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Clinical Investigation: Genitourinary Cancer

Preliminary Toxicity Analysis of 3-Dimensional Conformal Radiation Therapy Versus Intensity Modulated Radiation Therapy on the High-Dose Arm of the Radiation Therapy Oncology Group 0126 Prostate Cancer Trial

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Summary

An analysis of the high-dose arm of the randomized RTOG dose-escalation trial for prostate cancer shows that compared with 3D-CRT, IMRT reduces the volumes of bladder and rectum irradiated. Intensity modulated radiation therapy is associated with lower rates of acute and late toxicity. Acute side effects and large volumes of

Purpose: To give a preliminary report of clinical and treatment factors associated with toxicity in men receiving high-dose radiation therapy (RT) on a phase 3 dose-escalation trial.

Methods and Materials: The trial was initiated with 3-dimensional conformal RT (3D-CRT) and amended after 1 year to allow intensity modulated RT (IMRT). Patients treated with 3D-CRT received 55.8 Gy to a planning target volume that included the prostate and seminal vesicles, then 23.4 Gy to prostate only. The IMRT patients were treated to the prostate and proximal seminal vesicles to 79.2 Gy. Common Toxicity Criteria, version 2.0, and Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late morbidity scores were used for acute and late effects.

Results: Of 763 patients randomized to the 79.2-Gy arm of Radiation Therapy Oncology Group 0126 protocol, 748 were eligible and evaluable: 491 and 257 were treated with 3D-CRT and IMRT, respectively. For both bladder and rectum, the volumes receiving 65, 70, and 75 Gy were significantly lower with IMRT (all $P<.0001$). For grade (G) 2+ acute gastrointestinal/genitourinary (GI/GU) toxicity, both univariate and multivariate analyses showed a statistically significant decrease in G2+ acute collective GI/GU toxicity for IMRT. There were no significant

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rectum irradiated to high doses are associated with late rectal toxicity.

differences with 3D-CRT or IMRT for acute or late G2+ or 3+ GU toxicities. Univariate analysis showed a statistically significant decrease in late G2+ GI toxicity for IMRT ($P=.039$). On multivariate analysis, IMRT showed a 26% reduction in G2+ late GI toxicity ($P=.099$). Acute G2+ toxicity was associated with late G3+ toxicity ($P=.005$). With dose–volume histogram data in the multivariate analysis, RT modality was not significant, whereas white race ($P=.001$) and rectal V70 $\geq$15% were associated with G2+ rectal toxicity ($P=.034$).

Conclusions: Intensity modulated RT is associated with a significant reduction in acute G2+ GI/GU toxicity. There is a trend for a clinically meaningful reduction in late G2+ GI toxicity with IMRT. The occurrence of acute GI toxicity and large (>15%) volumes of rectum >70 Gy are associated with late rectal toxicity.

Introduction

A patient's treatment choice to manage localized prostate cancer depends on multiple factors, many of which are unrelated to the likelihood of long-term disease control (1). Techniques to minimize the risk of treatment-related toxicity have been introduced, but they have not been formally evaluated in the context of prospective clinical trials. This is especially relevant with external beam radiation therapy, for which dose-escalation trials have demonstrated improvement in biochemical disease control of prostate cancer while variably being associated with higher rates of toxicity.

Several single-institution series have reported a reduction in late toxicity with the introduction of intensity modulated radiation therapy (IMRT) compared with 3-dimensional conformal radiation therapy (3D-CRT), even with dose escalation (2-6). However, there are no reports of a contemporary cohort of patients treated to similar doses that compare toxicity between these 2 modalities. This report describes the toxicity outcomes of patients enrolled on the high-dose arm of a Radiation Therapy Oncology Group (RTOG) prospective phase 3 trial of conventional-dose versus dose-escalated radiation therapy, which allowed either IMRT or 3D-CRT.

Methods and Materials

Study design

Radiation Therapy Oncology Group protocol 0126 is a phase 3 trial that compares conventional-dose (70.2 Gy) radiation therapy with dose-escalated (79.2 Gy) conformal radiation therapy for the management of early-stage, intermediate-risk prostate cancer. The primary objective of the trial is to determine whether an improvement in overall survival can be achieved with dose escalation. In September 2003 the trial (Fig. 1) was amended to allow IMRT; treatment modality was added as a stratification variable, to help avoid treatment arm modality imbalances.

