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Clinical Investigation

Rectal Toxicity After Proton Therapy For Prostate Cancer: An Analysis of Outcomes of Prospective Studies Conducted at the University of Florida Proton Therapy Institute

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Summary

Proton therapy was associated with a low rate of grade 2 or higher gastrointestinal toxicity in patients undergoing both investigational and outcome tracking protocols, predominantly transient rectal bleeding, which was highly correlated with aspirin, anticoagulation, and rectal dose-volume histogram parameters.

Purpose: Study goals were to characterize gastrointestinal effects of proton therapy (PT) in a large cohort of patients treated for prostate cancer, identify factors associated with rectal bleeding (RB), and compare RB between patients receiving investigational protocols versus those in outcome-tracking protocols.

Methods and Materials: A total of 1285 consecutive patients were treated with PT between August 2006 and May 2010. Potential pre-existing clinical and treatment-related risk factors for rectal toxicity were recorded. Common Terminology Criteria for Adverse Events version 3.0 was used to score toxicity.

Results: Transient RB was the predominant grade 2 or higher (GR2+) toxicity after PT, accounting for 95% of gastrointestinal events. GR1 RB occurred in 217 patients (16.9%), GR2 RB in 187 patients (14.5%), and GR3 in 11 (0.9%) patients. There were no GR4 or GR5 events. Univariate analyses showed correlations between GR2+ RB and anticoagulation therapy ($P = .008$) and rectal and rectal wall dose-volume histogram (DVH) parameters ($P < .001$). On multivariate analysis, anticoagulation therapy ($P = .0034$), relative volume of rectum receiving 75 Gy (V75; $P = .0102$), and relative rectal wall V75 ($P = .0017$) were significant predictors for G2+ RB. Patients treated with investigational protocols had toxicity rates similar to those receiving outcome-tracking protocols.

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Conclusions: PT was associated with a low rate of GR2+ gastrointestinal toxicity, predominantly transient RB, which was highly correlated with anticoagulation and rectal DVH parameters. Techniques that limit rectal exposure should be used when possible.

Introduction

External beam radiation treatment (EBRT) is commonly used to treat localized prostate cancer. The most common source for EBRT has been x-rays. With sophisticated x-ray delivery techniques, such as intensity modulated radiation therapy (IMRT), which permit delivery of high doses of radiation to the prostate and low to moderate doses to normal tissues, patients have experienced a reduction in radiation toxicity (1). This reduction in toxicity has permitted dose escalation, resulting in increased efficacy (2, 3). The use of protons in lieu of x-rays as the source for EBRT may offer further reduction in toxicity and improvement in efficacy by reducing the incidental radiation dose to normal tissues. Reports from Loma Linda University Medical Center (LLUMC; Loma Linda, CA) in which proton therapy (PT) alone has been used to treat prostate cancer (4, 5) and studies of PT in combination with x-ray therapy (6) have shown grade 3 (GR3) rectal toxicity rates of $<1\%$.

Recent studies using the Medicare database, however, have implied higher rates of rectal toxicity (7-9) in patients receiving PT than previously reported and, in some instances, higher than in patients receiving IMRT. These studies have been criticized for dependence on correlative data (eg Medicare claims codes) rather than physician-assessed toxicity or patient-reported outcomes (10).

Early toxicity and 5-year results from 3 prospective PT protocols conducted at our institution showed low rates of gastrointestinal (GI) and genitourinary (GU) toxicity (11-13), mirroring the LLUMC reports. The purposes of the present study was to confirm our early findings with a larger population of patients and to identify clinical and treatment factors associated with rectal toxicity.

Methods and Materials

The medical records of 1538 consecutive patients with localized prostate cancer treated with PT at our institution between August 2006 and May 2010 were reviewed under institutional review board approval. Patients were excluded from analysis if they had hypofractionation protocols (n = 141), PT for salvage therapy (n = 14), or pelvic IMRT (n = 60) or had non-hemorrhoidal rectal bleeding (RB; n = 1) or colostomy (n = 2) prior to PT. Thirty-five additional patients were excluded for inadequate data contribution, including 19 who refused follow-up, 8 who refused to complete questionnaires, 3 who died of non−treatment-related causes, and 5 who discontinued treatment for non-GI toxicity. A previous report included 211 patients enrolled in early investigational protocols (IP) (11) (the primary purpose of which was to establish benchmarked outcomes for patients receiving PT for localized prostate cancer), including 2 excluded from this analysis because of death from non−treatment-related causes during or within a month of PT. The analysis thus consists of 1285 patients with baseline characteristics shown in Table 1, of whom 209 were undergoing IP. An additional 1076 patients were enrolled in an outcome-tracking protocol (OTP) in which data were collected prospectively at the same regular follow-up intervals as IP patients, with additional data collected between follow-up visits if toxicity, disease recurrence, or other serious adverse events developed. The primary difference between the IP and OTP was in exclusion criteria; the IP did not enroll patients whose medical history included a factor that could confound interpretation of outcomes, such as a previous malignancy, whereas all treated patients were eligible for the OTP.

All patients had outside pathology reviewed at our institution to ensure consistency of diagnosis and Gleason grading. All patients had pretreatment serum prostate-specific antigen (PSA) and complete blood count and blood chemistry tests, pelvic computed tomography (CT), and magnetic resonance imaging (MRI), unless contraindicated. Patients with intermediate- and high-risk disease had bone scans. After May 2009, screening colonoscopies were required before PT to lessen concerns about potential malignant sources of post-treatment RB.

