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Scientific Article

Simulating the Potential of Model-Based Individualized Prescriptions for Ultracentral Lung Tumors

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Purpose: The use of stereotactic body radiation therapy for ultracentral lung tumors is limited by increased toxicity. We hypothesized that using published normal tissue complication probability (NTCP) and tumor control probability (TCP) models could improve the therapeutic ratio between tumor control and toxicity. A proposed model-based approach was applied to virtually replan early-stage non-small cell lung cancer (NSCLC) tumors.

Methods and Materials: The analysis included 63 patients with ultracentral NSCLC tumors treated at our center between 2008 and 2017. Along with current clinical constraints, additional NTCP model-based criteria, including for grade 3+ radiation pneumonitis (RP3+) and grade 2+ esophagitis, were implemented using 4 different fractionation schemes. Scaled dose distributions resulting in the highest TCP without violating constraints were selected (optimal plan [$Plan_{opt}$]). $Plan_{opt}$ predictions were compared with the observed local control and toxicities.

Results: The observed 2-year local control rate was 72% (95% CI, 57%-88%) compared with 87% (range, 6%-93%) for $Plan_{opt}$ TCP. Thirty-nine patients had $Plan_{opt}$ with TCP > 80%, and 14 patients had $Plan_{opt}$ TCP < 50%. The $Plan_{opt}$ NTCPs for RP3+ were reduced by nearly half compared with patients' observed RP3+. The RP3+ NTCP was the most frequent reason for TCP of $Plan_{opt}$ < 80% (14/24 patients), followed by grade 2+ esophagitis NTCP (5/24 patients) due to larger tumors (>40 cc vs ≤40 cc; $P = .002$) or a shorter tumor to esophagus distance (≥5 cm vs <5 cm; $P < .001$).

Conclusions: We demonstrated the potential for model-based prescriptions to yield higher TCP while respecting NTCP for patients with ultracentral NSCLC. Individualizing treatments based on NTCP- and TCP-driven simulations halved the predicted relative to the observed rates of RP3+. Our simulations also identified patients whose TCP could not be improved without violating NTCP due to larger tumors or a near tumor to esophagus proximity.

Introduction

Stereotactic body radiation therapy (SBRT) has been demonstrated to be efficacious and safe for early-stage non-small cell lung cancer (NSCLC), halving the rate of local progression compared with conventional fractionation.[1-5] While high local control (LC) has been achieved

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with SBRT, it is associated with toxicity in the proximal bronchial tree (PBT), esophagus, and other mediastinal structures.[6] A phase 2 trial delivering 60 to 66 Gy in 3 fractions (fx) showed a higher rate of severe toxicity, 46% versus 17%, in central compared with peripheral tumors.[7] Also, dose-response effects on airway stenosis have been demonstrated for central tumors.[8,9] These concerns have been alleviated to some extent by using regimens with more fx, which showed similar overall survival (OS) as for peripheral lesions.[10]

Toxicity is especially heightened in a subgroup of patients termed *ultracentral*, defined as abutment of tumor with the PBT or the esophagus.[11] In a central tumor cohort from our own institution, higher toxicity, including grade (G) 5 (G5), was observed in the ultracentral subgroup.[12] Others have reported similarly high rates of treatment-related death also due to pulmonary hemorrhage.[13] Further, vascular endothelial growth factor (VEGF) inhibitors could potentiate toxicity after SBRT for ultracentral tumors.[11,14] As a result of these studies, we have adopted 50 Gy in 5 fx in patients with central tumors and 60 Gy in 8 to 15 fx in patients with ultracentral tumors,[11,15-17]

Risk of radiation pneumonitis (RP) has been associated with tumor size, location and presence of interstitial lung disease, and the total lung volume receiving >20 Gy (V_{20}) in 2-Gy dose equivalents[18] or V5.[19] While normal tissue complication probability (NTCP) models also exist for airway stenosis[20] and esophagitis,[21] pulmonary toxicity (PT), including respiratory failure and bronchopulmonary hemorrhage, are the most feared complications after SBRT for ultracentral NSCLC. In the recently published HILUS trial (N = 65) including 26 ultracentral tumors, D0.2cc to PBT was the strongest predictor of lethal hemorrhage,[22] whereas PBT V130 showed volume dependency for PT in another analysis (N = 200 with central tumors).[23]

