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Investigation of bladder dose and volume factors influencing late urinary toxicity after external beam radiotherapy for prostate cancer

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Abstract

Background—We sought to identify the bladder dose-volume factors associated with an increased risk of late urinary toxicity among prostate cancer patients treated with radiotherapy.

Materials and methods—This retrospective analysis included data from 128 prostate cancer patients treated on protocol with 2Gy/fraction to 46Gy followed by a boost to 78Gy. The end-point for this analysis was grade 1 or greater late genitourinary (GU) toxicity occurring within 2 years of treatment. The Lyman-Kutcher-Burman, mean dose, threshold dose, and hottest volume models were fitted to the toxicity data using the maximum likelihood method.

Results—Model fits based on dose volume histograms tended to fit the toxicity data better than models based on dose wall histograms. The hottest volume (hot-spot) model was found to be the best-fitting model investigated. The best fit was for the hottest 2.9% of bladder (95% C.I. 1.1% to 6.8%). This model has an area under the receiver operating characteristic curve of 0.74. The hot-spot model separated the patients into clinically meaningful subgroups with about 25% of the patients who received < 78Gy to the hottest 2.9% of bladder experienced GU toxicity at 8 years compared to about 50% when the dose was ≥ 78Gy ($p = 0.002$).

Conclusion—This provides the first evidence supporting that bladder “hot-spots” are related to GU toxicity within 2 years after external beam radiotherapy for prostate cancer. Confirming data are needed from other investigators. Particular attention should be given to hot spots higher than 78Gy in bladder in radiation treatment planning.

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There is no conflict of interest.

Keywords

Prostate cancer; radiotherapy; GU toxicity; NTCP

Introduction

Improved computer-aided visualization of the prostate and the surrounding normal tissues has allowed more conformal 3-dimensional radiotherapy (3D-CRT) and safe dose escalation. This increase in dose to the prostate has improved the biochemical outcome of prostate cancer [1] [2] [3]. Before the use of 3D-CRT, the prostate RT dose limit was thought to be 70Gy. The toxicity rates doubled when significantly higher doses were used to treat prostate cancer using conventional radiotherapy techniques [4]. In particular, late rectal toxicity associated with high dose external beam prostate cancer radiotherapy has been the subject of intense investigation in the past decade [5]. With careful attention to the dose volume histogram (DVH) constraints, late rectal toxicity has been maintained at an acceptable level even when prostate dose increased to 78Gy [6] [7]. The data on DVH constraints applicable to genitourinary (GU) toxicity are however less well understood and much more research is needed. Furthermore, the paucity of data also makes projecting late GU toxicity difficult when dose is further escalated beyond 78Gy.

This study examined features of the dose-volume histogram of the urinary bladder and bladder wall as related to the incidence of late GU toxicity among prostate cancer patients treated with 78Gy external beam radiotherapy. We compared several normal tissue complication probability (NTCP) models and identified the best fitting of these models. Our analysis suggests possible DVH constraints to better control late urinary toxicity after high-dose prostate cancer radiotherapy.

Materials and Methods

Patient cohort

The patients included in the present analysis comprised a subset of the patients enrolled on our institutional review board approved protocol (MDACC #93-001) which has been described previously [1]. We have also published the results of NTCP modeling using rectal toxicity data from the same patient cohort [7] [8] [9]. Briefly, all patients received definitive 3-dimensional conformal radiotherapy for prostate cancer at the University of Texas M.D. Anderson Cancer Center between 1992 and 1999. There were 128 patients for whom dose volume histogram (DVH) data were recovered. Minimum follow up for these patients was two years. The binary end-point for the present NTCP analysis was whether a grade ≥ 1 (i.e. any) late GU toxicity occurred within two years after the end of RT (yes or no). In this study, late complications were defined as those developing $\geq$3 months after RT completion. All late GU complications were graded per protocol using a modified scale and criteria from the Radiation Therapy Oncology Group [10], Late Effects Normal Tissue Task Force [11], and Fox Chase Cancer Center [12]. The details concerning grading of late GU toxicity are shown in Table 1. Follow-up clinical history and examinations were performed after the completion of RT at 3-6 month intervals during the first 2 years, every 6 months for 3 years, and annually thereafter.

RT techniques

The details of RT have been described previously [7,13]. Patients underwent simulation and treatment in the supine position with a full bladder. Immobilization devices were used and varied by year of treatment. CT image data sets for planning were acquired for 3D-CRT using a 5-mm slice thickness (Model 9800, General Electric Medical Systems, Milwaukee, WI).

Daily patient positioning was performed using skin marks and weekly portal films. The patients were initially treated to 46Gy at 2Gy/fraction to the isocenter using 18-MV photons and a conventional four-field box technique. A six-field 3D-CRT approach was used to boost the total isocenter dose to 78Gy at 2Gy/fraction. The clinical target volume (CTV) was defined as the prostate and seminal vesicles. For a limited number of patients, a portion of the seminal vesicles was excluded from the CTV to decrease the dose to the rectum. The block edge was placed 1.25–1.5 cm around the CTV in the anterior and inferior directions and 0.75–1.0 cm in the posterior and superior directions. This technique typically allowed the 95% isodose line for the 3D-CRT boost to cover the CTV.

