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CLINICAL INVESTIGATION **Prostate**

CHARACTERIZATION OF RECTAL NORMAL TISSUE COMPLICATION PROBABILITY AFTER HIGH-DOSE EXTERNAL BEAM RADIOTHERAPY FOR PROSTATE CANCER

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Purpose: Conformal radiotherapy (RT) has allowed radiation dose escalation to improve the outcome of prostate cancer. With higher doses, concern exists that rectal injury may increase. This study analyzed the utility and limitations of the widely used Lyman-Kutcher- Burman (LKB) normal tissue complication probability model in projecting the hazards of rectal complication with high-dose RT.

Methods and Materials: A total of 128 patients were included in this study. These patients were treated with three-dimensional conformal RT alone at the University of Texas M.D. Anderson Cancer Center between 1992 and 1999. Patients were treated to 46 Gy with a four-field box technique followed by a six-field arrangement to boost the total dose to 78 Gy. All doses were delivered at 2 Gy/fraction to the isocenter. The minimal follow-up was 2 years. The end point for analysis was Grade 2 or worse rectal bleeding by 2 years. The LKB model was fitted to the data using the maximal likelihood method.

Results: Of the 128 patients, 29 experienced Grade 2 or worse rectal bleeding by 2 years. For the entire cohort, the parameters obtained from the fit of the LKB model were as follows: the volume factor was $n = 3.91$ (95% confidence interval [CI] 0.031 to ∞), dose associated with 50% chance of complication for uniform whole rectal irradiation [$TD_{50}(1)$] was 53.6 Gy (95% CI 50.0–75.1), and a determinant of the steepness of the dose–response curve, (m), was 0.156 (95% CI 0.036–0.271). A statistically significant difference was found in the rate of postradiation rectal bleeding in patients with hemorrhoids vs. those without hemorrhoids. The parameters obtained for the patients without hemorrhoids were as follows: $n = 0.746$ (95% CI 0.026 to ∞), $TD_{50}(1)$ 56.7 Gy (95% CI 49.9–75.2), and m 0.092 (95% CI 0.019–0.189).

Conclusion: Our analysis suggests a dose response for rectal bleeding probability along with a volume effect. We found that the LKB model might have limited utility in determining a large volume effect. We further suggest that LKB model should be used with caution in clinical practice. **© 2004 Elsevier Inc.**

Prostate cancer, Radiotherapy, Dose escalation, Rectal NTCP, Lyman-Kutcher-Burman model.

INTRODUCTION

Prostate adenocarcinoma is the most common nonskin cancer in men. Most patients are diagnosed at a clinically localized stage in the prostate-specific antigen era (1). There has been a national trend over the past decade to increase the radiation dose to treat this malignancy (2). Conventional radiotherapy (RT) techniques for the treatment of prostate cancer have been limited by unacceptable rectal complications at >70 Gy (3, 4). Conformal RT has recently gained popularity. It allows radiation dose escalation to improve tumor control with acceptable toxicity (5–8). With higher doses, concern exists that the complication rate may increase. It has been demonstrated that the treatment dose and volume are predictive of the rectal complication rate (9–11). This study extended our previous analysis (11) by estimating the parameters of the best- fitting Lyman-Kutcher-Burman (LKB) normal tissue complication probability (NCTP) model (12, 13). Our analysis provides information on the utility and limitations of the LKB model for projecting the potential hazards of additional dose escalation.

METHODS AND MATERIALS

Patient cohort

The internal review board of the University of Texas M. D. Anderson Cancer Center (UTMDACC) approved this retrospective study. The patients included in the present analysis comprised a subset of the patients described previously (11,

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14). In brief, all patients received definitive three-dimensional conformal RT (3D-CRT) for biopsy-proven prostate cancer at the UTMDACC between 1992 and 1999. Their charts were retrospectively reviewed. There were 128 patients for whom dose–volume histogram (DVH) data could be recovered. The end point for this analysis was Grade 2 or greater late rectal bleeding occurring within 2 years after RT. Because the minimal follow-up for these patients was 2 years, the status of the rectal bleeding end point at 2 years was known for all patients. The range and median follow-up was, respectively, 2–8 years and 5.4 years. Late complications were defined as those developing ≥6 months after RT completion. One patient who developed rectal bleeding after 5 months was also scored as having late rectal bleeding. All late rectal complications were graded using a modified scale and criteria from the Radiation Therapy Oncology Group (15), Late effects Normal Tissue Task Force (16), and Fox Chase Cancer Center (17). Follow-up examinations were performed after the completion of RT at 6-month intervals during the first 2 years and annually thereafter. Rectal complications were determined retrospectively from the charts.