Treatment efficacy should also be evaluated in terms of tumor control probability (TCP). Although the commonly explored and empirical linear-quadratic model has been examined over high doses,[24,25] its applicability has been limited.[26] An alternative mechanistic TCP model was found to accurately predict TCP across a broad range of SBRT fractionation regimens in early-stage lung cancer.[27] Among strategies to improve treatment plan quality of ultracentral tumors are knowledge-based planning[28] and hierarchical optimization.[29] In parallel, efforts are ongoing to determine the maximum tolerated dose for SBRT of ultracentral tumors in the phase 1 SUNSET trial.[30] While an NTCP model-based approach is only currently used to some extent to stratify patients with head and neck cancer for proton therapy,[31,32] there are no ongoing or reported trials for ultracentral tumors that use both NTCP and TCP models to personalize treatments. The goal of this work is to demonstrate that NTCP in addition to TCP models relevant to lung SBRT can be used to optimize individual treatments with the potential to improve the therapeutic ratio.

Methods and Materials

Patient cohort and treatment

This retrospective study was approved by the local institutional review board, and the cohort consisted of patients with ultracentral tumors previously described in Wang et al.[33] Briefly, the cohort selected for the current analysis comprises patients with primary NSCLC (to match the data set explored for the TCP model[27]) treated between 2008 and 2017 where the gross tumor volume abutted the PBT or the planning tumor volume overlapped with the esophagus. The patients were treated to 45 Gy in 5 fx, 50 Gy in 5 fx, 60 Gy in 8 fx, or 60 Gy in 15 fx. The clinical target volume was created using a 2- to 3-mm expansion of the gross tumor volume and the planning tumor volume by adding a further 5 mm. Patients were treated with intensity modulated radiation therapy or volumetric arc therapy on a 6 MV linear accelerator with cone beam computed tomography image guidance. Clinical dose-volume constraints were either always applied (limits) or applied only if target coverage could be achieved (guidelines); refer to the summary of all constraints in Table E1.

Clinical outcome assessment

All patients had serial chest computed tomography imaging every 3 months for the first 2 years and every 6 to 12 months thereafter per the institutional standard. Esophagitis, hemoptysis, stenosis and PT were retrospectively scored by chart review using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.

TCP and NTCP models

The TCP at 2 years was calculated using the Jeong et al model.[27] This model estimates TCP mechanistically and incorporates hypoxia into the cell survival curves with the dose effect of hypoxic cells being scaled by the inverse of the oxygen enhancement ratio. In addition, based on our complete ultracentral cohort,[33] internally developed NTCP models for G2+ esophagitis (E2+), G2+ RP (RP2+), G3+ RP (RP3+), and lobar stenosis (LS) were also used to compute the respective NTCP values. All details regarding these NTCP models including equations, anatomic organs, and associated constraints are given in Table E2. These models were used to generate treatment

constraints (guidelines and limits). More specifically, a guideline did not supersede prescription dose, whereas a limit prevented treatment at higher dose. G3 and G5 PT (PT3+ and PT5) were assessed using the maximum dose NTCP model by Tekatli et al[23] but were slightly modified into the maximum dose to 0.1 cc (D0.1cc) to account for robustness as per our validation of published PT models.[34]

Plan scaling

Four candidate fractionation schemes were considered: 50 Gy in 5 fx, 60 Gy in 8 fx, 70 Gy in 10 fx, and 60 Gy in 15 fx. Normal tissue constraints were expressed as equivalent doses in 2-Gy fx (EQD2) and were created for our current clinical practice protocol of 50 Gy in 5 fx (Table E1), which is grounded in Radiation Therapy Oncology Group 0813.[17] From the 50 Gy in 5 fx protocol, constraints were extrapolated to the 3 other protocols using the linear-quadratic model. Constraints for RP3+ (guideline, 5%; limit, 10%), E2+ (limit, 30%), and LS (guideline, 5%) were developed by consensus among the treating thoracic radiation oncologists.