Statistical considerations

This is a preliminary analysis of patients treated on the high-dose arm of the trial, to evaluate potential associations between toxicity and radiation therapy modality. The Common Toxicity Criteria, version 2.0, and RTOG/European Organization for Research and Treatment of Cancer late morbidity scoring systems were used to prospectively collect toxicity data. Acute toxicities were those experienced within 90 days of the start of treatment, and late toxicities occurred more than 90 days from the start of treatment. Univariate acute toxicity modality comparisons were done using the χ^2 test. Multivariate comparisons were done using logistic regression (7). Cumulative incidence methods (8) were used to estimate rates of late toxicity, and univariate comparisons were done using Gray's test. Multivariate analyses for late toxicity were done using the Fine-Gray method (9).

Patient population

Patients had prostate adenocarcinoma diagnosed within 180 days of registration. Intermediate-risk disease with clinical stage T1b-T2b, Gleason score of 2-6 and prostate-specific antigen (PSA) level $\geq$10 ng/mL but <20 ng/mL, or a Gleason score of 7 with a PSA level <15 ng/mL was eligible. Patients required no evidence of metastases and no prior prostatectomy, pelvic irradiation, androgen deprivation therapy, 5-α reductase inhibitors, or chemotherapy.

Target volumes and organs at risk

For patients receiving 3D-CRT the clinical target volume (CTV) included the prostate and entire seminal vesicles for the first 55.8 Gy, followed by a boost to the prostate only to a total of 79.2 Gy. Because IMRT would have required 2 separate plans to deliver treatment in a similarly phased schedule, the decision was made to modify the high-dose target volume for IMRT cases to include the prostate and the proximal 1 cm of seminal vesicle tissue identified on the planning CT scan for the entire 79.2 Gy. This CTV modification was based on data demonstrating that 93% of 344 prostatectomy specimens had no cancer beyond the first 1 cm in the seminal vesicle tissue (10). All CTVs were required to have a planning target volume (PTV) margin of 0.5 to 1.0 cm surrounding them to account for organ motion or setup uncertainties. The bladder, rectum, penile bulb, and bilateral femora were defined previously in other RTOG trials (11, 12). The

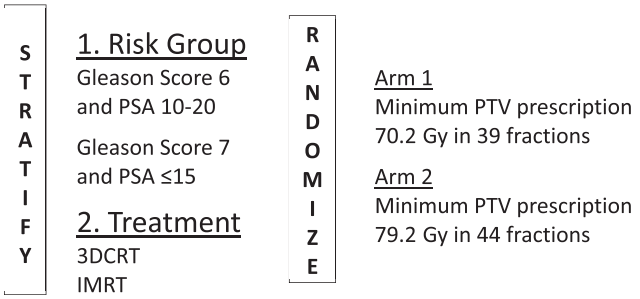

Fig. 1. Study schema.

bladder was contoured from its base to the dome, and the rectum from the anus (at the level of the ischial tuberosities) for a length of 15 cm or to the rectosigmoid flexure. Both these organs were contoured as solid structures.

Quality assurance

All treatment plans were submitted digitally to the Image-Guided Therapy QA Center (St. Louis, MO) for central review. All centers using IMRT had to successfully irradiate an anthropomorphic phantom from the Radiological Physics Center to demonstrate ability to comply with treatment planning constraints.

Treatment plans were scored as follows: (*1*) No variation (total coverage): prescription isodose surface covers ≥98% of the respective PTVs; (*2*) Minor variation (marginal coverage): prescription isodose surface coverage between ≥95% and <98% of the PTV; and (*3*) Major variation (suboptimal coverage): prescription isodose surface coverage <95% of the PTV, or <100% of CTV. The dose heterogeneity in the treatment plans was scored as follows: maximum dose to ≤ 2% of the PTV volume should not exceed the prescription dose by more than 7% (no variation: ≤7%; minor variation: >7 to ≤ 10%; major variation: >10%). This maximum dose volume of the PTV must not be shared by an "organ at risk." The protocol offered dose guidelines to the bladder, rectum, and penile bulb based on prior RTOG published experience (12-14).