Dose volume information

The original contours of the prostate and the surrounding normal tissues were restored from the institutional archives. Treatment plans were originally designed using an in-house 3D treatment planning system and archived using RTOG format (including full dose matrix and contoured structure sets). We have developed a conversion program that converts the RTOG file into a Pinnacle3 treatment plan (without re-computing dose). This has been verified using phantom and patient plans (compared the DVHs calculated for both treatment planning systems). The agreement was excellent. All dose-volume, dose-wall histograms were calculated using the Pinnacle3 treatment planning system (Philips Medical Systems, Bothell, WA) with the same converted dose distributions. A 5-mm thick bladder wall was assumed, with the inner contour generated automatically from the outer contour, and pseudo dose wall histograms (DWHs) were also computed. The dose bins for each DVH and DWH were 0.1Gy in size.

NCTP modeling

All data analyses were performed using Stata (StataCorp. 2005. Stata Statistical Software: Release 9. College Station, TX: Stata Corp LP). Four different dose-volume-response models were fitted to the grade ≥ 1 late GU toxicity within 2 years of treatment using the dose-volume information from either the DVH or the DWH. These widely used models have been described in detail elsewhere [8] [9]. Briefly, each model was based on a summary measure μ extracted from the DVH or DWH, which was then converted to a complication probability using a probit equation:

$$\mathrm{NTCP}(\mu) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{s(\mu-\mu_{50})} \exp\left(-u^2/2\right) du \quad (1)$$

Each of the models includes at least two unknown parameters, μ_{50} (determining the position of curve) and s (determining the slope of the curve, and often written in the form $s = (m \cdot \mu_{50})^{-1}$, as well as any other parameters used to define the summary measure μ . The models considered here correspond to the following summary measures of the DVH or DWH:

Lyman model

For the Lyman model [14] combined with the Kutcher-Burman DVH-reduction scheme [15], μ is equal to the effective dose, defined by [16]

$$D_{eff} = \left(\sum_i v_i \cdot D_i^{1/n}\right)^n \quad (2)$$

where v_i is the volume of the dose bin corresponding to dose D_i in the differential DVH or DWH. In addition to the parameters s and $\mu_{50} = D_{50}$, this model has a third parameter, n.

Mean dose model

For the mean dose model, the quantity μ is the mean dose (*MD*) to the organ:

$$MD = \sum_i v_i \cdot D_i \quad (3)$$

This model includes only the two probit parameters s and $\mu_{50} = MD_{50}$ and is a special case of the Lyman model corresponding to $n = 1$.

Threshold dose model

For the threshold dose model, μ represents the fractional volume VD_c of organ receiving a dose greater than or equal to a "threshold" dose D_c:

$$VD_c = \sum_{i \ni (D_i \geq D_c)} v_i \quad (4)$$

where the sum is over i such that $D_i \geq D_c$. This model has three parameters: the optimal dose, D_c , as well as the two probit parameters s and $\mu_{50} = VD_c(50)$. Both relative and absolute volumes of bladder and bladder wall were considered.

Hottest volume (hot-spot) model

By switching the roles of dose and volume in the threshold dose model, a similar model can be obtained. Instead of a threshold dose D_c as defined in the previous model, a threshold "hottest" volume, V_c, is specified, and we consider the minimum dose, DV_c, to the hottest volume of bladder of size V_c. Fitting the values of DV_c to the GU toxicity data using the probit link, a model with three parameters is again obtained: the optimal threshold volume, V_c, the value of DV_c corresponding to 50% complication probability, denoted $DV_c(50)$, and either s *or* m. Again, both the normalized relative volume and the absolute volume were considered.

All models were fitted to the data using maximum likelihood analysis. Confidence intervals for the model parameter estimates were obtained using the profile-likelihood method. Model comparisons were performed using bootstrap analysis, as described elsewhere [17] using 1000 bootstrap iterations unless otherwise stated. Curves showing freedom from toxicity as a function of time after radiotherapy were generated using the method of Kaplan and Meier. The area under the receiver operating characteristic (ROC) curve was computed for this best fitting model [18].

Late GU toxicity

Fig. 1 shows freedom from late GU toxicity among the 128 patients, respectively. All patients had follow up longer than 2 years and this time point was used for NTCP modeling. Fig. 1 illustrates that the majority of events within 2 years were grade 1. There were 19 patients who had grade ≥ 1 GU toxicity within 2 years of RT. Fig. 2 shows the average a) cumulative DVHs (cDVHs) and b) differential DVHs (dDVHs) for the patients with and without grade ≥ 1 GU toxicity within 2 years. The dose volume curve for patients with late GU toxicity is higher than that of the patients without side effects during this time period (Fig. 2a). Furthermore, the patients with late GU events within 2 years seem to have a stronger 'spike' at about 78Gy on their dDVHs (Fig. 2b).