Relative dose distributions for each fractionation scheme were scaled by factors in [0.5,1.5], and the scheme resulting in the highest TCP without violating clinical limits (and guidelines for factors >1) was selected as the optimal plan ($Plan_{opt}$). Scale factors outside this range were judged clinically infeasible. The fractionation simulations were all carried out in our open-source radiation therapy outcomes explorer, which is an extension of the widely used CERR.[35,36] Guidelines were only applied when the scale factor was >1. For $Plan_{opt}$, we computed the predicted TCP and NTCP for RP2+, RP3+, E2+, LS, PT3+, and PT5 and compared these values to the observed LC rates at 2 years as well as the observed toxicities. We also compared these values to those from the delivered treatment plan ($Plan_{del}$).

Table 1 Patient characteristics

Characteristic	No. (%) or median (range)
Total number of patients	63
Age (y)	75 (53-89)
Sex	
Male	25 (40%)
Female	38 (60%)
Smoking status	
Never smoker	11 (18%)
Former/current smoker	52 (82%)
History of COPD	27 (43%)
History of ILD	2 (3%)
Prior anti-VEGF therapy	5 (8%)
Anti-VEGF within 3 mo of SBRT	3 (5%)
Organ overlap/abutment	
Tracheal/GTV abutment	6 (10%)
PBT/GTV abutment	55 (87%)
Esophagus/PTV overlap	19 (30%)
Size (cm)	3.1 (1.1-6.9)
Metastasis	15 (24%)
Histology	
Adenocarcinoma	32 (51%)
Squamous cell carcinoma	28 (44%)
Other	3 (5%)
Prescription dose	
9 Gy × 5 fx	19 (30%)
10 Gy × 5 fx	20 (32%)
7.5 Gy × 8 fx	7 (11%)
4 Gy × 15 fx	17 (27%)

Abbreviations: COPD = chronic obstructive pulmonary disease; fx = fractions; GTV = gross tumor volume; ILD = interstitial lung disease; PBT = proximal bronchial tree; PTV = planning tumor volume; VEGF = vascular endothelial growth factor.

Results

Patient and tumor characteristics

A total of 63 patients were included (Table 1), of which 15 patients (23%) had metastatic disease, and the remaining patients had primary disease. The median age was 74 (range, 53-89) years, and 5 patients received anti-VEGF therapy. Patients were distributed among the 4 different fractionated regimens, with fewer patients treated with 8 fx.

Clinical outcomes

After a median follow-up time of 1.0 years (range, 0.15-6.2), the median OS was 2.9 years (95% CI, 1.3-4.0). The 2-year OS rate was 58% (95% CI, 46%-73%), and local failure was observed in 11 patients (17.5%; Fig. E1). The actuarial LC rate at 2 years was 72% (95% CI, 58%-91%). LS and/or atelectasis were more frequent (22%) than mainstem bronchial stenosis (3%), RP3+ was observed in 12% of patients, and G5 hemorrhage was observed in 4 patients, of whom 2 were exposed to anti-

Table 2 Observed clinical outcomes and toxicity and corresponding predicted TCP and NTCP values for $Plan_{del}$ and $Plan_{opt}$

Outcome	Clinically observed number (%)	Time from treatment (mo)	Predicted TCP or NTCP	$Plan_{del}$ (%), median (range)	$Plan_{scale}$ (%), median (range)
2-y LC	72 (CI, 58-91)		TCP	86 (74-88)	87 (6-94)
Stenosis/atelectasis					
Mainstem bronchi	2 (3)	7-11			
Lobar bronchi	14 (22)	2-19	LS NTCP	12 (0-25)	17 (5-40)
Radiation pneumonitis					
G1	2 (3)	28-51			
G2	8 (13)	0-10	RP2+ NTCP	23 (5-83)	23 (3-63)
G3	4 (6)	1-8	RP3+ NTCP	7 (2-43)	8 (2-21)
G5	4 (6)	2-8			
Esophageal toxicity					
G1	4 (6)	5-21			
G2	9 (14)	0-12	E2+ NTCP	8 (1-86)	8 (1-30)
G3	3 (5)	0-11			
Hemorrhage					
G2	1 (2)	48			
G5	4 (6)	7-12			
G3+ PT*	12 (21)	1-10	G3+ PT NTCP	8 (2-15)	6 (2-17)
Any G5 PT	7 (11)	2-12	G5 PT NTCP	6 (2-10)	4 (2-11)

Abbreviations: E2+ = grade 2+ esophagitis; G1-5 = grade 1-5; LC = Local control; LS = Lobar Stenosis; NTCP = normal tissue complication probability; $Plan_{del}$ = delivered plans; $Plan_{opt}$ = optimal plans; PT = Pulmonary toxicity; RP2+, RP3+ = grade 2+/3+ radiation pneumonitis; TCP = tumor control probability. *PT is defined per Tekatli et al[24] as any mainstem bronchus stenosis or atelectasis, RP or hemorrhage, or death from any treatment-related toxicity.