Treatment simulation and planning

The treatment simulation and planning processes have been described in detail previously (11). All patients underwent intraprostatic fiducial marker placement followed by CT simulation in a vacuum-locked body mold with 100 to 200 cm^3 saline instilled in the rectum. After May 2008, all patients had rectal balloons inflated with 80 to 100 cm^3 of saline for prostate stabilization. A planning MRI was also obtained with a Panorama model 0.23-T open MRI system (Philips, Amsterdam, the Netherlands) in patients able to tolerate MRI scanning, which was then fused with the CT for target and critical organ delineation. The rectum was manually contoured by dosimetrists, from the ischial tuberosity inferiorly to the sigmoid flexure superiorly. The rectal wall was constructed as 3-mm thick wall structures within the volume of the rectum.

The clinical target volume (CTV) included only the prostate in low-risk patients or the prostate and proximal

Table 1 Baseline characteristics for 1285 patients undergoing proton therapy for prostate cancer

Characteristics	No. of patients		
	All (n=1285)	OTP (n=1076; 84%)	IP (n=209; 16%)
Median age, y (range)	66 (41 to >89)	66 (42 to >89)	68 (41 to 88)
Ethnicity			
White	1173 (91%)	984 (91%)	189 (90%)
Black	78 (6%)	65 (6%)	13 (6%)
Other	34 (3%)	27 (3%)	7 (3%)
Body mass index			
<30	943 (73%)	779 (72%)	164 (78%)
≥30	342 (27%)	297 (28%)	45 (22%)
Diabetes			
No	1117 (87%)	939 (87%)	178 (85%)
Yes	168 (13%)	137 (13%)	31 (15%)
History of hemorrhoids			
No	819 (64%)	671 (63%)	148 (71%)
Yes	462 (36%)	401 (37%)	61 (29%)
Unknown	4 (<1%)	4 (<1%)	0 (0%)
Daily aspirin			
No	806 (63%)	690 (64%)	116 (56%)
Yes	479 (37%)	386 (36%)	93 (44%)
Anticoagulation*			
No	1167 (91%)	984 (91%)	183 (88%)
Yes	118 (9%)	92 (9%)	26 (12%)
Prostate size			
<60 cc	1094 (85%)	918 (85%)	176 (85%)
≥60 cc	187 (15%)	156 (15%)	31 (15%)
Unknown	4 (<1%)	2 (<1%)	2 (<1%)
Alpha-blocker use			
No	727 (57%)	643 (60%)	84 (40%)
Yes	558 (43%)	433 (40%)	125 (60%)
AUA score			
<15	1032 (82%)	864 (82%)	168 (80%)
≥15	228 (18%)	187 (18%)	41 (20%)
Unknown	25 (<0%)	25 (<0%)	0 (0%)
Risk group			
Low	540 (42%)	451 (42%)	89 (43%)
Intermediate	547 (43%)	466 (43%)	81 (39%)
High	198 (16%)	159 (15%)	39 (19%)
Gleason score			
5	6 (1%)	6 (1%)	0 (0%)
6	629 (49%)	524 (49%)	105 (50%)
7	483 (38%)	414 (38%)	69 (33%)
8+	167 (13%)	132 (12%)	35 (17%)
Tumor stage			
T1c	939 (73%)	804 (75%)	135 (65%)
T2	338 (26%)	269 (25%)	69 (33%)
T3/4	8 (1%)	3 (<1%)	5 (2%)
PSA ng/ml			
<4.0	204 (16%)	181 (17%)	23 (11%)
4.0-9.9	873 (68%)	730 (68%)	143 (68%)
10.0-19.9	170 (13%)	135 (13%)	35 (17%)
≥20.0	38 (3%)	30 (3%)	8 (4%)
Treatment start date			
Before May 2008	434 (34%)	225 (21%)	209 (100%)
May 2008 to May 2010	851 (66%)	851 (79%)	0 (0%)
Androgen deprivation therapy			
No	1060 (82%)	908 (84%)	152 (73%)
Yes	225 (18%)	168 (16%)	57 (27%)

(*continued on next page*)

Table 1 (*continued*)

Characteristics	No. of patients		
	All (n=1285)	OTP (n=1076; 84%)	IP (n=209; 16%)
Radiation dose, CGE			
<78	15 (1%)	14 (1%)	1 (0.5%)
78	1058 (82%)	920 (86%)	138 (66%)
>78	212 (17%)	142 (13%)	70 (33.5%)
Rectal wall V75			
<9.2%	499 (38.9%)	458 (42.6%)	41 (19.6%)
≥9.2%	785 (61.1%)	617 (57.4%)	168 (80.4%)
Relative rectum V75			
<9.4%	1058 (82.4%)	914 (85.0%)	144 (68.9%)
≥9.4%	226 (17.6%)	161 (15.0%)	65 (31.1%)

Abbreviations: AUA = asymptomatic urinary abnormalities; IP = investigational protocol; OTP = outcomes tracking protocol; PSA = prostate-specific antigen.

* Specific prescription anticoagulants, other than aspirin, included clopidogrel (Plavix) and warfarin (Coumadin).

2 cm of seminal vesicles in intermediate- and high-risk patients. The planning target volume (PTV) expansions were 8 mm and 6 mm beyond the CTV in the superior-inferior and axial planes, respectively; in May 2008, these expansions were reduced to 6 mm and 4 mm, respectively, after review of daily image guidance data with balloon stabilization. Patients were treated with lateral or lateral-oblique beams, typically with only 1 field each day. Prostate position was verified before delivery of each treatment field, using x-ray guidance and fiducial markers.

