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Clinical Investigation

Predictors of Pneumonitis After Conventionally Fractionated Radiotherapy for Locally Advanced Lung Cancer

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Purpose: Multiple factors influence the risk of developing pneumonitis after radiation therapy (RT) for lung cancer, but few resources exist to guide clinicians in predicting risk in an individual patient treated with modern techniques. We analyzed toxicity data from a state-wide consortium to develop an integrated pneumonitis risk model.

Methods and Materials: All patients (N = 1302) received conventionally fractionated RT for stage II-III non-small cell lung cancer between April 2012 and July 2019. Pneumonitis occurring within 6 months of treatment was graded by local practitioners and collected prospectively from 27 academic and community clinics participating in a state-wide quality consortium.

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Matthew R. McFarlane and Kimberly A. Hochstedler, contributed equally to this study.

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We are not authorized to share MROQC data. The data are individually owned by the member institutions of MROQC.

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Pneumonitis was modeled as either grade ≥2 (G2+) or grade ≥3 (G3+). Logistic regression models were fit to quantify univariable associations with dose and clinical factors, and stepwise Akaike information criterion−based modeling was used to build multivariable prediction models.

Results: The overall rate of pneumonitis of any grade in the 6 months following RT was 16% (208 cases). Seven percent of cases (n = 94) were G2+ and <1% (n = 11) were G3+. Adjusting for incomplete follow-up, estimated rates for G2+ and G3+ were 14% and 2%, respectively. In univariate analyses, gEUD, V5, V10, V20, V30, and mean lung dose (MLD) were positively associated with G2+ pneumonitis risk, whereas current smoking status was associated with lower odds of pneumonitis. G2+ pneumonitis risk of ≥22% was independently predicted by MLD of ≥20 Gy, V20 of ≥35%, and V5 of ≥75%. In multivariate analyses, the lung V5 metric remained a significant predictor of G2+ pneumonitis, even when controlling for MLD, despite their close correlation. For G3+ pneumonitis, MLD and V20 were statistically significant predictors. Number of patient comorbidities was an independent predictor of G3+, but not G2+ pneumonitis.

Conclusions: We present an analysis of pneumonitis risk after definitive RT for lung cancer using a large, prospective dataset. We incorporate comorbidity burden, smoking status, and dosimetric parameters in an integrated risk model. These data may guide clinicians in assessing pneumonitis risk in individual patients.

Introduction

Radiation pneumonitis is a common and potentially devastating adverse effect of thoracic radiation therapy (RT). Patients with locally advanced lung cancer are at the highest risk, as the standard of care for concurrent chemoradiation necessitates high doses (approximately 60 Gy) of radiation given to relatively large treatment volumes. Some have estimated the risk of pneumonitis of any grade as high as 30% to 40%.[1] In addition, patients with lung cancer are often in poor overall health at the time of their diagnosis; approximately three fourths of patients exhibit ≥1 comorbid medical condition, such as chronic obstructive pulmonary disease (COPD) and congestive heart failure, and many patients continue to smoke throughout their lung cancer treatment. Both clinical factors might synergize with radiation dose to affect the probability and severity of pneumonitis.[2] Because of its potential impact on quality of life, RT dose planning incorporates several constraints aimed at minimizing the risk of pneumonitis. For example, the volume of lung receiving >20 Gy of radiation (V20) and mean lung dose (MLD) are commonly used parameters.

These dosimetric constraints were based on older toxicity studies, most of which are small, single institution, retrospectively collected, or do not incorporate clinical factors. In addition, many were published before intensity modulated RT or concurrent chemotherapy became widely used. This has limited the ability to develop an accurate predictive model that can be used to optimize radiation dose distribution for the individual patient. In particular, the role of lung volume receiving low doses in the development of pneumonitis remains controversial. Volumetric modulated arc therapy−based techniques is capable of generating large volumes of lung receiving low doses of radiation to reduce the volumes receiving high doses, and but it is unknown whether this improves outcomes or whether additional parameters, such as V5, should be incorporated into planning optimization.

We reviewed the literature on pneumonitis risk during radiotherapy for lung cancer and identified 53 studies, including 2 meta-analyses (Table E1). We found that the median rate of G2+ pneumonitis reported was 18% (interquartile range [IQR], 14%-28%), and the median rate of G3+ pneumonitis was 9% (IQR, 5%-12%). The mean number of patients included per study was 102 (range, 8-1911). The most common predictors of pneumonitis were MLD and V20-V30, identified in 27 and 20 studies, respectively.

MROQC (Michigan Radiation Oncology Quality Consortium), a group of 27 academic and community practice treatment centers across the state of Michigan, maintains a large, prospective, multicenter patient database that aggregates clinical and dosimetric data for patients with lung cancer, and toxicity such as pneumonitis. We present the combined clinical and dosimetric data from 1302 MROQC patients—to our knowledge, the largest prospective cohort of patients analyzed for pneumonitis risk—and develop an integrated clinical-dosimetric pneumonitis risk model to estimate the probability of developing radiation pneumonitis using modern techniques in diverse community settings.