Results

Patient characteristics

Of the 1532 patients enrolled in the trial from March 2002 to August 2008, 748 of the 763 cases randomized to the high-dose arm were eligible and evaluable for this toxicity analysis. Fifteen cases were excluded from this analysis owing to withdrawal of consent (n=5), histologic diagnosis established more than 180 days before study entry (n=7), ineligible Gleason score, PSA level, or T-stage combination (n=2), or pre-entry laboratory results or imaging missing or out of protocol range (n=1). Table e1 (available online) lists the pretreatment characteristics. Patients treated at US institutions were significantly more likely to have been treated with IMRT. This finding may explain the racial imbalance and the preponderance of T1 stage in the IMRT group because US patients may have been more likely to be diagnosed by PSA screening. There were no significant differences in baseline urinary incontinence, urgency, or frequency or sexual impotence. The median follow-up for the 3D-CRT patients was 4.6 (range, 0.1-8.1) years and for the IMRT patients was 3.5 (0.1-6.3) years.

Radiation therapy plan review

The CTVs were defined per protocol or with acceptable variation in 87.2% of the 3D-CRT cases and 85.2% of the IMRT cases. The target volumes for 3D-CRT cases allowed for a volume reduction from prostate and seminal vesicles to prostate only after 55.8 Gy. Seventy-five percent of 3D-CRT cases underwent a volume reduction. The average size (± standard deviation) of the high-dose prescription volume for 3D-CRT cases was 134.8 ± 48.8 mL. The IMRT cases had a single target volume that consisted of the prostate and the proximal 1 cm of seminal vesicle tissue. The average size of the high-dose prescription volume for IMRT cases was larger than the 3D-CRT cases, 160.2 ± 61.2 mL. This larger volume is located predominantly at the anterior rectal wall and bladder trigone. The organs at risk were defined according to protocol or with acceptable variation in 94.5% of the 3D-CRT and 90.3% of the IMRT cases. The median dose to 98% of the PTV volume (D98) was 80.0 Gy and 79.2 Gy for the 3D-CRT and IMRT cases, respectively. None of the differences in target volume or normal organ definition were statistically significant.

Dosimetric comparison

The median percentages of the bladder receiving at least xGy (pVx) for pV65, pV70, and pV75 were 25.3%, 22.2%, and 17.7% for 3D-CRT and 19.7%, 16.6%, and 13.1% for IMRT, respectively. The median rectum pV65, pV70, and pV75 were 27.4%, 21.7%, and 15.8% for 3D-CRT and 23.0%, 18.2%, and 13.0% for IMRT, respectively. All the differences in organ at risk radiation doses between RT modalities were statistically significant (all $P<.0001$).

Acute gastrointestinal/genitourinary toxicity

Patients treated with 3D-CRT experienced a 15.1% rate of grade 2 or worse (2+) acute gastrointestinal (GI) and/or genitourinary (GU) toxicity, compared with a 9.7% rate in patients treated with IMRT ($P=.042$). A multivariate analysis that included radiation modality, age, and race confirmed that radiation modality and age were associated with lower rates of grade 2+ acute GI and/or GU toxicity (Table 1). Figure 2 shows the differences in combined acute GI/GU toxicity, but individually the differences in either GI or GU effects alone were not significantly different. There were no differences in acute grade 3+ GI or GU toxicities. There were no significant differences in acute grade 2+ or grade 3+ genitourinary toxicity rates. The most common acute side effects were diarrhea, proctitis, dysuria, urinary frequency, and urinary retention.

Late GI/GU toxicity

Intensity modulated radiation therapy was associated with a significant reduction in late GI toxicity. Patients treated with 3D-CRT had a 22.0% cumulative incidence at 3 years of grade 2+

Table 1 Grade 2+ acute GU/GI toxicity, multivariate analysis

Stratified variables	Variable categories	Observed risk	95% confidence interval	*P*
RT method	3D-CRT 79.2 Gy	RL	(0.379-0.999)	.049
	IMRT	0.615		
Age	≤70 y	RL	(0.361-0.861)	.008
	>70 y	0.558		
Race	White	RL	(0.487-1.519)	.604
	Non-white	0.860		

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; GI = gastrointestinal; GU = genitourinary; IMRT = intensity modulated radiation therapy; RL = reference level; RT = radiation therapy.

