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COMPARISON OF LATE RECTAL TOXICITY FROM CONVENTIONAL VERSUS THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY FOR PROSTATE CANCER: ANALYSIS OF CLINICAL AND DOSIMETRIC FACTORS

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ABSTRACT

Objectives. To compare late rectal toxicity (LRT) after definitive radiotherapy (DR) and salvage radiotherapy (SR) in prostate cancer using conventional (CONV) or three-dimensional conformal (3-D) techniques.

Methods. The outcomes and clinical factors of 212 patients with Stage T1a-T4 prostate cancer were evaluated (separated into DR and SR groups). The median prescribed dose was 66, 74, 66, and 70 Gy, for the CONV-DR, 3-D-DR, CONV-SR, and 3-D-SR groups, respectively. LRT was scored using both Radiation Therapy Oncology Group (RTOG) and modified RTOG and Late Effects Normal Tissue (mRTOG/LENT) scales.

Results. The 4-year biochemical relapse-free survival rate was 83% for all patients, with a trend toward improvement in the 3-D groups (78% CONV and 85% 3-D, $P = 0.12$). One patient (1%) in the CONV group and 24 (24%) in the 3-D group experienced grade 2 or worse LRT by the mRTOG/LENT scale. Patients undergoing DR experienced grade 2 or worse LRT of 1% versus 21% ($P = 0.003$) for the CONV and 3-D groups, respectively. Patients undergoing SR experienced grade 2 or worse LRT of 0% versus 40% for the CONV and 3-D groups, respectively. The following variables correlated significantly with LRT on both univariate and multivariate analyses: prescribed radiation dose ($P < 0.0001$), percentage of rectal volume receiving 60 Gy ($P < 0.005$), and percentage of rectal volume receiving 70 Gy ($P < 0.001$). The pretreatment clinical factors, when added to the dosimetric data, were not statistically significant on multivariate analysis ($P > 0.05$).

Conclusions. The prescribed radiation dose and percentage of rectal volume treated to 60 or 70 Gy had statistically significant correlations with increased LRT. The rate of grade 2 or worse LRT was greater for patients undergoing SR than for those undergoing DR. We believe that continued close attention to dosimetric variables is imperative for future studies of dose escalation. UROLOGY **65:** 114–119, 2005. © 2005 Elsevier Inc.

The rapid implementation of three-dimensional conformal radiotherapy (3-D) has been facilitated by desire to deliver higher radiation doses to tumor while minimizing normal tissue doses (enhance the therapeutic ratio). This ability to both escalate the dose and minimize gastrointestinal and genitourinary side effects has only been made available through modern radiation delivery approaches.[1–3] Advances such as computed tomography simulation, 3-D, and intensity-modulated RT have changed institutional practice patterns and the standard of care.[4,5] Dose-volume histogram-based evaluations of individual treatment plans and the development of biologic models have also greatly assisted clinicians in treatment planning decisions.[6–8] Because of these sophisticated computerized planning methods, the relationships among the rectal dose, rectal volume treated, and incidence of rectal complications can now be analyzed in greater depth.[6,8]

Although the feasibility of dose escalation in prostate cancer has been described, we initiated this study to evaluate how our institution's shift from conventional RT (CONV) to 3-D has specifically effected incidence and degree of late rectal

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Submitted: June 4, 2004, accepted (with revisions): August 20, 2004

0090-4295/05/$30.00
doi:10.1016/j.urology.2004.08.037

TABLE I. *Patient characteristics and radiation dose by treatment group*

Characteristic	CONV-DR	3-D-DR	CONV-SR	3-D-SR
Patients (n)	87	87	23	15
Age (yr)				
Median	71	73	70	62
Range	54–84	56–85	46–76	56–69
Stage (n)				
T1a	2	1	0	0
T1b	3	0	0	1
T1c	29	50	4	2
T2a	19	19	5	1
T2b	11	9	2	4
T2c	22	5	3	2
T3	1	3	8	5
T4	0	0	1	0
Initial PSA (ng/mL)				
Median	9.1	9.1	9.6	8
Range	2.2–128	2.8–100	5–64	4.5–140
Gleason score				
2–4	20	6	2	0
5–6	36	43	6	5
7	22	21	11	5
8–10	9	17	4	5
(+) Family history of prostate cancer	18	21	4	6
(+) Smoking history	33	20	7	3
(+) Coronary artery disease	29	23	2	1
(+) COPD	7	6	0	1
(+) Diabetes	9	8	1	2
Follow-up (mo)				
Median	86	36	82	27
Range	15–101	16–53	15–99	22–45
Radiation dose summary (cGy)				
Median	6600	7400	6600	7000
Range	5600–7020	6560–7800	5600–7000	5740–7400

