Updating Photon-Based Normal Tissue Complication Probability Models for Pneumonitis in Patients With Lung Cancer Treated With Proton Beam Therapy

Jain, Varsha; Niezink, Anne G. H.; Frick, Melissa; Doucette, Abigail; Mendes, Amberly; Simone, Charles B.; Langendijk, Johannes A.; Wijsman, Robin; Feigenberg, Steven J.; Levin, William

Published in:
Practical radiation oncology

Publication date:
2020

Practical Radiation Oncology® (2020) **10**, e330−e338

practical radiation oncology®
pro
www.practicalradonc.org

Basic Original Report

Updating Photon-Based Normal Tissue Complication Probability Models for Pneumonitis in Patients With Lung Cancer Treated With Proton Beam Therapy

Varsha Jain, MD, PhD,[a] Anne G.H. Niezink, MD,[b] Melissa Frick, MD,[c] Abigail Doucette, MPH,[a] Amberly Mendes, BS,[a] Charles B. Simone II, MD,[d] Johannes A. Langendijk, MD, PhD,[b] Robin Wijsman, MD, PhD,[b] Steven J. Feigenberg, MD,[a] William Levin, MD,[a] Keith A. Cengel, MD, PhD,[a] Arjen van der Schaaf, PhD,[b] and Abigail T. Berman, MD, MSCE[a,*]

[a]*Department of Radiation Oncology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania;* [b]*Department of Radiation Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands;* [c]*Department of Radiation Oncology, Stanford University, Stanford, California; and* [d]*New York Proton Center, New York City, New York*

Received 28 December 2019; revised 14 April 2020; accepted 28 April 2020

Abstract

Purpose: No validated models for predicting the risk of radiation pneumonitis (RP) with proton beam therapy (PBT) currently exist. Our goal was to externally validate and recalibrate multiple established photon-based normal tissue complication probability models for RP in a cohort with locally advanced nonsmall cell lung cancer treated with contemporary doses of chemoradiation using PBT.

Methods and Materials: The external validation cohort consisted of 99 consecutive patients with locally advanced nonsmall cell lung cancer treated with chemoradiation using PBT. RP was retrospectively scored at 3 and 6 months posttreatment. We evaluated the performance of the photon Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) pneumonitis model, the QUANTEC model adjusted for clinical risk factors, and the newer Netherlands updated QUANTEC model. A closed testing procedure was performed to test the need for model updating, either by recalibration-in-the-large (re-estimation of intercept), recalibration (re-estimation of intercept/slope), or model revision (re-estimation of all coefficients).

Results: There were 21 events (21%) of ≥grade 2 RP. The closed testing procedure on the PBT data set did not detect major deviations between the models and the data and recommended adjustment of the intercept only for the photon-based Netherlands updated QUANTEC model (intercept update: −1.2). However, an update of the slope and revision of the model coefficients were not recommended by the closed testing procedure, as the deviations were not significant within the power of the data.

Conclusions: The similarity between the dose-response relationship for PBT and photons for normal tissue complications has been an assumption until now. We demonstrate that the preexisting, widely used photon based models fit our PBT data well with minor

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Sources of support: No funding source.

Disclosures: The Department of Radiation Oncology of the University Medical Center Groningen (Groningen, The Netherlands) has research agreements with IBA, Elekta, RaySearch, Siemens, VisionRT, and Leoni.

* Corresponding author: Abigail T. Berman, MD, MSCE; E-mail: abigail.berman@uphs.upenn.edu

https://doi.org/10.1016/j.prro.2020.04.005

modifications. These now-validated and updated normal tissue complication probability models can aid in individualizing selection of the most optimal treatment technique for a particular patient.

Introduction

Lung cancer is the leading cause of cancer death in the United States,[1] with an estimated 228,150 new cases diagnosed in 2019.[2] Of all non-small cell cancer (NSCLC) cases, about two-thirds of patients are diagnosed with locally advanced disease with corresponding 5-year survival rates of 32.3%.[3] Radiation therapy (RT) combined with chemotherapy followed by immunotherapy is the standard treatment for locally advanced NSCLC.[4] However, when treating to definitive radiation doses, treatment-related toxicities can be significant and are often the dose-limiting factor. The most common and clinically important subacute toxicity of thoracic RT is radiation pneumonitis (RP).[5] It typically occurs 1 to 12 months after RT with most cases diagnosed within 6 to 8 months. The overall incidence of RP is estimated to be approximately 13% to 37%.[6-9] The need to minimize radiation-induced pneumonitis is more critical than ever, as immunotherapy itself, delivered standardly for a year after chemoradiation, increases the risk of pneumonitis (all grades) in addition to carrying its own independent risk of pneumonitis.[4] Additionally, the promise of durable systemic control and extended survival with these newer therapies, compared with our historical controls, further underscore the importance of minimizing toxicity, particularly radiation associated pulmonary morbidity.[10]