Target and normal tissue dosimetric specifications

In total, 98.8% of patients (99.5% of IP and 98.7% of OTP patients) received a treatment dose in the range of 78 to 82 Gy (relative biological effectiveness [RBE]). The median dose for all patients was 78 Gy (RBE) (range, 72-82.3 Gy [RBE]), 78 Gy (RBE) for IP patients (range, 76.0-82.0 Gy [RBE]) and 78 Gy (RBE) for OTP patients (range, 72-82.3 Gy [RBE]). Dosimetric specifications required that 95% of the target receive 100% of the prescribed dose and 100% of the target receive at least 95% of the prescribed dose. Dose constraints to organs at risk (OAR) included a rectal wall volume receiving at least 70 Gy (RBE) (V70) of <30% and V50 of <50% and a bladder wall V82 of <7 cm^3, a V80 of <8 cm^3, and a V30 of <35 cm^3. Patients in the low-risk IP received 78 Gy (RBE) to the prostate, whereas intermediate-risk IP permitted dose escalation to 78 to 82 Gy (RBE) to the prostate and proximal seminal vesicles when OAR dose constraints were met. High-risk IP patients received 78 Gy (RBE) with concomitant weekly docetaxel, followed by 6 months of androgen deprivation (ADT). OTP patients received predominantly 78 Gy (RBE) when OAR dose constraints were met; high-risk patients were also offered ADT. ADT was administered by referring physicians, and dose and duration of treatment were not recorded. Our recommendation was 6 months of ADT in patients with only 1 high-risk characteristic but up to 24 months in those with multiple high-risk features.

Outcome measurement and follow-up

Toxicity grading was based on Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE) (14) and occurred weekly during treatment and at 6-month intervals afterward. Specific GI symptoms evaluated included diarrhea, proctitis, abdominal cramping, fecal incontinence, and RB. Pre-existing clinical conditions that might contribute to toxicity, such as hemorrhoids, diabetes, and use of aspirin and anticoagulants, were recorded. Acute toxicity was defined as occurring either during PT or up to 90 days after completion of PT with late toxicity at any point after this. GR2 RB occurred acutely in only 2 of 1285 patients, both of whom had pre-existing hemorrhoids, so the focus of this report is on late rectal toxicity. Anticoagulant use was recorded prospectively at the time of initial consultation for radiation, although details regarding dose and duration of anticoagulant therapy were not recorded. In a few cases of prolonged rectal bleeding, anticoagulation was discontinued with approval of primary care physicians. For the purposes of further characterizing RB-related toxicity, CTCAE version 3.0-related GR2 RB was subdivided by intervention into medical (GR2A) such as prescribed rectal suppositories, procedural (GR2B), which included minor cautery and topical formalin application, and hyperbaric oxygen administration (GR2C). The minimum potential follow-up was 2 years; the median actual follow-up for all patients was 3.5 years, with 91% of patients with at least 2-year follow-up and 76% with 3-year follow-up, 37% with 4-year follow-up, and 14% with at least 5 years of follow-up.

Statistical analysis

Statistical computations were performed with SAS (SAS Institute, Cary, NC) and JMP software. The Kaplan-Meier product limit method and log-rank test were used to assess the impact of selected prognostic factors on GR2 or higher

(GR2+) RB. Both univariate and multivariate analyses were performed with proportional hazards regression. Backward selection assured the most parsimonious multivariate final model. Significant *P* values, hazard ratios, and confidence intervals for any significant variables reflect the final model, whereas non-significant *P* values, hazard ratios, and confidence intervals reflect their value in the full model. For both univariate and multivariate analyses, a post hoc Bonferroni adjustment was applied to the resulting *P* values; α value was increased proportionately to the number of prognostic factors considered. Prior to these analyses, the most optimal break points for each of a series of dosimetric parameters were determined with recursive partitioning. Each dosimetric parameter was reformatted as a binary variable based on the optimal break point before univariate and multivariate analyses. Two-sided *P* values of $\leq .05$ were considered statistically significant.

Results

Rates of rectal bleeding

The majority of GR2+ GI toxicity (95%) was related to RB. Most rectal bleeding was minimal, noted only with bowel movements, evident only as trace blood in stools or on toilet paper, and transient, beginning discretely some months after radiation and gradually completely resolving with or without intervention. Of the 1285 patients in this study, 415 (32.1%) admitted to post-treatment RB at some point during follow-up. The 217 patients (16.9%) with a maximum of GR1 RB included 195 patients who received no medications (15.2%) and 22 (1.7%) who took a short course of over-the-counter vitamin A, which has been shown to alleviate radiation proctitis (15, 16). The 187 patients with a maximum toxicity of GR2 (14.5%) were classified by intervention into GR2A medical, GR2B procedural, and GR2C hyperbaric oxygen. The 126 GR2A patients (9.8%) were given only rectal suppositories, 58 GR2B patients (4.5%) were treated with minor cautery or topical formalin application, and 3 GR2C patients (0.2%) received hyperbaric oxygen therapy. Eleven patients (0.9%) had a maximum of GR3 toxicity, including 8 (0.6%) who required transfusion, 2 who had formalin infusion (0.2%), and 1 (0.1%) who required a temporary, elective colostomy owing to development of hemorrhagic rectal ulceration following unauthorized biopsy of a telangiectatic rectal area performed by an outside gastroenterologist, which was subsequently successfully reversed. There were no GR4 or GR5 events. Post-treatment RB rates are shown in Figure 1. The overall GR2+ RB rate was 15.4% (198 patients). Ten patients had late GR2+ GI toxicities other than RB, including 7 patients with proctitis, 2 patients with transient episodes of rectal incontinence, and 1 patient with diarrhea.

