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Genitourinary Cancers

Five-Year Biochemical Results, Toxicity, and Patient-Reported Quality of Life After Delivery of Dose-Escalated Image Guided Proton Therapy for Prostate Cancer

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Summary

We report the clinical outcomes in men treated with image guided proton therapy for localized prostate cancer. In this cohort of 1327 men with a median follow-up time of 5.5 years, proton therapy provided excellent biochemical control rates for patients with low-risk, intermediate-risk, and high-risk prostate cancer. Proton therapy also preserves patient-reported quality of life and is associated with a low

Purpose: To report clinical outcomes in patients treated with image guided proton therapy (PT) for localized prostate cancer.

Methods and Materials: The medical records of 1327 men were reviewed. Each man was enrolled on an outcomes tracking study. Dual enrollment on a prospective clinical trial was allowed. Each patient was treated for localized prostate cancer with PT at our institution between 2006 and 2010. Ninety-eight percent of patients received 78 Gy (radiobiological equivalent [RBE]) or higher; 18% received androgen deprivation therapy (ADT). The 5-year freedom from biochemical progression (FFBP), distant metastasis-free survival, and cause-specific survival rates are reported for each risk group. Data on patient-reported quality of life and high-grade toxicities were prospectively collected and reported. A multivariate analysis was performed to identify clinical predictors of biochemical failure and urologic toxicity.

Results: The median follow-up time was 5.5 years. The 5-year FFBP rates were 99%, 94%, and 74% in low-risk, intermediate-risk, and high-risk patients, respectively. The actuarial 5-year rates of late grade 3+ Common Terminology Criteria for Adverse Events, version 4.0, gastrointestinal (GI) and genitourinary (GU) toxicity were 0.6% and 2.9%, respectively. Multivariate analysis showed a significant correlation between

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C. Bryant and T. L. Smith share first authorship of this work.

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incidence of high-grade urologic toxicity.

grade 3+ GU toxicity and pretreatment prostate reductive procedures ($P<.0001$), prostate volume ($P=.0085$), pretreatment α-blockers ($P=.0067$), diabetes ($P=.0195$), and dose−volume histogram parameters ($P=.0208$). The median International Prostate Symptom Scores pretreatment scores and scores at 5 years after treatment were 7 and 7, respectively. The mean Expanded Prostate Cancer Index Composite (EPIC) scores significantly declined for sexual summary for patients not receiving ADT (from 67 to 53) between baseline and 5 years.

Conclusions: Image guided PT provided excellent biochemical control rates for patients with localized prostate cancer. The actuarial rates of high-grade toxicity were low after PT. From pretreatment to 5 years of follow-up, a significant decline was found only in mean EPIC sexual summary scores. Prospective clinical studies are needed to determine the comparative effectiveness of PT and other radiation treatment strategies.

Introduction

More than 230,000 men received diagnoses of prostate cancer in 2014, making it the most common noncutaneous cancer among men in the United States (1). Numerous treatment strategies exist for managing localized prostate cancer, including external beam radiation therapy, brachytherapy, radical prostatectomy, and cryotherapy (2). Each strategy differs in cost, treatment efficacy, and side effect profile, making treatment decisions difficult. Furthermore, technological innovation improves each strategy over time, adding complexity to comparative effectiveness studies.

One such innovation within the category of external beam radiation therapy is proton therapy (PT). Although intensity modulated radiation therapy (IMRT) allows for the delivery of high-dose photon-based external beam radiation therapy with relative safety, PT provides an improvement over IMRT by reducing the radiation dose to normal tissue outside the volume targeted for cancer treatment. PT delivers less dose to normal tissues surrounding the prostate, like the rectum and bladder, compared with photon radiation (3-5), which may result in less toxicity and improved quality of life (QOL). To date, only a few studies have been published documenting the clinical outcomes in patients treated with PT for prostate cancer with more than 5 years of follow-up (6, 7), so the relative effectiveness of PT compared with other strategies is unknown (8).

Recently, we reported encouraging 5-year outcomes from 3 prospective trials in patients treated for localized prostate cancer with PT at our institution (7). The purpose of the present study was to update those findings, include them with a larger population of unselected consecutive patients, and identify factors predictive of either biochemical failure or urologic toxicity.