Several clinical and dosimetric parameters have been implicated in the development of RP.[9] Proton beam therapy (PBT) for lung cancer may provide a substantial improvement over tumor and organs at risk dose distributions than can be achieved by conventional photon radiation.[11] However, a recently published randomized phase 2 trial between protons versus photons using real-time assessment of outcomes failed to demonstrate this hypothesized benefit with regard to its primary endpoint of RP with protons.[12] However, this study was flawed by requiring patients to meet dosimetric constraints for both proton and photon treatment plans, and in fact the mean lung dose was similar between the proton and photon cohorts. Given these constraints, this trial may have resulted in decreased enrollment of patients who would have been most likely to benefit from PBT, highlighting that patient selection is key for deciding on an optimal treatment modality.

One way of selecting patients most likely to benefit from PBT is by using mathematical predictive models, such as normal tissue complication probability (NTCP) models, for predicting radiation toxicities. Although there is extensive literature on NTCP models in patients treated with photons,[13-18] similar data on patients treated with protons are currently lacking. Toward this end, we attempted to externally validate previously established photon-based NTCP models for RP in a cohort with locally advanced NSCLC treated with contemporary doses of chemotherapy and radiation therapy using PBT.

Methods and Materials

Patient selection

The study was approved by our institutional review board. The inclusion criteria for the study included patients who were >18 years of age, had a histologic diagnosis of NSCLC, American Joint Commission for Cancer seventh edition stage IIB-IVA disease, and were treated between 2011 to 2016 with PBT and platinum-based chemotherapy. Patients were excluded if they had inadequate follow-up (<3 months), received trimodality treatment with surgery in addition to RT and chemotherapy, or had evidence of disease progression while on radiation treatment.

Definition of target volume and organs at risk

All patients underwent a 4-dimensional free breathing computed tomography (CT) simulation scan approximately 2 weeks before treatment. Intravenous contrast was administered to most patients. A positron emission tomography scan was available for target delineation in each case. The gross tumor volume was defined as the primary tumor and pathologically or clinically involved lymph nodes. An internal target volume was created using all phases of the respiratory cycle retrieved from the 4-dimensional CT scan. The clinical target volume was defined as the internal target volume plus 6 to 8 mm isometric expansion around the primary tumor and 5 to 8 mm expansion around the nodes respecting the anatomic boundaries (heart, great vessels, esophagus, spinal cord) based on physician preference. No elective nodal radiation was performed. An additional 5-mm expansion was added for planning target volume to account for patient set-up errors and beam uncertainties.

Treatment planning

The patients were treated using double scattered or pencil beam scanning (PBS) proton therapy to a prescribed dose of 60 to 74 Gy in 1.8 Gy to 2 Gy daily fractions. The Eclipse Treatment Planning System,

version 10.0.28 (proton convolution superposition model) (Varian Medical Systems, Palo Alto, CA) was used to generate all plans; PBS plans were generated using the Xio Treatment Planning System, version 5.0 (pencil beam algorithm[19]; Impac Medical Systems, Maryland Heights, MO). For proton beam planning, proximal and distal margins were added in addition to the lateral margins to account for range uncertainties along the beam direction. Single field optimization planning was used for proton planning, and each proton field was designed to uniformly cover the target. All proton plans were designed by using a limited number (most commonly 2-3 fields) of predominantly posterior and posterior-oblique fields. All proton doses included a generic factor for mean relative biological effectiveness (RBE) of 1.1, as is the standard per the International Commission on Radiation Units and Measurements report 78,[20] and were reported in Gy (mean RBE).[21] For quality assurance, daily image guidance with kilovoltage-kilovoltage imaging was performed along with weekly offline CT evaluation.[22] Backup photon plans were created and delivered in cases of proton machine downtime. However, none of the included patients received >3 photon fractions.

Data acquisition and scoring of radiation pneumonitis

Patient demographic information was obtained from a retrospective chart review of patient records. RP was scored using the Common Toxicity Criteria (version 4.0) at 3 and 6 months post-RT completion. The endpoint used in this study was RP grade ≥2, which represents clinical symptoms leading to limitation of activities of daily living or requiring medical intervention such as steroids.