DVH vs. DWH

The median bladder volume among the 128 patients with DVH data available was 244.5 cc (range 52.5 to 999.6 cc). The median volume of bladder wall was 42.2 cc (range (21.1 to 69.8 cc). The volumes of bladder and bladder wall were highly correlated ($r = 0.988$, $p < 0.0001$). The mean dose to whole bladder had a median value of 44.4Gy (range 19.1 to 71.3Gy). The mean dose to bladder wall had a median value of 44.9Gy (range 21.1 to 68.8Gy). The mean doses to the two structures were highly correlated ($r = 0.994$, $p < 0.0001$).

NTCP modeling and bootstrap analysis

Table 2 lists the parameter estimates from the Lyman-Kutcher-Burman (LKB) model fitted to the grade ≥ 1 2-year GU toxicity data using the DVH data from whole bladder, regarded as a solid organ. Note that the parameter n is very close to zero, indicating that the maximum dose to bladder is important in determining toxicity. Fig. 3 shows the fit of LKB model to the GU toxicity data. Consistent with the estimate n≈0, the LKB model fits the data significantly better than the mean dose model, which corresponds to n=1 in the LKB model (P = 0.002, likelihood ratio test). In fact, the mean dose to bladder was not significantly associated with the incidence of grade ≥ 1 GU toxicity within 2 years in this patient cohort (p = 0.122, probit model).

Because the Lyman model points to the importance of the maximal dose, we examined the "hottest volume" model. The best fit was for the hottest 2.9% of bladder (95% C.I. 1.1% to 6.8%). Fig. 4 shows the fit of the hottest volume (hot-spot) model to the bladder toxicity data using the threshold volume of 2.9% of bladder.

A fit of the frequently used threshold-dose model identified 79Gy as the optimal dose threshold (95% CI 65.9Gy to 79.6Gy). Although the fit of this model also highlights the role of high doses in increasing the risk of grade ≥ 1 GU toxicity within 2 years, bootstrap analysis indicates that this model does not fit the data as well as the hottest volume model (P = 0.033). The hottest volume model was also compared to the LKB model using bootstrap analysis. Because of the computation time required to fit the Lyman model, the bootstrap was performed with only 200 replicates, of which 52 attempted fits failed to converge numerically to a set of LKB parameter estimates. The results from the 148 cases in which convergence was achieved suggest that the hottest volume model tends to fit the toxicity data better than the LKB model, though not significantly so (P = 0.088).

The threshold dose and hottest volume models were also fitted to the 2-year GU toxicity data using absolute bladder volumes in lieu of normalized relative volumes. The optimal threshold dose was 77.6 Gy (95% CI 63.8 Gy to 79.5 Gy) and the optimal absolute hottest volume was 5.3cc (95% CI <0.1cc to 15.3cc). There was trend for the relative hottest volume model to fit the data better than the absolute hottest volume model (P = 0.075, bootstrap analysis), but there was no consistent difference in the fits of the relative and absolute threshold dose models (P = 0.581, bootstrap analysis).

Each of the models was also fitted using the pseudo bladder-wall DWH data, and the corresponding fits were compared to one another using bootstrap analysis. The hottest relative volume model with a threshold volume of 2.9% of solid bladder fitted the toxicity data significantly better than the relative hottest wall-volume model with an optimal threshold of 2.7% of bladder wall. Similarly, the hottest absolute volume model with a threshold volume of 5.3cc of solid bladder fitted the toxicity data significantly better than the absolute hottest wall-volume model with an optimal threshold of 1cc of bladder wall (P = 0.018, bootstrap analysis). However, there were no significant differences between the relative or absolute threshold dose models and their counterparts for bladder wall, which had optimal threshold doses of 77.8 Gy in each case (P = 0.437 and P = 0.220, respectively).

Hot-spot model

Fig. 5 shows the ROC curve for this model. In particular, no patient experienced bladder symptoms unless the dose to the hottest 2.9% of bladder was 77.3 Gy or higher. More than half of the toxicities (11/19) occurred in patients receiving ≥ 78 Gy to 2.9% or more of bladder. Fig. 6 shows the time to grade ≥ 1 late GU events according to the dose to the hottest 2.9% of bladder: < 78Gy vs. ≥ 78Gy (p = 0.002).

Discussion

The development of 3D-CRT has allowed recent dose escalation for the treatment of prostate cancer [19]. This increase in dose to the prostate has improved the biochemical outcome of prostate cancer [1,20]. However, there is concern that dose escalation may also increase the normal tissue toxicity [21]. In contemporary series, late GU toxicity appears to be acceptable when prostate cancer is treated beyond 70Gy within the initial follow up time frame [22] [23] [24]. However, the rate of late urinary toxicity increases continuously with time to become a major side effect in longer term studies [25] [26] [27]. The radiation dose distribution to rectum has been shown to be highly correlated with late rectal toxicity [5] [7] [8] [9] [28]. The dose-volume response of the urinary bladder is much less well understood and is the subject of our study.