The onset of RB in most cases (98.1%) occurred within 3 years of completing treatment at a median of 12 months. RB began before 6 months in 32 patients (7.7%), between 6 and 12 months in 173 patients (41.7%), between 12 and 18 months in 112 patients (27.0%), between 18 and 24 months in 46 patients (11.1%), and between 24 and 36 months in 44 patients (10.6%).

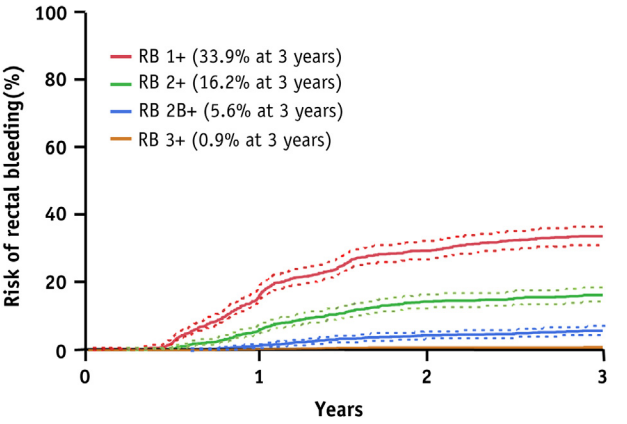

Fig. 1. Actuarial rate of rectal bleeding as a function of modified CTCAE v.3.0 severity scores. Grade 2+ includes all medical and procedural interventions for rectal bleeding, whereas GR2B+ includes only procedures such as cauterization and formalin and hyperbaric treatments, excluding those patients treated with suppositories. CTCAE v.3.0 = Common Terminology Criteria for Adverse Events, v3.0; GR2B+ = grade 2B or higher (toxicity).

Univariate and multivariate analyses of factors associated with rectal bleeding

Table 2 shows the results of univariate and multivariate analyses of factors potentially associated with GR2+ RB. On univariate analysis, anticoagulant use ($P = .008$) was significantly associated with GR2+ RB. Multiple rectum (RE) and rectal wall (RW) dose-volume histogram (DVH) parameters were also associated with GR2+ RB on univariate analysis, including both relative and absolute dose levels to both the RE and to the RW ranging from 30 Gy (RBE) to 75 Gy (RBE). Figure 2 shows the relationship between RB and increasing RE and RW DVH parameters with a table showing the most sensitive breakpoints for each DVH parameter. For simplification, only 4 DVH parameters were selected for evaluation in a multivariate analysis: percentage of RE (%RE) V30, %RE V75, %RW V30, and %RW V75. On multivariate analysis (Table 2), only the use of anticoagulants, %RE V75, and %RW V75 remained significant predictors for GR 2 + RB.

Tables 3 and 4 show the rate of GR2 overall and GR2B + RB, respectively, as a function of %RE V75, % RW V75, aspirin usage, and anticoagulation therapy. Patients not taking aspirin had rates of GR2B + RB of 4.3% versus 7.7% in those taking aspirin. Patients not taking anticoagulation regimens had rates of GR2B + RB of 4.5% versus 16.9% ($P < .0001$) in those receiving anticoagulation. The risk of GR2B + RB was highest (23%) in

Table 2 Factors associated with grade 2 or higher rectal bleeding

Factor	3-Year rate		Control group for hazard ratios	Univariate proportional hazards regression			Multivariate proportional hazards regression		
	Yes	No		*P* value	Hazard ratio	95% confidence interval	*P* value	Hazard ratio	95% confidence interval
Aspirin	19.4	14.3	Yes aspirin	.5820	0.7	0.5-1.1	.8041	0.8	0.5-1.2
Pretreatment diabetes	16.3	16.2	Yes diabetes	.9999	1	0.5-1.8	.9999	1.1	0.6-2.0
Anticoagulation	29.7	14.9	Yes anticoagulation	.0080	0.5	0.3-0.8	.0034	0.5	0.3-0.9
Pretreatment hemorrhoids	16.3	16.1	Yes hemorrhoids	.9999	1	0.6-1.5	.9999	0.8	0.5-1.3
Prostate volume <60 cm^3	16.5	14.5	≥60 cm^3	.9999	1.2	0.6-2.3	.9999	1.6	0.8-3.1
Alpha-blocker (pre- or post-treatment)	18.1	14.8	No alpha blocker	.9999	1.2	0.8-1.9	.9999	1.2	0.7-1.8
International prostate symptom score <15	16	17.7	≥15	.9999	0.9	0.5-1.5	.9999	0.8	0.5-1.4
Age, y < 60	14.3	16.7	≥60	.9999	0.9	0.5-1.5	.9999	0.9	0.5-1.7
Body mass index <30	16.1	16.5	≥30	.9999	1	0.6-1.6	-	-	-
Risk level*			Low risk	.9999	1.1	0.6-2.0	.9999	0.8	0.4-1.8
Androgen deprivation therapy	17.2	16.1	No androgen deprivation therapy	.9999	1.1	0.6-1.9	.9999	1	0.5-2.1
Dose ≤78 Gy(RBE)	15.1	22.2	>78 Gy	.3380	0.7	0.4-1.1	.9999	0.9	0.4-1.8
Ethnicity (white)	16.4	14.8	White	.9999	0.9	0.4-2.0	.9999	0.9	0.4-2.1
Treatment before May 2008	19.7	14.4	≥May 2008	.5500	1.4	0.9-2.1	.9999	0.8	0.5-1.4
Treatment before May 2009	17.1	14.3	≥May 2009	.9999	1.2	0.7-1.9	-	-	-
Treated on investigational protocol†	21	18.4	Yes protocol	.9999	0.8	0.4-1.6	-	-	-
Relative rectum V30 (%) < 26.4%‡	13.3	24.3	≥ 26.4%	.0006	0.5	0.3-0.8	.9999	0.9	0.4-2.3
Relative rectum V75 (%) < 9.4%‡	13.5	28.9	≥ 9.4%	<.0001	0.4	0.3-0.7	.0102	0.6	0.3-0.9
Relative rectal wall V30 (%) < 27.7%‡	13	23.5	≥ 27.8%	.0008	0.6	0.4-0.8	.9999	1	0.4-2.2
Relative rectal wall V75 (%) < 9.2%‡	8.3	21.1	≥ 9.2%	<.0001	0.4	0.2-0.7	.0017	0.5	0.3-0.9