Statistical methods

All statistical analyses were performed in R (version 3.4.2). Descriptive statistics were calculated to characterize patient, disease, and treatment features. Spearman correlation matrix was computed between various clinical and dose parameters.

A univariable logistic regression analysis for the endpoint of RP (grade ≥2) was performed with the following variables: World Health Organization performance status, gender, age (as continuous measure and as binary risk groups with >62 years as cutoff per the Appelt model and <60 years as an alternative threshold), smoking status (current, former, never), pre-existing pulmonary comorbidity (chronic obstructive pulmonary disease, interstitial lung disease, asthma: yes/no), cardiac comorbidity (hypertension, arrhythmia, valvular disease, myocardial infarction: yes/no), American Joint Commission for Cancer seventh edition tumor (T), node (N) and metastasis (M) stage, tumor location (upper, middle/hilar, lower), tumor laterality (right/left), chemotherapy (type and sequencing), and several dose volume parameters, including the mean dose and dose-volume parameters in 5 Gy bins to both lungs or either the ipsilateral or contralateral lung. For each variable, the goodness of fit to the data was calculated as the gain in -2 log likelihood (compared with a null model without any variables, ie, with only an intercept). This measure is larger than zero if the variable adds information that can be used to predict the patient responses, that is, RP. Its significance (*P* value; testing the null hypothesis that the gain is zero) was computed using a χ^2 test with degrees of freedom equal to 1 for continuous parameters and equal to the number of levels minus 1 for categorical parameters. We also calculated the discrimination performance of each variable using the area under the receiver operation characteristic curve (AUC). These analyses demonstrate the ability of each explanatory variable to predict the RP on their own and are used to discern independent from dependent predictors and poor predictors from collinear predictors later in multivariable analysis. Finally, multivariable analysis was performed using automatic forward stepwise logistic regression, based on the Bayesian information criterion (BIC).

We evaluated the performance of 3 established NTCP models for RP: (1) Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) pneumonitis (QP) model, which includes mean lung dose (MLD)[14]; (2) QUANTEC model adjusted for clinical risk factors (such as preexisting pulmonary comorbidity, mid or inferior tumor location, current/former smoker, old age, and sequential chemotherapy) presented by Appelt et al. (AQP)[15]; and (3) the recently published Netherlands updated QUANTEC pneumonitis model (NQP), which includes current smoking status.[23] Model performance was tested for goodness of fit (log-likelihood/BIC), discrimination (C-statistic or AUC), and calibration (Hosmer-Lemeshow test). A closed testing procedure as described by Vergouwe et al[24] was performed to test the need for model updating, either by calibration-in-the-large (re-estimation of model intercept), recalibration (re-estimation of intercept and slope), or model revision (re-estimation of all coefficients). For each model, the mean predicted NTCP reduction with proton treatment compared with photon treatment (ΔNTCP) was calculated for patients with the available photon treatment backup plan.

Results

We identified 134 consecutive patients treated with PBT for locally advanced NSCLC between 2011 and 2016 at our institution. Out of these, 35 patients were excluded, as they did not meet our inclusion criteria (19 had inadequate follow-up, 13 received trimodality

treatment, and 3 progressed while on treatment), leaving 99 patients for evaluation. Two of these were patients with stage IVA disease who had a solitary bone metastasis and were treated with a definitive intent. The 2 radiation courses were administered sequentially and there was no overlap between the 2 radiation plans. Ninety-three percent of patients were treated with double scattered and the rest with PBS. Corresponding backup photon plans were available for 48 of these patients.

Baseline patient characteristics

The median age of the patient cohort was 69 years (range, 31-97 years). Most patients were ≥60 years of age (87%), had a World Health Organization performance status of 0 or 1 (85%), were former smokers (77%), and had upper lobe tumors (67%). Additionally, most patients received platinum-based concurrent chemotherapy (98%) and had RT doses >60 Gy (96%). None of these patients received consolidation durvalumab, given the period analyzed was before the Food and Drug Administration approval of the drug. Four patients received RT doses <60 Gy secondary to complications during treatment (eg, malaise, esophagitis, pneumonia, other infections necessitating inpatient admission) (Table 1). The Spearman correlation between various baseline clinical variables was low (range, −0.33 to 0.41), implying that multicollinearity does not play a major role in multivariable analysis among these variables.