2-year hot-spot NTCP model and long-term GU toxicity

To ensure there were enough events for NTCP modeling, we included late GU toxicity events of any grades and types occurring within the first 2 years. We found that the mean doses to bladder and bladder wall were highly correlated, with correlation coefficient close to 1, and the shapes of the DVHs and DWHs were very similar. However, the DVH data fitted the toxicity data better than the DWH data – in some cases significantly so. Hence, we suggest that the whole-bladder DVH may be simpler and better to use in clinical treatment planning than the bladder-wall DWH.

We found a dose-volume response of the urinary bladder (Fig. 2a), and our analysis of the differential DVH (dDVH) suggested that there was a stronger dose “spike” (Fig. 2b) at about 78Gy for patients with late GU events. Our NTCP modeling identified the LKB model (Fig. 3) as the better model when compared with the mean dose model. Our fitted LKB parameters were quite different from what was previously thought, based on consensus: $n = 0.5$, $m = 0.11$, $TD50 = 80$Gy [29,30]. Our study revealed that volume factor n was close to zero (Table 2) suggested that maximal doses, quantified as the hot spots, might be important determinants of late GU toxicity.

From the hottest-volume NTCP modeling, we identified 2.9% of bladder volume as the optimal cut-point (95% C.I. 1.1% to 6.8%) (Fig. 4) and, using absolute volume, the dose to the hottest 5.3 cc of bladder (95% CI <0.1cc to 15.3cc) as significant determinants of late 2-year GU toxicity associated with high-dose prostate cancer radiotherapy. According to the fitted hot-spot model, the late (≥ 3months) GU toxicity is projected to be about 20% at 78Gy and increase steeply beyond that (Fig. 4). This model has an ROC area of about 0.74 (Fig. 5) suggesting that while this model is quite accurate other factors may also be important for late GU toxicity. Firstly, the bladder dose volume information was obtained from a single planning CT. However, we have observed that the daily filling of the bladder may not be uniform and this may affect the actual radiation dose and volume of the bladder [31]. Our future dose-volume response studies will incorporate these day-to-day variability data of the bladder volume. Secondly, the urethra dose that has been suggested to be important in brachytherapy related late GU toxicity [32] [33] was not considered in this study since the urethra could not be accurately contoured from our planning CT. Despite these factors, the “hot-spot” model remained quite accurate. Furthermore, our 2-year hot-spot model separated the patients into clinically meaningful groups. There was about 25% risk of grade 1 or above late urinary toxicity for patients received < 78Gy to the hottest 2.9% of bladder, for the others, there is about 50% risk of late GU toxicity (Fig. 6).

Future work

We analyzed late urinary toxicity data from 128 patients treated with external beam radiotherapy for prostate cancer to 78Gy on a randomized trial [1]. Similar to some other studies [22,34], the rate of late GU toxicity for these patients continued to increase with time for at least 8 years (Fig. 1). The rates of late rectal toxicity [7] and radiation induced erectile dysfunction [35] usually plateau after two years post RT, Therefore, data with 2-year follow-up is generally considered adequate for analysis of these endpoints. In the case of late GU toxicity, the choice of time point is not as clear as the cumulative incidence of late GU toxicity does not seem to level out [25] [26] [27]. Our data here suggest an initial wave of mostly grade 1 toxicities occurring within the first 2 years (Fig. 1 and Fig. 6), which may be distinct from the GU toxicity occurring later, appear to be adequate for NTCP modeling. Thus the curve separation occurs in Fig. 6 is mainly due to events occurring already by 2 years. Additional work is needed and are ongoing to model GU toxicity occurring later than 2 years that is consisted of relatively more grade 2 or above events. This will require a novel method of analysis allowing for censored time-to-toxicity data.

Conclusion

We here report the first evidence that supports the ‘hottest volume” model as potentially the best fitting model for predicting GU toxicity after external beam radiotherapy for prostate cancer. Confirming data are needed from other investigators. Particular attention should be given to hot spots higher than 78Gy in bladder in radiation treatment planning.