* Three-way comparison between low, intermediate, and high risks. Hazard ratios and confidence intervals in the table indicate the widest ranges.

† Analysis of rectal bleeding risks between patients undergoing interventional protocols (IPs) and the outcome tracking protocol was restricted to patients treated before 2008, when the IPs were ongoing, to avoid issues of differential follow-up between the groups.

‡ All dose-volume histogram absolute and relative values for the rectum and rectal wall were highly statistically correlated with the risk of rectal bleeding; for purposes of analysis, only data for lowest and highest values tested are shown.

the subset of patients receiving anticoagulants, with %RW V75 ≥ 9.2%. Figures 3 and 4 show the actuarial rates of GR2 and GR2B + respectively with respect to anticoagulant status and %RW V75. Three-year freedom from GR2 RB for patients with RW V75 of <9.2% not receiving anticoagulation therapy was 92.4% versus 62.7% for patients with RW V75 > 9.2% who were receiving anticoagulation. For GR2B + RB, the corresponding rates were 97.1% for patients not receiving anticoagulation with RW V75 < 9.2% and 77.3% for those with RW V75 > 9.2% who were receiving anticoagulation (P<.0001).

Discussion

This study presents the largest prospective assessment of rectal toxicity to date in cases if localized prostate cancer treated solely with PT. Our results demonstrate that the most physician-reported toxicity in prostate cancer treated with PT is transient RB. Our data show low rates of GR2 and GR3 RB (14.5% and 0.9%, respectively) compared with some previously reported 3-dimensional (3D) conformal RT (3DCRT) (17-19) and IMRT (20, 21) dose-escalated studies. Specifically for IMRT, DeMeerleer et al (20) and Vora et al (21) reported late GR2 GI toxicity rates (both studies used modified versions of the Radiation Therapy Oncology Group [RTOG] scale) of 18% and 24%, respectively, using IMRT up to 76 Gy, whereas for 3DCRT, Pollack et al (17) reported a GR2+ late GI toxicity rate of 26% in patients receiving 78 Gy in 39 fractions.

Some series (2, 22, 23) have reported lower rectal toxicity with dose-escalated IMRT above 78 Gy. For example, Spratt et al (2) reported a GR2+ GI toxicity rate (per CTCAE version 4.0) of 4% after doses of up to 86.4 Gy with IMRT. However, most of these appear to be predominantly retrospective studies, in contrast to the prospective study we report herein. Individual categorized toxicities such as rectal suppository use were not reported

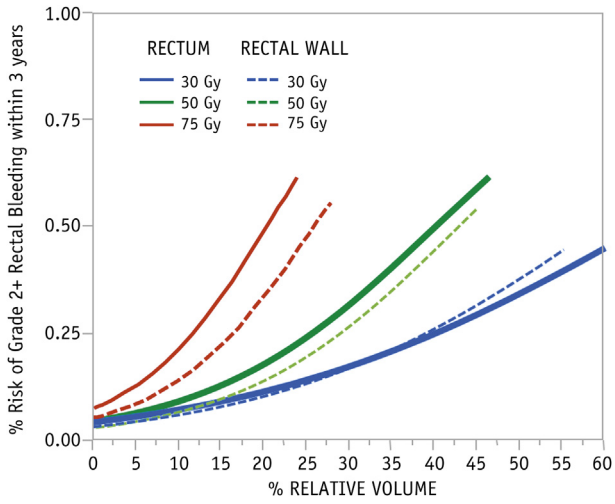

Fig. 2. Relationship between risk of GR2+ rectal bleeding and increasing percentage of rectal or rectal wall volumes receiving dose levels of 30, 50, and 75 CGE. Break points that best dichotomized the risk of GR2+ rectal bleeding for dose levels of 30, 50, and 75 CGE were 9.4%, 18.9%, and 26.4%, respectively, for the rectum and 9.2, 21.0, and 27.8%, respectively, for the rectal wall. GR2B+ = grade 2B or higher (toxicity).

in these series, in direct contrast to our study in which these individual toxicities were prospectively recorded and reported. A typical medical record might not consistently capture over-the-counter medical interventions or symptoms for which no intervention was given, so it is possible that studies not designed prospectively to capture such events could underestimate the prevalence of such symptoms and interventions.

Data in our study compare favorably to those of previously reported PT series (4, 6, 24, 25). LLUMC reported 3-year GR2+ GI toxicity rates of 21% (4), using the RTOG late effects scale (26). Zietman et al (6) reported GR 2 + GI toxicity of 17% in patients treated with 79.2 Gy with combined photons and protons, whereas Nihei et al (27) reported rates of GR2 rectal toxicity of 2% with PT, using a different scoring system, CTCAE version 2.0. (28). Again, just as with the dose-escalated IMRT series, specific interventions that were counted in the current study as GR2 toxicity (eg cortisone suppositories) are not specifically reported in previously published PT series, making direct comparisons difficult. In addition, scoring criteria vary among toxicity scoring systems, further complicating comparisons across studies regardless of treatment modality. Because most toxicity scoring systems are dependent on interventions and because preferences among physicians for interventions differ, standardized health-related quality-of-life questionnaires may be a useful tool for toxicity comparisons among different cohorts; Expanded Prostate Cancer Index Composite questionnaire data from this population is currently under analysis.