Methods and Materials

This analysis included patients who received conventionally fractionated (1.8-2.0 Gy/fraction) definitive RT for stage II-III non-small cell lung cancer from April 2012 through July 2019. Patient information was collected prospectively from 27 academic and community clinics participating in the Michigan Radiation Oncology Quality Consortium (MROQC). MROQC is a multicenter quality improvement collaborative that is funded by Blue Cross and Blue Shield of Michigan and Blue Care Network. It collects clinical, sociodemographic, treatment, dosimetric, and outcome data for patients receiving RT in Michigan. Data are collected on all eligible patients in MROQC practices, regardless of their insurance type. All data analyses were performed independently of the funding agency. Further information on data collection methods are available in other MROQC studies, available at https://www.mroqc.org/publications.

Information in the MROQC databases included patient demographics; tumor stage, location, and histology; and treatment information, including treatment plans, dose-volume histograms (DVHs), and use of chemotherapy. Each institution also provided prescription dose, separate from the DVH data.[3] Since 2018, DICOM planning images, RT structures, and dose, in addition to radiation plans, have been collected. During radiation treatment, patients were evaluated on a weekly basis by the treating radiation oncologist. Follow-up continued by the treating radiation oncologist for 1-, 3-, and 6-month visits after the conclusion of RT. At these evaluations, toxicities were scored using the Common Terminology Criteria for Adverse Events, version 4.0, on standardized forms. In this analysis, toxicities are reported as the maximum grade observed at any evaluation during the last week of RT or later.

Patient demographics were self reported. Patient smoking status was defined as "current," "former" (quit at least 1 month before diagnosis), or "never." Comorbidity information was obtained at the patient's initial visit. We summarized patient comorbidities as a simple count of the number of conditions that were reported, out of 19 listed (hypertension, diabetes mellitus, scleroderma, rheumatoid arthritis, lupus, cerebrovascular disease, COPD, congestive heart failure, connective tissue disease, confusion, hemiplegia, leukemia, malignant lymphoma, myocardial infarction, peripheral vascular disease, ulcer disease, liver disease, renal disease, malignant solid tumor [other than lung]). Information on the severity of comorbidities was not available. Clinical information on stage, chemotherapy, tumor size, and patient height and weight were also obtained at the patient's initial visit.

Pneumonitis

Two binary endpoints corresponding to grade ≥2 versus grade ≤1 (G2+) or grade ≥3 versus grade ≤2 (G3+) pneumonitis were analyzed. Because of variations in clinical practice, most patients were seen at only 1 or 2 of the 3 possible follow-up times. To account for missing follow-up data in our analysis, we calculated a patient-level weight so that patients seen at only 1 or 2 timepoints are weighted less in the analysis than patients seen at all 3 follow-up times. We calculated a weight for each follow-up time based on the relative frequency of G2+ pneumonitis at each timepoint. These weights were normalized to sum to 1, and patient-level weights were calculated as the sum of the follow-up time weights at non-missing timepoints. Patients who had a reported toxicity of grade ≥2 at any of these evaluations received full weight. Weights for G3+ analyses were computed using the same approach. This approach was taken—rather than a "time-to-event" or survival analysis—because it is possible for a patient to have G2+ pneumonitis in early months of follow-up that resolves before the latest 6-month visit.

DVH metrics

Relative lung volumes (in cubic centimeters) receiving doses from 5 to 60 Gy (V5, V10, V15, V20, V25, V30, V35, V40, V45, V50, V55, and V60) were calculated from lung DVHs. Both lungs minus the gross tumor volume or internal gross tumor volume were used as the normal lung evaluation structure. Absolute lung volumes receiving doses of 5 to 60 Gy were also considered, but they had lower predictive performance than relative measures and results are not included. MLD and generalized equivalent uniform dose (gEUD) were computed from lung DVHs. gEUD is defined according to Equation 1, and the α parameter was estimated via maximum likelihood with the constraint that $\alpha > 0$.

$$\mathrm{gEUD} = \left(\Sigma_i v_i D_i^{\alpha}\right)^{1/\alpha} \qquad \text{(Equation (1))}$$

where v_i is the i^{th} relative volume (fractional) for a given patient, and D_i is the i^{th} dose (Gy) for a given patient.

Statistical models

Weighted logistic regression models were used to describe the risk of pneumonitis toxicity as a function of dose and clinical covariates. Parameters were estimated using maximum likelihood. We used the fitted regression models to calculate the probability of toxicity at each dose value. In univariate and multivariable models, we then quantified the ability of each dose or clinical covariate to discriminate among patients who did or did not have toxicity, using nonparametric estimates of area under the receiver operating characteristic (ROC) curve (AUC). To build predictive models of G2+ and G3+ pneumonitis, we used a stepwise modeling procedure in which predictors were chosen using the Akaike information criterion (AIC). Stepwise regression was forward and backward. Variables considered in stepwise procedure were MLD, V5 − V60 (by 5), stage (II vs III), sex (binary), age (years), smoking status (current, former, or never), number of comorbidities, COPD (yes or no), receiving oxygen (yes or no), adjuvant chemotherapy (yes or no), concurrent chemotherapy (yes or no), neoadjuvant chemotherapy (yes or no), lower lobe location (left, right, both, or neither), treated after February 2018 (yes or no; proxy for immunotherapy), and total tumor volume.