RT techniques

The details of RT have been previously described (11, 14). In brief, patients underwent simulation and treatment in the supine position with a full bladder. The planning CT data were acquired at 5-mm intervals (Model 9800, General Electric Medical Systems, Milwaukee, WI). The patients were treated to 46 Gy at 2 Gy/fraction to the isocenter using 18-MV photons and a four-field technique. The isocenter was boosted to 78 Gy with 3D-CRT.

DVH information

DVHs were restored from the institutional archives. Either an in-house treatment planning system (COPPERPlan, M.D. Anderson Cancer Center) or a commercial planning system (Pinnacle, ADAC Laboratories, Milpitas, CA) was used for treatment planning. For the calculation of the DVH, the entire rectal volume was outlined to include the external rectal wall plus contents. The rectum was outlined about 11 cm in length starting at 2 cm below the inferior-most aspect of the ischial tuberosities.

NCTP modeling

Analysis algorithms were implemented in Stata (StataCorp, 2001, Stata Statistical Software, Release 7.0, Stata, College Station, TX) and Statistical Package for Social Sciences (SPSS, Chicago, IL). The Lyman NTCP model was fitted to the rectal complication data using maximal likelihood analysis. The Lyman model describes the probability of a complication after uniform radiation of a fractional volume (v) of normal tissue to a dose (D).

$$NTCP = F(t) = \frac{1}{\sqrt{2\pi}} \int_{\infty}^{t} e^{-\frac{u^2}{2}}\, du \qquad (1)$$

where

$$t = \frac{D - TD50(v)}{m \cdot TD50(v)} \text{ and } TD50(v) = TD50(1) \cdot (v)^{-n} \qquad (2)$$

$TD50(1)$ is the dose corresponding to a 50% chance of complications after uniform whole-organ irradiation, m characterizes the steepness of the sigmoid dose–response curve, and n determines the volume effect. When n is 0, there is no volume effect, and the volume effect increases with increasing n.

In practice, each patient's rectum receives a nonuniform dose, so a "histogram reduction" scheme such as that proposed by Kutcher and Burman (13) must be performed before the Lyman model can be applied. There are two equivalent DVH reduction schemes resulting in V_{eff} or D_{eff}. In this paper, we used the effective dose method to transform the DVH into a uniform effective dose D_{eff} to the entire organ ($v = 1$) based on the following equation:

$$D_{eff} = \left[\sum V_i \cdot (D_i)^{\frac{1}{n}} \right]^n \qquad (3)$$

where V_i is the fraction of the volume receiving a dose of D_i. Hereafter, we used the terms LKB model and NTCP model interchangeably. The parameters of the NTCP model, $TD_{50}(1)$, m, and n, were estimated using the maximal likelihood method. This method maximizes the probability of predicting grade 2 or worse rectal bleeding within 2 years for those patients who had complications and the probability of predicting no complications for the complication-free patients. The log likelihood was computed as follows:

$$Log - likelihood[m, n, TD50(1)] = \sum [R_i \cdot LnP_i + (1 - R_i) \cdot Ln(1 - P_i)] \qquad (4)$$

where P_i and R_i are, respectively, the predicted probability of rectal bleeding and observed occurrence of rectal bleeding for patient i. Ri = 1 if rectal bleeding occurred, otherwise $R_i = 0$. The confidence intervals were constructed using the profile-likelihood method (18). The area under the receiver operating characteristic curve (19) was used to measure the discriminatory power of the model.

RESULTS

We previously reported that a history of hemorrhoids is a risk factor for postradiation rectal bleeding in addition to dose and volume (14). Among the 128 UTMDACC prostate patients with DVH data in the present study, 44 had hemorrhoids. Fifteen of these (34%) experienced Grade 2 or worse late rectal bleeding within 2 years compared with 14 (17%) of the remaining 84 patients. This difference was statistically significant ($p = 0.025$, chi-square test). Figure 1 illustrates the difference in incidence of all Grade 2 or worse late rectal bleeding among the patients with and without hemorrhoids.

