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ANALYSIS OF RADIATION PNEUMONITIS RISK USING A GENERALIZED LYMAN MODEL

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Abstract

Purpose—To introduce a version of the Lyman normal-tissue complication probability (NTCP) model adapted to incorporate censored time-to-toxicity data and clinical risk factors, and to apply the generalized model to analysis of radiation pneumonitis (RP) risk.

Methods and Materials—Medical records and radiation treatment plans were reviewed retrospectively for 576 patients with non-small cell lung cancer treated with radiotherapy. The time to severe (grade 3) RP was computed, with event times censored at last follow-up for patients not experiencing this endpoint. The censored time-to-toxicity data were analyzed using the standard and generalized Lyman models with patient smoking status taken into account.

Results—The generalized Lyman model with patient smoking status taken into account produced NTCP estimates up to 27 percentage points different than from the model based on dose-volume factors alone. The generalized model also predicted that 8% of the expected cases of severe RP were unobserved because of censoring. The estimated volume parameter for lung was not significantly different from $n = 1$, corresponding to mean lung dose.

Conclusions—NTCP models historically have been based solely on dose-volume effects and binary (yes/no) toxicity data. Our results demonstrate that inclusion of non-dosimetric risk factors

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and censored time-to-event data can markedly affect the predictions of outcome made using NTCP models.

Keywords

Lyman model; NTCP; lung cancer; radiation pneumonitis; smoking

INTRODUCTION

The dose distribution to normal tissues during radiotherapy (RT) of malignant disease is known to influence the incidence of radiation-induced complications. Accordingly, various normal-tissue complication probability (NTCP) models have been proposed to estimate complication risk as a function of the normal-tissue dose-volume histogram (DVH). The most widely used NTCP model is the Lyman model¹, which is implemented in many radiation treatment-planning systems.

A feature of the Lyman model is that toxicity is regarded as a binary endpoint and scored as “yes” or “no” for each patient. This approach does not take into account the fact that some patients without toxicity might have experienced toxicity with longer follow-up. Moreover, the standard Lyman model does not incorporate non-dosimetric risk factors such as comorbidities and other patient characteristics.

Radiation pneumonitis (RP) among patients with inoperable non-small cell lung cancer (NSCLC) is an example of a normal-tissue toxicity for which analysis with the standard Lyman model may not be appropriate. When RP occurs, it is diagnosed within the first year after RT; unfortunately many patients with inoperable NSCLC succumb to disease during the same time period. As improvements in treatment are developed that improve survival for these patients, cases of RP are likely to occur that would otherwise have been masked by disease-related deaths. It would be desirable to have a model of RP risk that remains accurate as improvements in disease control are made.

There is considerable evidence to suggest that the risk of RP is influenced not just by dose-volume parameters but by non-dosimetric factors as well, notably smoking status. Consistent with other reports²⁻⁴, our recent analysis of data from 570 patients with lung cancer who were treated with RT found that the risk of RP was significantly lower among smokers (14% 1-year incidence of grade 3 RP) than among nonsmokers (37%), with an intermediate risk for former smokers (23%)⁵. Moreover, smoking status was found to be independent of every dose-volume factor investigated⁵. Thus, for RP and most likely for other normal-tissue endpoints as well, it is important to incorporate non-dosimetric factors into NTCP modeling.

The goal of the present study was to develop a generalization of the Lyman model incorporating censored time-to-toxicity data and non-dosimetric patient factors and to use the model to analyze the RP data from our cohort of 576 patients. The generalized Lyman model presented here has the mathematical form known as a mixture model, in which the complication probability and the distribution of event times are represented by separate components of the model⁶⁻⁹. This feature allows estimation of NTCP values while at the same time taking censoring into account.

MATERIALS AND METHODS

Patient population

The patient population for the present study was the same as that in our recent analysis of clinical and dosimetric risk factors for severe RP and is described in detail elsewhere⁵.