In all models, we enforced monotonicity of dose variables (so that higher dose could not decrease predicted risk of pneumonitis). Stepwise procedures were used to build predictive models of both G2+ and G3+ pneumonitis using only dosimetric predictors and using both dosimetric and clinical covariates. This analysis was done twice, once excluding gEUD-based models in favor of MLD or VX-based models. The AUC was calculated as the empiric value for univariable models. For the multivariable prediction models, 10-fold cross-validation was used in which the entire model-building procedure (specifically, variable selection and estimation) was included in the cross-

validation loop. Fold selection was repeated 10 times, and the resulting AUC estimates were averaged to remove variability associated with fold selection. SAS software version 9 (SAS)[4] and R V3.6.1 were used for analyses,[5] and the WeightedROC package was used for AUC calculations.[6] The stepAIC function used from MASS package in R. WeightedAUC and WeightedROC functions were used from the WeightedROC package.

Results

Clinical and toxicity information were available for 3000 patients with lung cancer. After exclusions, 1302 patients were included in our analysis, all of whom had stage II-III lung cancer treated in the state of Michigan between 2012 and 2019. Patients were excluded if they were treated twice per day (n = 82), were treated with surgery (n = 438), were stage 0, I, or OC (n = 400), did not have heterogeneity-corrected dose calculations (n = 76), were missing all pneumonitis follow-up evaluations (n = 293), had single lung definitions for normal lung volume calculations (n = 23), or had missing dose metrics or D95 to the planning target volume of <40 Gy (n = 384). Patient characteristics are summarized in Table 1.

Our cohort of patients were treated between April 2012 and July 2019 at 1 of 27 academic or community clinics. The group was equally divided between male and female, with a median age of 67 years. Racial composition was 80% white and 20% black/other; 40% of patients were current smokers, and 56% were former smokers. Median comorbidity count was 2, and >60% of patients had ≥2 comorbidities; 68% of patients had an Eastern Cooperative Oncology Group performance status of 0 or 1; 9.4% of patients were receiving supplemental oxygen at baseline; and 85% of patients received concurrent chemotherapy. The mean MLD for all patients was 15.2 Gy. Mean V5 and V20 were 57% and 26%, respectively. The overall rate of pneumonitis in the 6 months after RT was 16% (208 cases); 7% (94 cases) were grade ≥2 (G2+) and 1% (11 cases) were grade ≥3 (G3+). Adjusting for incomplete follow-up, estimated rates for G2+ and G3+ pneumonitis were 14% and 2%, respectively. The relative frequency of reported G2+ pneumonitis at each measured time point was as follows: end of treatment, 0.40%; 1 month, 2.60%; 3 months, 7.54%; and 6 months, 7.00%.

Univariate analysis

Univariate regression models for grade ≥2 (G2+) and grade ≥3 (G3+) pneumonitis are shown in Table 2. Dosimetric predictors of G2+ pneumonitis included MLD (odds ratio [OR], 1.11 per Gy; $P < .001$), V5 (OR, 1.34 per 10%; $P < .001$), V10 (OR, 1.34 per 10%; $P < .001$), V15 (OR, 1.63 per 10%; $P < .001$), V20 (OR, 1.79 per 10%; $P < .001$), V25 (OR, 1.63 per 10%; $P = .001$), V30 (OR, 1.48 per 10%; $P = .01$), and V35 (OR, 1.34 per 10%; $P = .048$),

Table 1 Characteristics of patients in the study cohort*

Characteristics	Overall (N = 1302)
Sex, n (%)	
Female	635 (48.8%)
Male	667 (51.2%)
Age (y)	
Mean (SD)	67.8 (9.77)
Median (range)	67.6 (38.7-94.1)
Race, n (%)	
African American, Other	260 (20.0%)
White	1042 (80.0%)
Smoking status, n (%)	
Current	517 (39.7%)
Former	723 (55.5%)
Never	51 (3.9%)
Missing	11 (0.8%)
Body mass index	
Mean, kg/m^2 (SD)	27.2 (6.69)
Median, kg/m^2 (range)	26.2 (13.3-69.0)
Missing, n (%)	125 (9.6%)
Stage, n (%)	
IIA	116 (8.9%)
IIB	91 (7.0%)
IIIA	749 (57.5%)
IIIB	346 (26.6%)
V5 (Gy)	
Mean (SD)	57.0 (3.84)
Median (range)	56.9 (1.56-100)
V20 (Gy)	
Mean (SD)	26.1 (7.90)
Median (range)	31.8 (0.789-90.7)
Mean lung dose (Gy)	
Mean (SD)	15.2 (3.84)
Median (range)	15.4 (2.70-34.3)
Comorbidities, n (%)	
Mean (SD)	1.98 (1.41)
Median (range)	2.00 (0.00-8.00)
Chronic pulmonary disease, n (%)	
No	665 (51.1%)
Yes	637 (48.9%)
Receiving oxygen, n (%)	
No	1147 (88.1%)
Yes	123 (9.4%)
Missing	32 (2.5%)
Lower lobe location, n (%)	
Left	162 (12.4%)
Right	249 (19.1%)
Both	2 (0.2%)
Neither	889 (68.3%)
Adjuvant chemotherapy, n (%)	
No	1150 (88.3%)
Yes	152 (11.7%)
Concurrent chemotherapy, n (%)	
No	190 (14.6%)
Yes	1112 (85.4%)
Neoadjuvant chemotherapy, n (%)	
No	1209 (92.9%)
Yes	93 (7.1%)

* Patient characteristics are evaluated before radiation therapy.