Table 1 shows the parameter estimates obtained when the

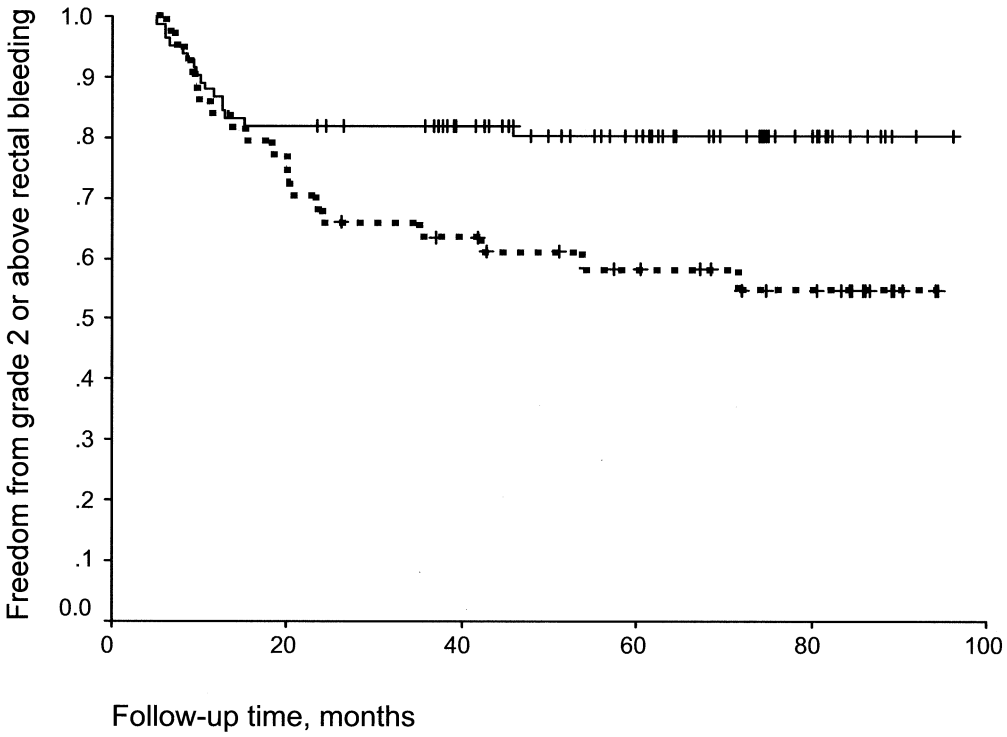

Fig. 1. Freedom from Grade 2 or worse late rectal bleeding as a function of time after end of RT among patients with (dotted line) and without (solid line) hemorrhoids.

LKB model was fitted to the data from all patients as a single cohort. We obtained an estimate of $n = 3.91$ (95% Confidence interval [CI] 0.031 to ∞) for the volume effect, an estimate of $TD_{50} = 53.6$ Gy (95% CI, 50.0–Gy–75.1Gy) for the dose associated with a 50% chance of complications after uniform whole rectal irradiation, and an estimate of $m = 0.156$ (95% CI, 0.036–0.271) for the parameter determining the steepness of the dose–response curve (Table 1).

To determine whether the model would fit better when the patients with or without hemorrhoids were separated, we compared the fit of a LKB model to all data with two separate fits to the hemorrhoid and nonhemorrhoid patients using the likelihood ratio test. Analyzing the two subsets of patients separately led to a marginally, although not significantly, better fit ($p = 0.077$). Given that it may be difficult to ascertain the true incidence of radiation-induced rectal bleeding in the background of hemorrhoid bleeding, we proceeded with NTCP modeling in the patients without hemorrhoids. The resulting parameter estimates are listed in Table 1. Figure 2 illustrate the derivation of the profile-likelihood 95% CIs. The parameter estimates CIs obtained for the patients without hemorrhoids were as follows: $n = 0.746$ (95% CI, 0.026 to ∞), $TD_{50} = 56.7$ Gy (95% CI, 49.9 Gy–75.2 Gy), and $m = 0.092$ (95% CI, 0.019–0.189). Figure 3 illustrates the goodness of the fit for the 84 nonhemorrhoid patients. The fit yields an area under the receiver operating characteristic curve of 0.841 (Fig. 4).

Table 1. The fitted parameters of the Lyman model for the subset of patients without hemorrhoids and for the whole cohort. The confidence intervals are determined from the profile-likelihood method.