Briefly, the medical and radiation records were reviewed for all patients with newly diagnosed NSCLC who received definitive 3-dimensional conformal radiotherapy or intensity modulated radiotherapy, with or without chemotherapy, at The University of Texas M. D. Anderson Cancer Center (UTMDACC) from 1999 to 2005. Patients were excluded from the analysis if they received a total dose < 50.4 Gy, had doses per fraction that varied over the course of treatment, or had treatment breaks totaling > 7 days. This retrospective study was approved by UTMDACC's Institutional Review Board.

Lung DVHs

All patients had RT simulation on regular or 4-dimensional (4-D) computed tomography (CT) scanners. The gross tumor volume (GTV) was defined as the total volume of the primary and nodal tumor masses visualized on any radiographic image. When a 4-D CT simulator was used, patient respiratory motion was monitored and the GTV was delineated on the maximal intensity projection (MIP) image, thus creating a MIP-GTV that combined the extension of the GTVs at the 10 phases of each respiratory cycle on the 4-D CT scan.

The normal lung was defined as the total lung minus trachea, main bronchi, and GTV (or MIP-GTV when 4-D CT scans were used). DVHs for normal lung were exported from the commercial treatment planning system (Pinnacle3; Philips Medical Systems, Andover MA) with 0.2-Gy bin sizes; doses represent physical doses calculated using a convolution/superposition algorithm for heterogeneity correction.

Scoring of radiation pneumonitis

Radiation pneumonitis was scored on the basis of clinical presentation and radiographic abnormalities and was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0¹⁰ as follows. Radiologically confirmed and symptomatic RP that interfered with daily activities or that required administration of oxygen was scored as grade 3; the need for assisted ventilation was scored as grade 4; and fatal RP was scored as grade 5.

The Lyman model

In the standard Lyman model¹, the probability of observing a specified complication after irradiation to dose D of subvolume V (expressed as a proportion of the whole organ or other reference volume) is modeled using a cumulative normal distribution, or probit function:

$$\text{NTCP}(D, V) = \frac{1}{\sqrt{2\pi}} \cdot \int_{-\infty}^t e^{-u^2/2} du \quad (1)$$

where

$$t = \frac{D - TD_{50}/V^n}{m \cdot TD_{50}/V^n} \quad (2)$$

The parameter TD_{50} is the tolerance dose corresponding to a 50% complication probability after irradiation of the reference volume, m is inversely related to the slope of the dose-response curve for the complication in question, and n is the volume parameter. The Lyman model is fitted to data using maximum likelihood (ML) analysis¹¹, with the contribution to the likelihood consisting of NTCP or $1 - \text{NTCP}$ for patients experiencing or not experiencing the endpoint, respectively.

In the typical clinical situation in which the dose distribution to the irradiated portion of the organ is nonuniform, Lyman suggested using a recursive algorithm to reduce the DVH to an equivalent (in terms of NTCP) single-step DVH in order to apply equations (1) and (2). Kutcher and Burman proposed a reduction scheme that leads to a DVH representing exposure of the effective volume V_{eff} to the maximum dose¹². In an alternative representation proposed by Mohan et al.¹³, the whole volume ($V=1$) is exposed to the effective dose, D_{eff} , defined by:

$$D_{\text{eff}} = \left(\sum_i v_i \cdot D_i^{1/n} \right)^n \quad (3)$$

In equation (3), n is the volume parameter from equation (2), D_i is the dose to subvolume v_i , and the sum extends over all dose bins in the DVH.

The Lyman model with covariates added

To incorporate covariates into the standard Lyman model, the quantity t (equation 2) can be replaced by

$$t = \frac{D_{\text{eff}} - TD_{50} \cdot \exp(\delta_1 \cdot Y_1) \cdot \dots \cdot \exp(\delta_k \cdot Y_k)}{m \cdot TD_{50} \cdot \exp(\delta_1 \cdot Y_1) \cdot \dots \cdot \exp(\delta_k \cdot Y_k)} \quad (4)$$

where the variables Y_1 through Y_k represent non-dosimetric risk factors. Typically these are indicator variables taking on values $Y_i = 1$ or $Y_i = 0$ to represent the presence or absence, respectively, of the risk factor. The quantity $\exp(\delta_i Y_i)$ is the dose-modifying factor (DMF) for TD_{50} in the presence of risk factor Y_i .