* Pulmonary toxicity is defined per Tekatli et al[24] as any mainstem bronchus stenosis or atelectasis, radiation pneumonitis or hemorrhage, or death from any treatment-related toxicity.

VEGF therapy within 3 months of receiving SBRT (Table 2).

TCP

The $Plan_{opt}$ was most frequently selected as 10 fx (n = 33, 52%), followed by 15 fx (n = 29, 46%; Fig. 1A). Only in 1 patient was the 5 fx selected, and the 8 fx was never selected. In 37 of 62 patients (59%), $Plan_{opt}$ achieved TCP > 80% while respecting all constraints, whereas in 16 patients (25%), TCP < 50%. More $Plan_{del}$ than $Plan_{opt}$ plans achieved TCP > 80% at the cost of higher RP3+ NTCP (Fig. 1B). The median TCP of $Plan_{del}$ and $Plan_{opt}$ were similar (86% vs 87%), but the range of TCP for $Plan_{opt}$ was wider (74%-88% vs 6%-94%). In 9 patients, a scale factor of 0.5 was used for $Plan_{opt}$, although this violated the clinical constraints. For $Plan_{opt}$ producing TCP < 80%, lung constraints were the primary reason (n = 17; 66%) followed by esophagus constraints (n = 7; 27%).

NTCP

The RP3+ NTCP was similar between $Plan_{del}$ and $Plan_{opt}$ (root mean square [RMS], 1.1%; Fig. 2A) when TCP of $Plan_{opt}$ was >80% but considerably higher (RMS, 9.8%) when $Plan_{opt}$ was limited by the RP3+ constraint. Similarly, as seen in Fig. 2B, the E2+ NTCP for $Plan_{del}$ agreed to a larger extent to $Plan_{opt}$ when TCP of $Plan_{opt}$ was >80% (RMS, 4.3% vs 23%). The LS NTCP was higher in $Plan_{opt}$ than in $Plan_{del}$ (Fig. 3A). The NTCP for PT3+ and PT5 for $Plan_{del}$ and $Plan_{opt}$ were similar (Fig. 3B, 3C).

Correlation between clinical characteristics and TCP/NTCP values for $Plan_{opt}$

Tumors >40 cc and those located <5 cm from the esophagus resulted in lower TCP for $Plan_{opt}$. For tumor volumes >40 cc, TCP of $Plan_{opt}$ was more likely to be <80% (P = .002; Fisher exact test) and RP3+ NTCP >