Table 2 Odds ratios, *P* values, and area under the receiver operating characteristic curve for univariate predictors of G2+ and G3+ pneumonitis

	Pneumonitis grade ≥2 vs ≤1(N = 1302)			Pneumonitis grade ≥3 vs ≤2(N = 1302)		
Predictors	OR	*P* value	AUC	OR	*P* value	AUC
gEUD (a = 0.01)	1.14*	<.001*	0.63*	—	—	—
MLD (Gy)	1.11*	<.001*	0.61*	1.27*	.005*	0.75*
V5 (per 10%)	1.34*	<.001*	0.62*	1.41	.08	0.68
V10 (per 10%)	1.34*	<.001*	0.61*	1.55*	.045*	0.70*
V15 (per 10%)	1.63*	<.001*	0.62*	2.12*	.007*	0.77*
V20 (per 10%)	1.79*	<.001*	0.62*	2.76*	.004*	0.79*
V25 (per 10%)	1.63*	.001*	0.59*	2.94*	.008*	0.74*
V30 (per 10%)	1.48*	.01*	0.58*	3.00*	.01*	0.72*
V35 (per 10%)	1.34*	.048*	0.56*	2.81*	.03*	0.69*
V40 (per 10%)	1.21	.20	0.54	2.62*	.046*	0.67*
V45 (per 10%)	1.10	.48	0.53	2.50	.07	0.66
V50 (per 10%)	1.10	.65	0.52	2.69	.07	0.67
V55 (per 10%)	1.00	.87	0.51	2.76	.08	0.68
V60 (per 10%)	1.00	.98	0.50	2.55	.17	0.63
Stage III (compared to stage II)	1.38	.30	0.52	0.54	.37	0.55
Male sex (compared to female)	1.12	.47	0.52	0.80	.72	0.53
Age	1.00	.99	0.49	1.06	.06	0.65
Former smoker†	0.58	.24	0.58	0.45	.47	0.58
Current smoker†	0.311	.02	—	0.26	.25	—
Comorbidity count	0.98	.79	0.51	1.57	.02	0.68
Adjuvant chemotherapy	1.05	.89	0.50	0.66	.70	0.52
Concurrent chemotherapy	0.97	.92	0.50	0.72	.67	0.52
Neo-adjuvant chemotherapy	0.66	.39	0.51	1.37	.77	0.51
Body mass index‡	1.03	.12	0.56	1.07	.07	0.71
Lung volume	1.00	.76	0.53	1.00	.26	0.61
Lower lobe location	1.48	.08	—	1.27	.71	—

Abbreviations: AUC = area under the receiver operating characteristic curve; OR = odds ratio.
Results are all from separate models.
* Predictors that are associated with G2+ or G3+ at the .05 significance level.
† Former smoker and current smoker are 2 levels in a single model, both compared to never smoker. Sample size for models was 1291.
‡ Sample size for models was 1177.

whereas clinical predictors of G2+ pneumonitis included current smoking status (OR, 0.311; $P = .02$). Lower lobe location trended toward an association with G2+ pneumonitis risk (OR, 1.48; $P = .08$), but was not significant in our analysis. The maximum likelihood estimate of the α parameter in gEUD was 0.01 (95% confidence interval [CI], 0-0.05). gEUD was significantly associated with risk of G2+ pneumonitis (OR, 1.14; $P < .001$).

To compare univariate predictors of G2+ pneumonitis, we plotted percent risk of G2+ pneumonitis as a function of MLD, V20, and V5 in separate graph panels (Fig. 1). We included commonly used dose constraints of MLD <20 Gy and lung V20 <35% in Figure 1 (red lines). In our data, these cutoffs both correspond to predicted risk of G2+ pneumonitis of 22%. The corresponding V5 value resulting in the same predicted risk is V5 ≥75%. We also included lines representing cutoffs that predict pneumonitis rates of less than 15% (blue lines), which correspond to MLD < 16 Gy, V20 < 27%, V5 < 58%.

Dosimetric predictors of G3+ pneumonitis were similar and included MLD (OR, 1.27 per Gy; $P = .005$), V10 (OR, 1.55 per 10%; $P = .045$), V15 (OR, 2.12 per 10%; $P = .007$), V20 (OR, 2.76 per 10%; $P = .004$), V25 (OR, 2.94 per 10%; $P = .008$), V30 (OR, 3.00 per 10%; $P = .02$), V35 (OR, 2.81 per 10%; $P = .03$), and V40 (OR, 2.62 per 10%; $P = .046$). Clinical predictors of G3+ pneumonitis included comorbidity count (OR, 1.57 per comorbidity; $P = .02$). Lower lobe location was not associated with G3+ pneumonitis (OR, 1.27; $P = 0.71$) in weighted univariable logistic regression models.

