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A Nomogram to Predict Radiation Pneumonitis, Derived from a Combined Analysis of RTOG 9311 and Institutional Data

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Abstract

Background—A previous analysis of our institutional database (WU) suggested that the superior-to-inferior tumor position, maximum dose, and D35 were valuable. We tested our institutional model against the RTOG 9311 patient database.

Methods—The entire dataset consists of 324 patients receiving definitive conformal radiation therapy for NSCLC (WU = 219, RTOG 9311 = 129). Clinical, dosimetric, and tumor location parameters were modeled to predict RP in the individual datasets and in a combined dataset. Association quality with RP was assessed using Spearman's rank correlation (R) for univariate and multivariate analysis comparison between subgroups was tested using Wilcoxon rank sum test.

Results—The WUSTL model to predict RP performed poorly for the 9311 data. The most predictive model in the RTOG dataset was a single parameter model, D15 ($r=0.28$). Combining the datasets, the best derived model was a two-parameter model consisting of MLD and GTV-SI ($r=0.303$). An equation and nomogram to predict the probability of RP was derived using the combined patient population.

Conclusions—Statistical models derived from a large pool of candidate models resulted in well-tuned models for each subset (WU or RTOG) which did not perform well when applied to the other dataset. However, when the data were combined, a model was generated which performed well on each data subset. The final model incorporates two effects: greater risk due to inferior lung irradiation, and greater risk for increasing normal lung mean dose. This formula and nomogram may aid clinicians during radiation treatment planning for lung cancer.

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Conflict of Interest Statement

No conflict of interest exists between the material contained within this manuscript and the authors of this manuscript.

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Keywords

Radiation pneumonitis; RTOG 9311; Nomogram

INTRODUCTION

Radiation pneumonitis (RP) is a frequent complication after definitive radiation therapy for lung cancer. RP causes symptoms of cough, fever, and shortness of breath, may require supplemental oxygen or oral steroids, and may even be fatal. Many investigators have identified factors to predict the risk for developing RP. The most commonly reported predictive factors are derived dosimetrically from treatment planning, including V20, V30, mean lung dose (MLD), and NTCP (normal tissue complication probability models).[1-4] The correlation between these factors varies: in our institutional dataset MLD is closely related to V15 and is slightly less correlated with other Vx values. These correlations, which are technique and patient population-specific, make it more difficult to accurately distinguish competing models. The choice of which parameter to use clinically is based largely on institutional preference.

Graham et al. originally published data from our institution showing that V20 correlated with RP following definitive radiation therapy.[1] Based on these data, the RTOG incorporated V20 as a stratification variable for RTOG 9311, a radiation dose escalation study where escalation of radiation dose was largely dependent on the V20 value.[5] We have continued to collect both clinical and dosimetric information for patients receiving definitive radiation therapy at our institution. In a recent analysis, Hope et al. demonstrated that a three-parameter model that included tumor position (inferiorly-located tumors had higher risk of RP), maximum dose, and D35 was a better predictor for RP than either V20 or MLD alone in our database.[6] However, substituting V20 or MLD for D35 achieved nearly as good a statistical performance. To further validate or modify these results, we present here an expanded analysis, in which we combine WU data with data extracted from RTOG 9311 trial treatment planning archives maintained by the Image-Guided Therapy QA Center. This greatly expands the range of dose distribution types over which the analysis is performed, which may make the model significantly more robust.