Patients without hemorrhoids		
Parameter	Estimate	95% Confidence Interval
TD50	56.7 Gy	49.9 Gy to 75.2 Gy
m	0.092 Gy^{-1}	0.019 Gy^{-1} to 0.189 Gy^{-1}
n	0.746	0.026 to ∞
Whole group		
Parameter	Estimate	95% Confidence Interval
TD50	53.6 Gy	50.0 Gy to 75.1 Gy
m	0.156 Gy^{-1}	0.036 Gy^{-1} to 0.271 Gy^{-1}
n	3.91	0.031 to ∞

DISCUSSION

Advances in anatomic imaging have allowed for better delineation of target and normal tissues and therefore made possible dose escalation to improve treatment outcomes (7, 8). When 3D-CRT has been used in conjunction with the DVH constraints, treating prostate cancer with higher doses has resulted in acceptable rectal and urinary complications rates (7, 8). In the UTMDACC randomized trial (8), in patients treated with 3D conformal techniques to 78 Gy, the urinary complication rates were similar in the two arms, 78 Gy and 70 Gy. With careful attention to the DVH of the

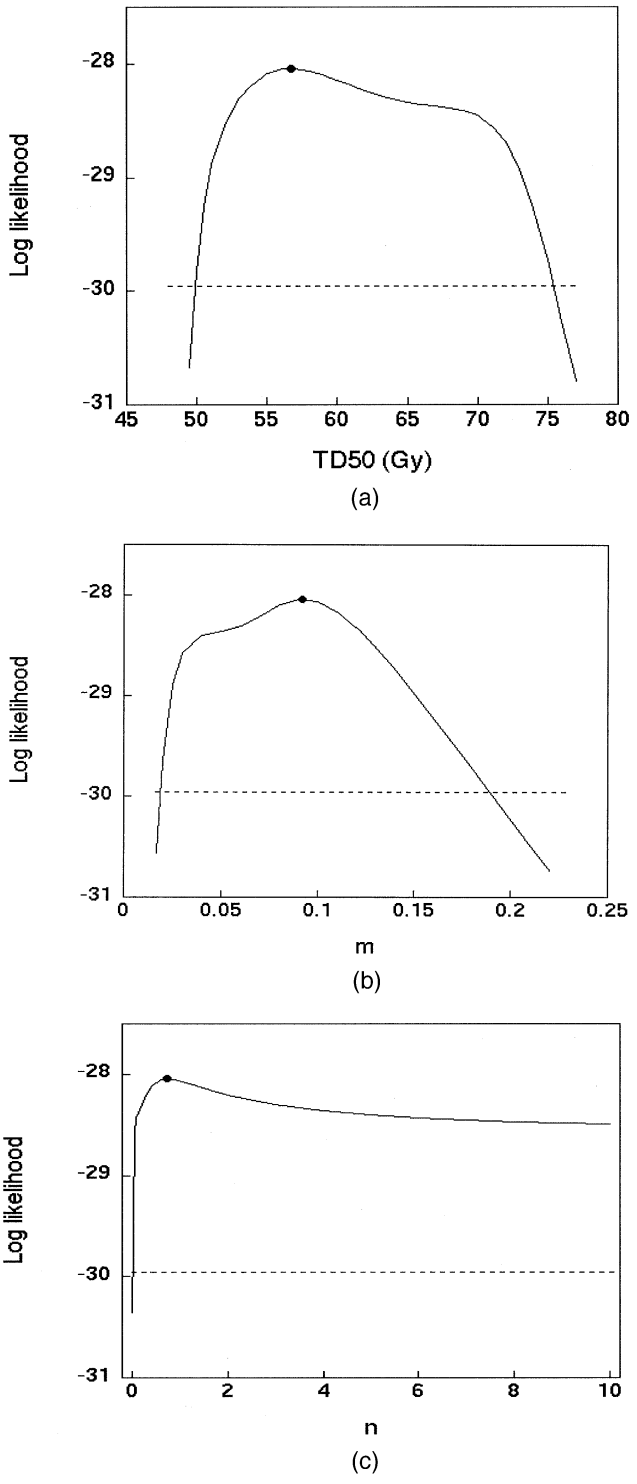

Fig. 2. Likelihood profiles of (a) $TD_{50}(1)$, (b) m, and (c) n for parameters of LKB model fitted to nonhemorrhoid patients alone. Dashed line represents log-likelihood values smaller than maximal likelihood by a value equal to Eq (1/2) $\chi^2_1(5\%) \approx 1.92$. Profile-likelihood CIs were derived from points at which likelihood profiles intersected dashed lines. Profile likelihood of n never returned below dashed line and was plotted out to $n = 10$ to illustrate its plateau.