KEY: CONV = conventional (radiotherapy); DR = definitive radiotherapy; 3-D = three-dimensional conformal (radiotherapy); SR = salvage radiotherapy; PSA = prostate-specific antigen; COPD = chronic obstructive pulmonary disease.

toxicity (LRT). The pretreatment clinical factors and dosimetric data (obtained from dose-volume histograms) were also statistically correlated with the incidence of LRT.

MATERIAL AND METHODS

We retrospectively reviewed the records of patients with prostate cancer treated from January 1995 to December 1996 (group 1) and January 1999 to December 2000 (group 2) at our institution. The hospital's institutional review board approved the study. The outcomes of 110 patients (group 1) and 102 patients (group 2) with Stage T1a-T4 prostate cancer were evaluated. The treatment for patients in group 1 (1995 to 1996) was by conventional four-field RT techniques (CONV groups), and the outcomes for this population were included for the purpose of comparison with those of group 2 (treated with 3-D). The median follow-up for the CONV group was 86 months (range 15 to 101) and for the 3-D group was 35 months (range 16 to 53). As a general rule, those patients treated definitively for high-risk disease in both treatment groups received hormonal therapy along with RT.

This analysis included only those patients with localized prostate cancer who were treated with RT in a definitive fashion (DR) or who underwent salvage RT (SR) after prostatectomy for a rising prostate-specific antigen (PSA) level. Those patients treated with RT in the adjuvant setting for positive surgical margins or nodal disease were excluded.

Patient Characteristics and Stratification

The patient characteristics for each treatment group are listed in Table I. The median age was 62 to 73 years old for all treatment groups. The median initial PSA levels were also similar between treatment groups (range 8.0 to 9.6 ng/mL). The presence of clinical factors such as a family history of prostate cancer, smoking history, and a history of coronary artery disease, chronic obstructive pulmonary disease, and diabetes were also collected for correlation with patient outcomes.

RT Techniques

In general, patients underwent simulation and treatment in the supine position with a full bladder. Bladder contrast material was used and retrograde urethrography performed as aid in treatment planning. In brief, the prostate and periprostatic tissues in the CONV-DR and CONV-SR groups were treated with a stationary four-field technique, with the dose prescribed to the isocenter. Customized blocking material with less than 5% beam transmission or multileaf collimation was used to comply with field margin and normal tissue dose re-

quirements. Wedges and filters were used to create a maximally homogeneous dose at depth. Portions of the urinary bladder and the posterior segment of the rectum were shielded on the lateral fields. RT was delivered to the prostate bed in the CONV-SR group with 6 to 15-MV photons based on localization using urethral, bladder, and rectal contrast at simulation.

Patients included in the 3-D group underwent computed tomography simulation in the treatment position. Immobilization devices were used to minimize interfractional and intrafractional positional variation. Computed tomography image data sets were acquired using a 5-mm slice thickness. For the 3-D group, each patient image set had contouring of the prostate, seminal vesicles, bladder, and rectum. The initial planning target volume was designated as 1 cm around the clinical target volume with decreased margins posteriorly (0.6 cm). Three-dimensional dose calculations were performed, and the dose was normalized to ensure coverage of the planning target volume by the prescribed isodose line.

Megavoltage energies were used to treat all patients (6 to 15 MV). Daily fractions of 1.8 to 2.0 Gy were used to deliver the prescribed dose. A summary of the prescribed radiation doses is also included in Table I. The median prescribed radiation dose was 66, 74, 66, and 70 Gy for the CONV-DR, 3-D-DR, CONV-SR, and 3-D-SR groups, respectively.