METHODS AND MATERIALS

Patients

Table 1 contains a list of abbreviations used in this manuscript. The Washington University dataset (WU) consists of 219 patients treated with conformal radiation therapy to a minimum dose of ≥ 50 Gy with or without chemotherapy for NSCLC. A description of this patient population was previously published.[6] Inclusion criteria required a minimum follow up of 6 months, or the observation of RP prior to 6 months. From the RTOG 9311 dataset, we were able to extract full 3 dimensional (3D) treatment planning data from 129 of the 179 patients enrolled. Fifty RTOG patients were not included: 31 with < 6 months follow up, 10 with irretrievable 3D image datasets, and 9 with missing follow up information. In total, 324 patients were available, after eliminating duplicate patients from our institution that were also enrolled on the RTOG 9311 trial. Patient-, tumor-, treatment-, and dosimetry-specific parameters were analyzed for both datasets. Patient parameters included age, last follow up date, status at follow up, pre-treatment weight loss, gender, performance status (Karnofsky scale), and smoking history). Analyzed tumor characteristics included tumor histology, gross tumor volume, and tumor stage. Analyzed treatment characteristics included many dosimetric characteristics extracted from treatment plan archives as well as clinical records, such as: radiation prescription dose (Gy), maximum radiation dose (Gy), overall treatment time, fraction size (Gy), V_x values (normal lung tissue volume receiving more than x Gy), D_x values (minimum dose to the hottest

x% of lung volume), and the use of either sequential or concurrent chemotherapy. The details of dosimetric parameters are described below. Dose, location, and contour information were made conveniently available by importing RTOG-format treatment plan archives into the Matlab-based plan analysis system CERR (computational environment for radiotherapy research) [7]. All modeled dose, volume, and positional factors were extracted using CERR. Model determination was performed using an open-source software system we have developed called DREES (dose response explorer system)[8]

Pneumonitis events

Pneumonitis events in the WU database were scored retrospectively after Institutional Review Board approval. All events were scored as Grades 1-5 according to our institutional grading system (Table 2), which required documentation of clinical RP. Our grading system is similar to that described by the Southwest Oncology Group (SWOG).[9] WU Grade 2 or greater events were scored as RP events in this analysis. Alternatively, the RTOG used its own grading system for 9311 and scored RP events prospectively. (Table 2). Grade 3 or greater events in 9311 patients were scored as RP events in this analysis. Both of these cutoffs include the use of oral steroids or supplemental oxygen as triggering events for scoring RP. The use of an oral anti-tussive would not be counted as an event by either system.

Structure definitions and analysis

Each patient treatment plan included contours describing total lung volume and GTV. All contours were checked for inconsistencies and recontoured within CERR (if necessary) by a single physician.

Dose calculation

Planned dose distributions were recovered from the archived treatment planning system data. For WU patients, patient charts were reviewed to confirm that these plans represented the dose that was delivered to the patient. Water-equivalent results were used for both datasets. Ideally, accurate dose calculations would be used in all cases, but older RTOG submissions as well as older WU calculation algorithms did not incorporate accurate heterogeneity corrections. Recent Monte Carlo-based dose recalculations by our group indicates that older heterogeneity corrections may be just as inaccurate as water-based calculations. Water-based calculations at least are consistent.

Dose-volume parameters

Multiple potentially predictive factors were included in a pool from which model variables were drawn. Analyzed dosimetric variables included total lung volume, mean lung dose, D_1 (close to the maximum dose) D_3 and D_x in 5% increments between 5-80%, and V_{5-80} in 5 Gy increments. All pulmonary dose-volume parameters were calculated with the total lung volume minus GTV. Mean lung dose was defined as the average dose to the total lung minus GTV. Maximum dose was also calculated per the International Commission of Radiation Units and Measurements (ICRU) maximum dose definition, defined as the highest mean dose to any subvolume of dimensions 1.5 cm^3 . Figure 1 shows an example dose-volume histogram of parameters of D_x and V_x . In addition, a Lyman-Kutcher-Burman type NTCP model was included in the pool.

Separately, the volume effect exponent in the generalized equivalent uniform dose equation was fitted separately to the datasets, to maximize the rank correlation between equivalent uniform dose and RP. Figure 2 shows the results. The best a parameter is usually between 0 and 1 (mean dose). Interestingly, if only high grade events are included, the 'best fit' is slightly

less than zero, which weights the low dose region of the DVH more than occurs when taking the mean dose.