Lung dose characteristics

The average MLD in the patient cohort treated with PBT was 15.6 Gy (interquartile range, 12.9 Gy to 18.8 Gy). In the patients (n = 48) in whom backup photon plans were available, the MLD was on average 1.3 Gy higher (interquartile range, 0.05 Gy to 2.7 Gy, $P < .001$) than the corresponding proton plans. Furthermore, the dose volume histogram values for backup photon plans were on average higher than the primary proton plans in the low dose range (V5-V25), but slightly lower in the high dose range (V30-V60). The Spearman correlation between baseline clinical and dose variables was low (range, -0.37-0.28), while the correlation between the dose variables was high (range, 0.47-1). Additionally, the correlation between proton and corresponding photon backup dose parameters was high (range, 0.72-0.81).

Radiation pneumonitis and univariable associations

We observed 21 events of grade ≥2 RP in our PBT cohort; of these, there were 4 events of grade 3 RP, and no patients had grade ≥4 RP. Additionally, 18 events occurred at 3 months. On univariable analysis, the following variables were found to be predictive of RP: the mean lung dose ($P = .012$) and several total lung dose volume histogram parameters ranging from V5 to V50, with the strongest association observed for V40 ($P = .004$) (Table 2). All clinical variables and other nonlung dose volume histogram parameters were not predictive of RP. The predicted ΔNTCP, which is the potential average toxicity reduction with PBT compared with photons, according to each univariable model for patients with available backup photon plans, ranged from −4.7% to 14.1% (Table 2).

Calibration

Patients were placed in 1 of the 3 groups/tertiles based on the highest one-third, medium one-third, and lowest one-third probability of developing RP. These 3 groups were used in the Hosmer-Lemeshow test owing to the limited number of observed events. For all 3 original models (QP, AQP, and NQP), the test showed significant deviation between the observed and expected event rates of RP. However, with adjustment of the intercept alone, these deviations were no longer found to be significant for the 3 tested models (Fig 1).

Closed testing procedure

The closed testing procedure on the PBT data set did not detect major deviations between the models and the data and recommended adjustment of the intercept only for the photon-based NQP model (Δ intercept, −1.2). The steepness of dose-response relationship was noted to be greater in the PBT data (0.0017/Gy) than in the QP (0.0013 /Gy) and AQP (0.0014/Gy) models but lower than in the NQP model (0.0030/Gy). However, an update of the slope, or revision of the model coefficients, was not recommended by the closed testing procedure, as the deviations were not significant within the power of the data (Table 3). Detailed results of model validation are presented in Table E1 (available online at https://doi.org/10.1016/j.prro.2020.04.005).

Model validation was also performed using the back-up photon plans, resulting in higher deviations for all 3 models than when the actual proton dose parameters were used. In the patients in whom backup photon plans were available, the average MLD of the PBT plans (15.6 Gy) was only slightly lower than that of the photon plans (16.2 Gy). Consequently, the predicted average NTCP reduction using protons instead of photons (ΔNTCP, Table E1, available online at https://doi.org/10.1016/j.prro.2020.04.005) was modest, ranging from 2.0% to 5.9% between the different models.

Redevelopment using stepwise analysis resulted in a model with the V40 dose volume parameter of the lungs as the only predictor and did not prove to fit better than existing QP and NQP models according to the BIC (Table E1). The

Table 1 Baseline patient characteristics

	All patients		Patients with back-up photon plans available	
	n	%	n	%
Total n	99	100	48	100
Sex				
Male	47	47.5	20	41.7
Female	52	52.5	28	58.3
Age				
Median (range)	69 (31-97)		69 (31-83)	
<60 y	13	13.1	5	10.4
≥60 y	86	86.9	43	89.6
WHO-PS				
0	32	32.3	16	33.3
1	52	52.5	24	50.0
2	13	13.1	6	12.5
3	2	2.0	2	4.2
Smoking status				
Current	17	17.2	12	25.0
Former	76	76.8	32	66.7
Never	6	6.1	4	8.3
Pulmonary comorbidity (COPD, interstitial lung disease asthma)				
Yes	39	39.4	19	39.6
No	60	60.6	29	60.4
Cardiac comorbidity (hypertension, arrythmia, valvular disease, ischemia)				
Yes	51	51.5	27	56.3
No	48	48.5	21	43.8
AJCC stage (7th ed)				
IIB	1	1.0	1	2.1
IIIA	67	67.7	29	60.4
IIIB	29	29.3	17	35.4
IVA	2	2.0	1	2.1
Tumor location				
Upper	66	66.7	32	66.7
Middle/hilar	12	12.1	6	12.5
Lower	21	21.2	10	20.8
Tumor laterality				
Right	57	57.6	26	54.2
Left	38	38.4	18	37.5
Unknown	4	4.0	4	8.3
Chemotherapy				
Concurrent	97	98.0	47	97.9
Sequential	2	2.0	1	2.1
Radiation pneumonitis (grade ≥ 2)				
3 mo	18	18.2	7	14.6
6 mo	21	21.2	8	16.7
RT dose				
<60 Gy	4	4.0	0	0.0
60-70 Gy	88	88.9	48	100.0
>70 Gy	7	7.1	0	0.0

Abbreviations: AJCC = American Joint Commission for Cancer; COPD = chronic obstructive pulmonary disease; RT = radiation therapy; WHO-PS = World Health Organization performance status.

