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CLINICAL INVESTIGATION **Prostate**

LATE RECTAL TOXICITY: DOSE–VOLUME EFFECTS OF CONFORMAL RADIOTHERAPY FOR PROSTATE CANCER

EUGENE H. HUANG, M.D.,* ALAN POLLACK, M.D., PH.D.,† LARRY LEVY, M.S.,‡ GEORGE STARKSCHALL, PH.D.,§ LEI DONG, PH.D.,§ ISAAC ROSEN, PH.D.,§ AND DEBORAH A. KUBAN, M.D.*

Departments of *Radiation Oncology, ‡Biomathematics, and §Radiation Physics, The University of Texas M. D. Anderson Cancer Center, Houston, Texas; †Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, PA

Purpose: To identify dosimetric, anatomic, and clinical factors that correlate with late rectal toxicity after three-dimensional conformal radiotherapy (3D-CRT) for prostate cancer.

Methods and Materials: We retrospectively analyzed the dose–volume histograms and clinical records of 163 Stage T1b-T3c prostate cancer patients treated between 1992 and 1999 with 3D-CRT, to a total isocenter dose of 74–78 Gy at The University of Texas M. D. Anderson Cancer Center. The median follow-up was 62 months (range 24–102). All late rectal complications were scored using modified Radiation Therapy Oncology Group and Late Effects Normal Tissue Task Force criteria. The 6-year toxicity rate was assessed using Kaplan-Meier analysis and the log–rank test. A univariate proportional hazards regression model was used to test the correlation between Grade 2 or higher toxicity and the dosimetric, anatomic, and clinical factors. In a multivariate regression model, clinical factors were added to the dosimetric and anatomic variables to determine whether they significantly altered the risk of developing late toxicity.

Results: At 6 years, the rate of developing Grade 2 or higher late rectal toxicity was 25%. A significant volume effect was observed at rectal doses of 60, 70, 75.6, and 78 Gy, and the risk of developing rectal complications increased exponentially as greater volumes were irradiated. Although the percentage of rectal volume treated correlated significantly with the incidence of rectal complications at all dose levels ($p < 0.0001$ for all comparisons), the absolute rectal volume appeared to be a factor only at the higher doses of 70, 75.6, and 78 Gy ($p = 0.0514$, 0.0016, and 0.0021, respectively). The following variables also correlated with toxicity on the univariate analysis: maximal dose to the clinical target volume, maximal dose to rectum, maximal dose to the rectum as a percentage of the prescribed dose, and maximal dose delivered to 10 cm^3 of the rectum. Of the clinical variables tested, only a history of hemorrhoids correlated with rectal toxicity ($p = 0.003$). Multivariate analysis showed that the addition of hemorrhoids increased the risk of toxicity for each dosimetric variable found to be significant on univariate analysis ($p < 0.05$ for all comparisons).

Conclusion: Dose–volume histogram analyses clearly indicated a volume effect on the probability of developing late rectal complications. Therefore, dose escalation may be safely achieved by adherence to dose–volume histogram constraints during treatment planning and organ localization at the time of treatment to ensure consistent patient setup. **© 2002 Elsevier Science Inc.**

Conformal radiotherapy, Prostate cancer, Rectal toxicity, Dose–volume effects.

INTRODUCTION

Dose escalation strategies through three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated RT are superseding conventional techniques in the treatment of prostate cancer. Although some increase in rectal bleeding has been observed, many series, including our own (1), have shown that dose escalation is possible using 3D-CRT without causing an unacceptable risk of major rectal complications (2–6). The sophistication of 3D treatment planning and analysis has enabled investigators to study the relationship between the rectal dose and volume (1, 3, 4, 7–11). Such findings must be incorporated into guidelines to limit rectal toxicity.