Biochemical and Clinical Endpoints

The included patients were evaluated for the clinical endpoints of biochemical relapse-free status, overall survival, and late gastrointestinal toxicity. Gastrointestinal toxicity was scored according to the modified Radiation Therapy Oncology Group (RTOG) and Late Effects Normal Tissue Task Force (mRTOG/LENT) criteria[9] and also by the RTOG criteria.[10] Biochemical failure was defined by the American Society for Therapeutic Radiology and Oncology consensus definition of three consecutive PSA rises.[11]

Statistical Analysis

The Kaplan-Meier method was used to estimate the time-adjusted morbidity, mortality, and biochemical relapse-free survival (bRFS) rates. The time to grade 2 or worse LRT was fit to a univariate proportional hazard regression model testing the included clinical and dosimetric factors independently. The dosimetric factors, age, stage, pretreatment PSA level, and Gleason score were treated as continuous variables and also analyzed at specific cutpoints of interest. For those statistically significant continuous variables, regression tree analysis was used to identify the optimal cutpoints that best discriminated a high risk of grade 2 or worse LRT. All comparisons were made using the log-rank statistic. A multivariate proportional hazards regression model was constructed to evaluate whether the clinical and dosimetric variables were statistically significantly associated with LRT.

RESULTS

A summary of degree (mRTOG/LENT and RTOG late toxicity scoring systems) and distribution by treatment group of LRT is listed in Table II. With stratification by treatment group, the incidence of grade 2 or worse LRT by mRTOG/LENT was 1%, 21%, 0%, and 40% in the CONV-DR, 3-D-DR, CONV-SR, and 3-D-SR groups, respectively. The corresponding incidence of grade 2 or worse LRT by the RTOG scale was 1%, 12%, 0, and 20%.

The actuarial 4-year bRFS and overall survival data were evaluated separately by group. The 4-year bRFS rate was 83% for all patients, with a trend toward improvement in the 3-D treatment group, although not statistically significant (78% CONV and 85% 3-D, $P = 0.12$). The calculated 4-year overall survival rate was 95%; the difference was also not statistically significant between the CONV (96%) and 3-D (94%) groups ($P = 0.62$).

Calculations of the actuarial 4-year freedom from grade 2 or worse LRT were made for each treatment group for comparative analysis. The 4-year freedom from grade 2 or worse toxicity rate was 98% for the CONV group versus 76% for the 3-D group ($P < 0.0001$). Additional stratification of the 3-D group (Fig. 1) revealed the 4-year freedom from grade 2 or worse toxicity rate to be 79% for the 3-D-DR group and 60% for the 3-D-SR group ($P = 0.10$) by mRTOG/LENT. The 4-year Kaplan-Meier proportion of grade 2 or worse toxicity and grade 3 toxicity for the 3-D group was 24% and 11%, respectively. No patient developed Grade 4 late rectal complications.

The univariate and multivariate analysis results revealed the dosimetric variables to be statistically significant predictors of grade 2 or worse LRT. The univariate regression analysis results of the clinical and dosimetric factors with respect to developing LRT are listed in Table III. Statistically significant variables with respect to the incidence of grade 2 or worse LRT included a prescribed RT dose of greater than 70 Gy ($P < 0.0001$), percentage of rectal volume treated to 60 Gy ($P = 0.005$), and percentage of rectal volume treated to 70 Gy ($P = 0.001$). The clinical factors analyzed, including family history of prostate cancer, smoking history, and history of coronary artery disease, chronic obstructive pulmonary disease, and diabetes were not statistically significant with respect to LRT. The optimal cutpoint for the percentage of rectal volume treated to 60 Gy or 70 Gy was 51.5% and 41.5% by regression tree analysis, respectively.

COMMENT

In this study, we evaluated how our institution's shift from conventional RT to 3-D conformal radiation therapy has led to changes in the incidence and degree of LRT. Although the pretreatment clinical factors (eg, diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease) did not correlate statistically with incidence of LRT, a prescribed radiation dose to greater than 70 Gy and the percentage of rectal volume treated to 60 or 70 Gy had statistically significant correlations with the probability of developing LRT.