Multivariable analysis

We next sought to determine which covariates retained predictive power of G2+ pneumonitis risk after controlling for V20, which is the most used planning constraint. We found that lung V5 remained significantly associated with G2+ pneumonitis risk, even after controlling for V20 (Fig. 2A) and despite the metrics being closely correlated ($r = 0.665$). Figure 2A illustrates this relationship at various values of V20; even at the highest decile, G2+ pneumonitis risk is positively associated with V5. In Figure 2B, we plot observed lung V5 versus V20 for all patients and indicate whether the

Table 3 Adjusted OR estimates, 95% CI, associated *P*-values and cross-validated AUC estimates for multivariable, weighted logistic regression models predicting G2+ and G3+ pneumonitis from dosimetric-only covariates or dosimetric and clinical covariates

Predictor	OR (95% CI)	*P* value
Pneumonitis grade 2+		
Dosimetric model, AUC: 0.602		
V5*	1.19 (1.00-1.42)	.053
V20*	1.37 (0.98-1.94)	.07
Dosimetric and clinical model, AUC: 0.600		
V5*	1.17 (0.98-1.55)	.08
V20*	1.41 (1.00-2.00)	.054
Former smoker†	0.62 (0.25-1.70)	.33
Current smoker†	0.33 (0.13-0.93)	.03
Pneumonitis grade 3+		
Dosimetric model, AUC: 0.752		
V20*	2.76 (1.40-5.70)	.004
Dosimetric and clinical model, AUC: 0.745		
Mean lung dose	1.31 (1.10-1.58)	.003
Age‡	1.35 (0.96-1.93)	.09
Comorbidity count	1.47 (0.98-2.17)	.053

Abbreviations: AUC = area under the receiver operating characteristic curve; CI = confidence interval; OR = odds ratio.

ORs may be interpreted as the multiplicative change in the odds of developing pneumonitis G2+ (or G3+) at any point during 1 to 6 months after radiation therapy, per unit increase (or compared to the reference group) of the given predictor, controlling for all other covariates.

* Per 10% increase.

† Reference group is "never smoked."

‡ Per 5-year increase.

patient experienced G2+ pneumonitis at any point during follow-up. Risk contours are presented to visualize the increasing risk of G2+ as a function of both V5 and V20. The risk gradient increases along both the V5 and V20 axes, indicating that both metrics are simultaneously useful for determining G2+ pneumonitis risk. These data were also analyzed using MLD in place of V20, with similar results (Figure E2).

Separately, we built a model to separately analyze G3+ pneumonitis. In this case, dosimetric predictors (V20 and MLD) and clinical comorbidities were analyzed together. Figure 3A demonstrates that, regardless of comorbidity count, lung V20 is still positively associated with the probability of developing G3+ pneumonitis. In Figure 3B, we plot the observed number of comorbidities versus V20 for all patients and indicate whether the patient experienced G3+ pneumonitis at any point during follow-up. One to twenty percent risk contours are presented to visualize the increasing risk of G3+ pneumonitis as a function of both comorbidity count and V20. We also note that, of the patients with observed G3+ pneumonitis, most had ≥ 4 comorbidities. These data were also analyzed using MLD in place of V20, with similar results (Figure E3).

Predictive modeling

Using a stepwise AIC procedure, we developed 4 predictive models for G2+ and G3+ pneumonitis risk (Table 3) using only dose terms or dose and clinical factors with candidate variables (all those listed in Table 2). The best dose-only

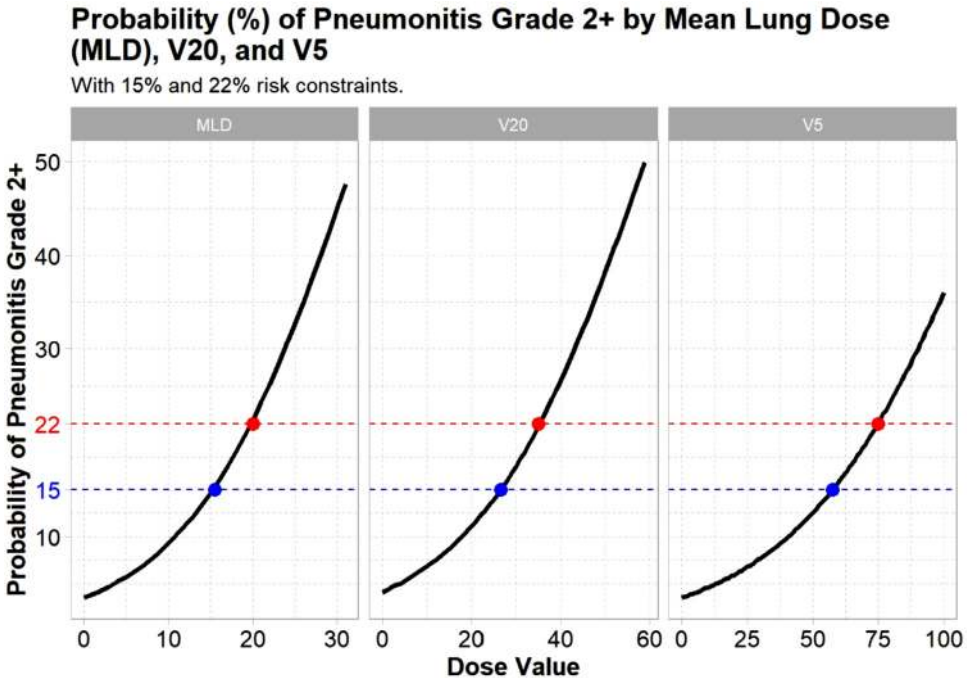

Fig. 1. Percent risk of developing G2+ pneumonitis as a function of mean lung dose, V20, and V5. Predictors of G2+ pneumonitis are represented in separate models. Horizontal dashed lines indicate dose metrics corresponding to 15% and 22% risk constraints for developing G2+ pneumonitis at any time during the 6 months following radiation therapy.

