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External validation of pulmonary radiotherapy toxicity models for ultracentral lung tumors

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A R T I C L E   I N F O

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A B S T R A C T

Introduction: Pulmonary toxicity is dose-limiting in stereotactic body radiation therapy (SBRT) for tumors that abut the proximal bronchial tree (PBT), esophagus, or other mediastinal structures. In this work we explored published models of pulmonary toxicity following SBRT for such ultracentral tumors in an independent cohort of patients.
Methods: The PubMed database was searched for pulmonary toxicity models. Identified models were tested in a cohort of patients with ultracentral lung tumors treated between 2008 and 2017 at one large center (N = 88). This cohort included 60 % primary and 40 % metastatic tumors treated to 45 Gy in 5 fractions (fx), 50 Gy in 5 fx, 60 Gy in 8 fx, or 60 Gy in 15 fx prescribed as 100 % dose to PTV.
Results: Seven published NTCP models from two studies were identified. The NTCP models utilized PBT max point dose (Dmax), D0.2 cm^3, V65, V100, and V130. Within the independent cohort, the $\geq$ grade 3 toxicity and grade 5 toxicity rates were 18 % and 7–10 %, respectively, and the Dmax models best described pulmonary toxicity. The Dmax to 0.1 cm^3 model was better calibrated and had increased steepness compared to the Dmax model. A re-planning study minimizing PBT 0.1 cm^3 to below 122 Gy in $EQD2_3$ (for a 10 % $\geq$grade 3 pulmonary toxicity) was demonstrated to be completely feasible in 4/6 patients, and dose to PBT 0.1 cm^3 was considerably lowered in all six patients.
Conclusions: Pulmonary toxicity models were identified from two studies and explored within an independent ultracentral lung tumor cohort. A modified Dmax to 0.1 cm^3 PBT model displayed the best performance. This model could be utilized as a starting point for rationally constructed airways constraints in ultracentral patients treated with SBRT or hypofractionation.

Introduction

In contrast to peripheral early stage non-small cell lung cancer (NSCLC), controversy exists in the use of stereotactic body radiation therapy (SBRT) for central tumors [1]. The concern with toxicity is especially heightened in a subgroup of patients termed ‘ultracentral’, defined as abutment of tumor with proximal bronchial tree (PBT), esophagus, or other mediastinal structures [2]. Definition of ultracentral tumors and reported toxicity rates vary in literature, which adds clinical uncertainty. High rates of toxicity, including fatal bronchopulmonary hemorrhage have been observed in the ultracentral subgroup of patients [3–5].

Various NTCP models have been studied to describe the toxicity associated with SBRT. Risk of radiation pneumonitis (RP) has been associated with tumor size, location and presence of interstitial lung disease, as well as the total lung volume receiving>20 Gy (V_{20}) in 2 Gy dose equivalents [6], or V5 [7]. Further use of local dose–effect relationship for lung perfusion loss has been shown to provide modest improvement in NTCP model fit for RP [8]. Similarly, models have been studied for airway stenosis [9], esophagitis [10], high grade pulmonary toxicity consisting of radiation pneumonitis, mainstem bronchial stenosis, and hemorrhage [4] and pulmonary hemorrhage events [5]. A recent review of predictive modeling in medicine identified a lack of external validation tests as a critical shortcoming [11].

High grade pulmonary toxicity, including respiratory failure and bronchopulmonary hemorrhage are the most feared complications for

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Table 1
Patient characteristics.

Characteristic	Number (%)
Total number of patients	88
Median age in years (range)	73.6 (24.9 – 91.3)
Gender	
Male	39 (44 %)
Female	49 (56 %)
Smoking status	
Never smoker	23 (26 %)
Former/current smoker	65 (74 %)
History of COPD	29 (33 %)
History of ILD	2 (2 %)
Prior anti-VEGF therapy	14 (16 %)
VEGF within 3 months of anti-VEGF	9 (10 %)
Organ overlap/abutment	
Tracheal abutment	8 (9 %)
PBT abutment	76 (86 %)
Esophagus overlap	23 (26 %)
Median size in cm (range)	3.0 cm (1.0 – 6.9)
Metastasis	35 (40 %)
Prescription dose	
9 Gy × 5	25 (28 %)
10 Gy × 5	29 (33 %)
7.5 Gy × 8	13 (15 %)
4 Gy × 15	21 (24 %)

SBRT in ultracentral lesions. The goal of this work was to explore the utility of published pulmonary toxicity models associated with dose to the airway structures after SBRT for ultracentral tumors in an independent institutional cohort of patients.