Late gastrointestinal toxicity from prospective dose-escalation trials of DR has been reported.[12–17] In our study, we found the incidence of grade 2 or worse LRT to be 1% for the CONV cohort and 24%

TABLE II. *Compared incidence of late rectal toxicity by modified RTOG/LENT score versus RTOG score*

Grade	CONV-DR (n)	3-D-DR (n)	CONV-SR (n)	3-D-SR (n)	Definition
Modified RTOG/LENT					
1	5 (6)	17 (20)	4 (17)	5 (33)	Excess bowel movements twice baseline; slight rectal discharge or blood
2	0 (0)	12 (14)	0 (0)	3 (20)	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	1 (1)	6 (7)	0 (0)	3 (20)	Two or more antidiarrheals/day; three or more coagulations or any transfusions for bleeding; prolonged steroids per enema; hyperbaric oxygen for bleeding/ulceration; regular dilation; persistent use of incontinence pads; regular narcotics for pain
4	0 (0)	0 (0)	0 (0)	0 (0)	Dysfunction requiring surgery; perforation; life-threatening bleeding
RTOG					
1	5 (6)	23 (26)	4 (17)	8 (53)	Minor symptoms requiring no treatment
2	1 (1)	12 (14)	0 (0)	3 (20)	Symptoms responding to simple outpatient management, lifestyle (performance status) not affected
3	0 (0)	0 (0)	0 (0)	0 (0)	Distressing symptoms altering patient's lifestyle (performance status); hospitalization for diagnosis or minor surgical intervention (eg, urethral dilation) may be required
4	0 (0)	0 (0)	0 (0)	0 (0)	Major surgical intervention (eg, laparotomy, colostomy, cystectomy) or prolonged hospitalization

KEY: RTOG = Radiation Therapy Oncology Group; RTOG/LENT = RTOG and Late Effects Normal Tissue; other abbreviations as in Table I.
Data in parentheses are percentages.

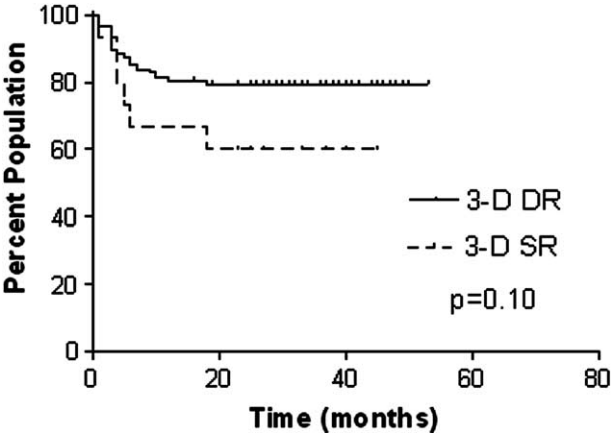

FIGURE 1. *Kaplan-Meier freedom from grade 2 or worse LRT after DR versus SR for 3-D conformal group.*

for the 3-D cohort by mRTOG/LENT criteria. A Phase I trial by Zelefsky *et al.*[13] found the incidence of grade 2 or worse toxicity in their cohort of 743 patients to be 8.8% using the RTOG scoring system. They have recently published a grade 2 or worse LRT rate of 4% for a large cohort of patients treated with intensity-modulated RT to 81 Gy.[18] The results of the Phase I-II dose escalation trial by Michalski *et al.*[14] reported grade 2 or worse toxicity (by the RTOG scoring system) of 4%, 8%, and 8% at the 68.4, 73.8, and 79.2-Gy dose level, respectively. The interpretation and comparison of reported toxicity results is complicated further because various toxicity scales have been used in these previous studies and the reported complication rates are highly dependent on which grading system was used. Owing to the recognized failure of early toxicity scales to represent late grade 2-4 toxicity accurately, Hanlon *et al.*[19] developed a scoring system similar to the mRTOG/LENT system for evaluation of late rectal bleeding (Fox Chase LENT score). For future meaningful comparisons to be made between institutions, we believe that a uniform scale, such as the mRTOG/LENT or Fox Chase LENT scoring system, should be used in future studies.