We previously reported the preliminary results of a Phase III randomized trial comparing 3D-CRT at a higher dose, 78 Gy, with a conventional four-field technique to 70 Gy (1). Although no significant increase in rectal toxicity was noted, our data indicated a dose–volume effect in the development of late rectal complications. Patients with >25% of the rectum irradiated to 70 Gy had a significantly higher

Reprint requests to: Deborah A. Kuban, M.D., Department of Radiation Oncology, Box 97, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030. Tel: 713-792-5862; Fax: 713-794-5573; E-mail: dakuban@mail.mdanderson.org

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Table 1. Patient characteristics

Patients (*n*)	163
Median follow-up (mo)	62 (24–102)
Median age (y)	63 (49–79)
Median pretreatment PSA (ng/mL)	7.9 (0.5–41.7)
Stage (AJCC 1992) (*n*)	
T1b	2
T1c	46
T2a	31
T2b	24
T2c	16
T3a	15
T3b	1
T3c	28
Gleason score (*n*)	
4, 5	16
6	70
7	55
8, 9	22

Abbreviations: PSA = prostate-specific antigen; AJCC = American Joint Commission on Cancer.

Numbers in parentheses are the range.

Table 2. Late GI toxicity grading using modified Radiation Therapy Oncology Group and Late Effects Normal Tissue Task Force criteria

Grade	Criteria
1	Excess bowel movements twice baseline; slight rectal discharge or blood
2	Two or more antidiarrheals/wk; two or fewer coagulations for bleeding; occasional steroids for ulceration; occasional dilation; intermittent use of incontinence pads; regular nonnarcotic or occasional narcotic for pain
3	Two or more antidiarrheals/d; three or more coagulations or any transfusion for bleeding; prolonged steroids per enema; hyperbaric oxygen for bleeding/ulceration; regular dilation; persistent use of incontinence pads; regular narcotics for pain
4	Dysfunction requiring surgery; perforation; life-threatening bleeding

risk of developing Grade 2 or higher complications. Furthermore, all Grade 3 complications occurred when >30% of the rectum received ≥70 Gy.

In this paper, we report the late rectal toxicity and analyze the dose–volume histograms (DVHs) of 163 patients treated at The University of Texas M. D. Anderson Cancer Center with 3D-CRT for localized prostate cancer after a median follow-up of 5 years.

METHODS AND MATERIALS

We reviewed the records for patients who received definitive 3D-CRT for prostate cancer at M. D. Anderson Cancer Center between 1992 and 1999. This analysis included only those patients with localized biopsy-confirmed prostate cancer who did not receive hormonal therapy. Of the 196 patients initially reviewed, 33 were excluded for the following reasons: 8 died before 24 months of follow-up, 1 lacked clinical follow-up information, and the DVH data for 24 patients could not be recovered from the archives.

The 163 remaining patients comprised this study cohort, and their characteristics are shown in Table 1. Of these, 128 were treated on a randomized institutional trial investigating 3D-CRT dose escalation to 78 Gy (12). The preliminary toxicity results of that trial have been previously reported (1). The other 35 patients were treated in an off-protocol setting (22 received 78 Gy, 12 received 76 Gy, and 1 received 74 Gy).

The median follow-up of all patients was 62 months (range 24–102). Follow-up clinical history and examinations were performed after the completion of RT at 6-month intervals during the first 2 years and annually thereafter. All late rectal complications were graded using a modified scale and criteria from the Radiation Therapy Oncology Group (13), Late Effects Normal Tissue Task Force (14), and Fox Chase Cancer Center (15) (Table 2). Late complications were defined as those developing ≥6 months after RT completion.

RT techniques

Patients underwent simulation and treatment in the supine position with a full bladder. Immobilization devices such as the alpha cradle, feet belt, or vacuum-lock bag 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 on a CT scanner (Model 9800, General Electric Medical Systems, Milwaukee, WI). Daily patient positioning was performed using skin marks and weekly portal films.

The details of RT have been previously described (16). In brief, patients were initially treated to 46 Gy at 2 Gy/fraction to the isocenter using 18-MV photons and a conventional four-field box technique. For the AP field, the lower border was typically set at the inferior aspect of the ischial tuberosities and was 11 cm × 11 cm. The lateral fields extended from the anterior aspect of the pubic symphysis and split the rectum posteriorly.

