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MODELING THE RISK OF RADIATION-INDUCED ACUTE ESOPHAGITIS FOR COMBINED WASHINGTON UNIVERSITY AND RTOG TRIAL 93-11 LUNG CANCER PATIENTS

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Abstract

Purpose—To construct a maximally predictive model of the risk of severe acute esophagitis (AE) for patients who receive definitive radiation therapy (RT) for non–small-cell lung cancer.

Methods and Materials—The dataset includes Washington University and RTOG 93-11 clinical trial data (events/patients: 120/374, WUSTL = 101/237, RTOG9311 = 19/137). Statistical model building was performed based on dosimetric and clinical parameters (patient age, sex, weight loss, pretreatment chemotherapy, concurrent chemo-therapy, fraction size). A wide range of dose–volume parameters were extracted from dearchived treatment plans, including Dx, Vx, MOHx (mean of hottest x% volume), MOCx (mean of coldest x% volume), and gEUD (generalized equivalent uniform dose) values.

Results—The most significant single parameters for predicting acute esophagitis (RTOG Grade 2 or greater) were MOH85, mean esophagus dose (MED), and V30. A superior–inferior weighted dose–center position was derived but not found to be significant. Fraction size was found to be significant on univariate logistic analysis (Spearman $R = 0.421$, $p < 0.00001$) but not multivariate logistic modeling. Cross-validation model building was used to determine that an optimal model size needed only two parameters (MOH85 and concurrent chemotherapy, robustly selected on bootstrap model-rebuilding). Mean esophagus dose (MED) is preferred instead of MOH85, as it gives nearly the same statistical performance and is easier to compute. AE risk is given as a logistic function of $(0.0688 * MED + 1.50 * ConChemo - 3.13)$, where MED is in Gy and ConChemo is either 1 (yes) if concurrent chemotherapy was given, or 0 (no). This model correlates to the observed risk of AE with a Spearman coefficient of 0.629 ($p < 0.000001$).

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Conclusions—Multivariate statistical model building with cross-validation suggests that a two-variable logistic model based on mean dose and the use of concurrent chemotherapy robustly predicts acute esophagitis risk in combined-data WUSTL and RTOG 93-11 trial datasets.

Keywords

Acute esophagitis; Lung cancer; NTCP; Radiotherapy

INTRODUCTION

Severe acute esophagitis (AE) is a common side effect of radiotherapy for non-small-cell lung cancer (NSCLC). When it occurs, AE typically peaks by Week 3 or 4 in a course of radiotherapy and is sometimes a dose-limiting toxicity (1, 2). Patient-related, tumor related and treatment-related risk factors reported to be statistically associated with the incidence or severity of AE include the following: age (3), tumor (4), nodal stage (5, 6), concurrent chemotherapy (2, 4), and body mass index (7). Two recent reviews have considered dosimetric predictors. Rose *et al.* (8) systematically reviewed 18 published radiation-induced esophagitis studies in NSCLC patients (2, 3, 5–7, 9–21) (11 of them assessed acute esophagitis, the rest of them assessed both acute and chronic radiation-induced esophagitis together). Five dosimetric parameters were identified as predictive of AE with or without chemotherapy: mean esophageal dose (MED), maximal esophageal dose, V20 (percentage of esophagus volume receiving >20 Gy), V35, and V60. In a separate review article, Werner-Wasik *et al.* (22) noted disparities in the dosimetric parameters identified as most predictive of AE. The situation is further confounded by the common practice of delivering one set of beams for several weeks before switching to spinal-cord sparing oblique beams for the remaining fractions. AE typically arises during or shortly after the first course finishes, and therefore the dose–volume characteristics of the cord-sparing beams probably confounds the dosimetric analysis, and may be a significant cause of the lack of consistency of reported results. Despite this obscuring factor, it is still useful to refine models that predict AE for such two-course treatments, such as the data in the current dataset.

Our previously published analysis (2) on 166 patients treated at Washington University concluded that the esophageal surface area receiving 55 Gy, the esophageal volume receiving 60 Gy, and the use of concurrent chemotherapy were the most statistically significant predictive factors for AE. In this study, we updated the previous Washington University cohort dataset and combined it with cohort data from Radiation Therapy Oncology Group (RTOG) trial 93-11, a dose escalation protocol for NSCLC. In addition, new dose-volume metrics are considered and modified statistical resampling methods are used to ensure an optimal model size and to increase confidence in the parameter selection process.