Table 2 Univariable analysis testing the association of various clinical and dosimetric variables with the risk of developing radiation pneumonitis

	Log likelihood gain	Degrees of freedom	*P* value	AUC	Predicted ΔNTCP (%)
Clinical variables					
Sex	1.0	1	.32	0.58	
Age	0.0	1	.91	0.55	
Age <62	0.0	1	.86	0.51	
Age >62	0.3	1	.59	0.52	
WHO-PS	2.4	3	.49	0.59	
Smoking status	1.3	3	.18	0.60	
Current smoker	3.6	1	.06	0.58	
Former smoker	1.3	1	.25	0.56	
Pulmonary comorbidity (COPD, interstitial lung disease, asthma)	2.9	1	.09	0.60	
Cardiac comorbidity (hypertension, arrythmia, valvular disease, ischemia)	0.2	1	.69	0.52	
AJCC stage (7th ed)	1.3	3	.73	0.53	
Tumor location (mid or low)	0.3	1	.61	0.53	
Tumor laterality	3.5	1	.22	0.57	
Sequential chemotherapy	0.8	1	.36	0.52	
Lung dose variables					
MLD	6.4	1	.012	0.71	3.7
V5	5.1	1	.024	0.68	14.1
V10	4.9	1	.026	0.68	6.5
V15	4.7	1	.030	0.68	2.5
V20	4.7	1	.031	0.69	0.9
V25	4.0	1	.045	0.69	0.1
V30	4.7	1	.031	0.70	−0.3
V40	8.1	1	.004	0.74	−1.9
V50	6.5	1	.011	0.69	−4.7
V60	2.3	1	.128	0.61	−3.9

Abbreviations: AJCC = American Joint Commission for Cancer; AUC = area under the curve; COPD = chronic obstructive pulmonary disease; MLD = mean lung dose; NTCP = normal tissue complication probability; WHO-PS = World Health Organization performance status.

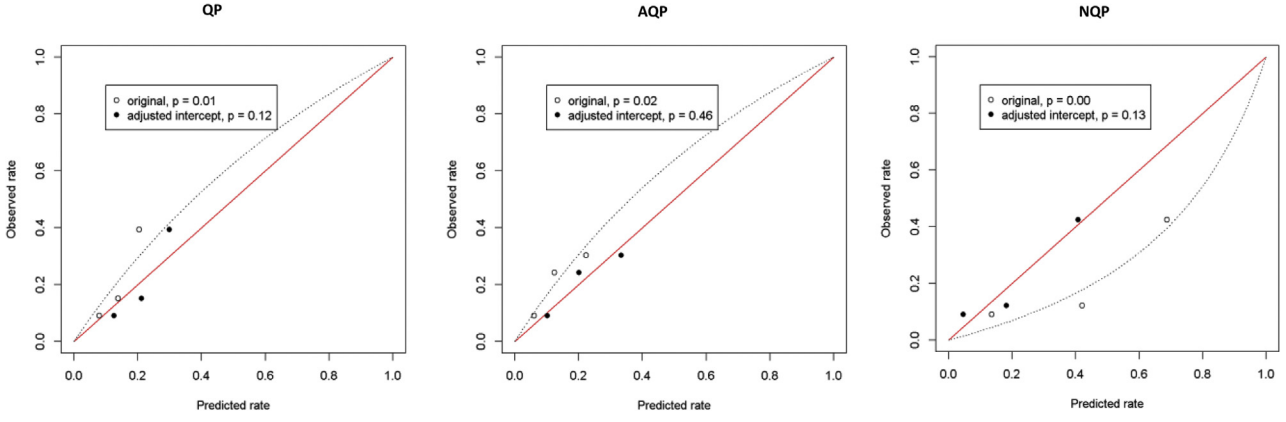

Figure 1 Calibration curves including original and intercept adjusted models in addition to Hosmer Lemeshow test results for QUANTEC pneumonitis (QP), QUANTEC model adjusted for risk factors (AQP), and Netherlands updated QUANTEC (NQP) models. Points denote the averages in the risk groups of the Hosmer Lemeshow test (white dots = original, filled = adjusted model). The red line is the identity reference. The dashed line represents the calibration offset before intercept adjustment. QUANTEC = Quantitative Analyses of Normal Tissue Effects in the Clinic.