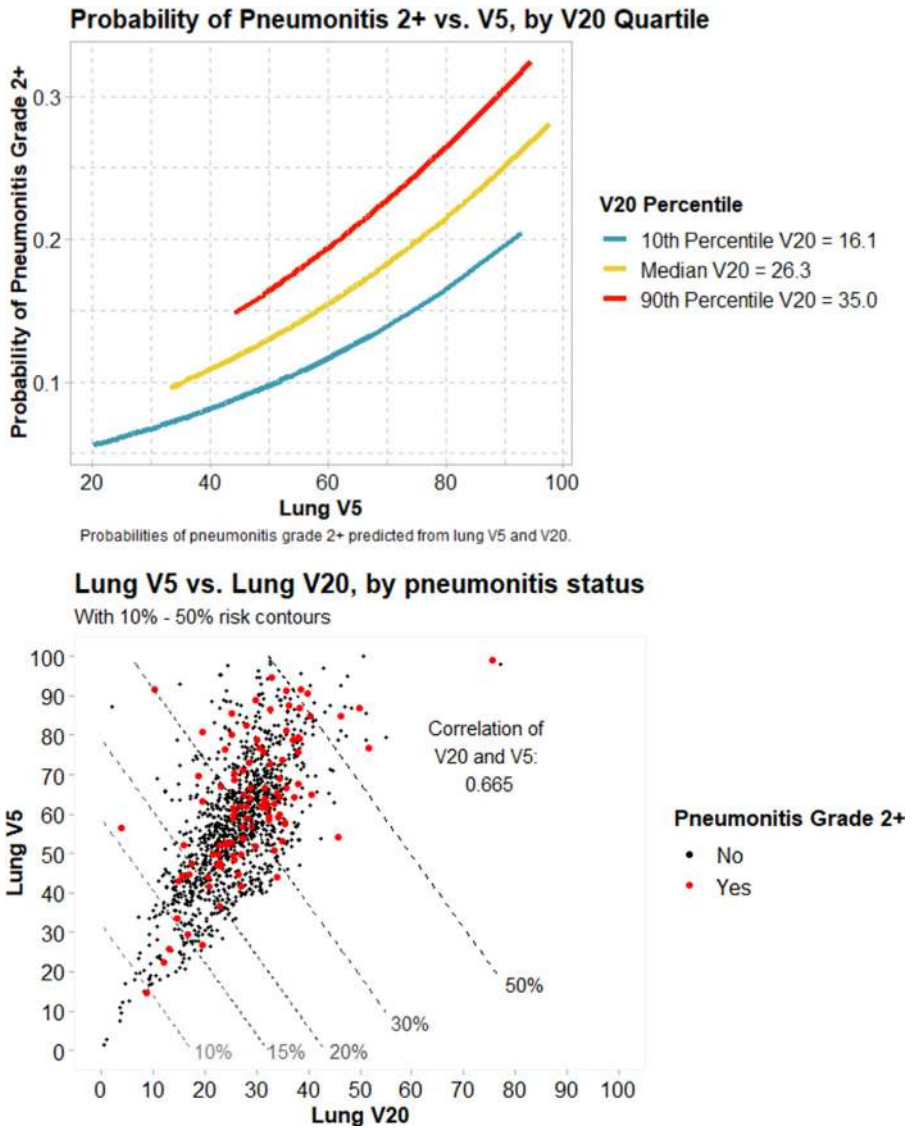

Fig. 2. (A) Probability of developing G2+ pneumonitis at any time during 1 to 6 months after radiation therapy versus lung V5, with separate lines corresponding to lung V20 percentile. (B) Lung V5 versus lung V20 observations, with points colored by G2+ pneumonitis status. The dashed line indicates V5 and V20 values associated with a 20% predicted risk of G2+ pneumonitis. Background shading corresponds to predicted probability of V5 and V20, ranging between 0% and 80%. V5 and V20 are highly correlated, with $r = 0.665$.

predictive model for G2+ pneumonitis includes only gEUD. No other dose terms significantly improved model fit when added to a model including gEUD. The best dose and clinical factor model included gEUD (OR, 1.13) and whether the patient is a current or former smoker (OR, 0.56 and 0.29, respectively). Because gEUD is not commonly used, we also repeated the AIC-based model building while excluding gEUD from consideration. The resulting dose-only model for G2+ pneumonitis included V5 and V20, and the cross-validated estimate of the model AUC was 0.61. Including clinical factors in modeling resulted in a model with V5 (OR, 1.19 per 10% increase), V20 (OR, 1.37 per 10% increase), and whether the patient is a current or former smoker (OR, 0.33 and 0.62, respectively). Adding smoking status to the model with V5 and V20 significantly improved model fit (as quantified by AIC), although the cross-validated estimate of this model AUC remained 0.60.