Methods and Materials

Patients

This study was approved by our institutional review board and was based on a review of the medical records of 1538 men with biopsy-proven localized prostate cancer treated consecutively with PT at our institution between 2006 and 2010 on a prospective outcome tracking protocol (OTP). The patients could also be dual enrolled on clinical trials. During the early part of the study, 3 prospective clinical trials designed to establish benchmark outcomes with PT delivered with standard dose and fractionation accrued patients with localized prostate cancer (7, 9). The first trial, PR01, included low-risk prostate cancer patients treated with PT to 74 to 78 Gy(radiobiological equivalent [RBE]) at 2 Gy(RBE) per fraction (n = 89). The second was a dose-escalation trial, PR02, which included patients with intermediate-risk prostate cancer who were treated to 74 to 82 Gy(RBE) of PT at 2 Gy(RBE) per fraction (n = 81). The third prospective trial, PR03, included high-risk prostate cancer patients treated with PT to 74 to 78 Gy(RBE) at 2 Gy(RBE) per fraction to the prostate and proximal seminal vesicles with concurrent weekly docetaxel (20 mg/m^2) without pelvic node irradiation, followed by androgen deprivation therapy (ADT) for 6 months (n = 39). In total, 209 patients accrued in 2006 and 2007 were dually enrolled on the early benchmark trials and the general OTP and were included in this study. Patients were excluded from this analysis if they had nodal metastasis present before treatment (n = 13), prior local treatment for prostate cancer (n = 14), did not complete PT (n = 5), refused, were ineligible for or withdrew from the outcomes tracking protocol (n = 19), or if no clinical follow-up information was available (n = 11). Later during the timeframe of this study (2008-2010), other clinical trials were conducted involving hypofractionation in low-risk and intermediate-risk patients (n = 141) and pelvic node irradiation and concurrent chemotherapy (n = 8) in high-risk patients; because the focus of the current study was to report overall outcomes of standard fractionation PT, these patients were not included in the current analysis. A total of 1327 patients were included in this study, and biochemical, clinical, and QOL data were collected prospectively from each patient at regular intervals. For the analysis of the 2 endpoints of freedom from disease progression and toxicity after PT, other specific exclusions were made. In the toxicity analysis, 34 patients

who received IMRT for elective nodal irradiation and 4 patients who did not have any gastrointestinal (GI) or genitourinary toxicity (GU) follow-up information were excluded, leaving a total of 1289 patients (Table 1). In the biochemical disease control analysis, because the focus was on tumor control after PT, patients who received concurrent chemotherapy (n = 53) and patients with less than 2 years of biochemical follow-up for reasons other than death (n = 60) were also excluded, leaving 1214 patients for the biochemical disease control analysis (Table 1).

The pretreatment workup for all patients included medical history, digital rectal examination, and in-house pathology review of prostate biopsy specimens to verify the diagnosis and Gleason score. The workup also included prostate-specific antigen (PSA), 1.5-Tesla to 3.0-Tesla magnetic resonance prostate imaging (MRI) and computed tomography (CT) scans of the pelvis, and bone scans in patients with intermediate-risk and high-risk disease.

The patients' histories were reviewed, and potential risk factors for treatment failure and toxicity were recorded, including maximum PSA, clinical stage, the results of pretreatment staging studies, prostate size per transrectal ultrasonographic findings at the time of fiducial marker placement, maximum Gleason score, maximum percentage of involvement in any biopsy core, percentage of zones involved on prostate biopsy, and the use of ADT. A 10-zone or more prostate biopsy was recommended within 6 months of beginning PT. The patient characteristics for this cohort are listed in Table 1.

Treatment simulation, planning, and delivery

The treatment planning procedures have also been previously described (9). The clinical target volume (CTV) for low-risk patients included only the prostate as visualized on fused MRI and CT images; the CTV in intermediate-risk and high-risk patients also included the proximal 2 cm of seminal vesicles. In the OTP population, reduction off of the seminal vesicles was allowed in patients with intermediate-risk disease. For high-risk patients with a risk for pelvic node involvement >15%, IMRT was delivered to the initial CTV, which included the pelvic nodes, the proximal seminal vesicles, and the prostate. The CTV was expanded by 5 mm axially and 8 mm in the superior and inferior axes to create a planning target volume (PTV); in 2008, the parameters for PTV expansion were reduced to 4 mm axially and 6 mm in the superior and inferior axes as the result of an internal intrafraction motion analysis. Lateral or oblique fields were used with PT. The edge of the brass aperture was placed 1 cm beyond the PTV in the superior, inferior, and anterior directions and 7 mm in the posterior direction. Treatment was planned with an Eclipse system (Varian Medical Systems, Palo Alto, CA) using a CT Hounsfield conversion algorithm (10). Distal and proximal range uncertainty margins of 5 mm and a smearing value of 19 mm were used.