Table 3 Results of model validation using the Hosmer Lemeshow test and closed testing procedure

	Slope of MLD (Gy^{-1})	# of events	Update indicated by Hosmer Lemeshow test	Update indicated by closed test procedure	Intercept update (Δ)	AUC
Actual model	0.0017	21 (predicted)				
QP	0.0013	14	Intercept only	None	0.51	0.71
AQP	0.0014	13	Intercept only	None	0.64	0.63
NQP	0.003	41	Intercept only	Intercept only	−1.21	0.72

Abbreviations: AQP = Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) model adjusted for risk factors; AUC = area under the curve; MLD = mean lung dose; NQP = Netherlands updated QUANTEC model; QP = QUANTEC model.

apparent AUC of the redeveloped model was 0.74, which was not corrected for optimism associated with the applied variable selection. Because the average V40 was slightly higher in the proton plans than in the photon backup plans (19.8% vs 18.8%), the predicted ΔNTCP was negative (−1.9%) for this model.

Discussion

The similarity between dose-response relationship between photons and PBT for normal tissue complications has largely been an assumption until now. Our results demonstrate that the widely used NTCP models for RP that were developed using dosimetric data from photon treatments are also valid for PBT with minor modifications.

Several previous studies have proposed NTCP models to predict RP incorporating varying clinical and dosimetric factors.[15-17,25,26] However, all of the models published thus far were based on data from photon treatment plans. To the best of our knowledge, this is the first study to develop and present an NTCP model for RP in a cohort of patients with locally advanced NSCLC treated with PBT. We used a closed testing procedure to select the appropriate method for updating the currently available NTCP models. This method allows one to incorporate the previous knowledge of the relative predictor strengths and update the original prediction model rather than re-estimate the effect of all predictors.[24] This is particularly advantageous in cases such as the current study where the original models were developed with a relatively large sample size and hence had greater power compared with our PBT update sample.

We evaluated the performance of 3 available NTCP models. The first was the QUANTEC model, which incorporated published data from >70 studies to develop a complication probability model as a function of MLD.[14] This model fit our PBT data well with no update (slope or intercept) indicated by the closed testing procedure. The second model tested was an update of the QUANTEC model as proposed by Appelt et al.[15] This model incorporated additional clinical factors such as pre-existing pulmonary comorbidity, mid or inferior tumor location, current/former smoker, old age, and sequential chemotherapy with the goal of providing an individualized estimate of a patient's risk of RP compared with a lung dose-only approach. Our data fit well with the AQP model, again with no adjustment recommended by the closed testing procedure, however, with a lower performance than the more simplistic QUANTEC model. Apparently, the extra variables in the AQP model do not improve the model performance as expected. The last model tested was the NQP model, which is newer (presented in abstract form at European Society for Radiotherapy 2017)[23] and developed in a cohort of patients treated with contemporary doses and regimens of RT and chemotherapy. For this model, only an adjustment of the intercept was indicated by the closed testing procedure for our PBT data. This indicates that the average event rate in the prediction model versus the update sample was different, although the overall dose-response relationship as measured by the slope of the model was similar within the power of our data.

It is interesting to note that a negative adjustment of the intercept was recommended for the NQP model, indicating that the event rate of RP predicted by the model was higher than that observed in our PBT data. One of the reasons for this average higher event rate of RP could be the use of gemcitabine-based chemotherapy in the model development cohort, which is a potent radiosensitizer and has been associated with a higher incidence of RP.[27,28] This may also explain the higher coefficient for the mean dose in the model, that is, the steeper dose-response relationship of this model. Another reason could be that proton therapy generally results in markedly smaller volumes receiving a low irradiation dose (eg, V5- V20), which may contribute to the development of RP but is not included in the existing models so far.