The selected dose-only predictive model for G3+ pneumonitis includes only V20 (OR, 1.41) with a cross-validated AUC of 0.75. Our predictive model using dosimetric and clinical covariates for G3+ pneumonitis includes MLD (OR, 1.31 per Gy increase), age (OR, 1.35 per 5-year increase), and comorbidity count (OR, 1.47 per comorbidity). Although adding age and comorbidities to the model with V20 significantly improved model fit (as quantified by AIC), the cross-validated AUC remained 0.75. Equations giving predicted risk based on these models are presented in Figure E1, and a web calculator is available at http://ppa.mroqc.org, which allows users

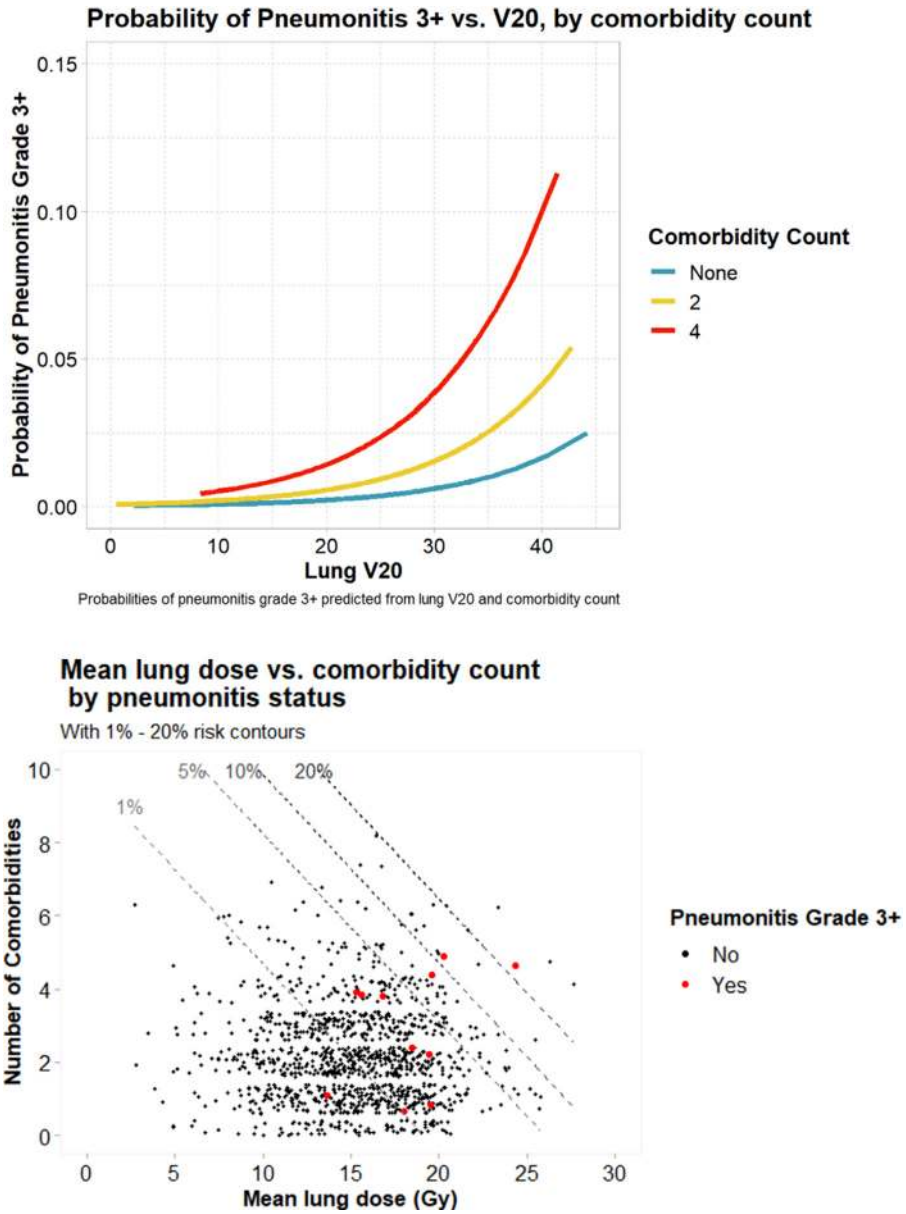

Fig. 3. (A) Probability of developing G3+ pneumonitis at any time during 1 to 6 months after radiation therapy versus lung V20, with separate lines corresponding to comorbidity count. (B) Patient comorbidity count versus lung V20 observations, with points colored by G3+ pneumonitis status. The dashed line indicates comorbidity count and V20 values associated with a 5% predicted risk of G3+ pneumonitis. Background shading corresponds to predicted probability of G2+ pneumonitis, as a function of comorbidity count and V20, ranging between 5% and 95%.

to easily estimate the pneumonitis risk of an individual patient based on readily available clinical and dosimetric parameters. Model calibration was checked graphically through HL type plots of observed vs predicted risk (Fig E4). Each of the predictive models was well calibrated.

Discussion

Herein, we have analyzed the clinical toxicity from 1302 patients receiving definitive RT for lung cancer. Data were collected prospectively from 27 academic and community clinics participating in a state-wide quality consortium. We have used these data to develop integrated risk models for both G2+ and G3+ pneumonitis.

As expected, our results indicate that both G2+ and G3+ pneumonitis risk depends primarily on overall lung dose. MLD and nearly all VX metrics from V5-V35 are statistically significant univariate predictors of both G2+ and G3+ pneumonitis (the only exceptions were near-significant: V35 for G2+ [$P = .05$] and V5 and V10 G3+ [$P = .08$ and $P = .05$, respectively]).