GTV location

To study potential effects of high-dose location within the lung, the center of mass (COM) of the GTV was defined for each patient relative to lateral, anterior-posterior, and superior-inferior dimensions. COM location was defined relative to the maximal extent of contoured lung volume within the CT dataset. For each dimension, the bounding box describing the extent of the lung was normalized to continuous values ranging from 0–1 inferior-to-superior, 0–1 right-to-left (for patients with only one lung, value was normalized between 0–0.5 or 0.5-to-1, depending on which lung remained), and 0-to-1 posterior–anterior for each patient. Another variable (0–1) describing lateral position defined the midthorax as 0 and either lateral chest wall as 1, with tumor position was normalized to describe the medial–lateral dimension. The center of mass of the contoured GTV was calculated for each of these normalized coordinates using a batched processed routine in CERR/Matlab.

Statistical analysis

Univariate correlations with RP were calculated using Spearman's rank correlation (r), which is the analog of Pearson's correlation but defined for discrete inputs. Comparisons of subgroups were performed using the Wilcoxon rank sum method.[10] As described elsewhere, outcomes modeling is performed as a two-step process: in the first step we study correlation vs. prediction of best fit models as a function of the number of allowed parameters. [8] We compute bootstrap and leave-one-out predictive performance as a function of allowed parameters (usually similar, but not always). The model is fit for data included and tested against data excluded. These processes are repeated many times for statistical validity. Once the model order is determined, to study variable selection robustness, we perform bootstrap simulations of the entire fitting process, and tabulate a histogram of the different groups of variables selected. Models with variables which are highly correlated are coalesced into a single model and the process is repeated. Ultimately, a histogram is produced describing how often different variable sets were selected. Finally, the variable set most often selected is refit to the entire dataset, to maximize predictive power. The intent of these methods is to avoid over-fitting and under-fitting the model, and to select model variables which are robust against small variations in the dataset.

RESULTS

Patient characteristics for both groups are shown in Table 3. The mean tumor volume in the WU dataset was larger than in the RTOG 9311 dataset, with median volumes of 91.9 cm³ vs 36.5 cm³ ($p < 0.0001$), respectively. Table 4 shows the univariate correlations for dosimetric variables derived from radiation treatment planning from both patient groups. The results show that several dosimetric variables have similar predictive value for RP in both groups (MLD, V20, V13, D35, and D15)). Given that the dosimetric variables tend to be closely interrelated, none are clearly superior. D₁₅ had the highest correlation with outcome in the 9311 patient cohort ($r = 0.28$); V₂₀ also correlated well ($r = 0.26$). However, the V₂₀ method was used for assigning dose level on RTOG 9311. It is possible that the use of V₂₀ to assign the prescription dose added a hidden factor to the effect of V₂₀ in this cohort. The variable with the highest predictive value for the WU patients was superior-to-inferior GTV position (GTV-SI)($r = 0.23$), inferior irradiations being riskier. In contrast, this variable was not as well correlated with pneumonitis for 9311 patients ($r = 0.13$)(Figure 3). This is further discussed below. Variables that were not predictive for RP by univariate analysis in either dataset include age, gender, performance status, tumor histology, and the use of chemotherapy.

In order to understand why our RP modeling methods showed differences between the two patients groups, we plotted maximum dose versus V_{20} for both populations (Figure 4). Patients treated on RTOG 9311 received higher doses at lower V_{20} values as designed in the investigation. Whereas patients treated at WU had larger V_{20} values as a result of larger tumor volumes and received lower maximum radiation doses.

The best multi-metric model from WU patients was the three-variable combination of GTV-SI, D_{35} , and maximum dose ($r = 0.279$). [6] The best WU model was a poor performer when applied to the RTOG dataset. Applying the WU model directly to RTOG 9311 will yield $r = 0.06$. If the parameters were to be re-fitted, then $r = 0.143$. If the WU data were included in the fitting, then $r = 0.159$. Combining the datasets, the best derived model was the two-variable model consisting of MLD and GTV-SI ($r = 0.303$) (Figure 5).