Our study provides a description of the most significant intervention for patient toxicity, which may offer patients more accurate expectations regarding toxicity risks. Most patients required minimal or no intervention. In contrast with dose-escalated IMRT experiences (2), which suggest a steady increase in bowel toxicity over time, in the LLUMC experience of 1255 patients, Slater et al (4) reported that all severe GI toxicity from PT manifested in the first 2.5 years after treatment. Similarly, Nihei et al (27) reported that RB, which was the most common late rectal toxicity, occurred within 2 years of treatment. In our study, 98.3% of cases of RB started within 3 years of PT and 87.7% within 2 years. Because 91% and 76% of patients had a minimum actual 2- or 3-year follow-up, it is likely that most of the physician-reported rectal toxicity occurring within this time frame was captured in our analysis. Clearly, longer follow-up is needed to confirm this possible difference in the pattern of late bowel toxicity between IMRT and PT; it is possible that other patterns of late GI toxicity will emerge with longer follow-up after PT.

We found toxicity outcomes in patients treated with specific IPs that were the same as those treated with OTPs. Because surveillance strategies for the IPs and OTPs were identical, this finding confirms the low toxicity rates previously reported in patients in IPs (11), and the generalizability of these findings to other patients treated with PT in a similar fashion with similar doses.

Previous reports from the Surveillance, Epidemiology, and End Results database (7-9) and Medicare claims data have suggested that PT may be associated with greater GI toxicity than IMRT. Criticism of these studies includes the

Table 3 Rate of grade 2 or higher rectal bleeding as a function of predictive factors

	No. of patients/total no. of patients (%)			
	Aspirin therapy		Anticoagulation therapy	
Factor	No	Yes	No	Yes
Grade 2+/total	109/806 (13.5%)	89/479 (18.6%)	166/1167 (14.2%)	32/118 (27.1%)
Relative rectum V75 (%)				
<9.4	73/668 (10.9%)	63/390 (16.2%)	112/960 (11.7%)	24/98 (24.5%)
≥9.4	36/137 (26.3%)	26/89 (29.2%)	54/206 (26.2%)	8/20 (40.0%)
Relative rectal wall V75 (%)				
<9.2	21/314 (6.7%)	20/185 (10.8%)	35/454 (7.7%)	6/45 (13.3%)
≥9.2	88/491 (17.9%)	69/294 (23.5%)	131/712 (18.4%)	26/73 (35.6%)

Table 4 Rate of grade 2B or higher rectal bleeding as a function of predictive factors

	No. of patients/total no. of patients (%)			
	Aspirin therapy		Anticoagulation therapy	
Factor	No	Yes	No	Yes
Grade 2B+/Total	35/806 (4.3%)	37/479 (7.7%)	52/1167 (4.5%)	20/118 (16.9%)
Relative rectum V75 (%)				
<9.4	25/668 (3.7%)	29/390 (7.4%)	38/960 (4.0%)	16/98 (16.3%)
≥9.4	10/137 (7.3%)	8/89 (9.0%)	14/206 (6.8%)	4/20 (20.0%)
Relative rectal wall V75 (%)				
<9.2	9/314 (2.9%)	8/185 (4.3%)	14/454 (3.1%)	3/45 (6.7%)
≥9.2	26/491 (5.3%)	29/294 (9.9%)	38/712 (5.3%)	17/73 (23.3%)

use of correlative endpoints (Medicare claims) rather than actual clinical outcomes, the comparison between large, population-based data for IMRT and 3DCRT and small-population data from a single institution for PT, and the absence of critical prognostic data, such as radiation prescription dose, fractionation, and DVH parameters (significantly associated with RB rates in the present study). The actual low rate of significant GI toxicity documented in our study underscores the possibility that studies relying on such surrogate data may lead to erroneous conclusions.

Two prognostic factors were found to be significantly associated with RB: the volume of RE or RW exposed to various radiation dose levels and the use of anticoagulants. These RE or RW DVH parameters were correlated with other factors such as prescribed dose, prostate size, and treatment and prostate stabilization techniques. Higher radiation doses for prostate cancer have been associated with higher rates of GI toxicity, for example, Zietman et al (6), reporting long-term outcomes of the PROG 9509 study randomizing patients between 70.2 CGE and 79.2CGE (50.4 Gy by photons followed by a proton boost), demonstrated an increased risk of GR2+ GI toxicity with higher doses of PT (13% vs 24%, respectively). The distinction between rectal DVH factors and prescribed dose to the prostate target volume (29) as the primary risk factor for rectal injury is critical as technical variations now and in the future may achieve rectal tissue dose constraints while permitting dose escalation or hypofractionation strategies that achieve better outcomes in terms of disease control or patient convenience. In the current study, the use of a rectal balloon permitted a reduction in PTV expansion, which we believe accounts for the reduction in GR2+ RB rates over time. Techniques currently under investigation that increase the distance between the prostate target volume and the RW by inserting slow absorption gels (30) may have a significant impact on rectal toxicity in the future. For now, the current study clarifies the relationship between rectal injury from PT and dose-volume relationships for rectal tissue that may be helpful in establishing future treatment planning guidelines for protection of OARs.