Methods

Patient cohort and treatment

This retrospective study was approved by our institutional review board (IRB #16–142) and the selected cohort consisted of patients with ultracentral thoracic lesions previously described in Wang et. al. [12]. Briefly, this cohort was identified as patients with NSCLC or lung metastases treated at our institution between 2008 and 2017 where the gross tumor volume (GTV) abutted the PBT or planning tumor volume (PTV) overlapped with the esophagus (Table 1). The patients were treated with one of the following schemes: 45 Gy in 5 fractions (fx), 50 Gy in 5 fx, 60 Gy in 8 fx, or 60 Gy in 15 fx prescribed as 100 % dose to PTV. Motion management was performed by 4 dimensional CT to create an internal target volume (ITV) or using deep inspiratory breath-hold technique. The clinical target volume (CTV) was generated by a 2–3 mm expansion and PTV by a further 5 mm margin expansion. Patients were treated with intensity modulated radiation therapy (IMRT) or volumetric arc therapy (VMAT) using a 6 MV linear accelerator with cone beam CT image guidance. All current normal tissue and tumor dose/volume constraints and guidelines are summarized in Table S1. Patients were followed with serial chest CT imaging every 3 months for the first 2 years and every 6–12 months thereafter. Pulmonary toxicity in addition to other toxicities not part of the current analysis (esophageal toxicity, stenosis and hemoptysis) were scored using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.

NTCP model validation

The PubMed database was scrutinized for toxicity models evaluating pulmonary and airway toxicity for SBRT or hypofractionated radiation treatment for central tumors in the lung. The following search term criteria were used: (central) AND (lung tumor) AND (normal tissue complication probability) AND (radiation). The PBT, defined as trachea 2 cm above the carina to the primary lobar bronchi, was systematically and manually segmented for all patients by one radiation oncologist prior to analysis [12]. All doses were converted to equivalent dose of 2 Gy per fraction (EQD_2) computed using $EQD_2 = D \times (d + \alpha/\beta)/(2 + \alpha/\beta)$, where D is the total dose, d is the dose per fraction, and α/β of 3 Gy was used for PBT [4]. Model performance was judged graphically comparing the agreement between predicted and observed toxicity, in addition to the steepness S of the dose–response curves. More specifically, calibration was defined as the agreement between the observed toxicity in the independent cohort and a model's predicted toxicity based on the number of quintiles enclosed in the model's 95 % confidence interval (ideally 5/5 quintiles fall within the 95 %CI).

Table 2
Model steepness and the agreement between each model and the independent cohort data.

Toxicity	Model	Model steepness 5th to 1st quintile	No. of quintiles within model 95 %CI
≥ Grade 3 Pulmonary	Max point dose	0.10	2
	D0.1 cm^3	0.09	4
	D1 cm^3	0.09	3
	D3 cm^3	0.07	1
	V100	1.32	1
	V130	0.00	0
Grade 5 Pulmonary	Max point dose	0.06	3
	D0.1 cm^3	0.09	3
	D1 cm^3	0.06	4
	D3 cm^3	0.06	2
	V65	1.21	2
	V100	1.20	0
Grade 5 Hemorrhage	D0.2 cm^3	0.79	2

Results

The search strategy identified a total of seven NTCP models: one D0.2 cm^3 model for lethal hemorrhage from the recently published HILUS trial of 65 patients with central lung tumors, of which 26 were located ultracentrally [5]. In addition, six NTCP models for clinical pulmonary toxicity were identified from a pooled analysis of nearly 200 patients with central lung tumors [4]. Pulmonary toxicity in this paper was defined as any ≥ grade 3 radiation pneumonitis, ≥grade 3 hemoptysis, atelectasis due to main stem bronchus occlusion, or any multifactorial respiratory failure. Of these six models, three were for ≥ grade 3 and three for grade 5 toxicity and included bronchial max point dose, V65, V100, and V130.