The treatment planning guidelines included goals for both target coverage and dose constraints for organs at risk (OARs), including the bladder, bladder wall, rectum, rectal wall, and femoral heads. For target coverage, 95% of the PTV received 100% of the prescribed dose, and 100% of the PTV received at least 95% of the prescribed dose. Minor adjustments were allowed when dose constraint goals to the OARs could not be met, including a reduction in total dose, a reduction in dose per fraction, and treatment of both rather than only 1 field per day. In total, 1311 (99%) patients were treated with 2-Gy(RBE) fractions. The dose to the PTV was 78 to 80 Gy(RBE) in 1141 (86%) patients and 81 to 82 Gy(RBE) in 161 (12%) patients. Failure to meet the dose constraints to OARs, issues relating to patient preference, or both resulted in 24 patients (1.8%) receiving 73.8 to 77.4 Gy(RBE) in 1.8- to 2.0-Gy(RBE) daily doses. One patient discontinued treatment after 72 Gy(RBE) over 36 fractions. All patients treated with 1.8-Gy(RBE) fractions had both fields treated each day, and 1 patient was treated in the prone position in an effort to improve the daily dose distribution. Thus, 1324 patients (99.0%) received ≥75 Gy(RBE), and 1302 (98%) received ≥78 Gy(RBE).

Androgen deprivation therapy was primarily recommended for patients with high-risk prostate cancer for a duration of 6 to 24 months. Most ADT prescriptions for patients with low-risk or intermediate-risk disease had been prescribed by outside physicians before consultation for PT. Two hundred forty-four patients (18%) received neoadjuvant, concurrent, or adjuvant hormone therapy. The treatment characteristics for the patient cohort are listed in Table 1.

Follow-up and observed outcome

Follow-up included medical history review and physical examinations at 6-month intervals after treatment. PSA tests were performed every 3 months for 3 years and then semianually. Biochemical failure was determined according to the Phoenix definition (nadir + 2 ng/mL) (11). The time to reported biochemical outcomes was calculated from the radiation start date. Clinical failure (local, regional, or distant) was based on available clinical, histologic, or radiographic evidence of disease recurrence. In the event of biochemical failure, patients underwent bone scans, pelvic MRI, and occasionally positron emission tomography−CT. Biopsy of the prostate was not performed unless the results of pelvic MRI or digital rectal examination suggested possible local disease progression.

The patients were seen at 6-month intervals after treatment to prospectively assess toxicity according to the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAEv3) (12). The patients also prospectively completed International Prostate Symptom Score (IPSS) and QOL assessments (Expanded Prostate Cancer Index Composite; EPIC) at 6-month intervals after treatment for 5 years, then annually thereafter. The EPIC summary and subscales were calculated and reported using a scale of 0 to 100, with higher scores indicating better outcomes.

Table 1 Patient and treatment characteristics (N = 1327)