The use of anticoagulant agents was also associated with an increased risk of GR2+ RB. This risk with anticoagulants was double the risk with aspirin. Patients taking anticoagulants also required procedural interventions such as

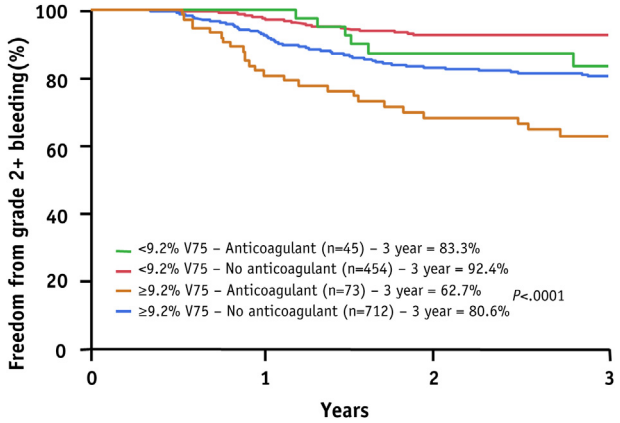

Fig. 3. Actuarial rate of freedom from GR2+ rectal bleeding with respect to anticoagulant use and rectal wall %V75. %V75 = percentage of the target volume receiving 75 Gy. GR2B+ = grade 2B or higher (toxicity).

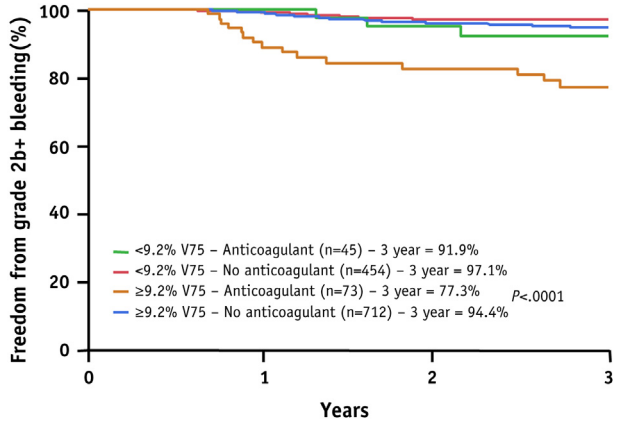

Fig. 4. Actuarial rate of freedom from GR2B + rectal bleeding with respect to anticoagulant use and rectal wall % V75. % V75 = percentage of the target volume receiving 75 Gy. GR2B+ = grade 2B or higher (toxicity).

topical formalin and minor cautery 3.7 times more frequently than patients not using anticoagulants. Some investigational studies exclude patients receiving anticoagulation therapy (25), making toxicity results less generalizable to the overall population. Takeda et al (31) also reported increased GR2+ GI toxicity in patients taking anticoagulants treated with 3DCRT or IMRT. In 718 men treated with EBRT to doses ≥75 Gy, Hamstra et al (32) reported GR2+ GI toxicity rates of 26.4% in patients taking anticoagulants compared to 11.3% in patients not taking anticoagulants ($P = .004$).

More stringent dose constraints to the RE and RW may be warranted in patients taking anticoagulants. Patients may benefit from education by their health-care team regarding RB expectations and risk minimization strategies such as maintenance of regular bowel function and avoidance of potentially harmful interventions. Current colonoscopies before PT can reduce the concern for RB related to other causes and the need for colonoscopic examinations during the risk period for RB. Prospective patient education on the pathophysiology of RB, potential benefits of avoiding dehydration or constipation, early notification of the health-care team if RB is observed, and the value of hemoglobin and hematocrit monitoring may allay patient concerns and pre-empt unnecessary potentially harmful interventions. In our experience, most cases of RB resolve without intervention. When RB occurs, we encourage good bowel function with hydration and stool softeners and rely on observation unless bleeding is prolonged, occurs outside normal bowel movements, or there is evidence of hemoglobin drop. When intervention is deemed necessary, our preferred order of interventions is: (*1*) over-the-counter vitamin therapy; (*2*) rectal suppositories, if necessary; and (*3*) topical formalin applications, only if deemed necessary by an experienced gastroenterologist and colorectal surgeon. Occasionally, hyperbaric oxygen therapy or multiple topical formalin applications are recommended. Rarely, formalin rectal infusion has been recommended. Patients are strongly encouraged to avoid invasive procedures such as cautery and argon plasma laser coagulation as some patients have anecdotally had clinical deterioration with these interventions. Rectal biopsy should be discouraged unless there is evidence suggesting prostate cancer progression (eg PSA rise or increasing mass on MRI or digital rectal examination) or a rectal tumor.

Conclusions

In our study, PT was associated with low rates of GR2+ GI toxicity, the most common event being transient RB. RB is typically minimal and resolves without intervention. Radiation exposure to rectal tissue and anticoagulant use are correlated with the risk of GR2+ RB following PT. Although rates of GR2+ RB are low, even among anticoagulated patients, patients taking such medications may benefit from more intensive monitoring after PT. Techniques that limit rectal exposure should be used when possible. In patients undergoing anticoagulation therapy, stricter dose constraints for rectal tissue may be warranted.