A total of 88 patients were identified for inclusion in the independent cohort. The median follow-up time was 20 months. Of these patients, 46 had primary NSCLC, 7 recurred locally, and 35 patients had lung metastases from non-lung primaries. In the independent cohort, the grade 5 hemorrhage rate was 7 % compared to the published 12 % rate in [5], while the ≥ grade 3 toxicity and grade 5 pulmonary toxicity rates were 18 % and 10 % (compared to the published 15 % and 8 % rates in [4]). Although with fairly shallow response curves ($S = 0.08$ and 0.05 for ≥ grade 3 and grade 5 pulmonary toxicity, respectively), the max point dose model from [4] reflected the ≥ grade 3 and grade 5 pulmonary toxicity (Figures 1 and S1; Table 2). Other models failed the validation test since the corresponding dose–response curves were although steeper ($S = 1.9$–7.7), but not well calibrated (0–2 quintiles within 95 % CI of the corresponding dose–response curve) as depicted in Figures 2 and S1, S2, and Table 2.

In general, the pulmonary toxicity models from [4] underestimated the pulmonary toxicity rates in the independent cohort (Figures 1, S1 and S2), while the HILUS hemorrhage model overestimated the corresponding hemorrhage rate (Fig. 2). The max point dose model from [4] was made more robust by focusing on the max dose to 0.1 cm^3, 1 cm^3 and 3 cm^3 (D0.1 cm^3, D1 cm^3, D3 cm^3) of PBT. The D0.1 cm^3 dose–response curve was steeper than that of the max point dose ($S = 0.11$ vs 0.08 for ≥ grade 3 pulmonary toxicity), and the model better adhered

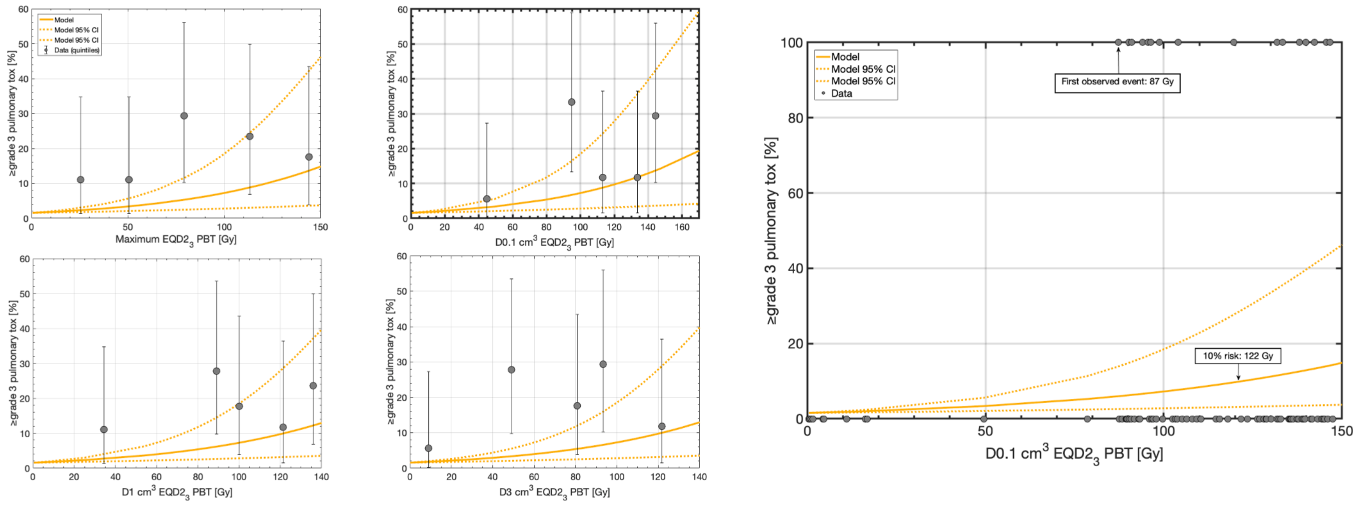

Fig. 1. The models published in [4] for ≥ grade 3 pulmonary toxicity applied to the independent cohort data. Left: Dose-response curves for the published max dose model (upper left) along with robustness variations (D0.1 cm^3, D1 cm^3, D3 cm^3). Right: The best dose–response curve (D0.1 cm^3; right) in which the dose at a 10 % predicted risk and the dose at the first ≥ grade 3 toxicity event was observed. Observed data is also aggregated in quintiles (at the average dose value in each quintile) with error bars given by 95 % binomial confidence intervals.