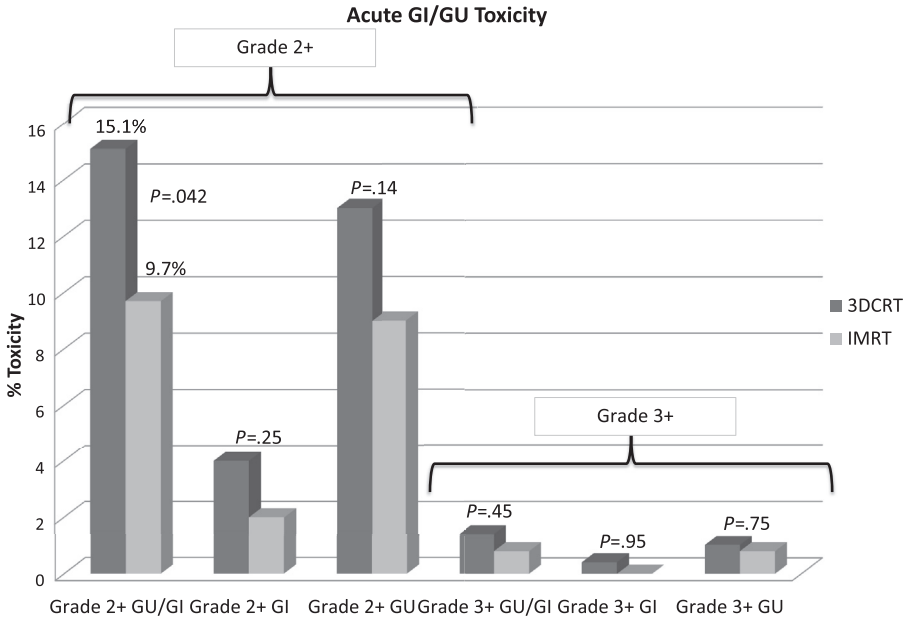

Fig. 2. Incidences of grade 2+ and grade 3+ acute gastrointestinal (GI) or genitourinary (GU), acute gastrointestinal, and acute genitourinary toxicity by radiation modality.

toxicity, compared with only 15.1% at 3 years for patients treated with IMRT ($P = .039$). Intensity modulated radiation therapy was associated with a reduction in the cumulative incidence at 3 years of grade 3+ late GI toxicity (5.1% vs 2.6%), although this trend was not statistically significant ($P = .09$). Figure 3 illustrates the improvement in time to late GI toxicity associated with IMRT compared with 3D-CRT. All reported toxicities are listed in Table e2. There were no significant differences in time to late grade 2+ or grade 3+ GU toxicities.

Intensity modulated radiation therapy was associated with a 27% reduction in time to grade 2+ late GI toxicity in a multivariate analysis that included radiation modality, age, and race, although this difference was not statistically significant ($P = .077$). Non-white race was associated with a significant reduction in the cumulative incidence of grade 2+ GI toxicity ($P = .001$). The cumulative incidence at 3 years of grade 2+ GI toxicity was 24% for whites, compared with 9% for non-whites ($P = .0001$; Fig. e1, available online). There were no significant GU toxicity differences related to race. There was an association between experiencing an acute effect and developing a late toxicity. Patients who had experienced acute grade 2+ GI toxicity were significantly more likely to have grade 3+ late toxicity. This association of acute toxicity and the development of late toxicity was independent of the racial differences described above. The most common late effects were radiation proctitis and rectal bleeding.

Partial volume effects

Small volumes of the rectum exceeding high-threshold radiation doses were associated with a nearly 2-fold risk of late grade 2+ toxicity. If more than 10% or 15% of the rectum exceeded 75 Gy or 70 Gy, respectively, patients had a significantly greater risk of late GI toxicity (Fig. 4). When both modality and the dose thresholds were included in the GI toxicity analysis, there was still a separation between the 3D and IMRT arms at each dose constraint level, with a larger, but not statistically significant, separation for the >10% dose constraint groups (Fig. 5).