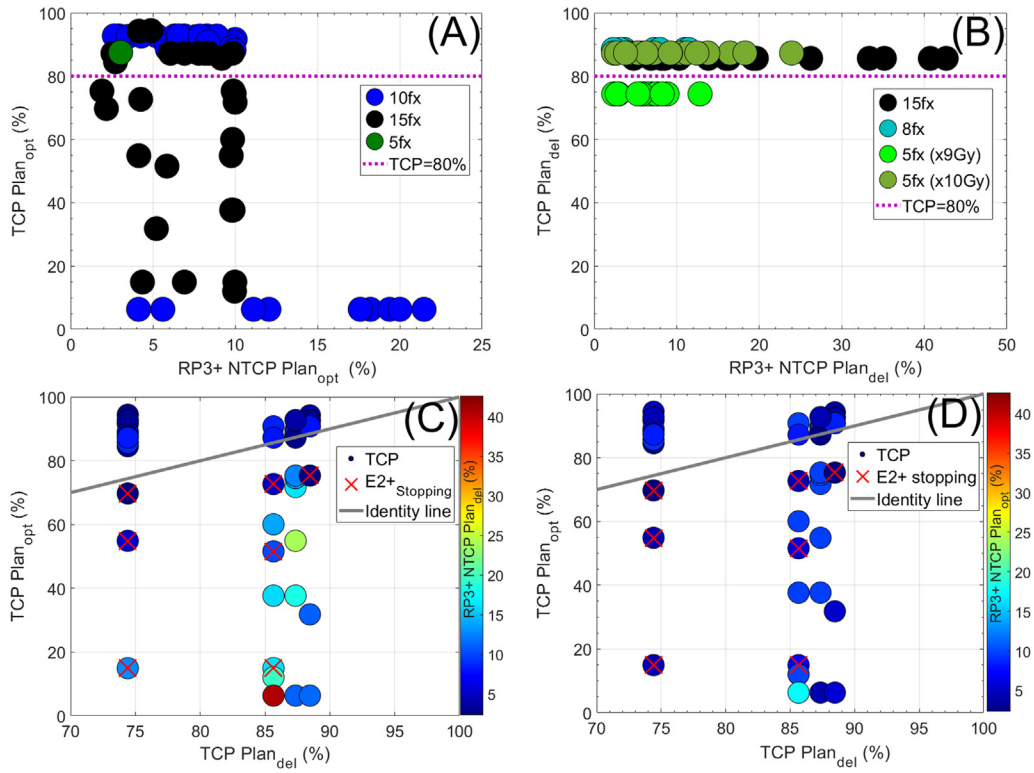

Figure 1 (A) Predicted grade 3+ radiation pneumonitis (RP3+) normal tissue complication probability (NTCP) and tumor control probability (TCP) for the 3 fractionations (fx) selected for the optimal plans ($Plan_{opt}$). Infeasible plans with low TCP and RP3+ NTCP exceeding 10% are denoted in red. (B) Predicted RP3+ NTCP and TCP for delivered plans ($Plan_{del}$). Predicted TCP $Plan_{opt}$ versus $Plan_{del}$, color coded by (C) RP3+ NTCP $Plan_{del}$ and (D) RP3+ NTCP $Plan_{opt}$. *Abbreviation:* E2+ = grade 2+ esophagitis.

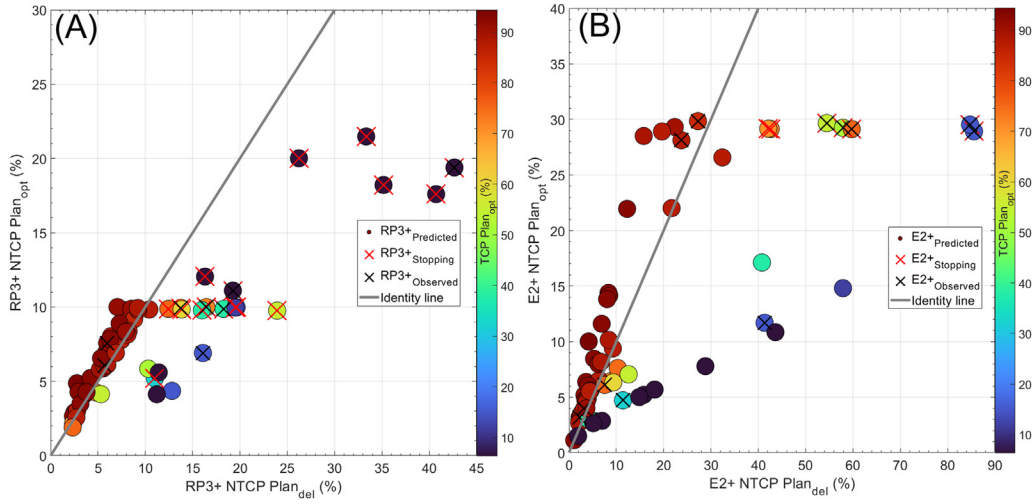

Figure 2 Predicted (A) grade 3+ radiation pneumonitis (RP3+) normal tissue complication probability (NTCP) and (B) grade 2+ esophagitis (E2+) NTCP of optimal plans ($Plan_{opt}$) versus delivered plans ($Plan_{del}$) with respective stopping criteria and clinically observed events color scaled by tumor control probability (TCP) $Plan_{opt}$.