The finding that V5 is still a significant predictor of pneumonitis after adjusting for MLD or V20 is important

because it differs from a secondary analysis of the RTOG 0617 randomized trial, in which neither lung V5 nor MLD was significantly associated with grade 3 pneumonitis, suggesting that "spreading out" low dose using volumetric modulated arc therapy might be an effective means of limiting toxicity.[7] In contrast, our data join other recent publications[8] in suggesting that low doses to large volumes of lung might not be an optimal strategy to reduce lung toxicity, although this must be balanced against other considerations such as dose to heart[9] and esophagus.[10] The data also suggest that strategies being tested in ongoing clinical trials to further reduce low dose volumes, such as adaptive replanning or proton therapy, might show clinical benefit in appropriately designed and powered randomized trials. Although the only published randomized lung proton therapy trial failed to show a decrease in toxicity, this was in the context of a passive scattering proton technique that resulted in larger high-dose lung volumes compared with the intensity modulated RT controls, which confounds the interpretation of benefit from reducing low-dose volumes.[11]

Although our model for G2+ pneumonitis that included gEUD modestly outperformed the one incorporating V5 and V20 (Table E2), we have emphasized the VX metric −based model because the AIC difference was small, and VX-based constraints will be more familiar and readily calculated by most practicing physicians. Because gEUD, by definition, integrates more DVH data than discrete VX metrics, this is to be expected; however, the modest improvement in AIC obtained using gEUD suggests that V5 and V20 collectively contain most of the predictive power of the DVH. Interestingly, the optimized gEUD α value determined with the model was 0.01, which suggests that the low-dose area of the DVH contains the most predictive power, once again underscoring the importance of incorporating low-dose metrics, such as V5, into pneumonitis risk algorithms.

Our predictive model for G3+ pneumonitis reveals a somewhat different predictive model. In contrast to G2+ pneumonitis, age and comorbidity burden appear to significantly influence the development of G3+ pneumonitis, possibly because poor overall health might make patients more prone to hospitalization, which defines grade 3 lung toxicity in Common Terminology Criteria for Adverse Events. Interestingly, our prior work demonstrated the opposite regarding esophagitis, in which age decreased, rather than increased, the risk.[10]

Smoking status appeared markedly protective against G2+ pneumonitis risk (OR, 0.311; $P = .02$); this is consistent with literature showing that smoking decreases the risk of hypersensitivity pneumonitis, possibly because of an immunosuppressive effect.[12,13] Interestingly, smoking does not appear to be protective against pneumonitis induced by immune checkpoint inhibition.[14] Smokers are less rather than more likely to develop toxicity than nonsmokers; this suggests that one should resist applying the logic of surgical decision-making to RT patients, in whom active smoking has been associated with increased surgical risk and poorer outcomes in lung cancer, causing many surgeons not to offer lobectomy surgery to active smokers.[15] Indeed, our data suggest that smoking patients might actually tolerate treatment better than their nonsmoking counterparts.

In line with previously published data,[16] we found a trend toward association of pneumonitis with cancer involvement of lower lung lobes, although this was marginally significant and was not selected for our multivariate model. We were surprised to find that the receipt of concurrent chemotherapy was not associated with increased pneumonitis risk, as has been reported previously. Because this was not a randomized trial, patient selection might account for the observed lack of association.

Our study has many strengths, including the large multicenter patient cohort with prospective data collection and the ability to analyze clinical and dosimetric data together. There are, however, several limitations. First, this is a registry analysis, not a clinical trial, and as such is subject to inherent limitations, such as a lack of independent evaluators and prespecified radiologic confirmation. This limitation might affect reproducibility, although as noted our results are in line with previously published data on this topic. Second, our event rate, particularly for G3+ pneumonitis, is small. Our overall event rate for pneumonitis was also low by historical standards, at 16%. This is likely the result of having recorded only the first 6 months from diagnosis and reflects undercounting of the 1-year incidence. Clearly defining pneumonitis can be challenging because many patients have underlying pulmonary disease or may present with concurrent infectious etiologies. To better capture pulmonary toxicity, we have recently started collection of patient hospitalization related to any pulmonary etiology.

Another limitation of our analysis is that we use a crude comorbidity count rather than a more sophisticated metric such as the Charlson Comorbidity Index,[17] which assigns weighted values. However, our list of collected comorbidities, which includes all common comorbidities such as prior stroke and myocardial infarction, congestive heart failure, and chromic pulmonary disease, closely mirrors those used to calculate the CCI. The major differences include (1) severity of diabetes and of liver/kidney disease not differentiated; (2) stage (localized vs metastatic) of concurrent (nonlung) malignancies was not captured; and (3) HIV status was not collected. In select cases, our metric might "underestimate comorbidity burden" by "underweighting" severe conditions; however, for most patients, the crude number of comorbidities tracks closely with Charlson score.

Conclusions

Despite these limitations, these data represent a powerful, modern toxicity model for patients undergoing RT

for advanced lung cancer. We show that grade 2+ pneumonitis is heavily influenced by smoking status and normal lung dosimetry and that most of the variability can be captured with moderate (V20) and low (V5) dose volumes. We also show that G3+ pneumonitis is influenced by age and pre-existing patient comorbidities, which might be the result of a higher propensity of those patients to be hospitalized by a decline in lung function. Our data might be useful for clinicians to compare plans, estimate the expected likelihood of toxicity in their patients, and identify patients who are most likely to experience adverse toxicity outcomes, who might therefore be counseled and followed appropriately.

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