Characteristics	No. of patients	Biochemical and clinical freedom from progression analysis		Urologic toxicity analysis	
		Excluded	Included	Excluded	Included
Total number of patients	1327	113	1214	38	1289
Median age, y (range)	66 (41-88)	68 (41-84)	66 (42-88)	70 (50-87)	66 (41-88)
Race and ethnicity					
African-American	85 (6%)	12 (11%)	73 (6%)	4 (10%)	81 (6%)
Asian-Pacific	12 (1%)	0 (0%)	12 (1%)	0 (0%)	12 (1%)
Hispanic	23 (2%)	0 (0%)	23 (2%)	1 (3%)	22 (2%)
White	1207 (91%)	101 (89%)	1106 (91%)	33 (87%)	1174 (91%)
T stage*					
TX	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)
T1	953 (72%)	75 (66%)	878 (72%)	14 (37%)	939 (73%)
T2a	229 (17%)	14 (12%)	215 (18%)	3 (8%)	226 (17%)
T2b	90 (7%)	12 (11%)	78 (6%)	10 (26%)	80 (6%)
T2c	34 (3%)	6 (5%)	28 (2%)	2 (5%)	32 (2%)
T3	20 (2%)	6 (5%)	14 (1%)	9 (24%)	11 (1%)
Gleason score					
≤6	643 (48%)	40 (35%)	603 (50%)	5 (13%)	638 (50%)
7 = 3 + 4	332 (25%)	17 (15%)	315 (26%)	5 (13%)	327 (25%)
7 = 4 + 3	161 (12%)	8 (7%)	153 (13%)	2 (5%)	159 (12%)
8	122 (9%)	30 (27%)	92 (8%)	11 (29%)	111 (9%)
9-10	69 (5%)	18 (16%)	51 (4%)	15 (40%)	54 (4%)
PSA					
Median (range)	6 (0.3-134)	6.4 (0.5-90.4)	6 (0.3-134)	14.6 (4.3-58.6)	6.0 (0.3-134)
<10	1090 (82%)	77 (68%)	1013 (83%)	11 (29%)	1079 (84%)
10 to <20	183 (14%)	16 (14%)	167 (14%)	11 (29%)	172 (13%)
≥20	54 (4%)	20 (18%)	34 (3%)	16 (42%)	38 (3%)
Risk category					
Low	547 (41%)	33 (29%)	514 (42%)	3 (8%)	544 (42%)
Intermediate	551 (42%)	19 (17%)	532 (44%)	1 (3%)	550 (43%)
High	229 (17%)	61 (54%)	168 (14%)	34 (89%)	195 (15%)
Maximum percentage core involvement					
Unknown	41	3	38	3	38
<50%	844 (66%)	61 (55%)	783 (67%)	9 (26%)	835 (67%)
≥50%	442 (34%)	49 (45%)	393 (33%)	26 (74%)	416 (33%)
Percentage of prostate zones positive on biopsy					
Unknown	7	2	5	0	7
<50%	889 (67%)	66 (59%)	823 (68%)	9 (24%)	880 (69%)
≥50%	431 (33%)	45 (41%)	386 (32%)	29 (76%)	402 (31%)
Perineural invasion					
Yes	251 (19%)	31 (27%)	220 (18%)	18 (46%)	233 (18%)
Dose					
<75 Gy(RBE)	3 (<1%)	2 (2%)	1 (<1%)	1 (3%)	2 (<1%)
75-77 Gy(RBE)	22 (2%)	0 (0%)	22 (2%)	10 (26%)	12 (1%)
78-80 Gy(RBE)	1141 (86%)	104 (92%)	1037 (85%)	26 (68%)	1115 (87%)
81-82 Gy(RBE)	161 (12%)	7 (6%)	154 (13%)	1 (3%)	160 (12%)
Elective pelvic node radiation					
Yes	34 (3%)	0 (0%)	34 (3%)	34 (89%)	0 (0%)
Elective radiation to seminal vesicles					
Yes	743 (56%)	77 (68%)	666 (55%)	35 (92%)	708 (55%)
Concurrent chemotherapy	49 (4%)	49 (43%)	0 (0%)	0 (0%)	49 (4%)
Androgen deprivation therapy	244/1327 (18%)	59/113 (52%)	185/1214 (15%)	25/38 (66%)	219/1289 (17%)
Low risk	37/547 (7%)	1/33 (3%)	36/514 (7%)	0/3 (0%)	37/544 (7%)
Intermediate risk	56/551 (10%)	3/19 (16%)	53/532 (10%)	1/1 (100%)	55/550 (10%)

(*continued on next page*)

Table 1 (*continued*)