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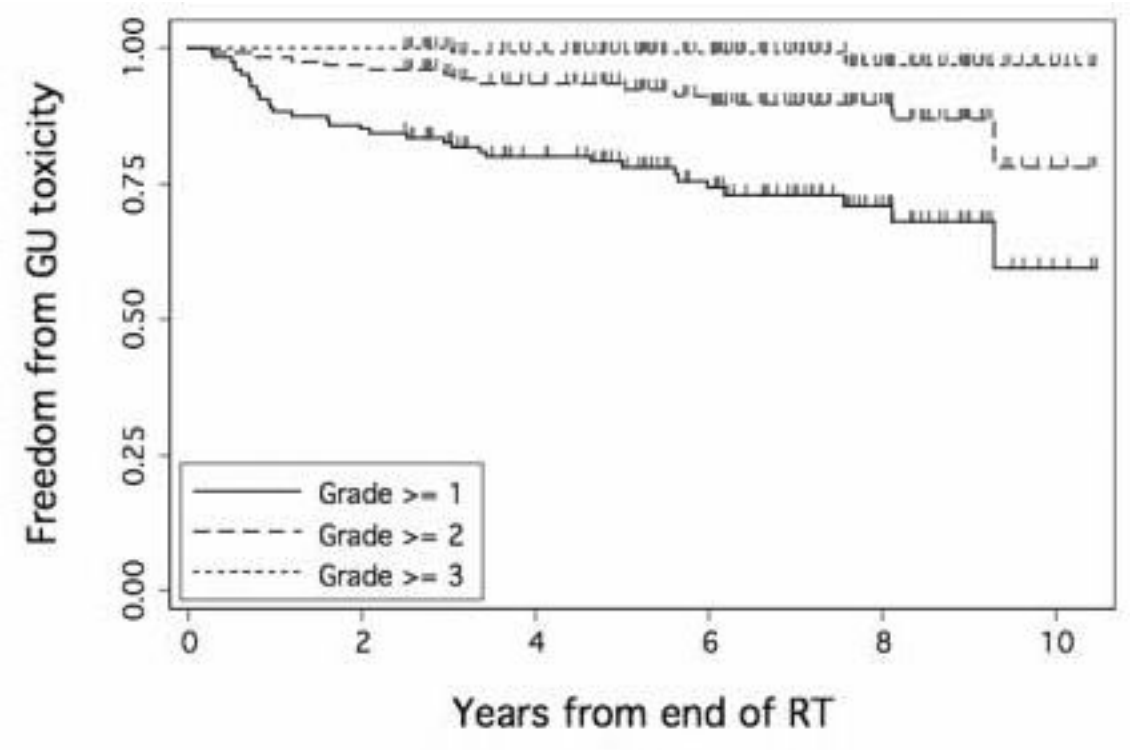

Fig. 1.
Proportion of the 128 patients free from grade ≥ 1, grade ≥ 2, or grade ≥ 3 late GU toxicity after 78Gy external beam radiotherapy for prostate cancer.

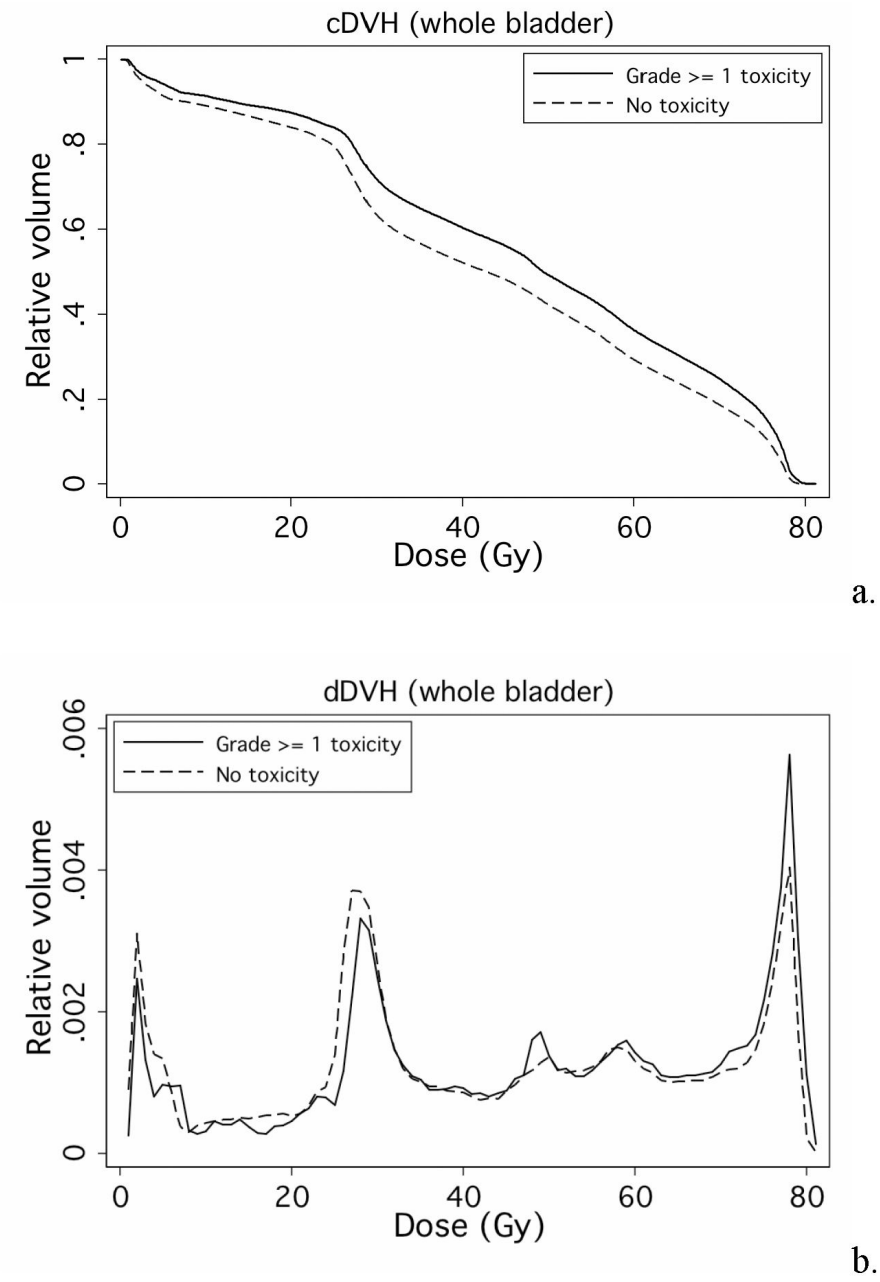

Fig. 2.