rectum, the complication rate could be lowered to 16% when ≤25% of the rectum received ≥ 70 Gy. The Grade 2 or worse long-term rectal toxicity rate increased to 46%

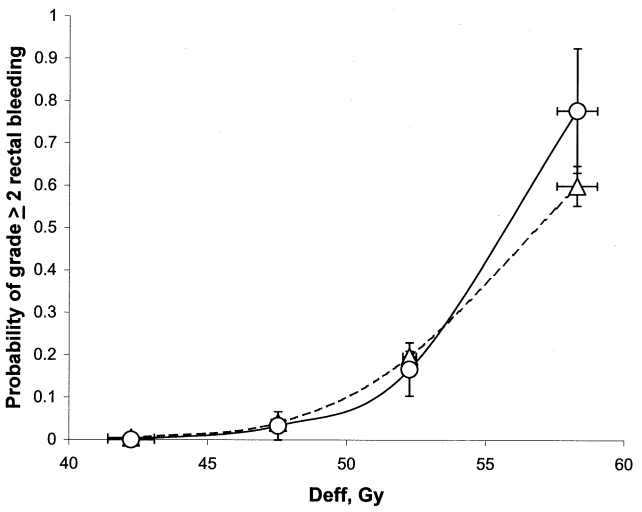

Fig. 3. Observed vs. fitted incidence of Grade 2 or worse rectal bleeding after RT. Cohort of 84 patients without hemorrhoids was used for this fit. Open circles and triangles represent, respectively, observed and predicted rates of rectal bleeding. D_{eff} = effective dose calculated from DVH reduction scheme. Error bars indicate standard errors.

when >25% of the rectum received ≥70 Gy. We have reported that radiation dose, irradiated volume, and a history of hemorrhoids were important predictive factors for radiation-induced rectal toxicity (11). Here, we estimated the parameters of the best-fitting LKB NTCP model (12, 13).

NTCP model of late rectal bleeding

In the era of 3D CRT, severe rectal toxicities are rare. To have enough events for model fitting, we used Grade 2 or worse rectal bleeding as the end point. This is consistent with other reports (14, 20). In our cohort, 29 of the 33 patients experiencing Grade 2 or worse rectal bleeding did so by 2 years after RT. In particular, the rectal bleeding rate appears to plateau after 2 years for nonhemorrhoid patients (Fig. 1). Hence, we selected Grade 2 or worse rectal bleeding by 2 years as an end point for our NTCP modeling. This differs from the end points such as rectal stenosis and rectal necrosis that are caused by more severe rectal tissue damage. Thus, our estimates of the n and TD_{50} parameters are different from the estimates based on the types of rectal complications resulting from conventional RT (21). In particular, Burman *et al.* (21) reported that there was little or no volume effect in severe radiation-induced rectal injury. Our current study (Table 1, Fig. 2) and other recent studies (9, 10, 22) have found more pronounced volume effects. Using the fitted parameters, we found close correspondence between the predicted and observed rates or rectal bleeding (Fig. 3). Furthermore, the fitted LKB model has a high discriminatory power to distinguish between those with and without bleeding as measured by the area under the receiver operating characteristic curve (Fig. 4).