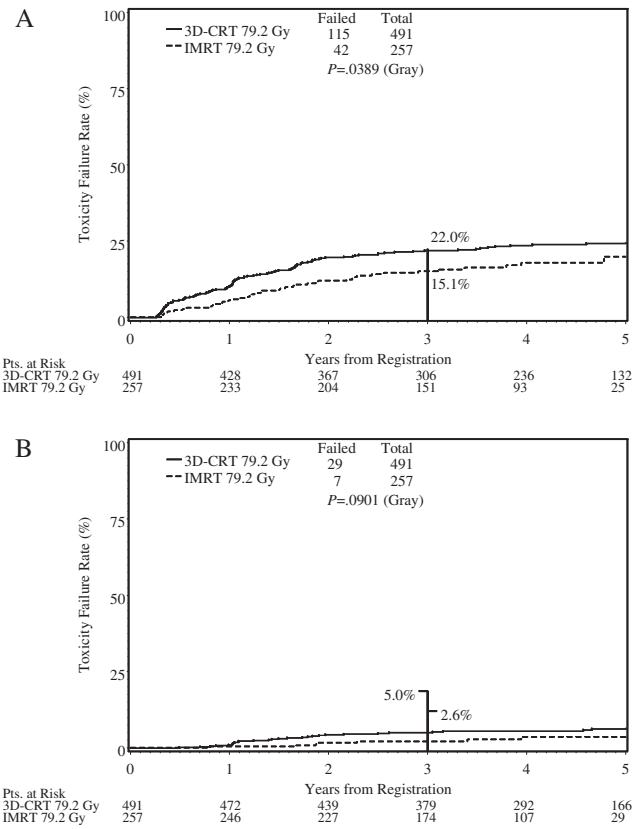

Fig. 3. Actuarial time to the development of (A) grade 2+ and (B) grade 3+ late gastrointestinal toxicity by radiation modality. 3D-CRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy.

Discussion

Dose escalation

Over the past decade modern radiation therapy planning and delivery techniques have allowed safe escalation of radiation dose for early-stage prostate cancer (15, 16). Several clinical trials have been conducted to test the value of dose-escalated radiation therapy (17-20). In these studies, a 9 Gy to 10 Gy increase in radiation dose was associated with an improvement in biochemical disease-free survival. In the University of Texas MD Anderson and Medical Research Council trials, the increase in radiation dose was also associated with an improvement in clinical disease-free survival (18, 19). However, none of these trials has demonstrated nor was powered to detect a difference in overall survival. Radiation Therapy Oncology Group protocol 0126 was designed to determine whether dose escalation will lead to a survival advantage and is currently in follow-up for the primary endpoint of overall survival.

In all the published dose-escalation trials there have been statistically significant increases in late rectal toxicity reported in the high-dose radiation arms (17-20). The Dutch trial reported a 2-fold increase in the incidence of late rectal bleeding or fecal incontinence in the high-dose arm (17). The Proton Radiation Oncology Group trial showed an increased rate of acute grade 2+ toxicity for the patients receiving a high dose (20). The Proton Group also reported a 24% incidence of late grade 2+ GI toxicity

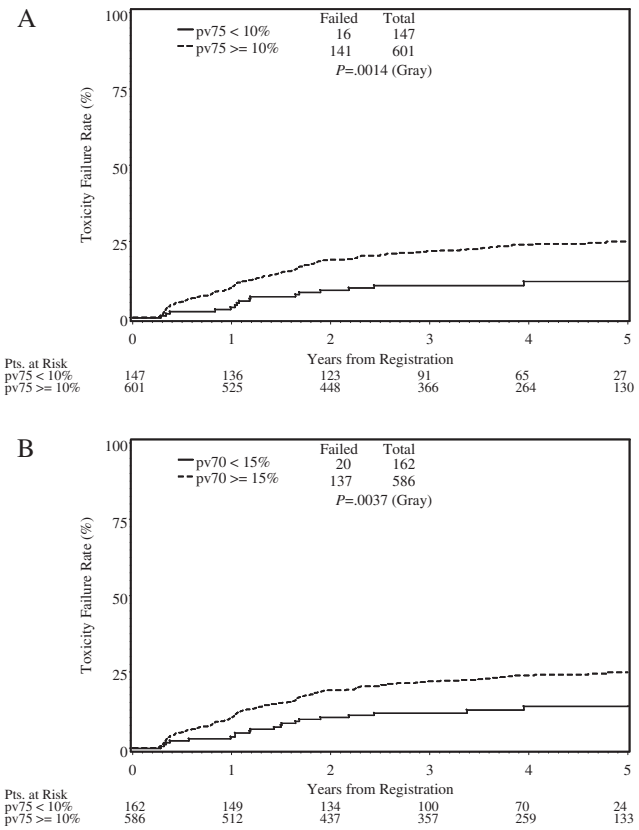

Fig. 4. Actuarial time to the development of grade 2+ late gastrointestinal toxicity by dose–volume metrics; (A) pV70 <15% or (B) pV75 <10%.

