Int. J. Radiation Oncology Biol. Phys., Vol. 78, No. 4, pp. 1253–1260, 2010

0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.01.069

PHYSICS CONTRIBUTION

LATE RECTAL TOXICITY ON RTOG 94-06: ANALYSIS USING A MIXTURE LYMAN MODEL

Susan L. Tucker, Ph.D.,* Lei Dong, Ph.D.,† Walter R. Bosch, D.Sc.,‡§ Jeff Michalski, M.D.,§ Kathryn Winter, M.S.,¶ Radhe Mohan, Ph.D.,† James A. Purdy, Ph.D.,‖ Deborah Kuban, M.D.,** Andrew K. Lee, M.D.,** M. Rex Cheung, M.D., Ph.D.,** Howard D. Thames, Ph.D.,†† and James D. Cox, M.D.**

Departments of *Bioinformatics and Computational Biology, †Radiation Physics, **Radiation Oncology, and ††Biostatistics, The University of Texas M.D. Anderson Cancer Center, Houston, TX; ‡Image-Guided Therapy QA Center and §Department of Radiation Oncology, Washington University, St. Louis, MO; ¶American College of Radiology, Philadelphia, PA; and ‖Department of Radiation Oncology, University of California Davis Cancer Center, Sacramento, CA.

Purpose: To estimate the parameters of the Lyman normal-tissue complication probability model using censored time-to-event data for Grade ≥2 late rectal toxicity among patients treated on Radiation Therapy Oncology Group 94-06, a dose-escalation trial designed to determine the maximum tolerated dose for three-dimensional conformal radiotherapy of prostate cancer.

Methods and Materials: The Lyman normal-tissue complication probability model was fitted to data from 1,010 of the 1,084 patients accrued on Radiation Therapy Oncology Group 94-06 using an approach that accounts for censored observations. Separate fits were obtained using dose–volume histograms for whole rectum and dose–wall histograms for rectal wall.

Results: With a median follow-up of 7.2 years, the crude incidence of Grade ≥2 late rectal toxicity was 15% (n = 148). The parameters of the Lyman model fitted to dose–volume histograms data, with 95% profile-likelihood confidence intervals, were TD_{50} = 79.1 Gy (75.3 Gy, 84.3 Gy), m = 0.146 (0.107, 0.225), and n = 0.077 (0.041, 0.156). The fit based on dose–wall histogram data was not significantly different. Patients with cardiovascular disease had a significantly higher incidence of late rectal toxicity (p = 0.015), corresponding to a dose-modifying factor of 5.3%. No significant association with late rectal toxicity was found for diabetes, hypertension, rectal volume, rectal length, neoadjuvant hormone therapy, or prescribed dose per fraction (1.8 Gy vs. 2 Gy).

Conclusions: These results, based on a large cohort of patients from a multi-institutional trial, are expected to be widely representative of the ability of the Lyman model to describe the long-term risk of Grade ≥2 late rectal toxicity after three-dimensional conformal radiotherapy of prostate cancer.

Prostate cancer, Radiation Therapy Oncology Group, Rectal toxicity, Dose–volume histogram, Lyman model.

INTRODUCTION

Patients undergoing external beam radiotherapy (RT) of prostate cancer may develop late rectal complications, and many investigators have sought to identify characteristics of the rectal dose–volume histogram (DVH) associated with toxicity risk. At least four studies (1–4) have analyzed late rectal data using the Lyman normal-tissue complication probability (NTCP) model (5) combined with the DVH reduction scheme of Kutcher and Burman (6).

In fitting the Lyman-Kutcher-Burman (LKB) model to data, the approach used in previous studies of rectal toxicity has been to score patients as responders or nonresponders according to whether or not toxicity was observed, although it is recognized that some ''nonresponders'' would have experienced the endpoint with longer follow-up. As a consequence of these false negatives, NTCP models fitted to such data tend to underestimate the true complication risk. To address this problem, some previous studies have specified a time point for risk assessment, *e.g.,* 18 months for the study of Rancati *et al*. (1) and 3 years for the study of Peeters *et al*. (3). However, excluding patients with shorter follow-up leads to a loss of data, and estimates of risk at specified time points can be

Reprint requests to: Susan L. Tucker, Ph.D., Department of Bioinformatics and Computational Biology – Unit 1410, The University of Texas M.D. Anderson Cancer Center, P.O. Box 301402, Houston, TX 77230-1402. Tel: (713) 792-2613; Fax: (713) 563-4242; E-mail: sltucker@mdanderson.org

Supported in part by grants R01 CA104342, U24 CA81647, U10 CA21661, U10 CA37422, and U10 CA32115 from the National Cancer Institute, the National Institutes of Health.

Presented in part at the 49th annual meeting of the American Society for Therapeutic Radiology and Oncology, October, 2007.

Conflict of interest: none.

Received Aug 24, 2009, and in revised form Jan 19, 2010. Accepted for publication Jan 25, 2010.

substantially lower than the ultimate long-term risk level, depending on the time course over which toxicity appears.