Average a) cDVHs and b) dDVHs for the patients with (solid line) and without (dotted line) grade ≥ 1 GU toxicity within 2 years.

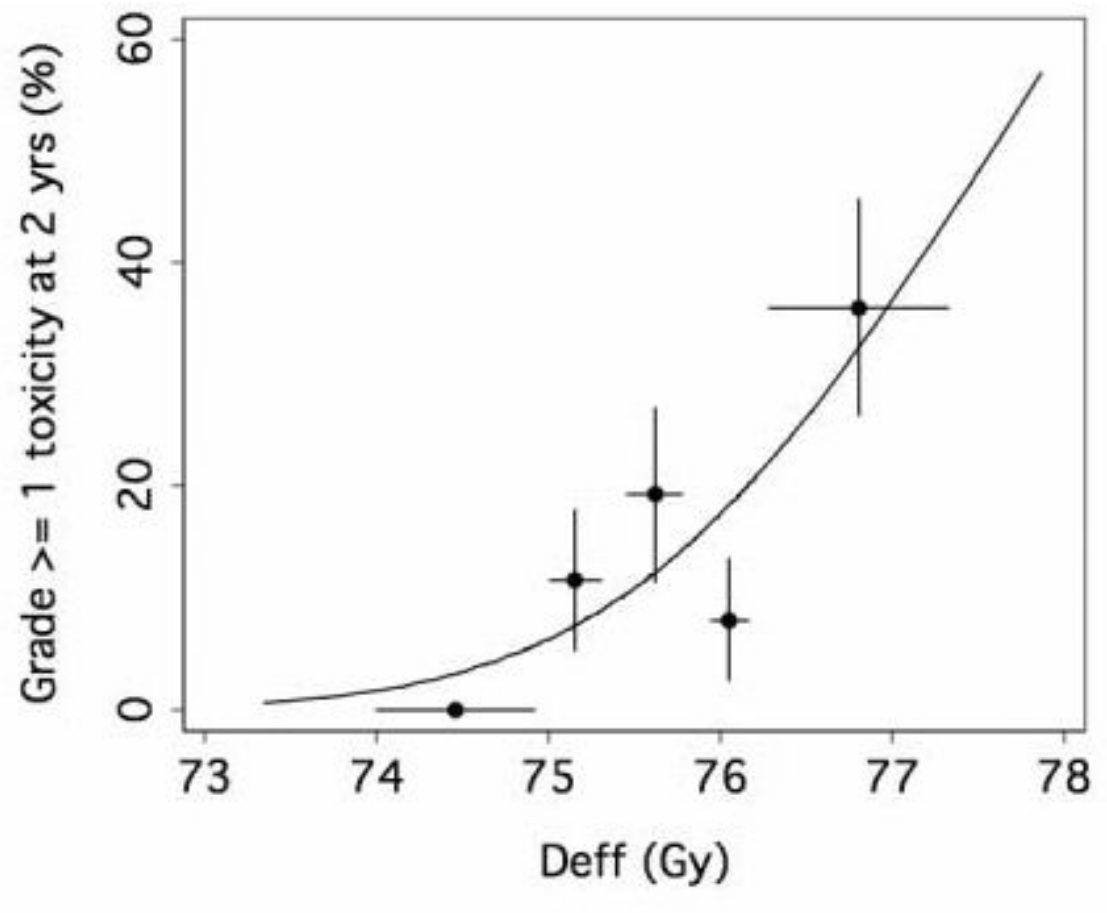

Fig. 3.

The points represent the incidence of toxicity in each of 5 equal subgroups of patients (25-26 patients each), plotted at the mean value of effective dose D_{eff} (Eq. 2) in the subgroup. The horizontal error bars represent ± 1 standard deviation of the mean D_{eff} in each group, and the vertical error bars represent ± 1 standard deviation calculated from the observed incidence of complications, assuming binomial statistics.