TABLE III. *Univariate regression analysis statistics with respect to grade 2 or worse late rectal toxicity*

Variable	Hazard Ratio	*P* Value	Optimal Cutpoint	Reference Category
Age at initial diagnosis	0.509	0.133	72	56–72
PSA at initial diagnosis	1.206	0.654	10	2.8–9.9
AJCC T Stage				
T2	0.676	0.404		T1
T3	2.451	0.118		T1
Gleason score	1.155	0.724		4–6
Family history of prostate cancer	2.116	0.070		No
Smoking history	1.357	0.496		No
CAD	1.150	0.768		No
COPD	1.140	0.859		No
DM	1.275	0.694		No
Prescribed radiation dose (70–78 Gy)	1.151	<0.0001		0–70
Maximal rectal dose (77.71–84.10 Gy)	2.177	0.101	77.7	63.00–77.70
Rectal volume irradiated to 60 Gy (52–58%)	5.463	0.005	51.5	5–51
Rectal volume irradiated to 70 Gy (42–55%)	7.025	0.001	41.5	0–41

KEY: *PSA = prostate-specific antigen; AJCC = American Joint Committee on Cancer; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus.*

The treatment-related morbidity of post-prostatectomy RT has been described in most reports to be mild to moderate in severity.[20–23] A report by Song *et al.*[23] revealed that 18% of patients treated with RT for a rising or persistent PSA level developed occasional rectal bleeding (although none warranted referral for intervention). Crane *et al.*[21] also reported that the only late gastrointestinal complication noted after post-prostatectomy RT was grade 2 chronic proctitis. Grade 1-3 LRT was also reported in 9% of patients in a retrospective series by Pisansky *et al.*[22] In our series, we found that the LRT incidence was exaggerated for post-prostatectomy patients with a rate of grade 2 or worse toxicity equal to 40% using the mRTOG/LENT toxicity scale. The conventional rationale would explain the increased toxicity as due to treatment of a hypoxic tumor bed and the increased rectal volume/circumference treated to higher radiation doses owing to the absence of prostatic tissue.

As supported by our study results, the volume of rectum treated to higher radiation doses may be the most statistically significant factor determining the occurrence of late toxicity. Jackson *et al.*[24] correlated patients' rectal bleeding (from radiation doses of 70.2 to 75.6 Gy) with statistically significant increases in the mean dose-volume histogram. Wachter *et al.*[25] also found that grade 2 LRT was associated with patients who had more than 57% of the rectum irradiated to 60 Gy. Storey *et al.*,[26] in their preliminary report of a randomized 3-D dose-escalation trial, found that patients with more than 25% of the rectal volume irradiated to 70 Gy or greater developed grade 2 or worse toxicity. This has been supported by Kuban *et al.*[27] in their findings that the risk of grade 2–3 complications can be markedly diminished by adhering to strict dose-volume constraints such as limiting the volume of the rectum treated with 70 Gy to less than 26%. These analyses further support the importance of close attention to dosimetric variables in future radiation dose escalation trials.

In light of the continued evidence of increased toxicity risk with radiation dose escalation, recent studies have reported experience with novel techniques to improve the therapeutic ratio. Zelefsky *et al.*[18] reported decreased rectal toxicity using intensity-modulated RT to 81 Gy compared with 3-D techniques prescribed to the same dose. Another recent innovative technique includes the use of a rectal balloon catheter and ultrasound localization in CRT for rectal wall sparing.[28] Prostate localization using transabdominal ultrasound imaging has also provided a rapid means of correcting interfraction positional variations.[29,30]

CONCLUSIONS

We found that statistically significant greater rates of grade 2 or worse LRT occurred in the 3-D group compared with the CONV group for both DR and SR. We also found that a prescribed radiation dose to greater than 70 Gy and the percentage of rectal volume treated to 60 or 70 Gy had statistically significant correlations with the probability of developing LRT. We believe that continued close attention to dosimetric variables is imperative for future studies of dose escalation. Continued long-term follow-up is warranted and will be necessary to evaluate fully whether dose escalation will translate to im-

proved bRFS or overall survival in specific subsets of patients with adenocarcinoma of the prostate.

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