Recent randomized phase II clinical trials comparing toxicities between photons versus protons have reinforced that patient selection is key to determine patients most likely to benefit from PBT.[12] This study was designed as a Bayesian trial, which used an adaptive randomization using real time assessment of outcomes to allocate more patients to the better treatment arm if a difference was observed. Although the study failed to show superiority of protons in terms of higher RP or local failure, it should be

noted that the study required patients to meet dosimetric constraints for both proton and photon plans, and thus may have resulted in decreased enrollment of patients who would have been most likely to benefit from PBT. Of note, there was no statistically significant difference in the mean lung dose between proton and photon plans, a dosimetric variable well established to be associated with the risk of RP. Additionally, all events of RP in the proton arm occurred during the earliest period of trial enrollment, whereas these were spread out evenly by time among the photon arm, where intensity modulated radiotherapy treatment guidelines had been established before the start of the study, suggesting a learning curve associated with the newer proton technology. Lastly, this trial also used double scatter PBT as opposed to pencil beam PBT, which has theoretical advantages. It is unclear if the results would have changed with more experience with planning or the newer PBT technology. There is an ongoing phase III randomized trial comparing overall survival after proton versus photon chemoradiation for inoperable locally advanced NSCLC (Radiation Therapy Oncology Group 1308). This trial is specifically assessing RP as 1 of the secondary endpoints and we await the trial's final results.

A model-based approach toward treatment modality selection is a step forward in this direction. In fact, the Netherlands has published a proposed methodology that can aid in selecting the most appropriate patients for a particular treatment modality using a model-based dual track approach.[29] The default track is a relatively noncontroversial, standard-of-care indication based on available level 1 and 2 evidence. However, in the absence of high-level evidence, as is the case with protons, an alternate track using a ΔNTCP approach will be invoked. At the PBT center, optimized photon and proton plans will be generated. These plans will be assessed for toxicity complication probability, and if the ΔNTCP of most concern for photons exceeds that of protons by some nationally preagreed upon difference (ΔNTCP threshold), then the patient will be treated with PBT. This approach provides for an efficient and transparent mechanism for both patients and clinicians to be able to understand and justify the chosen treatment pathway. We envision that an updated proton-based model such as the one developed in the current study would aid in the treatment modality selection process. In the analyzed data set, the differences in mean lung dose were small between proton plans and photon backup plans, resulting in only a small estimated benefit of protons, which again reinforces the importance of patient selection.

Our work has several limitations. First, our study suffers from small patient numbers, which may have affected the power of the model validations and the accuracy of the model development. Second, the NTCP models investigated in this report are all based on logistic regression, which relies on several assumptions about dose-toxicity relationships. Incorporation of additional nonparametric or machine learning approaches in future models can help alleviate this issue to some extent.[30] Lastly, these models were based on the dose planned, but were not adapted to the dose actually delivered to the target and organs at risk. Uncertainties in contouring of the targets, treatment planning, and delivery as well as uncertainties in RBE were not taken into account in these models.

In conclusion, the similarity between the dose-response relationship for PBT and photons for normal tissue complications has been an assumption until now. We demonstrate that the widely used QP, AQP, and the recently developed NQP models fit our PBT data well with minor modifications. NTCP models, such as the one developed, can aid in individualizing selection of the most optimal treatment technique for a particular patient. In the next phase, we hope to include photon data in the analysis to develop a model that generalizes to both protons and photons.

Supplementary data

Supplementary material for this article can be found at https://doi.org/10.1016/j.prro.2020.04.005.

References

1. Torre LA, Siegel RL, Jemal A. Lung cancer statistics. *Adv Exp Med Biol*. 2016;893:1-19.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69:7-34.
3. Noone AM, Howlader N, Krapcho M, et al (eds). Cancer Statistics Review, 1975-2015 - SEER Statistics. SEER Cancer Statistics Review. Available at: https://seer.cancer.gov/csr/1975_2015/. Accessed January 1, 2020.
4. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379:2342-2350.
5. Simone CB. Thoracic radiation normal tissue injury. *Semin Radiat Oncol*. 2017;27:370-377.
6. Rodrigues G, Lock M, Souza D, Yu E, Van Dyk J. Prediction of radiation pneumonitis by dose-volume histogram parameters in lung cancer - A systematic review. *Radiother Oncol*. 2004;71:127-138.
7. Graves PR, Siddiqui F, Anscher MS, Movsas B. Radiation pulmonary toxicity: From mechanisms to management. *Semin Radiat Oncol*. 2010;20:201-207.
8. Mehta V. Radiation pneumonitis and pulmonary fibrosis in non-small-cell lung cancer: Pulmonary function, prediction, and prevention. *Int J Radiat Oncol Biol Phys*. 2005;63:5-24.
9. Vogelius, Bentzen IS. A literature-based meta-analysis of clinical risk factors for development of radiation induced pneumonitis. *Anta Oncol*. 2013;51:975-983.
10. Gray JE, Villegas A, Daniel D, et al. Three-year overall survival with durvalumab after chemoradiotherapy in stage III NSCLC—Update from PACIFIC. *J Thorac Oncol*. https://doi.org/10.1016/j.jtho.2019.10.002.
11. Giaddui T, Chen W, Yu J, et al. Establishing the feasibility of the dosimetric compliance criteria of RTOG 1308: Phase III randomized trial comparing overall survival after photon versus proton