The generalized Lyman model

In the generalized Lyman model, NTCP is modeled in the same way as for the standard Lyman model (equation 1), with t given by equation (4) or equation (2), depending on whether or not covariates are to be included. However, the NTCP does not represent the probability of observing a complication, but the probability that the complication would eventually occur if the patient survived and were followed for a sufficient amount of time. Thus the NTCP includes the probability of toxicities that are censored by incomplete follow-up for any reason, including patient death.

Among patients who would eventually experience toxicity with sufficiently long follow-up, the distribution of times to toxicity (the latency distribution) is modeled in the present study using a log-normal distribution, which has parameters μ and σ and density function

$$f(\tau) = \frac{1}{\sigma\tau\sqrt{2\pi}} \cdot e^{-(\ln \tau - \mu)^2 / 2\sigma^2} \quad (5)$$

Other choices are also possible, such as the log-logistic distribution or an empirical distribution based on the observed event-time data. Also, the latency parameters (μ and σ) could be functions of D_{eff} and/or Y_1 through Y_k , in which case additional parameters could be introduced to describe this dependence.

The generalized Lyman model is a mixture of 2 components, the incidence component, NTCP, and the latency component, $f(\tau)$. In fitting the model to data using ML analysis, the contribution to the likelihood for a patient experiencing toxicity at time τ is

$$\text{NTCP}(D_{\text{eff}}, Y_1, \dots, Y_k) \cdot f(\tau) \quad (6)$$

whereas for a patient followed to time τ without experiencing toxicity, the contribution to the likelihood is

$$1 - \text{NTCP}(D_{\text{eff}}, Y_1, \dots, Y_k) \cdot F(\tau) \quad (7)$$

where $F(\tau)$ is the cumulative distribution function corresponding to $f(\tau)$. Expression (7) is the sum of 2 terms, one representing patients for whom toxicity will not occur regardless of length of follow-up ($1 - \text{NTCP}$) and the other representing patients who would experience toxicity at a later time if follow-up were sufficiently long ($\text{NTCP}(1 - F(\tau))$).

Statistical methods

Curves representing overall survival or freedom from RP were calculated using the method of Kaplan and Meier¹⁴. RP incidence levels in patient subgroups were computed as 1 minus the Kaplan-Meier estimate of freedom from RP at the specified time point. Confidence intervals for model parameter estimates obtained by maximum likelihood analysis were derived using the profile likelihood method¹¹. Comparisons between the fits of nested models were performed using the likelihood ratio test. All calculations were performed using Stata (Stata Statistical Software, Release 10, 2007; Stata Corp LP, College Station, TX).

RESULTS

Overall survival and incidence of RP

Figure 1 shows overall survival and freedom from severe RP (grade 3) during the first year after start of RT for the 576 patients in the study cohort. There was a reduction in survival of more than 20% over the time period during which RP was diagnosed. Thus, there are patients without severe RP who would likely have experienced the endpoint had they lived longer. This illustrates the need for an NTCP model incorporating censored time-to-toxicity data.

Time to severe RP

The distribution of times to grade 3 RP (the latency distribution) is shown in Figure 2 for the 117 patients experiencing the endpoint, adjusted to take into account the number of patients alive and at risk of RP at each time point. The distribution is well described by a log-normal function (equation 5), as illustrated by the dashed curve, and supports use of this latency model for the present data.

Fits of the generalized Lyman model

Table 1 (column 1) lists the parameter estimates obtained by fitting the generalized Lyman model to the censored time-to-toxicity data. Smoking status was included in the model by regarding smokers as the baseline group ($N = 156$), with 2 covariates, Y_1 and Y_2 , representing former smokers ($N = 374$) and nonsmokers ($N = 46$), respectively.