Characteristics	No. of patients	Biochemical and clinical freedom from progression analysis		Urologic toxicity analysis	
		Excluded	Included	Excluded	Included
High risk	151/229 (66%)	55/61 (90%)	96/168 (57%)	24/34 (71%)	127/195 (65%)
Comorbidities					
Diabetes	175 (13%)	18 (16%)	157 (13%)	6 (16%)	169 (13%)
No diabetes	1152 (87%)	95 (84%)	1057 (87%)	32 (84%)	1120 (87%)
Aspirin	491 (37%)	42 (37%)	449 (37%)	11 (29%)	480 (37%)
No aspirin	836 (63%)	71 (63%)	765 (63%)	27 (71%)	809 (63%)
Prescription anticoagulant	121 (9%)	14 (12%)	107 (9%)	2 (5%)	119 (13%)
No prescription anticoagulant	1206 (91%)	99 (88%)	1107 (91%)	36 (95%)	1170 (87%)
Pretreatment urologic function					
Pretreatment α-blockers	252 (19%)	26 (23%)	226 (19%)	6 (16%)	246 (19%)
No pretreatment α-blockers	1075 (81%)	87 (77%)	988 (81%)	32 (84%)	1043 (81%)
Pretreatment α-reductase inhibitors	102 (8%)	9 (8%)	93 (8%)	1 (3%)	101 (8%)
No pretreatment α-reductase inhibitors	1225 (92%)	104 (92%)	1121 (92%)	37 (97%)	1188 (92%)
Pretreatment TURP†	96 (7%)	14 (12%)	82 (7%)	0 (0%)	96 (7%)
No pretreatment TURP† or unknown	1231 (93%)	99 (88%)	1132 (93%)	38 (100%)	1193 (93%)
International Prostate Symptom Score					
Not available	28	3	25	2	26
<15	1060 (82%)	83 (75%)	977 (82%)	27 (75%)	1033 (82%)
≥15	239 (18%)	27 (25%)	212 (18%)	9 (25%)	230 (18%)
Prostate volume					
Not available	5	2	3	1	4
<Median (36 cm^3)	649 (49%)	66 (59%)	583 (48%)	19 (51%)	630 (49%)
≥Median (36 cm^3)	673 (51%)	45 (41%)	628 (52%)	18 (49%)	655 (51%)
<40 cm^3	777 (59%)	74 (67%)	703 (58%)	27 (73%)	750 (58%)
40-59 cm^3	355 (27%)	19 (17%)	336 (28%)	8 (22%)	347 (27%)
≥60 cc	190 (14%)	18 (16%)	172 (14%)	2 (5%)	188 (15%)
Follow-up, y					
PSA median (range)	5.1 (0.1-8.8)	1.9 (0.1-8.2)	5.3 (0.3-8.3)	3.9 (0.5-7.0)	5.2 (0.1-8.8)
Toxicity median (range)	5.5 (0.5-8.8)	5.5 (0.7-8.4)	5.5 (0.5-8.8)	4.7 (0.5-7.0)	5.5 (0.6-8.8)

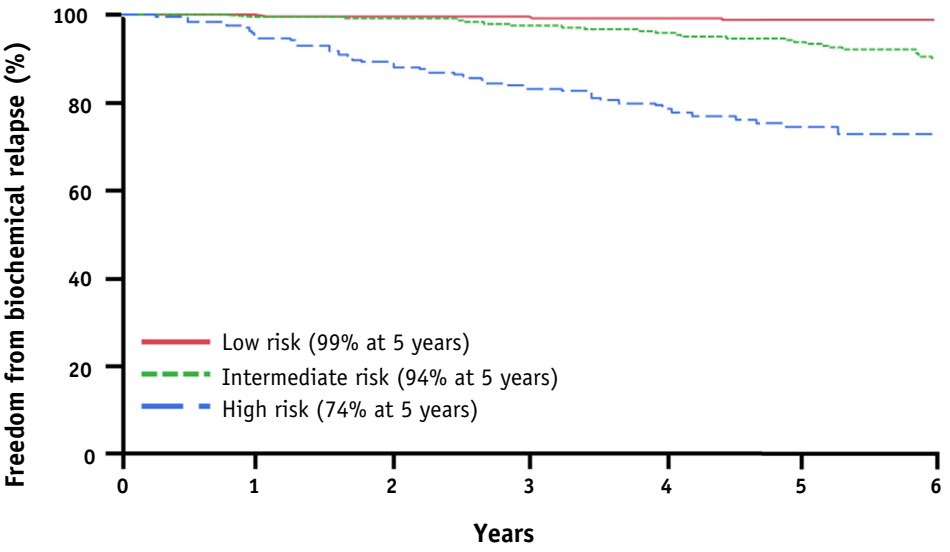
Abbreviation: TURP = transurethral resection of the prostate.
* T stage missing in 1 patient because prior colectomy precluded digital rectal examination.
† Includes all prostate reductive procedures.