After the initial 46 Gy, a six-field 3D-CRT approach was used to boost the total isocenter dose to 74, 76, or 78 Gy. The six-field coplanar arrangement consisted of two lateral fields and four oblique fields at 30–40° above or below the lateral fields. All patients were treated at 2 Gy/fraction using 18-MV photons prescribed to the isocenter. 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 removed 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. The field arrangement was also designed to limit doses >60 Gy to <50% of the bladder and rectum. This guideline was usually met; how-

Table 3. Distribution of patients by late rectal toxicity

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Late rectal toxicity (*n*)	73 (44.8)	52 (31.9)	29 (17.8)	9 (5.5)	0
Frequency		7 (4.3)	2 (1.2)	0	
Discomfort		0	2 (1.2)	0	
Incontinence		2 (1.2)	1 (0.6)	0	
Bleeding		43 (26.4)	24 (14.7)	9 (5.5)	

Numbers in parentheses are percentages.

ever, adjustments were not usually made if this criterion was not satisfied.

Conformal plan evaluation

DVHs for the treatment plans were restored from the institutional archives and analyzed for each patient. Depending on the date at which the treatment plan was generated, either an in-house treatment planning system (COPPERPlan, M. D. Anderson Cancer Center) or a commercial planning system (Pinnacle [3], ADAC Laboratories, Milpitas, CA) was used to evaluate the treatment plans and provide specific information on several dosimetric and anatomic variables. For the calculation of the DVH, the entire rectal volume was outlined to include the external rectal wall plus contents. The rectum was outlined 11 cm in length starting at 2 cm below the inferiormost aspect of the ischial tuberosities.

Univariate analysis

The time to Grade 2 or higher late rectal toxicity was fit to a univariate proportional hazards regression model testing several clinical, anatomic, and dosimetric factors, independently. The clinical factors were treated as 0,1 variables and included a history of diabetes, diverticulitis, inflammatory bowel disease, hemorrhoids, and previous abdominal surgery. The anatomic and dosimetric variables were continuous values and included CTV, rectal volume, maximal dose to the CTV, maximal dose to the rectum, and the volume and percentage of the rectum receiving $>$60, 70, 75.6, and 78 Gy. For those dosimetric variables found to be significant, classification and regression tree analysis was used to identify the cutpoints that best discriminated those patients at high risk of Grade 2 or higher toxicity. That is, patients whose treatment plans had a dosimetric factor above a certain cutpoint were associated with a higher rate of rectal complications. The 6-year actuarial rate of late rectal toxicity was assessed using Kaplan-Meier survival analysis (17), and comparisons were made using the log–rank test (18).

Multivariate analysis

A multivariate proportional hazards regression model was used to analyze further those anatomic and dosimetric variables that were significantly associated with rectal toxicity. Various clinical factors were added one at a time to the univariate model to determine whether the hazard would be significantly altered by the presence of the clinical factor. These included a history of diabetes, diverticulitis, hemorrhoids, inflammatory bowel disease, and abdominal surgery.

RESULTS

The distribution of patients according to grade and type of late rectal toxicity is shown in Table 3. Of the 163 patients studied, 38 had Grade 2 or higher late rectal complications (6-year rate 25%; Fig. 1). The 6-year Kaplan-Meier proportion of Grade 2 and 3 complications was 21% and 6%, respectively. No patient developed Grade 4 complications. The median time to developing Grade 2 or higher complications was 12 months (range 6–72). The vast majority of late complications occurred within 2 years of completing RT. Of the 29 patients who had Grade 2 toxicity, 23 (79%) developed the complications at $\leq$24 months. All Grade 3 complications developed at $<$24 months.

Univariate regression analyses (Table 4) of the DVH data showed that several dosimetric variables were highly significant with respect to developing Grade 2 or higher complications. Furthermore, the risk of rectal toxicity increased exponentially as a function of the dosimetric variables rather than linearly. These variables included the maximal dose to the CTV, maximal dose to the rectum, maximal dose to the rectum as a percentage of the prescribed dose, and maximal dose to the rectum delivered to 10 cm^3 of rectum. The percentage of the volume of rectum irradiated to 60, 70, 75.6, and 78 Gy was also found to be highly significant. The absolute volume of the rectum irradiated to the higher doses of 70, 75.6, and 78 Gy was also associated with Grade 2 or higher complications.