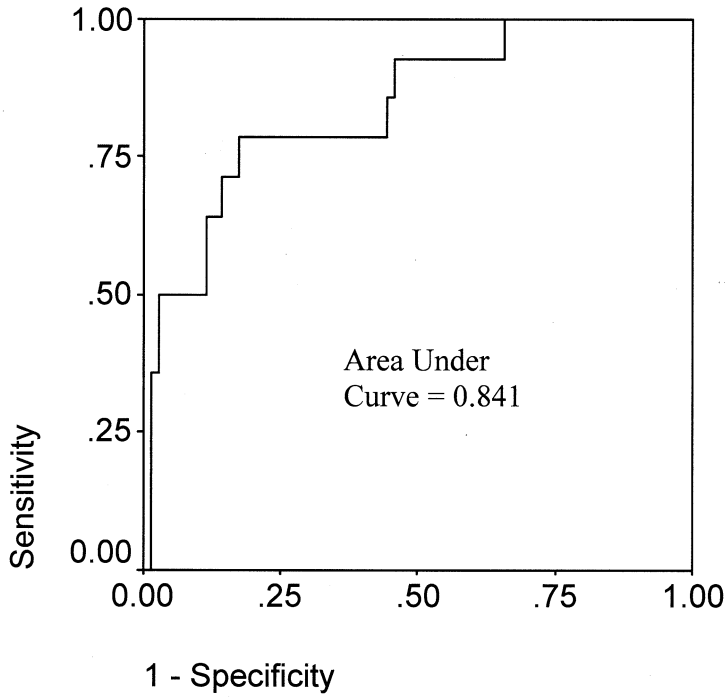

Fig. 4. Receiver operating characteristic curve of Normal Tissue Complication Probability (NTCP) model fitted to 84 nonhemorrhoid patients.

Limitations of LKB model

To account for the inhomogeneous nature of the rectal irradiation, the LKB model assumes that volume effect can be approximated by a power law (13). This requirement of DVH reduction is largely based on the desire for a relatively simple model. Its validity remains to be verified clinically in RT of prostate cancer. On the basis of our analysis of the entire group of patients, we found that TD_{50} and m could be accurately estimated. However, the volume effect n had a large confidence interval (Table 1). We reanalyzed our data using only the subset of patients without hemorrhoids and found that the CI of n continued to be large. Figure 2c shows that the upper limit of the CI for n is ∞ because the profile likelihood appears to reach a plateau. Hence, the likelihood profile of n never dropped to the level of the dashed line on the upper end. Therefore, the volume effect n may be considerably larger than the optimal value of 0.746. However, it is clinically unrealistic that the rectum will have an infinitely large volume effect. More likely, this suggests that the LKB model failed in ascertaining the upper bound of n based on our data set. Thus, the LKB model should be used with caution in fitting the data set with a potentially large-volume effect for n.

Iso-NTCP dose escalation

There is a keen interest in using NTCP models such as this one in guiding dose escalation in RT for prostate cancer. Tumor control probability analysis has indicated that doses 85 Gy may be needed to treat high-risk patients (23). Doses 85 Gy have been shown to be feasible with intensity-modulated RT (24) with acceptable rectal toxicity. The use of NTCP models to guide RT in other sites such as the lung (25, 26) and liver (27) has also been proposed. In this study, we evaluated the utility and limitation of the LKB model in this regard. Figure 5 illustrates that when the volume of the irradiated rectum decreases, the predicted tolerance radiation dose increases. According to the LKB model, the rectal radiation tolerance increases dramatically according to the power law (Eq. 2). For example, assuming that the 15% late rectal bleeding rate is the tolerated rectal toxicity level, then by reducing the fraction of rectal irradiation from 75% to 50%, the putative uniform dose may be escalated from 65 to 85 Gy. This predicted shift in rectal tolerance appears to be exceedingly large. We suggest that the LKB model should be used with caution clinically.

Furthermore, the LKB model assumes a uniform irradiation dose to a fraction of rectum. This implies that the rest of the rectum completely is unirradiated. In practice, most of the rectum will receive some dose in RT for prostate cancer. Hence, there is no direct way to translate the prediction into routine clinical practice. Some may argue that simple cutpoints on DVHs may be more practical and clinically useful. For example, we have suggested that to maintain rectal toxicity at $<$16%, $\leq$25% of the rectum should receive $\geq$70 Gy (11).

Challenges of rectal NTCP modeling and opportunities for improvement

NTCP modeling is inherently difficult (28). Uncertainties in the position of the prostate and rectum exist (29, 30). This study did not take into account the effect of rectal motion on NTCP modeling. Intuitively, one may reasonably hypothesize