METHODS AND MATERIALS

Patient cohort

All patients (2) treated at WUSTL between 1991 and January 2001 who received a minimal target dose of 60 Gy were included, unless computer-generated 3D-CRT plan was not retrievable or key clinical data were unavailable. Patients who were treated under RTOG 93-11 and definitively during this era at WUSTL for small-cell lung cancer were included unless the treatment planning or clinical data was missing. The fraction size of WUSTL patients range from 1.8 to 2.5 Gy; fraction size of the majority of RTOG patients ranged from 1.8 to 2.5; of the patients, 5 had nonstandard fractionation radiotherapy (fraction size range as 3.7, 3.9, 4.5, 7.0, and 18 Gy). General patient characteristics are given in Table 1. Of 374 NSCLC patients included in the modeling, 247 were Washington University in St.

Louis (WUSTL) patients, and 137 (non-WUSTL) were from RTOG trial 93-11 (23). Treatment plans were retrieved either from WUSTL data archives or from RTOG archives kept by the Advanced Technology Consortium. Retrieved archives were analyzed using the research tool, CERR (24). All archives were converted to CERR format and then reviewed for correctness by a physician.

Treatment characteristics

All WUSTL patients were treated with “two-course” radiotherapy: a parallel opposed (anterior–posterior/ posterior–anterior) beams for a few weeks, then followed by off-cord oblique beams to spare part of esophagus. For the RTOG patients, all fields were treated within each fraction per protocol requirements. Chemotherapy regimes varied over time, and details of agents and dosing were not available beyond concurrent vs. pretreatment.

AE events

An AE complication is defined for modeling as any RTOG Grade 2 event (requiring medical attention or care), according to criteria given in Table 2. In the WUSTL cohort, 101 of 237 patients (42.6%) developed AE; 19 of 137 RTOG 93-11 trial patients (13.9%) developed AE. The esophagitis grade distribution over each subset is given in Table 3.

Dose–volume parameters

A wide range of dose–volume parameters for the esophagus were extracted for modeling. The entire length of the esophagus was contoured. Dx is defined as the minimum dose to the x% volume of the esophagus receiving the highest dose; Vx is the percent volume of the esophagus receiving at least x dose; MOHx is defined as the mean dose of the hottest x% of the esophagus; MOCx is defined as the mean of dose values of the coldest x% of the organ. MOHx and MOCx were included, as they could potentially be more robust predictors of dosimetric effect than Dx and Vx because of their averaging property compared with focusing on a single dose–volume histogram point.

Statistical analysis

More than 50 parameters were initially included in the analysis. Dosimetric parameters of esophagus included the following: D5-D100; V5-V100; MOH5-MOH100; MOC5-MOC100, all in 5% increments; mean dose, ICRU maximum dose (highest mean dose to any cuboid volume at least 1.5 cm on a side), ICRU minimum dose (lowest mean dose to any cuboid volume at least 1.5 cm on a side). A positional variable was also derived: which is the dose-weighted midpoint of the high-dose region (COMSI_eso), which ranged from 0 to 1 along the superior–inferior direction. Patient parameters included age, sex, race, performance status, weight loss, use of pretreatment chemotherapy or concurrent chemotherapy, histology, and clinical stage. Univariate logistic analysis for each available parameter was conducted, and the Spearman rank correlation coefficient (R) was used to assess univariate logistic correlation with AE risk. Any model that demonstrates a high Spearman rank correlation with the observed outcome can be used to classify risk.

The model building methodology has several steps. First, the number of Dx and Vx variables under consideration was pruned to leave only variables between which inter-variable Pearson (linear) correlations were less than a 0.85. Overfitting was avoided, and an optimal model order was defined by automating forward step regression and computing average prediction performance on cross-validation. The leave-one-out method was used, testing the predictive power of logistic regression models of increasing order for each left-out data point, in turn. Thus, a rank correlation between predictions and observations was formed, and the peak performance of this statistic as a function of number of model

variables was used to select the optimal model size. The robustness of the variable sets selected was tested by cataloging the frequency of variable sets selected based on model refitting of bootstrap datasets (25). Further details for this data-mining method to select variables and define models are described in (25, 27).