The parameter estimates obtained by restricting the volume parameter in the generalized Lyman model to $n = 1$, corresponding to the case in which $D_{\text{eff}} = \text{mean lung dose (MLD)}$, are also listed in Table 1 (column 2). This fit is not significantly different from the fit with $n = 0.53$ ($P = 0.159$, likelihood ratio test). The dose-modifying factors for former smokers and nonsmokers correspond to TD_{50} estimates of 34.8 Gy (95% CI 29.7-46.9 Gy) and 26.0 Gy (95% CI 20.6-36.2 Gy) in those patient subgroups, respectively. Figure 3 shows the NTCP values predicted by the generalized Lyman model with $n = 1$, plotted as a function of mean lung dose. The fit of the model to data is illustrated by plotting the estimates of RP incidence at 1 year for subgroups of smokers, former smokers, and nonsmokers grouped

according to mean lung dose. Figure 4 provides another illustration of the model fit; patients were divided into 5 subgroups according to their NTCP values, which ranged from 4% to 70%, with a median of 21%. The 1-year incidence rates of severe RP in patient subgroups with NTCP < 10%, 10-20%, 20-30%, 30-40% and > 40% were 5%, 17%, 27%, 27%, and 47%, respectively.

Dependence of latency on NTCP

To investigate whether the time to occurrence of severe RP depended on the severity of tissue damage, we tested whether the fit of the generalized Lyman model was improved if the latency parameter μ was modeled as a linear function of NTCP by inclusion of one additional parameter. However, this modification did not significantly improve the fit ($P = 0.384$).

Impact of censoring

To investigate the effect of taking censoring into account in the NTCP modeling, the NTCP values obtained from the generalized Lyman model fitted to censored time-to-toxicity data were compared to the NTCP values obtained from the standard Lyman model fitted to binary (yes/no) data. For both models the volume parameter was fixed at $n = 1$ and patient smoking status was taken into account (equation 4). Because the generalized model “anticipates” unobserved toxicities by means of equation (7), it produced NTCP values that were an average of 2 percentage points higher than those from the standard model, ranging up to 8 percentage points higher. The average relative difference in NTCP values was 9%, ranging up to 22%. Overall, the generalized model predicted that an additional 10 patients, i.e. 127 patients in total, would have experienced severe RP with unlimited follow-up, compared to the 117 cases that were observed. Thus the generalized Lyman model estimated that 8% of the expected cases of severe RP were unobserved because of censoring.

Impact of smoking status

The impact of excluding important covariates from the generalized Lyman model was investigated by comparing the NTCP values obtained from the fit of the generalized Lyman model to those obtained from a fit in which smoking status was omitted (i.e., in which equation 4 was replaced by equation 2). With smoking status included in the model, the generalized Lyman model produced NTCP values that were up to 27 percentage points lower for smokers and up to 23 percentage points higher for nonsmokers than the NTCP values obtained by omitting smoking status from the fit. Relative differences in NTCP ranged from -44% for smokers to +62% for nonsmokers. For the present data, therefore, inclusion in the model of important non-dosimetric covariates (i.e., smoking status) had a large impact on estimated NTCP values, and in fact the impact was larger than the effect of taking censoring into account.

DISCUSSION

The present study presents an alternative to the standard Lyman NTCP model suitable for analysis of radiation toxicities such as RP that might be unobserved in some patients because of censoring. The value of such a model is that it should remain more accurate in its NTCP predictions than the standard Lyman model as evolving treatment regimens lead to prolonged patient survival. Accordingly, the generalized model leads to higher NTCP estimates than the standard Lyman model.

The mathematical form used here to generalize the Lyman model is that of a mixture model, in which the incidence and latency of the endpoint are modeled separately⁶⁻⁹. The mixture model is a theoretically appealing approach for NTCP modeling because it incorporates the

assumption that only a proportion of the subjects will express the injury, even with unlimited follow-up. This is in contrast to the proportional hazards approach, in which the underlying assumption is that all subjects will eventually experience the complication with sufficiently long follow-up¹⁵.