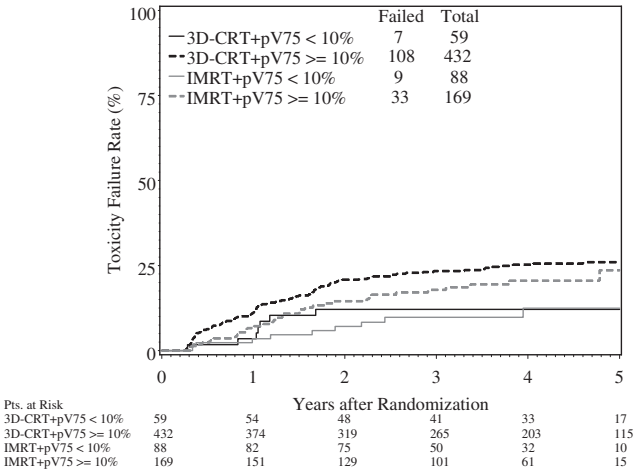

Fig. 5. Actuarial time to the development of grade 2+ late gastrointestinal toxicity by pV75 and radiation modality. 3D-CRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy.

in the high-dose arm, compared with only 13% in the standard-dose arm ($P = .09$) (20). Dearnaley et al (18) reported a 47% increase in grade 2+ late GI toxicity with a modest dose escalation with 3D CRT, from 64 Gy to 74 Gy. None of the trials has shown any significant differences in acute or late GU toxicity.

With the exception of the proton trial, each of these previous studies used 3D-CRT, or in the case of the MD Anderson trial conventional RT with a 3D-CRT boost. All the studies used uniform techniques in both dose arms, and IMRT was not available or allowed in them. Dosimetric analyses reported from some of these trials have demonstrated an association of dose to the rectum and the development of late grade 2+ GI or rectal toxicity (21, 22). In the MD Anderson trial, when at least 25% of the rectum was treated to more than 70 Gy, the grade 2+ complication rate 6 years after therapy was significantly increased, from 16% to 46% (22). In a report by Peeters et al (21), the incidence of rectal bleeding increased from 1% to 9% when the volume of the anorectal wall exceeding 65 Gy increased from 19% to 43%. In the present study, dosimetric analyses of patients treated to 79.2 Gy demonstrates an association for significant improvement in rectal, bladder, and penile bulb dosimetry with IMRT compared with 3D-CRT. Intensity modulated radiation therapy is more likely to achieve the dose constraints on the rectum than is 3D-CRT, and it would be expected to lead to a lower rate of late rectal toxicity.

In this study, IMRT was associated with a significantly lower rate of grade 2+ acute GI or GU toxicity. Although acute effects are reversible, there have been reports of an association between acute toxicity and the development of subsequent late complications. From the Dutch phase 3 trial, Peeters et al (21) reported that prior acute GI toxicity was a significant factor for persistent stool frequency (≥6 stools per day). In a review of their institutional experience, Vargas et al (23) reported that any acute tenesmus or diarrhea was associated with chronic rectal toxicity. Zelefsky et al (24) also reported an association of acute GI toxicity and late grade 2+ rectal toxicity. In a prospective trial testing the use of sucralfate to prevent late GI toxicity, O'Brien et al (25) reported that acute symptoms predicted for late radiation proctitis. Patients with moderate to severe pain were 3 times more likely to experience late rectal toxicity. Our data demonstrate an association of

grade 3+ late GI effects with previous acute grade 2+ GI toxicity. Whether patients who develop acute effects are predisposed to develop late effects or whether there is a direct relationship of acute injury and subsequent inflammation or late injury is unknown.