RESULTS

Univariate logistic regression analysis

Mean, median, and range values for representative Dx, Vx, and MOHx variables for esophagus are listed in Table 4. Figure 1 plots Spearman coefficients vs. Dx; Fig. 2 shows the Vx plot; and Fig. 3 shows the MOHx plot. Figure 1-3 demonstrate that a wide range of dose-volume variables highly correlate with AE risk with spearman coefficient 0.5 ($p < 0.00001$) including D10-D45, V5-V60, and MOH15-100. The variables with Spearman coefficients >0.5 are listed in Table 5. In particular, MOH85 ($R_s = 0.583$, $p < 0.0000001$), MED ($R_s = 0.575$, $p < 0.0000001$), V30 ($R_s = 0.573$, $p < 0.0000001$), and ConChemo (concurrent chemotherapy, $R_s = 0.5$, $p < 0.000001$) had the highest correlations with AE risk. Fraction size is also significantly, but less highly correlated with AE risk ($R_s = 0.421$, $p < 0.00001$).

Multivariate logistic analysis

A two-variable model was suggested as the optimal order by cross-validation evaluation. The stability of variable selection was tested by performing the variable selection process on bootstrap pseudo-datasets. The variable combination of MOH85 and ConChemo was nearly always selected. However, we substitute mean esophagus dose (MED) for MOH85, as MED gives nearly the same numerical performance and would be easier to implement in clinical treatment planning systems. The fact that mean dose has no adjustable parameters may also make it more likely to perform better when generalizing to other datasets. The resulting risk of AE as a function of MED and concurrent chemotherapy (ConChemo, 1 if delivered, 0 if not delivered) is given by:

$$NTCP = \frac{1}{1 + \exp(-x)}$$

where NTCP denotes normal tissue complication probability, and

$$x = 0.0688 \times \text{MED} + 1.50 \times \text{ConChemo} - 3.13$$

The Spearman coefficient of this risk model on the combined cohort was 0.629 ($p < 0.000001$). The corresponding individual 95% confidence intervals (Wald intervals) for the model parameters are given in Table 6. Figure 4 shows the estimated logistic regression curves as a function of mean esophageal dose, with and without concurrent chemotherapy.

Figure 5 compares the model-predicted incidence of AE and the observed incidence, with patients divided into six equal-number bins, according to the model-predicted risk. The ratio of the observed AE rate between the one-third of patients at highest risk and the one-third of patients at lowest risk is 25.6 when classified by model predictions, which is another indicator that the model usefully distinguishes between high-risk and low-risk treatments. Note, however, that concurrent chemotherapy is much more common now, which makes the lowest risk levels less likely to be attained.

Figure 6 is a scatter plot showing the effect of increasing mean dose for patients with and without concurrent chemotherapy. Figure 7 shows the area under the receiver operating characteristics curve of the model applied to the current dataset.

DISCUSSION

Previous reviews of dosimetric predictors indicate a confusing array of potentially predictive dose-volume factors, as noted. The present report indicates a strong correlation between mean esophageal dose and AE, for a dataset that is both large and interinstitutional. Although concurrent chemotherapy has become more common, future regimens may change and so it is still desirable to explicitly model the impact of concurrent chemotherapy. Unlike analyses of clinical trials, it is desirable for predictive risk modeling datasets to have a wide range of dose-volume characteristics, to increase the likelihood that truly causative parameters are selected (26). Note that, in the current analysis, we did not observe a preference for any high dose parameters (*e.g.*, V60).

We add the important caveat, however, that the treatments in question are primarily those of the “two-course” kind, as noted. Treatment regimes that use the same fields every day may result in more predictive models for AE. Going beyond this observation, mean dose is probably just a surrogate for the rate of accumulation of dose (*e.g.*, mean dose accumulated per week, fraction size), which might be more causally related to the actual induction of acute esophagitis during a course of radiotherapy. Indeed, in this dataset, fraction size was significantly correlated to AE risk on univariate analysis, but was not selected in the multivariate model. On general principles, increasing fraction size would be expected to increase the risk of acute esophagitis more than increasing the number of daily fractions for the same increase in mean dose. Similarly, the naive application of the linear-quadratic model would not necessarily be expected to track changes in complication risk for this endpoint (or indeed any acute endpoint observed during therapy), because most of the total dose is delivered after the endpoint is observed and of course cannot “cause” an increase in complication probability. Despite these caveats, the observed ability of the model to distinguish between high-risk and low-risk plans, and the corresponding high AUC (0.83), supports further testing and potential refinement on independent datasets.