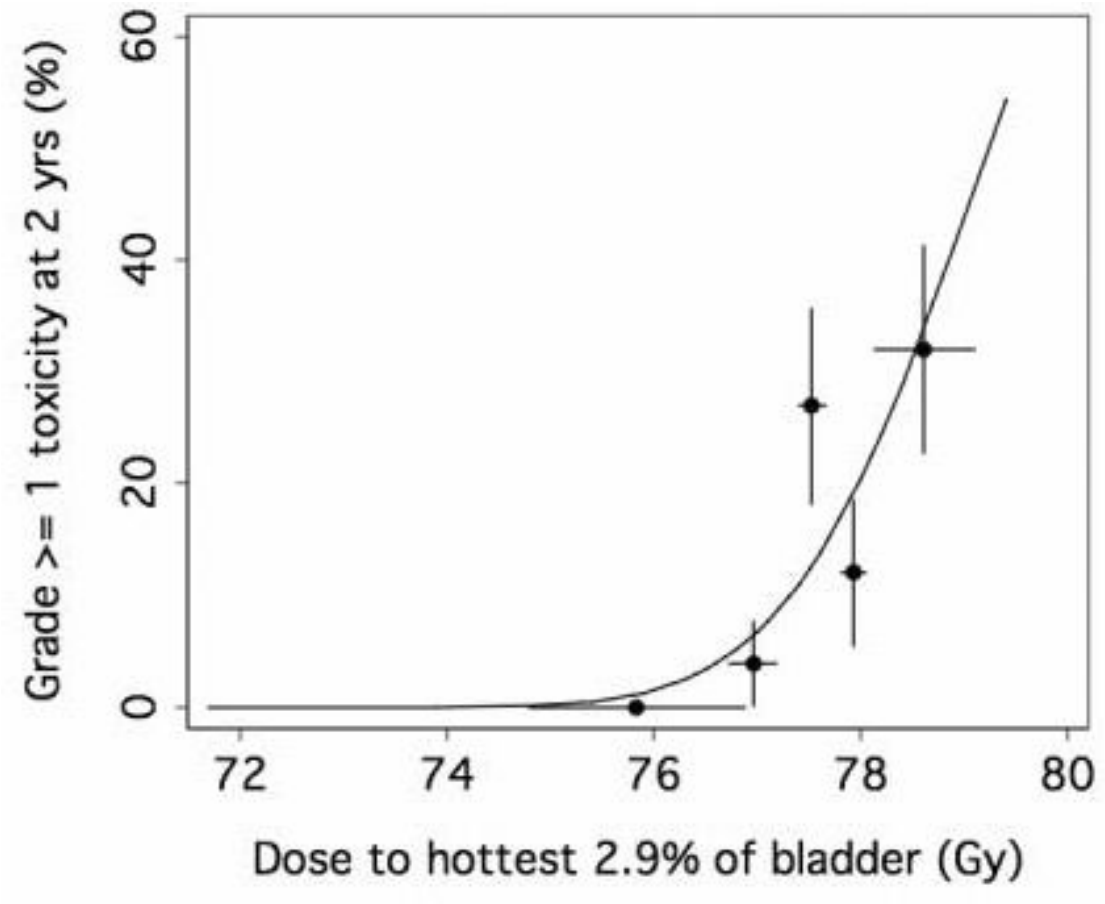

Fig. 4.

Fit of absolute hottest volume (hot-spot) models to the late GU toxicity data. The points represent the incidence of toxicity in each of 5 equal subgroups of patients (25-26 patients each), plotted at the mean value of dose to hottest 2.9% volume in the subgroup. The horizontal error bars represent ± 1 standard deviation of the mean in each group, and the vertical error bars represent ± 1 standard deviation calculated from the observed incidence of complications, assuming binomial statistics.