For these continuous variables, classification and regression tree analysis identified the optimal cutpoints (Table 4) that differentiated patients at high risk of late toxicity from those at low risk. The cutpoint for the percentage of the volume of the rectum irradiated to 60, 70, 75.6, and 78 Gy was 40.6%, 26.2%, 15.8%, and 5.1%, respectively. The cutpoint for the absolute volume of the rectum irradiated to 75.6 and 78 Gy was 3.8 and 1.4 cm^3, respectively. For the purposes of clinical utility, Fig. 2 shows the Kaplan-Meier freedom from Grade 2 or higher late rectal toxicity according to the percentage of volume of the rectum receiving 70 Gy. The 6-year rate of rectal complications was 54% for patients who had $>$26.2% of rectum irradiated to 70 Gy vs. 13% for those who had $\leq$26.2% irradiated to 70 Gy.

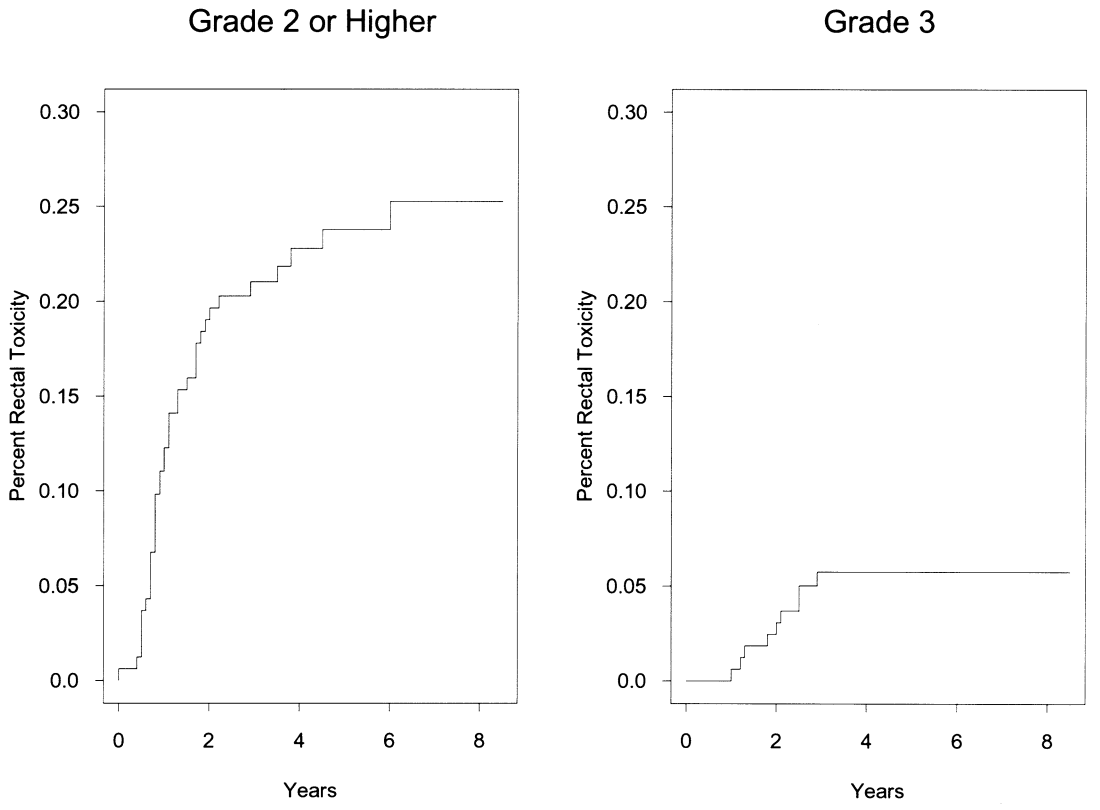

Fig. 1. Kaplan-Meier actuarial rate of late rectal complications.