CONCLUSION

A predictive model for the probability of severe acute esophagitis (as indicated by medical management) was derived from a large and heterogeneous dataset. The heterogeneity of the dataset and resulting good separation between high-risk and low-risk plans supports the potential use or refinement of the model as an aid in clinical treatment planning for lung cancer. As for any newly proposed predictive model, further validation is needed before possibly advancing to routine use in radiotherapy clinics.

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Fig. 1.

Univariate correlation of acute esophagitis (AE) events with dosimetric variable Dx of esophagus for the combined dataset and each subset. Dx is the minimum dose to the X% volume receiving the highest dose. Note: Although the WUSTL dataset does not show a strong x-value preference, hotter dose values to small volumes (small $\times$ values of Dx) have higher correlations for the RTOG dataset.

Fig. 2.

Univariate Spearman's coefficient correlation of acute esophagitis (AE) events with the dosimetric variable V_x of esophagus for the combined dataset and each subset. V_x is the percent volume receiving at least $\times$ dose (x has units of Gy).

Fig. 3.

Univariate Spearman's coefficient correlation of acute esophagitis (AE) events with the dosimetric variable MOHx of esophagus for the combined dataset and each subset. MOHx is the mean dose of the hottest x% of esophagus. Note: hotter dose values to small volumes (small $\times$ values of MOHx) have higher correlations for the RTOG dataset.

Fig. 4. Estimated dose response curves for Grade 2 or greater acute esophagitis, with and without concurrent chemotherapy (error bars represent the 95% confidence intervals of the estimated curve).

Fig. 5.

Predicted rate of AE vs. observed rates for patients binned by predicted risk. Patients are binned according to predicted risk of AE by the two-variable model (MED, and ConChemo) with equal patient numbers in each bin. The mean predicted and observed event rates in each bin are (risk, events/patients): (0.0486, 1/62), (0.0835, 2/62), (0.1773, 19/62), (0.3047, 19/62), (0.5184, 29/62), (0.7720, 48/62). Good calibration and the large difference in risk between the high-risk and low-risk patients indicate that this might be a useful clinical model.

Fig. 6.

Scatter plots of the mean esophageal dose, for patients who did or did not have concurrent chemotherapy. Scatter points are laterally perturbed to avoid visual overcrowding.

Fig. 7.

Receiver operating characteristic curve based on the best two-variable logistic regression model, a function of mean esophagus dose and concurrent chemotherapy, with area under the curve of 0.83. This demonstrates a promising ability to separate patients into those with and without acute esophagitis (AE) risk.

Table 1

Patient characteristics

Characteristic	Value for WUSTL	Value for RTOG
Age, y, mean (range)	65.3 (31–94)	70.6 (37–92)
Sex, n (%)		
Male	123 (51.9)	77 (56.2)
Female	114 (48.1)	60 (43.8)
Race		
White	177	NA
Black	57	NA
Other	3	NA
KPS (%)		
70	215 (90.7)	137 (100)
70	22 (9.3)	0
Weight loss (%)		
< 5%	183 (77.2)	103 (75.2)
5%	54 (22.8)	34 (24.8)
Fraction Size	1.8–2.5 Gy	1.8–18 Gy*
Clinical Stage		
I	39 (16.5)	62 (45.3)
II	14 (6.0)	11 (8.0)
IIIA	107 (45.1)	40 (29.2)
IIIB	61 (25.7)	23 (16.8)
Recurrent	9 (3.8)	
Histological Type		
Squamous cell carcinoma	97 (40.9)	52 (38.0)
Adenocarcinoma	71 (30.0)	45 (32.8)
Undifferentiated large cell	4 (1.7)	11 (8.0)
NSCLC, NOS	65 (27.4)	29 (21.2)
Chemotherapy		
None	109 (46.0)	120 (87.6)
Sequential	62 (26.2)	17 (12.4)
Concurrent	87 (36.7)	0

Abbreviations: KPS = karnofsky performance status; NSCLC = non–small-cell lung carcinoma; NOS = not otherwise specified.