Thus, chosen from many candidate models for predicting RP, an equation was derived based on both patient populations:

$$\text{RP risk} = \text{logistic fn} \{ -1.5 + (0.11 \times \text{MLD}) - (2.8 \times \text{GTV-SI position}) \}$$

Fitting this equation to leave-one-out datasets and applying the result to the removed data point resulted in an average Spearman's coefficient of $r = 0.284$ ($p < 0.0001$).

Based on this equation, a nomogram was constructed for the purpose of predicting the risk of RP based on this two-variable model. With MLD plotted on the left and the inferior-to-superior position plotted on the right, the intersection of the line connecting these two values corresponds to the predicted RP probability (NTCP) (Figure 6A). In order to demonstrate the range of patients for each combination of COM-SI and MLD, Figure 6B shows the number patients in the shaded regions. Please note that no data exist for COM-SI locations between 0 -0.2 and 0.8-1. Likewise, no data exist for MLD below 6 Gy and above 30 Gy.

With regard to the effect of concurrent chemotherapy on RP, the only patients who received concurrent chemotherapy were in the WU dataset ($n=81$). In analyzing the WU dataset, there was no correlation between RP and the use of concurrent chemoradiation therapy ($r=0.0185$, $p=0.392$). Additionally, when these patients are excluded from the combined analysis, the significance of the two dominant factors, MLD and COM-SI, is unchanged ($r = 0.28$, $p<0.00001$).

DISCUSSION

Models to predict RP following thoracic radiation therapy can be extremely valuable. Treatment plans for patients projected to have a high risk of symptomatic RP based on both dose-volume parameters and tumor location may be modified to lower this risk. Examples of modifications include the use of systemic neoadjuvant chemotherapy to reduce tumor volume, the use of IMRT to decrease the volume of normal lung receiving radiation therapy, or the use of gating to reduce the amount of normal lung moving in and out of the radiation field during tidal ventilation.

The most commonly employed dosimetric variables that predict for RP are MLD, V_{20} , V_{30} , V_{eff} (corresponding to the equivalent uniform dose), and the Lyman-Kutcher-Burman type NTCP model. [1-4] Most of the previously reported parameters is based on institutional datasets that are dependent on the radiation techniques employed by that institution. Important exceptions include the Kwa study, which combined DVHs from five different institutions (including WU), and the later study by Seppenwoold et al. which combined data from the Netherlands Cancer Institute (NKI) and the University of Michigan. We had previously shown that a three parameter model of tumor location (inferiorly-located tumors with higher risk),

maximum dose, and D35 was superior to either V20 or MLD in our own database.[6]. At the same time, we obtained permission to test this model within the RTOG 9311 database.

Perhaps surprisingly, the best model derived based on WUSTL data (a combination of tumor location, maximum dose, and D35) alone had negative prognostic performance when applied to the RTOG 9311 database. Within the RTOG dataset, D15 (minimum dose to the hottest 15% of the lung) was the single most significant dosimetric factor examined ($r = 0.28$, Tables 2 and 3). D15 was, however, not particularly powerful when applied to our own database ($r=0.11$, Table 2). Likewise, inferior tumor position, though of value, was less important in the 9311 database ($r = 0.13$). There were some similarities between the databases. Parameters such as age, gender, performance status, tumor histology, and the use of chemotherapy were not predictive in either.

This discrepancy is likely due to the differences in the databases, both in terms of tumor characteristics and resulting treatment parameters. RTOG tumors were on average smaller, and tended to be more superior in location, which may have decreased the impact of inferior position in that dataset. As seen in Figure 4, the RTOG dataset contains more tumors with higher maximum doses and lower V20's.