However, the mixture model is not without its own limitations. In particular, if there is no clear indication from the data that the observation period adequately covers the time frame during which complications occur, then the model parameters may not be identifiable¹⁶⁻¹⁸. That is, it may not be possible to distinguish between 2 fits to the data, one in which there is a high long-term incidence of the endpoint and a long tail to the latency distribution, and another in which there is a lower incidence of the endpoint and a shorter average latency. Moreover, the mixture model requires specification of a latent-time distribution. The mixture model appears to be well suited to the analysis of severe RP, however, because the observed events occurred relatively early compared to average patient follow-up (Figure 1), and the latent-time distribution is well described by a log-normal model (Figure 2).

The generalized Lyman model used here also incorporates non-dosimetric risk factors. In fact, inclusion of smoking status in the model was found to have a pronounced effect on estimated NTCP values, and illustrates the importance of taking relevant non-dosimetric factors into account during dose-volume modeling.

The method used here to incorporate additional covariates into the Lyman model requires that the response curves for each subgroup have the same value of the parameter m (equation (2)). This is the same approach taken by Peeters et al. in their analysis of rectal toxicity¹⁹. Alternatively, one could require the slopes of the dose-response curves to be constant across subgroups. However, a bootstrap analysis²⁰ performed using the present data indicated that a fit requiring a common m value was, on average, superior to one requiring a common slope, although the difference in fits did not reach statistical significance ($P=0.286$). A third approach, requiring additional parameters, is to allow both the slope and TD_{50} to be fitted freely in each patient subset; for the present cohort, however, a fit of separate dose-response curves to the cohorts of smokers, former smokers and nonsmokers (although with common values of the latency parameters from equation (5)) was not significantly different from the fit shown in Table 1 ($P = 0.759$).

Despite the large size of our study cohort (576 patients, with 117 cases of severe RP), we were unable to detect a significant improvement in the fit of the generalized Lyman or model over a fit in which the volume parameter was fixed at $n = 1$, i.e. the generalized mean dose model. This conclusion is consistent with the findings of numerous other studies in which the mean lung dose has been found to predict the incidence of pneumonitis as well or better than any other parameter considered^{2, 21-28}.

In our previous analysis of the data from the present study cohort, we identified a set of dose-volume constraints associated with the incidence of severe RP⁵. Specifically, patients whose lung DVHs satisfied $V_{20} \leq 25\%$, $V_{25} \leq 20\%$, $V_{35} \leq 15\%$, and $50 \text{ Gy} \leq 10\%$, (where V_{20} is the percentage of normal lung exposed to doses $> 20 \text{ Gy}$, and similarly for V_{25} , V_{35} and 50 Gy), had only a 2% incidence of severe RP at 1 year. Among subgroups of patients whose DVHs did not meet these strict constraints but met increasingly relaxed dose-volume constraints, the 1-year rates of severe RP were progressively higher and differences in incidence of RP by smoking status became more and more apparent⁵. While it is useful to identify risk levels using a small number of dose-volume constraints, the modeling approach described in the present study has certain advantages. It takes the entire lung DVH into account and avoids the suggestion that there are dose thresholds (e.g. 25 Gy or 50 Gy) at

which risk levels suddenly change. Moreover, it allows estimation of risk for individual patients, instead of simply for patient subgroups.

It should be noted, however, that there remains significant room for improvement in modeling RP risk. In particular, the dose-response curves shown in Figure 3 are relatively shallow, and NTCP estimates in the range 20-40% do not define distinct risk groups in the present cohort (Figure 4). To steepen and/or further separate the dose-response curves, thereby improving predictive accuracy, it may be important to incorporate additional covariates into the modeling. In particular, several groups have shown that the anatomic region of lung exposed to radiation has an impact on complication risk.^{23, 28-36} Although we did not find any non-dosimetric factors other than smoking status to be associated with differences in risk of severe RP in our study cohort⁵, others have reported the impact of patient and clinical factors such as COPD or use of chemotherapy³⁷. Markers of individual susceptibility to RP, such as genetic information or cytokine expression levels, are also likely to improve prediction of RP risk. If smoking status plays as important a role in affecting RP risk as our studies have suggested, there would also likely be a benefit in incorporating better measures of tobacco exposure than were considered here, where patients were divided into just 3 broad groups: smokers, former smokers and nonsmokers. It may also be the case that the Lyman model is inherently limited in its ability to accurately predict RP risk, and we are also pursuing other modeling approaches.