Of the clinical variables tested using univariate analysis, only the presence of hemorrhoids was found to significantly increase the risk of Grade 2 or higher toxicity. In multivariate analysis, each of the clinical variables was added one at a time to the previous model of dosimetric variables. Again, only the presence of hemorrhoids was found to significantly

Table 4. Univariate regression analysis

Variable	Hazard ratio	*p*	Optimal cutpoint	Mean ± SD
Clinical				
Diabetes	1.030	0.956		
Diverticulitis	–	0.196		
Hemorrhoids	2.703	0.003*		
Inflammatory bowel disease	–	1.000		
Abdominal surgery	0.906	0.775		
Anatomic				
CTV (cm^3)	1.000	0.9460		95.0 ± 29.9
Volume of rectum (cm^3)	0.994	0.1067		121.0 ± 49.5
Dosimetric				
Maximal dose to CTV (Gy)	1.006	0.0026*	78.2	79.2 ± 0.9
Maximal dose to CTV (% of prescribed)	1.308	0.0825		101.8 ± 1.0
Maximal dose to rectum (Gy)	1.006	0.0001*	77.8	78.4 ± 1.3
Maximal dose to rectum (% of prescribed)	1.490	0.0003*	102.4	100.7 ± 1.5
Maximal dose delivered to 10 cm^3 of rectum (Gy)	1.003	0.0005*	75.6	75.0 ± 3.8
Volume of rectum receiving 60 Gy (cm^3)	1.008	0.3261		41.0 ± 18.9
Volume of rectum receiving 70 Gy (cm^3)	1.021	0.0514		26.2 ± 13.5
Volume of rectum receiving 75.6 Gy (cm^3)	1.040	0.0016*	3.8	12.7 ± 9.2
Volume of rectum receiving 78 Gy (cm^3)	1.048	0.0021*	1.4	3.7 ± 6.2
Percent of rectum receiving 60 Gy (%)	1.063	0.0001*	40.6	34.5 ± 10.3
Percent of rectum receiving 70 Gy (%)	1.092	0.0001*	26.2	22.0 ± 8.4
Percent of rectum receiving 75.6 Gy (%)	1.101	0.0001*	15.8	10.6 ± 6.5
Percent of rectum receiving 78 Gy (%)	1.096	0.0001*	5.1	3.1 ± 4.8

* $p < 0.05$.