The inapplicability of the 'best' model derived from one dataset shows that our methods are sensitive to the details of the underlying datasets and the available parameter range which is being modeled. The resulting models are 'well-tuned' to the input datasets. We conclude from this that to generate a model which works well for both datasets, they must be jointly modeled. Thus, we generated a best-performing model which uses MLD as well as S-I tumor position. No other parameters were selected as being likely to improve the fit. The lack of effect from chemotherapy is consistent with other publications.[11,12,6,13,1] Figure 5 shows a histogram of the most frequently selected model sets on bootstrap refitting simulations. The two-parameter model using MLD and S-I tumor position is clearly superior.

With regard to effect of concurrent chemotherapy on the risk of RP, our data indicate that there was not an increased risk for RP in the WU patients. Thus, there was no overall effect of concurrent chemotherapy on RP in the combined dataset. However, the number of patients receiving concurrent chemotherapy in this analysis is limited. Trials that are controlled for the effect of chemotherapy would be more ideal to answer this question.

Though this analysis does not clearly identify a superior parameter(s) that is most predictive for RP in both databases, it does support the inclusion of S-I tumor position as an important variable in the overall dataset, and at least consistent with both subsets. Inferior tumor position had been identified as significant in some previous publications.[14,15] The commonly used values of V20 and MLD do not take tumor position into account. This equation and nomogram (Figures 6A, B, and C) perform well for a wide variety of irradiation patterns in this large database. The nomogram is based from 3DCRT treatment plans. It may not apply to IMRT applications where the normal lung receives a higher percentage of low dose irradiation. We believe the application of this RP risk equation will potentially aid clinicians in evaluating radiation treatment plans. We encourage and hope others will test the value of MLD and S-I tumor position with the RP risk nomogram within their own database.

Conclusions

Statistical models derived from a large pool of candidate models resulted in well-tuned models for each subset (WU or RTOG) which did not perform well when applied to the other dataset. However, when the data were combined, a model was generated which performed well on each data subset. This exercise indicates the advantage in generating robust models based on multi-institutional datasets. The final model incorporates two effects: greater risk due to inferior lung

irradiation, and greater risk for increasing normal lung mean dose. This formula and nomogram may aid clinicians during radiation treatment planning for lung cancer.

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DVH Refresher: V_x and D_x

Figure 1.
Definitions of V_x and D_x on the dose volume histogram.

Figure 2.

Changes in Spearman's correlation coefficient as the 'a' parameter in the GEUD equation (= $1/n$ in the LKB NTCP model) is changed. The label 'combined mixed' refers to including all the grades in the rank correlation.

Figure 3.

Radiation pneumonitis events for both datasets. Circles represent the development of pneumonitis shown as the center of mass location on an AP view of the chest. Inferior location is significantly associated with RP in the WUSTL patients. This is suggested in the 9311 patients, though does not reach statistical significance.

Figure 4.

Non-pneumonitis and pneumonitis events scored by maximum PTV dose and V20. The RTOG 9311 patients received higher doses to lower V20 values than did WUSTL patients.

Figure 5. Bootstrap multimetric modeling for the combined WUSTL and RTOG 9311 population. The most frequently selected model is a two-parameter model of MLD and COM-SI.

Figure 6C

Figure 6.

Figure 6A: A nomogram to predict the incidence of radiation pneumonitis (NTCP, middle line) based on the mean lung dose (left) and the inferior-to-superior (0-1) (right) position of the center of mass. The NTCP value is obtained by connecting the MLD and tumor position with a straight line. Figure 6A contains an example. The nomogram is based on delivered doses using 3DCRT, not IMRT.

Figure 6B: Same as Figure 6A, without the example

Figure 6C: An accompanying plot of COM-SI according to MLD showing the number of patients (shaded area) for each combination of the two parameters; MLD and COM S-I position. No data exist for the extreme scenarios within the nomogram (i.e. COM-SI locations between 0 – 0.2 and between 0.8 – 1; MLD locations under 6 Gy and above 30 Gy).