References

1. Michalski JM, Yan Y, Watkins-Bruner D, et al. 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. *Int J Radiat Oncol Biol Phys* 2013;87:932-938.
2. Spratt DE, Pei X, Yamada J, et al. Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2013;85:686-692.
3. Pahlajani N, Ruth KJ, Buyyounouski MK, et al. Radiotherapy doses of 80 Gy and higher are associated with lower mortality in men with Gleason score 8 to 10 prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;82:1949-1956.
4. Slater JD, Rossi CJ Jr., Yonemoto LT, et al. Proton therapy for prostate cancer: The initial Loma Linda University experience. *Int J Radiat Oncol Biol Phys* 2004;59:348-352.
5. Rossi CJ Jr., Slater JD, Yonemoto LT, et al. Influence of patient age on biochemical freedom from disease in patients undergoing conformal proton radiotherapy of organ-confined prostate cancer. *Urology* 2004;64:729-732.
6. Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: Long-term results from proton radiation oncology group/american college of radiology 95-09. *J Clin Oncol* 2010;28:1106-1111.
7. Sheets NC, Goldin GH, Meyer AM, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. *JAMA* 2012;307:1611-1620.
8. Kim S, Shen S, Moore DF, et al. Late gastrointestinal toxicities following radiation therapy for prostate cancer. *Eur Urol* 2011;60:908-916.
9. Yu JB, Soulos PR, Herrin J, et al. Proton versus intensity-modulated radiotherapy for prostate cancer: Patterns of care and early toxicity. *J Natl Cancer Inst* 2013;105:25-32.
10. Mendenhall NP, Schild S, Slater J. Radiation therapy modalities for prostate cancer. *JAMA* 2012;308:450-451. author reply 451-452.
11. Mendenhall NP, Li Z, Hoppe BS, et al. Early outcomes from three prospective trials of image-guided proton therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;82:213-221.
12. Mendenhall NP, Hoppe BS, Nichols RC, et al. Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2014;88:596-602.
13. Henderson RH, Hoppe BS, Marcus RB Jr., et al. Urinary functional outcomes and toxicity five years after proton therapy for low- and intermediate-risk prostate cancer: Results of two prospective trials. *Acta Oncol* 2013;52:463-469.
14. National Cancer Institute. Common terminology criteria for adverse events, v3.0. 2006. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed May 1, 2014.
15. Mendenhall WM, McKibben BT, Hoppe BS, et al. Management of radiation proctitis. *Am J Clin Oncol* 2013;37:517-523.
16. Ehrenpreis ED, Jani A, Levitsky J, et al. A prospective, randomized, double-blind, placebo-controlled trial of retinol palmitate (vitamin A) for symptomatic chronic radiation proctopathy. *Dis Colon Rectum* 2005;48:1-8.
17. Pollack A, Zagars GK, Starkschall G, et al. Prostate cancer radiation dose response: Results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002;53:1097-1105.
18. Dearnaley DP, Sydes MR, Graham JD, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: First results

from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007; 8:475-487.
19. Michalski JM, Winter K, Purdy JA. Trade-off to low-grade toxicity with conformal radiation therapy for prostate cancer on Radiation Therapy Oncology Group 9406. *Semin Radiat Oncol* 2002;12:75-80.
20. De Meerleer GO, Fonteyne VH, Vakaet L, et al. Intensity-modulated radiation therapy for prostate cancer: Late morbidity and results on biochemical control. *Radiother Oncol* 2007;82:160-166.
21. Vora SA, Wong WW, Schild SE, et al. Analysis of biochemical control and prognostic factors in patients treated with either low-dose three-dimensional conformal radiation therapy or high-dose intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2007;68:1053-1058.
22. Zelefsky MJ, Chan H, Hunt M, et al. Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. *J Urol* 2006;176:1415-1419.
23. Nath SK, Sandhu AP, Sethi RA, et al. Target localization and toxicity in dose-escalated prostate radiotherapy with image-guided approach using daily planar kilovoltage imaging. *Technol Cancer Res Treat* 2011;10:31-37.
24. Slater JD, Yonemoto LT, Rossi CJ Jr., et al. Conformal proton therapy for prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1998;42:299-304.
25. Coen JJ, Bae K, Zietman AL, et al. Acute and late toxicity after dose escalation to 82 GyE using conformal proton radiation for localized prostate cancer: Initial report of American College of Radiology Phase II study 03-12. *Int J Radiat Oncol Biol Phys* 2011;81:1005-1009.
26. RTOG/EORTC late radiation morbidity scoring schema. Available at: http://www.rtog.org/ResearchAssociates/AdverseEventReporting/RTOGEORTCLateRadiationMorbidityScoringSchema.aspx. Accessed May 1, 2014.
27. Nihei K, Ogino T, Onozawa M, et al. Multi-institutional phase II study of proton beam therapy for organ-confined prostate cancer focusing on the incidence of late rectal toxicities. *Int J Radiat Oncol Biol Phys* 2011;81:390-396.
28. National Cancer Institute. Common Toxicity criteria, v2.0 April 1999. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf. Accessed May 1, 2014.
29. McGee L, Mendenhall NP, Henderson RH, et al. Outcomes in men with large prostates ($\geq$ 60 cm(3)) treated with definitive proton therapy for prostate cancer. *Acta Oncol* 2013;52:470-476.
30. Song DY, Herfarth KK, Uhl M, et al. A multi-institutional clinical trial of rectal dose reduction via injected polyethylene-glycol hydrogel during intensity modulated radiation therapy for prostate cancer: analysis of dosimetric outcomes. *Int J Radiat Oncol Biol Phys* 2013; 87:81-87.
31. Takeda K, Ogawa Y, Ariga H, et al. Clinical correlations between treatment with anticoagulants/antiaggregants and late rectal toxicity after radiotherapy for prostate cancer. *Anticancer Res* 2009;29:1831-1834.
32. Hamstra DA, Stenmark MH, Ritter T, et al. Age and comorbid illness are associated with late rectal toxicity following dose-escalated radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2013; 85:1246-1253.