Finally, estimation of RP risk will undoubtedly improve as methods are developed to reduce uncertainty in the data. It is well recognized that the DVHs obtained from treatment-planning CT scans are not fully representative of the radiation exposure to lung, owing to motion of the thorax during each daily treatment and to possible changes in patient anatomy over the course of therapy. Technologies such as 4-dimensional CT scanning have been developed to address this issue, and future data will therefore include more accurate lung DVHs. Furthermore, the scoring of the pneumonitis endpoint is subject to considerable subjectivity, and there may be more than 1 etiology involved³⁸. The development of more consistent and objective measures of lung injury would markedly improve our ability to predict risk.

CONCLUSIONS

The generalized Lyman model presented here provides a technique to take into account the effects of censoring when analyzing late toxicity data, provided the observation period adequately covers the latent time for occurrence of toxicity. In addition, the generalized models allow non-dosimetric risk factors such as smoking status to be easily incorporated into NTCP estimation. Analysis of censored time-to-toxicity data and inclusion of non-dosimetric risk factors can significantly impact the predictions of NTCP models that have historically been based solely on dose-volume effects and binary (yes/no) toxicity data.

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Figure 1. Overall survival and freedom from grade ≥ 3 RP and during the first 12 months after start of radiotherapy.

Figure 2.

Histogram showing the distribution of times to grade 3 RP, adjusted to take into account the number of patients alive and at risk of RP at each time point. The dashed curve represents a log-normal density function with parameters $\mu = 1.31$ and $\sigma = 0.42$ (equation 5).

Figure 3.

NTCP values computed from the fit of the generalized Lyman model as a function of mean lung dose (model parameters from column 2 of Table 1). Points show Kaplan-Meier estimates of RP incidence at 1 year in patient subgroups. The cohorts of smokers and former smokers were divided into 4 groups each according to mean lung dose: MLD < 15 Gy, 15-20 Gy, 20-25 Gy, and > 25 Gy. The cohort of nonsmoking patients was divided into two subgroups with MLD < 20 Gy and MLD > 20 Gy. Points are plotted at the average MLD value for each subgroup. Horizontal error bars indicate ± 1 standard deviation in MLD; vertical error bars indicate ± 1 standard error in the estimated RP incidence.

Figure 4. Freedom from grade ≥ 3 RP among patient subgroups defined by NTCP value from the fit of the generalized Lyman model with $n = 1$ (Table 1, column 2).

Table 1

Parameter estimates of the generalized Lyman model for risk of grade 3 RP.

Parameter	Model	
	Full model	Fix n=1 (MLD model)
n	0.57 (0.26, 1.32) *	1 **
m	0.43 (0.27, 0.70)	0.56 (0.43, 0.77)
TD_{50} (smokers) (Gy)	54.1 (38.8, 99.2)	52.4 (35.9, 171)
DMF *** (former smokers)	0.79 (0.40, 0.98)	0.67 (0.24, 0.94)
DMF(nonsmokers)	0.65 (0.27, 0.89)	0.50 (0.15, 0.79)
μ	1.31 (1.23, 1.39)	1.31 (1.23, 1.39)
σ	0.41 (0.36, 0.47)	0.41 (0.36, 0.47)

* 95% confidence intervals are shown.

** Volume parameter fixed at $n = 1$; comparison with fit of the full model is $P = 0.159$ (likelihood ratio test).

*** DMF = Dose-modifying factor