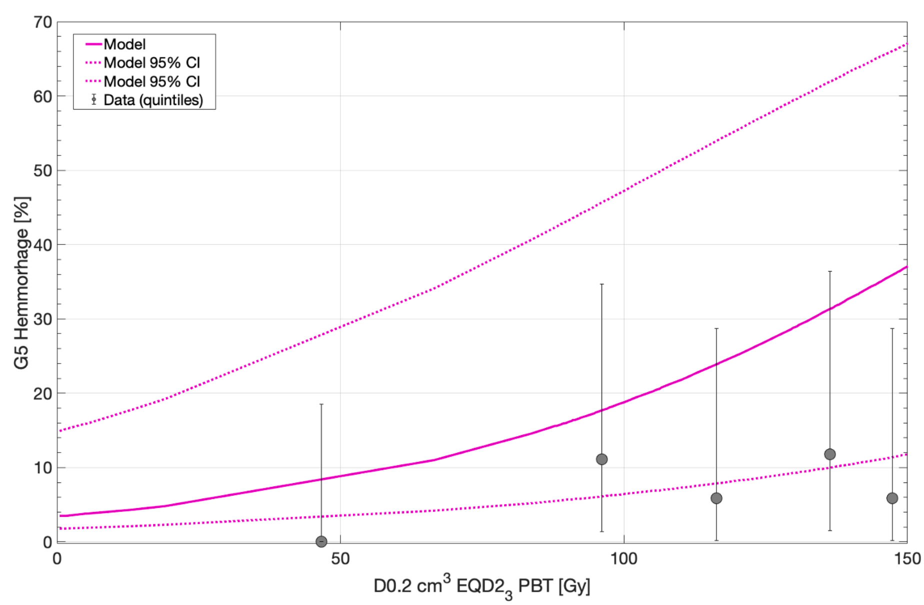

Fig. 2. The dose–response curve for the published D0.2 cm^3 Hemorrhage model from [5] applied to the independent cohort data. Observed data is binned into quintiles (at the average dose value in each quintile) with error bars given by 95 % binomial confidence intervals.

to the data (2 vs 4 quintiles within 95 %CI of the corresponding dose–response curve); Fig. 1; Table 2. The observed 15 % ≥grade 3 toxicity in the independent cohort corresponded to a D0.1 cm^3 of 150 Gy, while the first event of ≥ grade 3 toxicity was observed at D0.1 cm^3 of 87 Gy. Aiming for a reduced rate of ≥ grade 3 toxicity from the observed 15 % to 10 % would correspond to D0.1 cm^3 of 122 Gy.

A re-planning study was conducted to explore the feasibility of adhering to D0.1 cm^3 < 122 Gy. More specifically, the six patients that had received D0.1 cm^3 > 122 Gy (D0.1 cm^3 range: 132–147 Gy) and that had experienced ≥ grade 3 toxicity without receiving anti-VEGF were re-planned aiming for D0.1 cm^3 < 122 Gy while still adhering to all clinical constraints, applying the same treatment technique and fractionation as in the original and delivered treatment plans. The D0.1 cm^3 was converted to the D0.1 cm^3 in the two given fractionation schemes (10Gyx5: D0.1 cm^3 < 48 Gy; 7.5Gyx8fx: D0.1 cm^3 < 59 Gy). In four of the 6 patients, the new constraint was adhered to, and on average D0.1 cm^3 was reduced from 55 Gy to 48 Gy in the 5 fraction scheme and from 65 Gy to 59 Gy in the 8 fraction scheme (Fig. 3). This new constraint was nearly also met in a fifth patient, whereas not at all in the sixth patient, but importantly PBT D0.1 cm^3 was considerably reduced in all six patients compared to in the original treatment.

Discussion

The goal of this work was to validate identified NTCP models for pulmonary toxicity in an independent cohort of patients with ultra-central lung tumors from one large center. Bronchial-tree related toxicity is under-studied, and published data is relatively scarce. We explored the NTCP models for pulmonary toxicity published by Tekatli et al [4] and the NTCP model for hemorrhage from the HILUS trial [5]. However, the models in [4] underestimated our institutional pulmonary toxicity rates, while the HILUS model overestimated our hemorrhage