radiochemotherapy for inoperable stage II-IIIB NSCLC. *Radiat Oncol.* https://doi.org/10.1186/s13014-016-0640-8.
12. Liao Z, Lee JJ, Komaki R, et al. Bayesian adaptive randomization trial of passive scattering proton therapy and intensity-modulated photon radiotherapy for locally advanced non−small-cell lung cancer. *J Clin Oncol.* https://doi.org/10.1200/JCO.2017.74.0720.
13. Yorke ED. Parameters for and use of NTCP models in the clinic The 1991 Data Set 1991 to Now. *Ppt.*:1-8. Available at: https://www.aapm.org/meetings/amos2/pdf/29-7787-23771-420.pdf. Accessed June 24, 2020.
14. Marks L, Bentzen S, Deasy J, Kong F. Radiation dose volume effects in the lung. *Int J Radiat Oncol Biol Phys*. 2010;76:70-76.
15. Appelt AL, Vogelius IR, Farr KP, Khalil AA, Bentzen SM. Towards individualized dose constraints: Adjusting the QUANTEC radiation pneumonitis model for clinical risk factors. *Acta Oncol (Madr)*. 2014;53:605-612.
16. Seppenwoolde Y, Lebesque JV, De Jaeger K, et al. Comparing different NTCP models that predict the incidence of radiation pneumonitis. *Int J Radiat Oncol Biol Phys*. 2003;55:724-735.
17. Tsougos I, Nilsson P, Theodorou K, et al. NTCP modelling and pulmonary function tests evaluation for the prediction of radiation induced pneumonitis in non-small-cell lung cancer radiotherapy. *Phys Med Biol*. 2007;52:1055-1073.
18. Semenenko VA, Li XA. Lyman-Kutcher-Burman NTCP model parameters for radiation pneumonitis and xerostomia based on combined analysis of published clinical data. *Phys Med Biol*. 2008;53:737-755.
19. Hong L, Goitein M, Bucciolini M, et al. A pencil beam algorithm for proton dose calculations. *Phys Med Biol*. 1996;41:1305-1330.
20. International Commission on Radiation Units and Measurements Report 78, J ICRU 2007;7. Oxford: Oxford University Press; 2007.
21. Paganetti H, Niemierko A, Ancukiewicz M, et al. Relative biological effectiveness (RBE) values for proton beam therapy. *Int J Radiat Oncol Biol Phys*. 2002;53:407-421.
22. Veiga C, Janssens G, Teng CL, et al. First clinical investigation of cone beam computed tomography and deformable registration for adaptive proton therapy for lung cancer. *Int J Radiat Oncol Biol Phys*. 2016;95:549-559.
23. Van Der Schaaf A, Lodeweges J, Niezink A, Langendijk JA. Updating QUANTEC and clinically adjusted QUANTEC models for pneumonitis at external validation. *Radiother Oncol*. 2017;123:S68.
24. Vergouwe Y, Nieboer D, Oostenbrink R, et al. A closed testing procedure to select an appropriate method for updating prediction models. *Stat Med*. 2017;36:4529-4539.
25. Brodin NP, Kabarriti R, Garg MK, Guha C, Tomé WA. Systematic review of normal tissue complication models relevant to standard fractionation radiation therapy of the head and neck region published after the QUANTEC reports. *Int J Radiat Oncol Biol Phys*. 2018;100:391-407.
26. Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose−volume effects in the lung. *Int J Radiat Oncol Biol Phys*. 2015;76:S20-S27.
27. Yamada M, Kudoh S, Hirata K, Nakajima T, Yoshikawa J. Risk factors of pneumonitis following chemoradiotherapy for lung cancer. *Eur J Cancer*. 1998;34:71-75.
28. Leprieur E, Fernandez D, Chatellier G, Klotz S, Giraud P, Durdux C. Acute radiation pneumonitis after conformational radiotherapy for nonsmall cell lung cancer: Clinical, dosimetric, and associated-treatment risk factors. *J Cancer Res Ther*. 2013;9:447.
29. Langendijk JA, Lambin P, De Ruysscher D, Widder J, Bos M, Verheij M. Selection of patients for radiotherapy with protons aiming at reduction of side effects: The model-based approach. *Radiother Oncol*. 2013;107:267-273.
30. Lambin P, Zindler J, Vanneste BGL, et al. Decision support systems for personalized and participative radiation oncology. *Adv Drug Deliv Rev*. 2017;109:131-153.