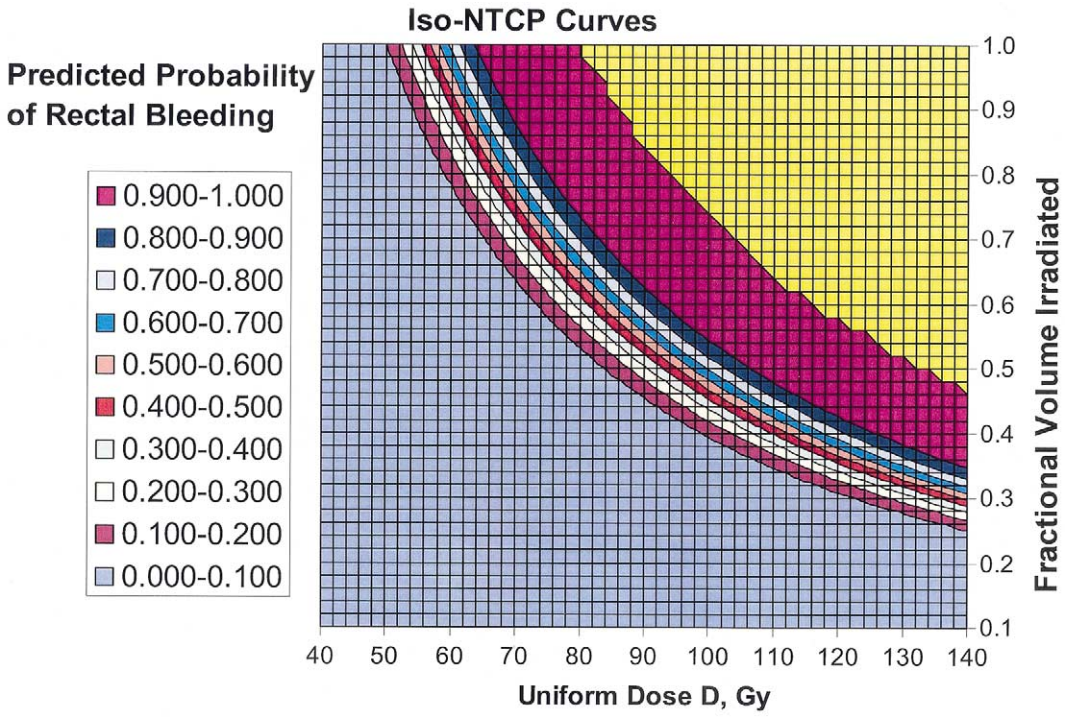

Fig. 5. Normal Tissue Complication Probability (NTCP) models of post-RT Grade 2 or worse rectal bleeding with partial rectal irradiation under uniform irradiation dose *D*. Parameters: $n = 0.746$, $m = 0.092$, and $TD_{50}(1) = 56.7$ Gy. Dotted line indicates 15% rectal bleeding rate.

that the daily variations of rectal position may have some impact on rectal NTCP modeling. However, some authors have suggested that patient-specific uncertainties in setup and organ movement had only minor effects on dose–volume response modeling. Only the systematic setup error might have the greatest impact on dose response modeling (31, 32). In the case of the prostate, we have used a daily ultrasound localization technique to measure the systematic positional variations for 147 consecutive prostate patient treatments. We found that the the standard deviation for systematic shifts was 3.4 mm, 3.2 mm, and 1.9 mm in the AP, superoinferior, and lateral directions, respectively (33). Because the rectal position is intimately related to that of the prostate, it is conceivable that the rectum may also have similar systematic shifts. Furthermore, the potential impact of rectal shape variation has also been described (34). Unfortunately, current clinical practice does not capture this daily rectal volumetric information during a patient's routine treatment. To evaluate fully the impact of organ motion, we have an active protocol that will use an in-room CT scanner (35) to measure the volumetric variations of the rectum and prostate for 30 patients, who each will undergo three CT scans weekly in an 8-week period immediately before each treatment. These future studies will provide more information related to rectal motion.

Uncertainties also exist in the biologic models used to model NTCP. Models have been proposed to include the existence of a threshold dose for injury (36), a susceptible subvolume (37), a parallel architecture (38), and distinct functional units (39). We are currently investigating alternative models that may further improve rectal NTCP modeling; the results will be reported separately.

CONCLUSION

For this analysis, we used the widely used LKB model (12). We have found that the predictive power of the fitted NTCP is high and in excess of 0.8. This is quite encouraging as a first approximation given the various biologic and technical uncertainties involved in the targeting and modeling. The remainder of the improvement may come from more precisely ascertaining the true prostate position during treatment and refinement in the modeling schemes. Because of the various limitations we discussed concerning the LKB model, clinical use of the LKB remains unwarranted at this time.

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