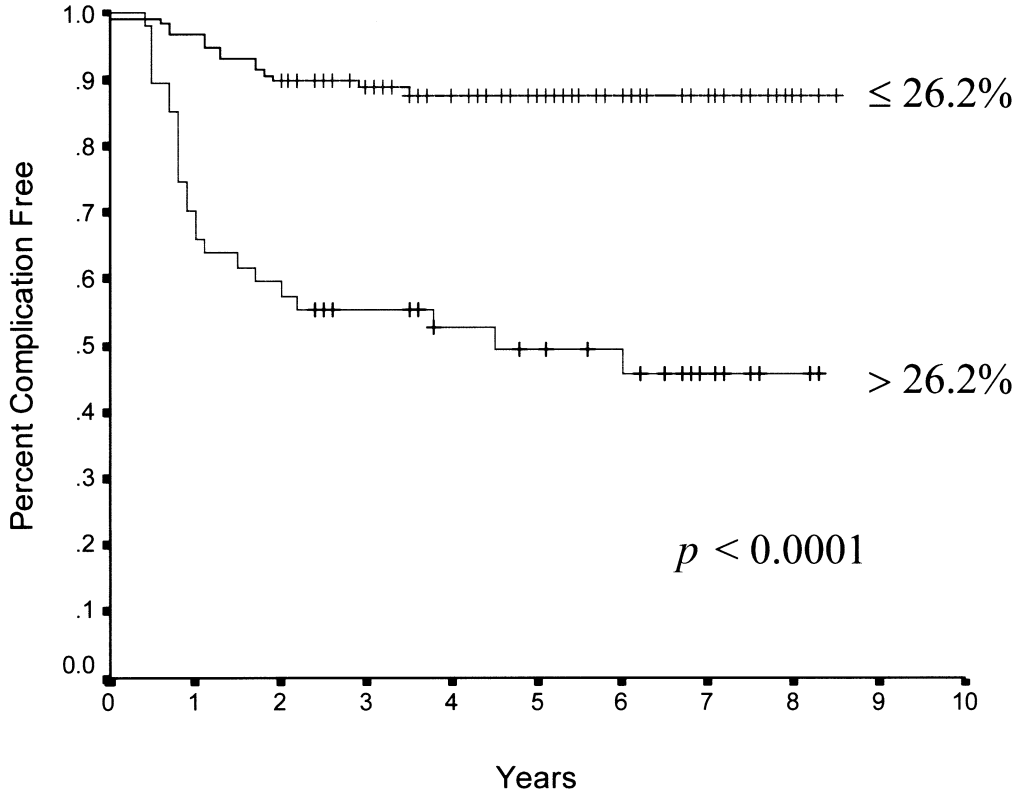

Fig. 2. Kaplan-Meier freedom from Grade 2 or higher late rectal complications according to the percentage of rectal volume receiving ≥70 Gy.

increase the risk of developing late toxicity (Table 5). The risk of rectal complications increased exponentially both with and without the additional risk factor of hemorrhoids (Fig. 3).

DISCUSSION

Our preliminary report of a randomized 3D-CRT dose-escalation trial (1) suggested the presence of a dose–volume effect in late rectal toxicity. Patients with >25% of the rectum irradiated to ≥70 Gy developed Grade 2 or higher complications. With a larger cohort, longer follow-up >5 years, and more extensive DVH analysis, the importance of dose–volume effects in late rectal toxicity has been further strengthened. Our results demonstrate that dose and volume behave as continuous interrelated variables, because both the absolute and the percentage of rectal volume correlated significantly with late toxicity across a range of dose levels from 60 to 78 Gy. In addition, our data indicated that the risk of developing late rectal complications grows exponentially as a greater volume of the rectum is irradiated to a defined dose.

Table 5. Multivariate regression analysis

Variable	Hazard ratio	*p*
Percent of rectum receiving 60 Gy	1.055	0.0005
Hemorrhoids	2.166	0.0229
Percent of rectum receiving 70 Gy	1.081	0.0001
Hemorrhoids	2.013	0.0419
Percent of rectum receiving 75.6 Gy	1.091	0.0001
Hemorrhoids	2.099	0.0299
Percent of rectum receiving 78 Gy	1.084	0.0001
Hemorrhoids	2.257	0.0166

Furthermore, this risk increased significantly in those patients who had a clinical history of hemorrhoids. That radiation appears to exacerbate hemorrhoidal bleeding is intuitive; however, the component due to telangiectasia vs. hemorrhoidal bleeding cannot be separated out. Overall, the data would seem to suggest that limiting the rectal volume may be especially important in this cohort of patients. Our analysis did not find diabetes to be a significant risk factor for developing Grade 2 toxicity. The report of Herold *et al.* (19) examining a larger cohort of patients treated at the Fox Chase Cancer Center, however, showed diabetes to be an important predictor of late rectal toxicity. This difference may have been due to the small number of diabetic patients available for analysis in our series. A previous study from the Fox Chase Cancer Center with fewer patients failed to show diabetes to be a significant factor (20). Similarly, the number of patients with diverticulitis (3 patients) or inflammatory bowel disease (no patients) was too small in our series to test these factors in the regression model. However, of the 3 patients who had diverticulitis, 1 developed Grade