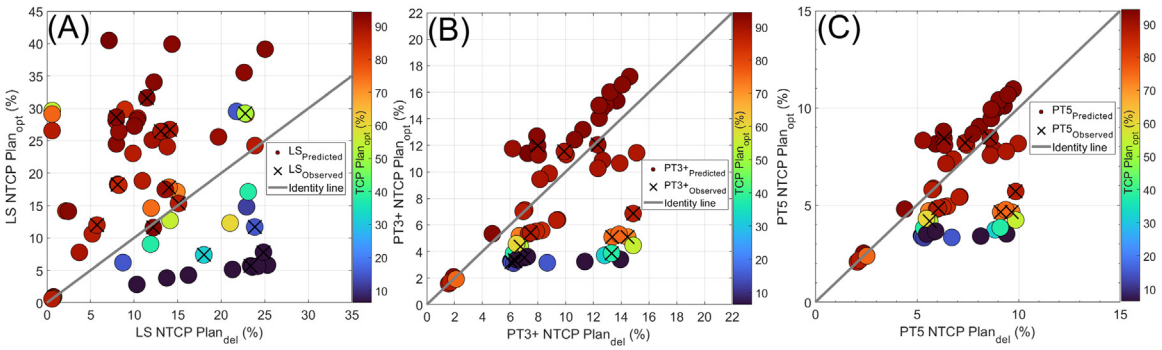

Figure 3 Predicted normal tissue complication probability (NTCP) optimal plans ($Plan_{opt}$) versus delivered plans ($Plan_{del}$) color coded by tumor control probability (TCP) $Plan_{opt}$ for (A) lobar stenosis (LS), (B) grade 3+ pulmonary toxicity (PT3+), and (C) any grade 5 PT (PT5).

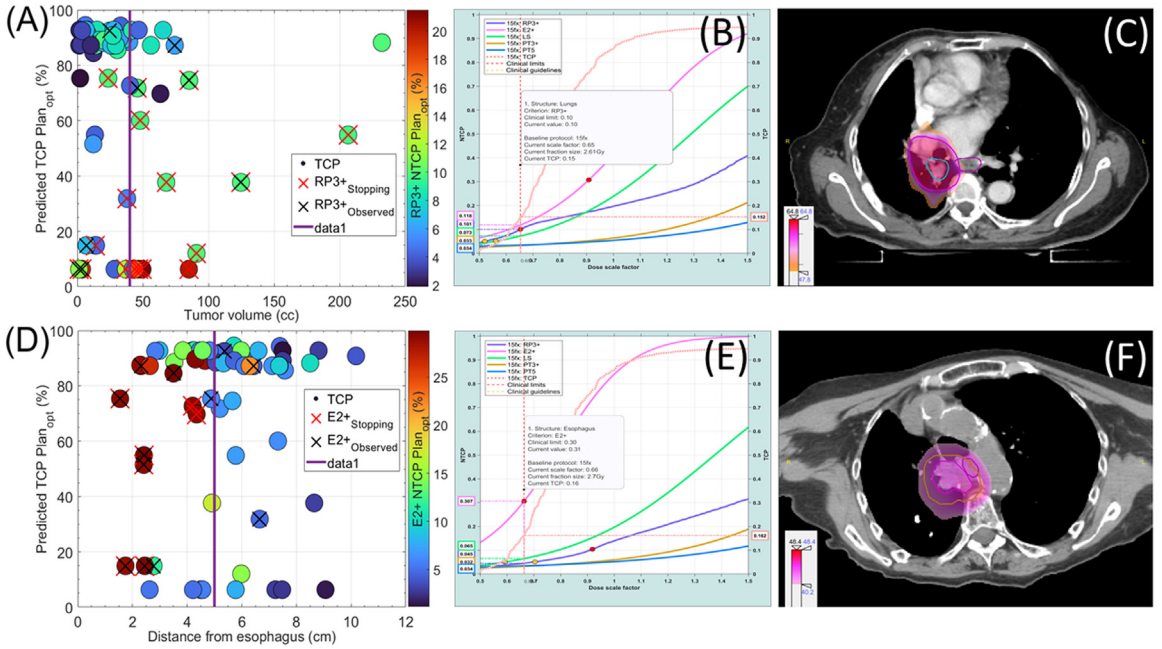

Figure 4 (A) Predicted tumor control probability (TCP) optimal plans ($Plan_{opt}$) versus tumor volume; purple vertical line: tumor volume = 40 cc. (B) TCP and normal tissue complication probability (NTCP) curves for a patient whose TCP scaling was restricted by the grade 3+ radiation pneumonitis (RP3+) NTCP limit. (C) Axial overlay of gross tumor volume (GTV), planning tumor volume (PTV), esophagus, and dose color wash in the patient with prior right lower lobe lobectomy. (D) Predicted TCP $Plan_{opt}$ versus distance from esophagus; purple vertical line: distance from esophagus = 5 cm. (E) TCP and NTCP curves for a patient whose TCP scaling was restricted by the E2+ NTCP limit. (F) Axial overlay of GTV, PTV, esophagus, and dose color wash illustrating the abutment of tumor and esophagus.