The goal of the present study was to fit the LKB model to late rectal toxicity data using a technique that explicitly takes into account the possibility of censored events and thereby avoids false negatives and the loss of data that results from specification of a minimum follow-up time (7). The generalized LKB model can be called the ''mixture Lyman model'' by analogy with ''mixture cure'' models from the statistical literature (8). Such models assume that some patients will experience the event of interest with sufficiently long follow-up whereas others will not, and the goal is to estimate the risk that a patient belongs to the former category (the NTCP). In fitting the model to data, patients without toxicity at last follow-up are regarded as having some probability of experiencing the endpoint at a later time, depending on the current length of follow-up and on the DVH and other relevant risk factors. As noted previously (7), censored cases include patients who die without toxicity, which implies that NTCP estimates from the mixture Lyman model are expected to remain accurate in settings where survival is improved.

The data analyzed in this study are from Radiation Therapy Oncology Group (RTOG) 94-06, a large multi-institutional trial designed to establish the maximum tolerated dose during three-dimensional conformal RT of clinically localized (T1–T3) adenocarcinoma of the prostate. Participating institutions were required to meet specific criteria for technology and quality assurance, although each institution used its own in-house conformal techniques for treatment. Patients enrolled on the trial were followed up regularly at prescribed intervals and scored prospectively according to strictly defined toxicity criteria. The uniformity in the collection and scoring of data from a large number of patients, combined with the variation in treatment designs among participating institutions, makes the data from RTOG 94-06 an excellent resource for investigating the dose–volume response of the rectum.

METHODS AND MATERIALS

Patient accrual and treatments on protocol RTOG 94-06

Protocol RTOG 94-06 accrued 1,084 patients from 42 different institutions between 1994 and 2000. Details of the trial and results of primary analyses have been presented elsewhere (9–12). Briefly, the trial included five prescription dose levels: 68.4 Gy, 73.8 Gy, and 79.2 Gy (levels I– III) given in 1.8-Gy fractions, and 74.0 Gy and 78.0 Gy (levels IV–V) given in 2-Gy fractions. Patients were stratified into three groups according to the estimated risk of seminal vesicle invasion (13). Patients in Group 1 were treated to the prostate only, patients in Group 2 were treated to the prostate and bilateral seminal vesicles for the first 55.8 Gy (levels I–III) or 54 Gy (levels IV–V) and to the prostate only for the remainder of treatment, and Group 3 patients were treated to the prostate plus bilateral seminal vesicles throughout RT. Neoadjuvant androgen suppression was permitted if it began 2 to 6 months before study registration.

DVH data

Treatment planning computed tomography scans were acquired in the same position and under the same conditions (*e.g.,* full vs. empty bladder) as for treatment. The rectum was empty unless contrast medium was used, and was contoured from the level of the ischial tuberosities to the rectosigmoid flexure. The rectal DVH was computed for rectum as a solid volume based on the dose matrix submitted by the participating institution. For a few cases in which the dose matrix did not encompass the entire rectum, the volume of rectum outside the dose matrix was added to the 0-Gy dose bin of the DVH. For patients who did not complete planned treatment, the rectal DVH represented the dose actually delivered.

A dose–wall histogram (DWH) was calculated for an approximate rectal wall structure obtained by retracting the outer rectal contour inward by 3 mm. As described previously (14), the choice of 3 mm is supported by a study in which rectal wall thicknesses were measured by ultrasound (15).

Patient follow-up and toxicity scoring

After treatment, patients were followed up every 3 months for the first year, every 4 months during the second year, every 6 months during the next 3 years, and annually thereafter. Toxicity was scored using RTOG criteria (16). Consistent with previous analyses of these data (9–12), late rectal toxicity was defined as toxicity starting or persisting at least 120 days after the start of RT. Time to Grade $\geq$2 late rectal toxicity was computed from the RT start date, and patients not experiencing the endpoint were censored at the date of last follow-up.

The data analyzed here were extracted from the RTOG database in October 2007. This retrospective secondary analysis was approved by the RTOG Publications Committee and by the Institutional Review Boards of UTMDACC, the Washington University Medical Center, and the American College of Radiology.

Data analysis

Data were analyzed using the mixture Lyman model (7), in which the NTCP after indefinitely long follow-up is modeled using the standard LKB formula, with parameters TD_{50}, m, and n:

$$\mathrm{NTCP} = \frac{1}{\sqrt{2\pi}} \cdot \int_{-\infty}^{t} e^{-u^2/2} du \tag{1}$$

where

$$t = \frac{D_{eff} - TD_{50}}{m \cdot TD_{50}} \tag{2}$$

and

$$D_{eff} = \left(\sum (D_i)^{1/n} \cdot v_i \right)^n \tag{3}$$

The expression for effective dose, given by equation (3), D_i is the dose to relative organ volume v_i, and the sum extends over all dose bins in the DVH (17).

The mixture Lyman model also includes a formula for the distribution of times at which toxicity occurs among patients who will experience the endpoint. In the present study, latent times were modeled using a lognormal distribution, which has parameters μ and σ and probability density function

$$f(\tau) = \frac{1}{\sigma\tau\sqrt{2\pi}} \cdot e^{-(\ln\tau - \mu)^2/2\sigma^2} \tag{4}$$

Mixture Lyman model was fitted to data using maximum likelihood analysis (18). As described in detail elsewhere (7), the contribution to the likelihood for a patient experiencing toxicity at time τ is