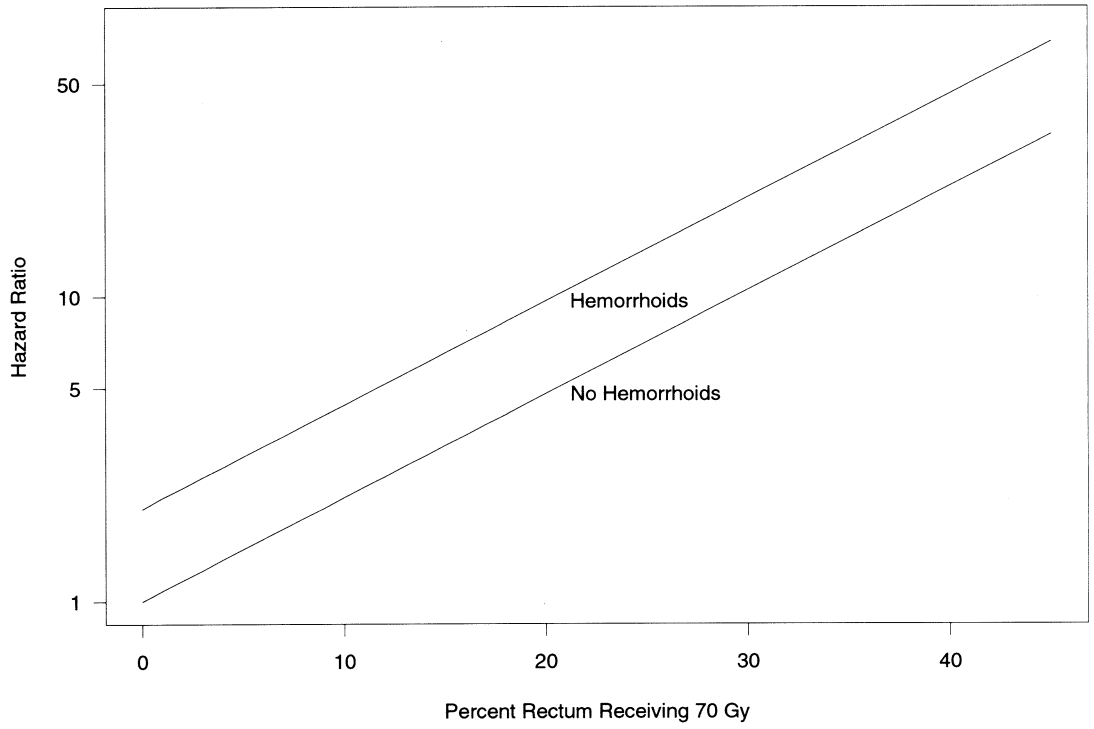

Fig. 3. Risk of developing Grade 2 or higher late rectal complications as a function of rectal volume (percentage of rectum irradiated to 70 Gy) for patients with or without a history of hemorrhoids.

1 rectal bleeding; the other 2 patients did not develop any rectal complications.

In the future, the dosimetric variables that correlate with late rectal toxicity can be used as benchmark parameters to evaluate 3D treatment plans. Classification and regression tree analyses identified the optimal cutpoints within these variables that most significantly discriminate those patients at high risk of late toxicity from those at low risk. To reduce the risk of late toxicity, $<$40% of the defined rectal volume should receive 60 Gy, $<$25% should receive 70 Gy, $<$15% should receive 75.6 Gy, and $<$5% should receive 78 Gy. At the higher dose levels, <4 cm^3 of the absolute rectal volume should be irradiated to 75.6 Gy and <2 cm^3 to 78 Gy. The percentage of rectal volumes and the maximal rectal dose were the dosimetric variables that correlated most significantly with late toxicity. Since our preliminary report of the 3D-CRT dose-escalation trial (1), our institution has been using $\leq$25% of the rectum receiving 70 Gy as a principal DVH constraint, although it has been increasingly recognized that the DVH is a continuum of relationships and not a single dose point.

Other investigators have previously reported the dose–volume effects related to late rectal toxicity after 3D-CRT, particularly at doses of $\geq$60 Gy. Schultheiss *et al.* (7) and Lee *et al.* (3) have reported that patients with rectal shielding on the lateral fields for the final 10 Gy of treatment (total doses of 77–80 Gy) had significantly less Grade 2–4 rectal toxicity, 13% vs. 43%. Wachter *et al.* (11) found that Grade 2 rectal complications were associated with patients who had $>$57% of the rectum irradiated to 60 Gy. Similarly, Boersma *et al.* (4) reported that the percentage of rectum irradiated correlated significantly with Grade 3 rectal bleeding. Finally, in a series of 41 patients treated at the Massachusetts General Hospital using a proton boost to a total dose of 75.6 Gy, rectal bleeding correlated with a range of dose–volume combinations from 60 Cobalt Gray Equivalent to $\geq$70% of the anterior rectal wall to 75 Cobalt Gray Equivalent to $\geq$30% (8, 21).

