: 4% and 25% at a dose of approximately 74 Gy and 86 Gy, respectively. Kelsey et al¹² analyzed the bronchial stenosis of the mainstem bronchus in 18 patients with CT scans and found in 17 of the 18 patients a decrease in the airway caliber ranging from 6%-57%. The stenosis appeared to be dose dependent ($p = 0.08$), progressed with

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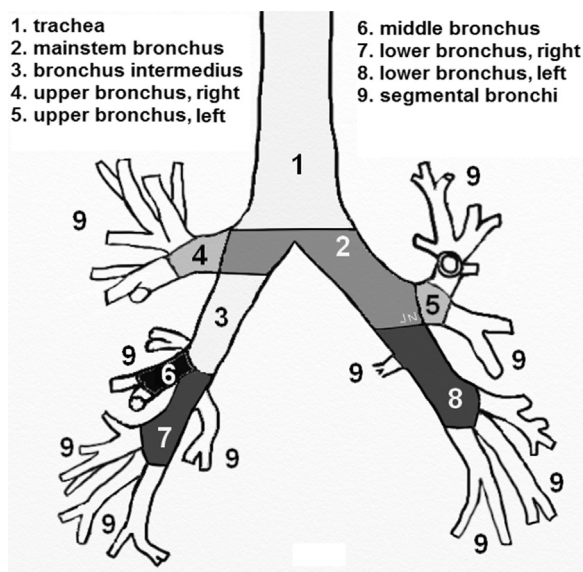


Figure 1 Bronchial structures.

increasing time after radiotherapy ($p = 0.04$) and was worse in patients who also received chemotherapy ($p = 0.04$). Although 17 of the 18 patients were diagnosed with stenosis, only 2 were known to have symptomatic bronchial stenosis.

Despite those records, there is still no clear consensus about the dose-related side effects of the bronchial structures in SBRT. Therefore, the aim of this study was to calculate the dose to the bronchial structures, such as trachea; mainstem bronchi; intermediate bronchus; upper-, middle-, and lower-lobe bronchus; and the segmental bronchi, to determine the time for the onset of side effects and to calculate the normal tissue complication probability (NTCP) of the side effects as seen on a CT scan for each of these structures.

Methods

Patients

From July 2006–December 2012, 134 patients with 143 central tumors were treated with SBRT on a robotic Cyberknife (Accuray Inc, Sunnyvale, CA) treatment unit.¹³ The planning target volume (PTV) was constructed by adding a 5-mm margin to the gross tumor volume (GTV). The PTV dose was prescribed at the 70%–95% isodose line, which covered at least 80% of the PTV. It was allowed to underdose the GTV or PTV or both to

respect the constraints of the organs at risk (OAR). For the first 102 patients, dose calculations were performed using the ray-tracing algorithm implemented in the MultiPlan treatment planning system. For the other patients, a novel Monte Carlo (MC) dose-calculation algorithm was used in MultiPlan.

According to the tumor location, various dose-prescription schedules were used. Tumors located near the esophagus (less than 2 cm) were in the first part of the study treated with 6 fractions of 8 Gy ($n = 26$), later with 7 fractions of 8 Gy ($n = 8$), and when the MC calculation algorithm was available with 7 fractions of 7 Gy ($n = 9$). All other central tumors (close to the mainstem bronchus, but not the esophagus) were initially treated with 5 fractions of 9 Gy ($n = 5$). This dose was subsequently escalated to 5 fractions of 10 Gy ($n = 18$) and later to 5 fractions of 12 Gy ($n = 23$). When the MC calculation algorithm was available, these tumors were treated with 5 fractions of 11 Gy ($n = 19$). A patient was treated with 3 fractions of 20 Gy. Over time, the constraints to the OAR changed, because no severe toxicity was seen and the prescription changed because of the use of the MC calculation algorithm. The current dose constraints for the bronchial structures and OAR are shown in Table 1.

Dose (Re-)Calculation for the Study

For the purpose of the study, dose distributions for the first 102 patients, planned with the ray-tracing algorithm, were recalculated with the more advanced MC dose-calculation algorithm. To compare doses in the OAR across the various fractionation schemes, all doses were converted into an equivalent dose of 2 Gy (EQD₂) and a biologically equivalent dose (BED). The BED and EQD₂ were calculated using the following formulas: $BED = D \times (1 + (d/(\alpha/\beta)))$ and $EQD_2 = D \times (d + \alpha/\beta)/(2.0 + \alpha/\beta)$ where D = total dose and d = dose per fraction. For the tumors and normal tissues, we assumed α/β ratios of 10 and 3 (late side effects), respectively. The D_{max} was the maximum dose of a structure in a point calculated by the planning system. Apart from D_{max} , the volumes receiving an EQD₂ of 65, 80, 90, 100, and 130 Gy, and the volume receiving a BED of 100 Gy were calculated. Patients whose bronchial structures received an EQD₂ lower than 65 Gy were excluded in the analyses.

Assessment of Side Effects of the Bronchi and Survival

In total, 690 bronchial structures were delineated in the planning CT scan together with the PTV and GTV, and the

Table 1 Currently Used Dose Constraints

Organ	Volume	Dose Constraints For	
		55 Gy (5 Fractions) Total dose, Gy	49 Gy (7 Fractions) Total dose, Gy
Spinal cord	Any point	27.5	32.9
Esophagus	Any point	35	42
Trachea	Any point	45	49
Main bronchus	Any point	55	49
Brachial plexus	Any point	30	35
Lung	30%	16	18

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