10% (P = .01), as seen in Fig. 4A. Similarly for cases where the tumor was located within 5 cm of the esophagus, the NTCP of EP2+ was more likely to be >20% (P < .001; Fig. 4B).

Discussion

The use of SBRT has demonstrated a high rate of LC in NSCLC; however, there is considerable concern regarding its safety for treating patients with ultracentral lung tumors.[7,11,12,14,22,33] In this work, we combined patient-specific LC and toxicity from a cohort with ultracentral tumors together with published TCP and NTCP models with the goal to simulate treatment plans that would achieve higher TCP while also minimizing NTCP. As demonstrated in Fig. 1, fewer plans achieved TCP > 80% when incorporating constraints from the NTCP models ($Plan_{opt}$); however, in $Plan_{del}$ the higher TCP came at the cost of an increased rate of predicted toxicity in addition

to an increased rate of observed toxicity. Constraints for the normal lung and esophagus were the most frequent reason preventing a higher TCP to be achieved, and in some patients, higher TCP could not be achieved without violating constraints (illustrated in Fig. 4). Figure 4B and 4C demonstrate an instance where the dose scaling factor was limited by NTCP of RP3+. In this case, the patient, with a right-sided tumor, had a prior right lower lobe lobectomy. The lowered lung volume could have resulted in prediction of higher toxicity. The RP3+ NTCP for $Plan_{opt}$ was 10% whereas that of $Plan_{del}$ was 20%. However, clinically, the patient only experienced RP2, displaying the limitation of predictive modeling in this case. Figure 4E and 4F show an instance of abutment of the tumor with the esophagus, which limited the scaling of the TCP curve by EP2+. Clinically, this patient experienced an event of EP3 a month into treatment. Tumor volume and proximity to the esophagus was associated with higher NTCP.

Weaknesses of this analysis include the retrospective nature of this work and the associated biases. Additionally, the $Plan_{opt}$ was created by scaling pre-existing delivered treatment plans. A more ideal scenario likely yielding treatment plans with higher TCP and lower NTCP overall could have involved replanning and incorporating constraints from the NTCP models. In the complete internal cohort including 88 patients with ultracentral lung tumors,[33] the NTCP models for E2+, RP2+, and RP3 were found to accurately predict the respective toxicities. An extension of the published NTCP model for PT3+ and PT5[23] was found to be valid as part of a parallel validation effort,[34] whereas the validity of the mechanistic TCP model was not fully explored in the current cohort. Since the TCP model was derived for primary NSCLC, we aimed to limit bias due to cohort differences by focusing on the 63 of 88 patients with ultracentral tumors that were primary NSCLC.

The Radiation Therapy Oncology Group 0813 trial evaluated the maximum tolerated dose for SBRT in central tumors with incremental increase from 50 to 60 Gy in 5 fx and showed comparable LC with a higher rate of dose-limiting toxicity in the higher dose arms.[17] The ongoing phase 1 dose-escalation study for ultracentral tumors (SUNSET) uses a time-to-event continual reassessment method, with accrual starting at 60 Gy in 8 fx and systematic escalation or de-escalation to identify safe dose-fractionation regimen for these tumors.[30] However, as demonstrated by the results of the aforementioned analysis, the NTCP and TCP are patient-dependent; therefore, we believe that an individualized prescription approach is the optimal strategy to maximize the therapeutic ratio in patients with ultracentral tumors.

Conclusion

This study demonstrates the value of model-based personalization, allowing for more informed patient decision making weighing risks versus benefits. For patients identified to have a higher rate of toxicity, the greater risk could become part of the informed consent discussion with shared decision making. These patients can also be targeted for more rigorous follow-up to, *e.g.*, improve clinical outcomes or to decrease the likelihood of hospitalization.

Disclosures

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.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101285.

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