Intensity modulated radiation therapy has been reported to be associated with a lower rate of late rectal toxicity compared with 3D-CRT in patients receiving definitive RT for localized prostate cancer. In the prospective series of dose escalation at Memorial Sloan-Kettering, Zelefsky et al (24) reported a reduction in grade 2+ late rectal toxicity after the introduction of IMRT. The 10-year incidence of grade >2 GI toxicity for patients receiving 70.2 Gy, 75.6 Gy, and 81 Gy was 7%, 18%, and 5%, respectively. The reduction in the rate of late toxicity was attributed to the use of IMRT in the high-dose group. Although other single-institution studies have also reported a reduction in toxicity with the use of IMRT compared with 3D-CRT, they have been complicated by using either different radiation doses or different treatment volumes between the comparison groups (4-6). In an observational cohort study using 2002 to 2004 claims data from the Surveillance, Epidemiology, and End Results Medicare database, Bekelman et al (26) reported reductions in composite bowel complications and proctitis/hemorrhage related to the use of IMRT compared with 3D-CRT. In a propensity score-adjusted analysis of Surveillance, Epidemiology, and End Results data from 2000 to 2009, Sheets et al (27) confirmed a reduction in gastrointestinal toxicity associated with IMRT compared with conformal radiation therapy. The present analysis of the high-dose arm of the RTOG 0126 phase 3 trial confirms the association of lower rates of late rectal toxicity with IMRT.

Like other dose-escalation trials there did not seem to be any difference in late genitourinary toxicity by radiation technique (24). This may be related to the fact that with both 3D-CRT and IMRT the bladder neck and prostate urethra are unavoidably part of the target volume. Furthermore, variable bladder filling makes the development of models of partial organ irradiation complex. Finally, the expression of late bladder toxicity typically is years later than with rectal toxicity, and our follow-up is too short to identify any latent differences.

A strength of the present study is the relatively uniform treatment patients received on the trial. On average, IMRT patients had larger high-dose target volumes than 3D-CRT patients. This was related to the allowance of a target volume reduction on the 3D-CRT cases. Although the magnitude of the volume reduction is small, it is specifically at the anterior rectal wall and base of the bladder. This may impact the expression of GI and GU toxicities. Toxicity endpoints were reported and collected consistently, irrespective of treatment modality. Many of the patients treated on this trial received treatment during the era that IMRT was being adopted in many clinics, and normal tissue dose constraint guidelines were not as clearly established as they are today (28). Whether current practice would yield similar or better outcomes is worthy of further investigation.

Because this trial did not randomize patients to the different treatment techniques, the conclusions are not definitive. Furthermore, the treatment target volumes used were different from 3D-CRT to IMRT. In the preceding dose-escalation trial, RTOG 9406, patients with intermediate-risk disease received treatment to the prostate and seminal vesicles to a dose of 55.8 Gy, following which the prostate gland was boosted to 79.2 Gy (15). Because IMRT techniques require 2 separate treatment plans for this target volume approach, the investigators chose to treat the prostate and proximal 1 cm of seminal vesicle tissue to the study dose. This CTV of prostate and proximal seminal vesicle was supported by a pathologic analysis demonstrating that 1 cm of seminal vesicle tissue encompasses 93% of cancer extension from the prostate gland (10). This results in the IMRT patients having a slightly larger high-dose CTV than the 3D-CRT patients. It is expected that the larger volume to the total prescription dose would bias for more toxicity in the IMRT group; however, excess toxicity was not observed.

The evaluation of rectal volume and dose parameters confirms the association of partial rectal volumes exceeding defined threshold doses with complications. In this study, if <15% of the rectum exceeded 70 Gy (pV70 <15%) or <10% exceeded 75 Gy (pV75 <10%) there was a significant reduction in grade 2+ rectal late effects. Lower dose thresholds in the 40-Gy to 60-Gy range did not predict for rectal toxicity. This finding is consistent with the QUANTEC review that supported high dose limits being more important than lower doses to larger volumes (28).

An unexpected finding was the association of significantly less late rectal toxicity in non-white patients. There was no association of race with acute toxicity. Whether this observation reflects a different biology and response to radiation therapy or a bias in patient or physician reporting requires further analysis.

Conclusions

The use of IMRT in the high-dose treatment of men with localized prostate cancer was associated with significantly lower doses of radiation delivered to the rectum and bladder. Lower incidence of acute GI or GU toxicity is associated with the use of IMRT. Intensity modulated radiation therapy is also associated with a lower cumulative incidence of late grade 2+ rectal toxicity. When planning radiation therapy, keeping the volume of rectum exceeding 70 Gy or 75 Gy to <15% and <10%, respectively, is associated with lower rates of GI toxicity.

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