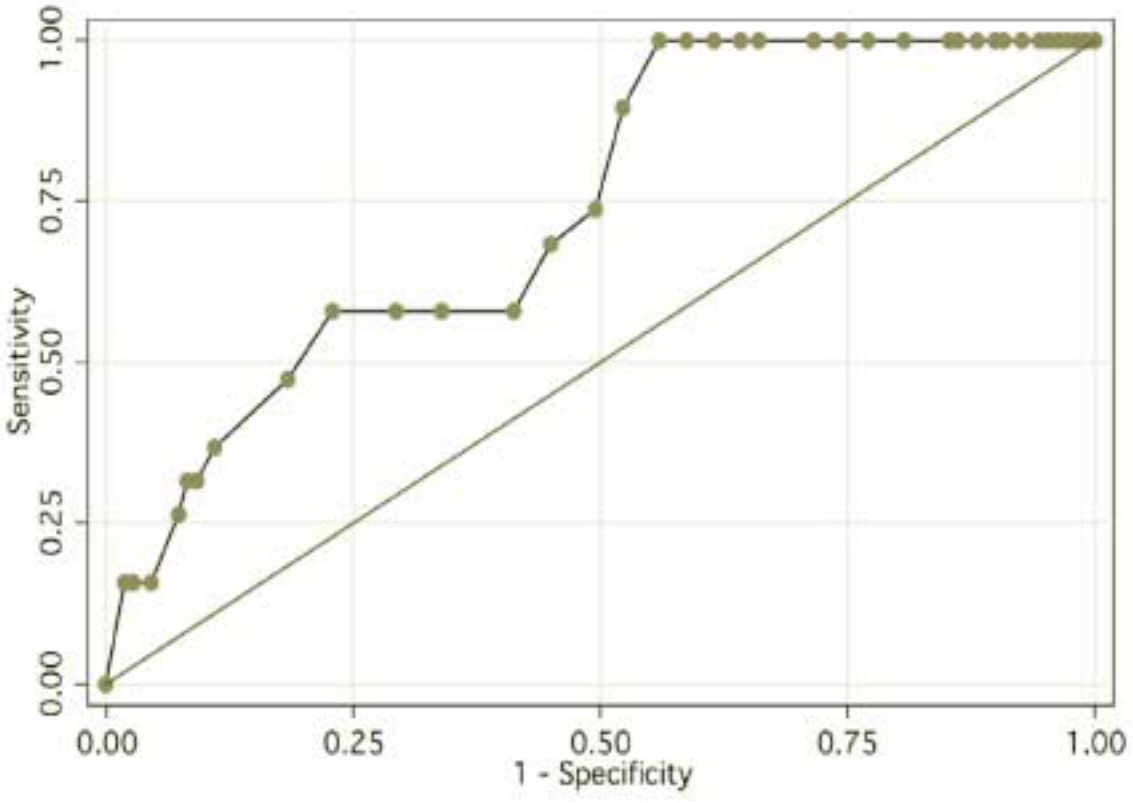

Fig. 5.
ROC curve for the best-fitting "hot-spot" late GU NTCP model.

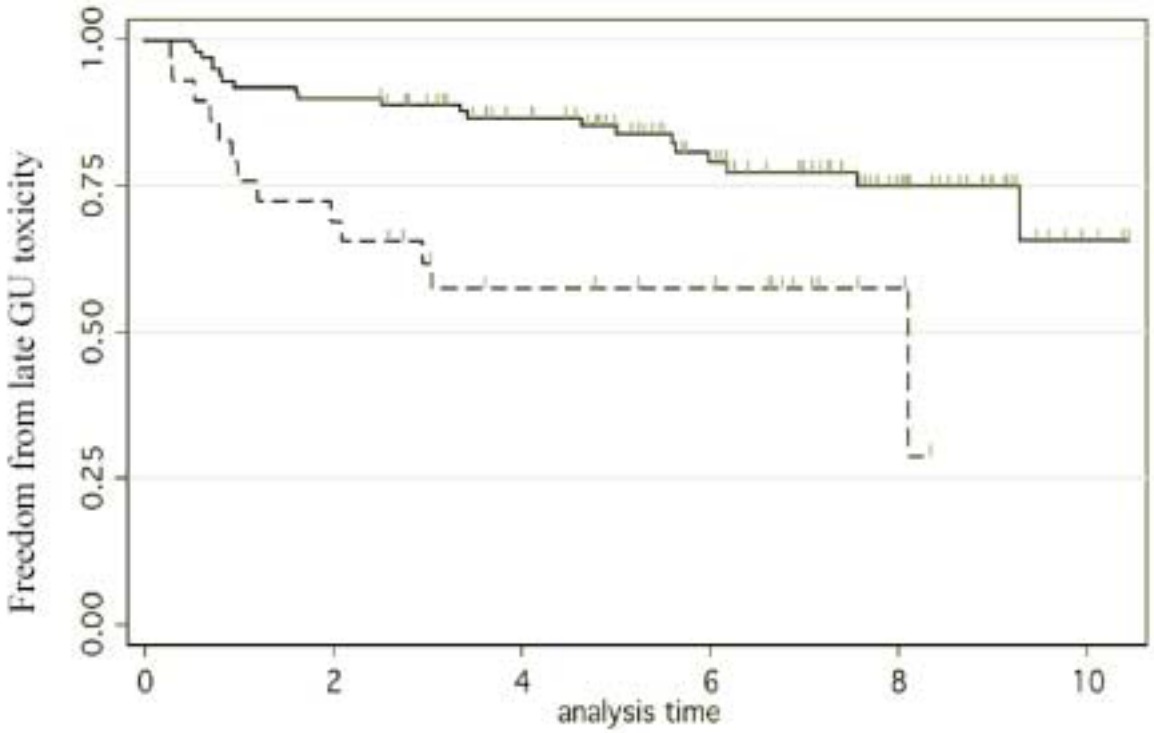

Fig. 6.

Freedom from grade ≥ 1 late GU toxicity after prostate cancer radiotherapy. The two groups are respectively the patients who received < 78Gy to the hottest 2.9% of their bladders (solid line) versus those who received ≥ 78 Gy to the hottest 2.9% of their bladders (dotted line) ($p = 0.002$).

Table 1

The grading system used for late genitourinary radiation side effects.

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nocturia twice baseline. Microscopic hematuria. Light mucosal atrophy and minor telangiectasia.	Moderate frequency. Nocturia more than twice baseline. Generalized telangiectasia. Intermittent macroscopic hematuria. Two or fewer blood transfusions. Two or fewer coagulations. Regular non-narcotic or occasional narcotic for pain.	Severe frequency and dysuria. Nocturia more frequent than once every hour. Reduction in bladder capacity (150 cc). Frequent hematuria. More than two transfusions. More than one coagulation for hematuria. Regular narcotic for pain.	Severe hemorrhagic cystitis. Ulceration. Requirement for urinary diversion and/or cystectomy.	Fatal toxicity

Table 2

Parameter estimates of the Lyman-Kutcher-Burman model fitted to the late GU toxicity data (Grade ≥ 1 toxicity within 2 years), with 95% profile-likelihood confidence intervals shown in parentheses.

n = 0.00995 (0, 0.059)
m = 0.022 (0.013, 0.089)
D50 = 77.6Gy (74.4Gy, 80.3Gy)