Table 1**Abbreviations List**

WU	Washington University patient dataset
RTOG	Radiation Therapy Oncology Group
SWOG	Southwest Oncology Group
NSCLC	Non-small cell lung cancer
RP	Radiation pneumonitis
3DCRT	Three dimensional conformal radiation therapy
IMRT	Intensity modulated radiation therapy
DVH	Dose volume histogram
Gy	Gray
ICRU	International Commission on Radiation Units and Measurements
GTV	Gross tumor volume
S-I	Superior-to-inferior
MLD	Mean lung dose
NTCP	Normal tissue complication probability
V _{eff}	Effective volume (analogous to equivalent uniform dose)
COM	Center of mass
CERR	Computational environment for radiation research
DREES	Dose response explorer system
V _x	Normal lung tissue volume exceeding x Gy
V15	Normal lung volume (right + left – GTV) exceeding 15 Gy
V20	Normal lung volume exceeding 20 Gy
V30	Normal lung volume exceeding 30 Gy
D _x	Minimum dose to the hottest $x\%$ of lung volume
D15	Minimum dose to the hottest 15% of the lung volume
D35	Minimum dose to the hottest 35% of the lung volume

Table 2**Radiation Pneumonitis Grading**

Grading System	Grade	Definition
Washington University	1	Mild symptoms of dry cough or dyspnea on exertion not requiring clinical intervention or radiographic evidence of pneumonitis without clinical symptoms
	2	Steroids given for clinically significant pulmonary
	3	Hospitalization for symptoms of dyspnea requiring supportive care (oxygen)
	4	Severe respiratory insufficiency/continuous oxygen or assisted ventilation
	5	Fatal
Southwest Oncology Group	1	Normal radiographic changes, symptoms do not require steroids (non-infectious)
	2	Steroids required or tap of effusion
	3	Oxygen required
	4	Requires assisted ventilation
	5	Fatal
Radiation Therapy Oncology Group	1	Mild symptoms of dry cough or dyspnea on exertion
	2	Persistent cough requiring narcotic anti-tussive agent/dyspnea with minimal effort but not at rest
	3	Severe cough unresponsive to narcotic anti-tussive agent or dyspnea at rest/clinical or radiologic evidence of acute pneumonitis; intermittent oxygen or steroids may be required
	4	Severe respiratory insufficiency/continuous oxygen or assisted ventilation
	5	Fatal

Table 3**Patient Characteristics**

Parameter	WUSTL (n = 219)	RTOG (n = 129)
Age (y), median (range)	65.2 (31-94)	71 (49-92)
Gender (%)		
Male	108 (49)	70 (54)
Female	111 (51)	59 (46)
Performance Status <70 (%)	17 (7.7)	0 (0)
Weight loss >5% (%)	47 (21.5)	23 (17.8)
Total lung volume (cm ³), mean (range)	3594 (1461-7054)	4201 (1959-8688)
GTV volume (cm ³), mean (range)	142 (0.4-1321)	62 (1.8-554)
Primary histology (%)		
Squamous cell	93 (42)	53 (41)
Adenocarcinoma	62 (28)	42 (33)
NSCLC (NOS)	64 (30)	34 (26)
Prescription dose (Gy), median (range)	70 (50-84)	77.4 (32.2-93.5)
Chemotherapy (%)		
Neoadjuvant	60 (27)	20 (15.5)
Concurrent	81 (37)	0 (0)

Table 4
Univariate Correlations Predicting RP

Parameter	9311 (Spearman's)	WU (Spearman's)
MLD	0.22	0.18
V ₂₀	0.26	0.18
V ₁₃	0.20	0.18
D ₃₅	0.20	0.19
D ₁₅	0.28	0.11
GTV-SI	0.13	0.23
GTV-AP	0.06	0.02