In a series of 171 patients treated with 3D-CRT at the Memorial Sloan-Kettering Cancer Center, Jackson *et al.* (9) studied the relationship between the rectal wall volume and toxicity at intermediate doses of 40–50 Gy. Grade 2 or higher rectal bleeding correlated with the percentage of the volume of rectal wall exposed to 46 Gy. Patients who developed bleeding had an average of 10% more rectal wall volume irradiated to doses of 30–50 Gy and 5% more volume at doses $>$50 Gy. This observation continued to be significant even if the total rectal wall volume was small, clearly indicating the presence of a volume effect in rectal bleeding. No correlation was observed with respect to the absolute rectal volumes.

Our patients received 3D-CRT for only a portion of their treatment, so our 6-year rate of 25% of patients developing Grade 2 or greater complications may be higher than those treated with conformal techniques throughout the entire treatment. Also, the modified scoring system that we used is much more sensitive than the Radiation Therapy Oncology Group system (15). Most of the complications were generally mild, and most of the Grade 3 complications were

graded as such because the patient required three laser coagulations to control the rectal bleeding.

One of the limitations of this study was that the entire rectum, including the rectal cavity and its contents was contoured, rather than just the rectal wall. We believe, however, that outlining the rectum in this fashion provides data that are more reproducible because it circumvents the difficulty of distinguishing the rectal wall from the rectal contents. Second, because the rectum is a thin tube, it is often difficult to contour the wall in a way that consistently reflects its thickness at any point. We also believe that there is a proportional relationship between the volume of the whole rectum and the volume of the wall structure. Using both the rectal wall and the entire rectum have produced meaningful results in analyzing dose tolerance levels. One must be mindful, however, of which is being used, as well as the total length of rectum being contoured, because the volume percentages vs. dose will vary accordingly.

Perhaps the most important limitation of this study was that this analysis did not take into account the effects of setup variability and internal organ motion because the DVHs were generated from the pretreatment planning scans. Prostate and rectal motions are not yet entirely understood, and this movement could cause significant variation in the actual dose distribution across the rectal mucosa over a full course of treatment. Studies investigating organ motion have reported movement of up to 1 cm or more in the AP directions, most likely because of rectal filling by gas and stool (22–25). Data from our own institution using an ultrasound localization system (BAT, Nomos, Sewickley, PA) during intensity-modulated RT have shown that although intrafraction organ motion is clinically insignificant (26), interfraction movement is considerable, with $>$25% of treatments having shifts $>$5 mm (range 0–32) (27). The dominant motion was found to occur in the anterior direction, affecting not only target coverage, but also possibly exposing a greater volume of the rectum to higher doses. Because of this uncertainty in organ location, using the pretreatment planning scan to assess the total dose delivered to the rectal mucosa may not accurately reflect the actual dose distribution. Therefore, the dosimetric variables correlating with late toxicity identified from DVH analysis must be regarded as surrogates.

CONCLUSION

Dose escalation using 3D-CRT can carry a substantial risk of late rectal toxicity. DVH analyses clearly indicate the presence of a volume effect with respect to Grade 2 or higher complications across doses of 60–78 Gy. This risk grows exponentially as greater volumes of the rectum are irradiated and may be significantly enhanced by comorbidities such as a history of hemorrhoids. Our data suggest that it is the percentage of rectal volume, rather than the absolute volume, that correlates more significantly with late toxicity. If possible, the percentage of rectal volume irradiated to 60, 70, 75.6, and 78 Gy should be limited to 40%, 25%, 15%, and 5%, respectively. Efforts to reduce the risk of rectal toxicity include minimizing the volume of rectum exposed to higher doses by adopting appropriate DVH constraints and improving treatment planning and delivery systems such as incorporating intensity-modulated RT in conjunction with a method to account for daily setup variation and organ motion. Preliminary studies from the Memorial Sloan Kettering Cancer Center (5) and our own institution indicate that intensity-modulated RT seems to allow for higher prostate doses while abiding by recommended rectal constraints. Further exploration of methods to document prostate position is underway.

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