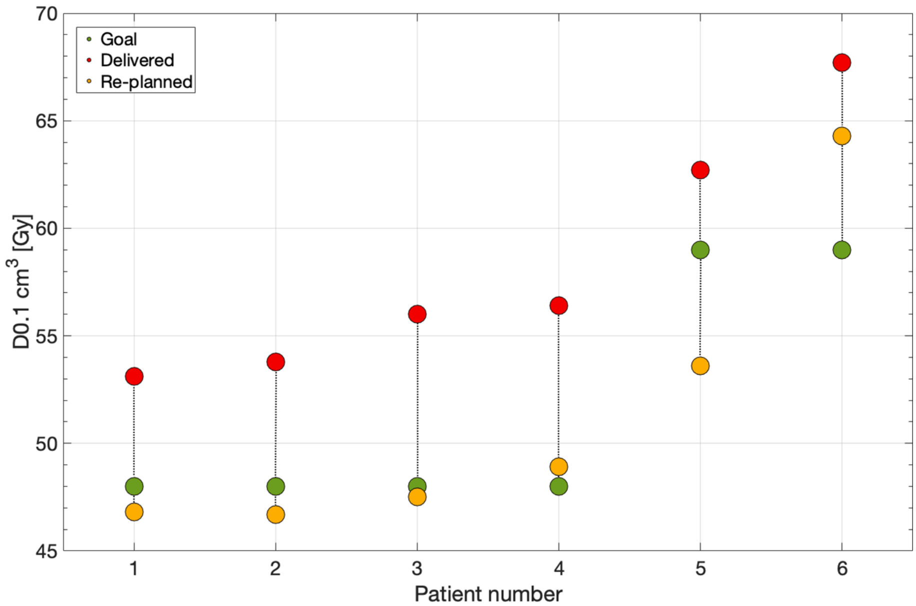

Fig. 3. Results of the D0.1 cm^3 re-planning study in the six patients that experienced ≥ grade 3 pulmonary toxicity and had a delivered D0.1 cm^3 > 122 Gy; red denotes the D0.1 cm^3 in the delivered plans; orange the re-planned D0.1 cm^3 and green the ideal D0.1 cm^3 goal of D0.1 cm^3 $EQD2_3$ < 122 Gy (10Gyx5: D0.1 cm^3 < 48 Gy (patients 1–4); 7.5Gyx8fx: D0.1 cm^3 < 59 Gy (patients 5 and 6)). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

rates. A possible explanation of the underestimation of the model by Tekatli et al [4] could be due to that model being developed from a mixture of central (lesion within 2 cm of the PBT) and ultracentral lung lesions with only 33 % of the population having ultracentral lesions. The hemorrhage model from the HILUS trial [5] that on the contrary overestimated our hemorrhage rates could be due to dose being prescribed to the 67 % isodose line compared to our institutional linac-based practice of prescribing 100 % dose to PTV. Of note, this NTCP model was derived from a cohort of ultracentral and central patients, in which the ultracentral patients accounted for the majority of fatal hemorrhagic toxicity events.

The max point dose models from [4] were made more robust by using Dx cm^3 parameters, among which the D0.1 cm^3 model agreed with our pulmonary toxicity data to the largest extent. We used this NTCP model in our own data to determine a tentative dose-volume threshold of D0.1 cm^3 < 122 Gy $EQD2_3$ dose to PBT that would ideally keep the risk of pulmonary toxicity under 10 %. We demonstrated that by replanning treatments with this constraint, the dose to PBT could be considerably lowered compared to previous plans while still adhering to all internal and currently used clinical constraints for ultracentral lung tumors without compromising target coverage. This could potentially translate to lower rates of clinically observed pulmonary toxicity. However, we do acknowledge the fairly shallow dose–response curves for all explored models (including also the D0.1 cm^3 model), which is partially explained by the low number of events for the studied toxicities. A possible reason confounding this could be the use of anti-VEGF therapy, which has been demonstrated to predispose for risk of pulmonary toxicity [13] and potentially also the follow-up time not being long enough to catch the complete spectrum of pulmonary toxicity. One way forward and to further promote model generalizability is to pool data across institutions [14]. Using such an approach and based on individual dose and toxicity data for 989 prostate cancer patients treated at five institutions, the study by Thor et al [15] identified a novel dose range being most critical for the development of late rectal bleeding.

From a model validation perspective and in accordance with the recommendations for model reporting made by QUANTEC [16], we would like to emphasize the importance of publishing NTCP model parameters with associated errors in order to allow for reconstruction of the dose–response function. To enable validation of the models in [4] and [5], the authors of [4] and [5] provided their model coefficients, which were not included in their original publications. These coefficients are summarized in Table S2.

In summary, despite the lack of large data sets, trends towards increasing risk of severe pulmonary toxicity are apparent in particular in the D0.1 cm^3 model fit, supporting its clinical relevance. Although more data is ultimately needed, the results further support that avoiding high maximum dose (and alike parameterizations) to the proximal bronchial tree is important to further limit pulmonary toxicity for patients with ultracentral lung tumors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2022.10.012.

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