* Only 5 patients had nonstandard fractionation radiotherapy (fraction size ranges as 3.7, 3.9, 4.5, 7.0, and 18 Gy).

Table 2

Radiation Therapy Oncology Group (RTOG) scoring criteria for acute esophagitis

Score	Description
0	No change in baseline
1	Mild dysphagia or odynophagia; may require topical anesthetic, nonnarcotic agents, or soft diet
2	Moderate dysphagia or odynophagia; may require narcotic agents or puree/liquid diet
3	Severe dysphagia or odynophagia with dehydration or weight loss (> 15% from pretreatment baseline) requiring nasogastric feeding tube, i.v. fluids, or hyperalimentation
4	Complete obstruction, ulceration, perforation, or fistula
5	Death

Table 3

Esophagitis grade distribution for both subsets: Washington University in St. Louis (WUSTL) and Radiation Therapy Oncology Group (RTOG)

Grade	WUSTL patients, <i>n</i> (%)	RTOG patients, <i>n</i> (%)
0	76 (32.07)	86 (62.77)
1	60 (25.32)	32 (23.36)
2	73 (30.8)	19 (13.87)
3	23 (9.7)	0
4	5 (2.11)	0
5	0	0

Table 4

Summary of dosimetric statistics for the esophagus

	Variable	Mean/Median (Gy)	Range (Gy)
Dx	D10	49.44/59.43	0.0188–90.78
	D20	44.45/51.23	0.0063–90.43
	D30	38.57/47.58	0.0063–89.08
	D40	32.00/40.05	0.0063–85.58
	D50	25.01/16.70	0.0063–76.978
	D60	17.82/4.10	0.0063–73.98
	D70	10.12/1.63	0.0063–66.73
	Variable	Mean/Median (%)	Range (%)
Vx	V10	49.35/52.82	0.00–100
	V20	43.04/48.29	0.00–100
	V30	39.47/44.37	0.00–93.41
	V40	36.45/39.98	0.00–92.21
	V50	27.39/25.74	0.00–86.74
	V60	16.47/8.65	0.00–82.26
	V70	6.79/0	0.00–67.06
	Variable	Mean/Median (Gy)	Range (Gy)
MOHx	MOH10	52.17/61.95	0.025–90.96
	MOH20	49.57/59.24	0.011–90.80
	MOH30	46.86/54.85	0.011–90.49
	MOH40	43.85/52.12	0.011–89.76
	MOH50	40.73/49.82	0.011/88.01
	MOH60	37.38/44.49	0.011/85.89
	MOH70	33.84/38.67	0.011–83.32
	MOH80	29.92–32.61	0.011–74.27
	MOH90	26.57/29.47	0.011–67.20
Other	MED	25.05/27.60	0.017–61.85
	Minimum dose	0.43/0.025	0.006–25.03
	Maximum dose	57.91/67.90	0.025–91.88

Table 5

Variables with highest univariate correlation with acute esophagitis (AE) incidence (all significant at $p < 0.0001$)

Parameter	Rs (Spearman)	
MOH85	0.5825	<0.000000001
MOH95	0.5794	<0.000000001
MOH90	0.5752	<0.000000001
MED	0.575	<0.000000001
MOH80	0.5733	<0.000000001
V30	0.5734	<0.000000001
V35	0.5710	<0.000000001
V40	0.5677	<0.000000001
MOH15-MOH75	0.5015–0.5694	<0.000000001
D35	0.5403	<0.000000001
V45	0.5393	<0.000000001
V15	0.5380	<0.000000001
V55	0.5368	<0.000000001
V10	0.5324	<0.000000001
D40	0.5318	<0.000000001
D30	0.5289	<0.000000001
V5	0.5315	<0.000000001
D25	0.5272	<0.000000001
D20	0.5243	<0.000000001
D45	0.5230	<0.000000001
V60	0.5193	<0.000000001
V50	0.5096	<0.000000001
D10	0.5034	<0.000000001
ConChemo	0.500	<0.000000001

Table 6

Model coefficients and individual 95% confidence intervals (Wald intervals)

Parameter	Estimated coefficient	95% Confidence interval	<i>p</i> value
Mean esophagus dose	0.0688	(0.0575 to 0.0801)	0.000000001
ConChemo	1.5021	(1.1942 to 1.81)	0.0000011
Constant	−3.1298	(−3.4924 to −2.8219)	