Toxicities occurring ≥6 months after PT were scored as "late," and those occurring during treatment or <6 months after PT were scored as "acute." CTCAE, version 4.0 (CTCAEv4) (13) was published in 2009; all patients with CTCAEv3 grade 3 toxicities were also retrospectively categorized according to CTCAEv4 criteria.

Grade 3 urologic toxicity included the following: urinary frequency or urgency resulting in urination ≥1 time per hour or necessitating a catheter; urinary retention requiring more than daily catheterization or surgical intervention such as transurethral resection of the prostate (TURP), transurethral needle ablation, or indwelling suprapubic catheter; hematuria requiring blood transfusion(s); hyperbaric oxygen (HBO) treatment; or a surgical intervention such as a cystoscopy with a procedure (either a biopsy specimen showing necrosis or cauterization). Cystoscopies revealing normal bladder and not requiring an intervention (such as biopsy, cautery, or resection) were not scored as a grade 3 toxicity. Specific GI symptoms evaluated included diarrhea, proctitis, abdominal cramping, fecal incontinence, and rectal bleeding; a detailed analysis of factors associated with GI toxicity has been reported (14).

Statistical analysis

Statistical analyses were performed with SAS and JMP software (SAS Institute, Cary, NC). The Kaplan-Meier product-limit method provided estimates of freedom from biochemical recurrence, death of disease, and death of any cause. For each of these outcomes, the log-rank test statistic was used in a series of univariate analyses to assess the level of statistical significance between strata of selected prognostic factors. Proportional hazards regression with backward selection was then used for multivariate analysis. A P value of <.05 was considered statistically significant.



Risk Group	1 year No. of pts at risk (%)	2 year No. of pts at risk (%)	3 year No. of pts at risk (%)	4 year No. of pts at risk (%)	5 year No. of pts at risk (%)	6 year No. of pts at risk (%)
Low	512 (99.8%)	508 (99.8%)	486 (99.6%)	436 (99.2%)	316 (98.9%)	153 (98.9%)
Intermediate	527 (99.6%)	521 (99.1%)	489 (97.5%)	442 (95.8%)	322 (93.9%)	157 (90.0%)
High	160 (95.2%)	148 (88.6%)	130 (83.0%)	108 (78.3%)	67 (74.0%)	30 (72.7%)

Fig. 1. Freedom from biochemical failure by risk group.

The Kaplan-Meier product-limit method was used to estimate freedom from grade 3+ GU toxicity; the log-rank test statistic was used to assess statistical significance of these estimates after stratification by selected prognostic factors. Multivariate analysis of these same prognostic factors was performed with proportional hazards regression; a backward selection procedure was added to assure the most parsimonious final model for each toxicity endpoint. The most optimal breakpoints for each of a series of dosimetric parameters were determined with recursive partitioning before the multivariate analysis. Each dosimetric parameter was then reformatted as a binary variable based on the optimal breakpoint. Two-sided P values of $\leq .05$ were considered statistically significant. For EPIC patient-reported QOL comparisons, the mean and median scores are reported. The mean score change between baseline values and 5-year values was calculated, and significant differences were reported using the minimally important difference technique published by Skolarus et al for the EPIC composite short form (15).

Results

Disease control

The median follow-up time for biochemical outcomes was 5.3 years (range, 0.3-8.3 years). The median time to PSA nadir was 3.6 years (range, 0.3-8.4 years), and the median PSA nadir was 0.2 ng/mL for all patients. The median PSA nadir was 0.3 ng/mL for patients who did not receive ADT. By risk group, the median PSA nadir was 0.3 ng/mL for low-risk, 0.2 ng/mL for intermediate-risk, and 0.1 ng/mL for high-risk patients. The median times to nadir by risk group were 4.2, 3.6, and 1.1 years, respectively. For patients who did not receive ADT, the median PSA nadir by risk group was 0.3 ng/mL for low-risk, 0.2 ng/mL for intermediate-risk, and 0.3 ng/ml for high-risk patients. The median times to nadir by risk group for patients who did not receive ADT were 4.2, 3.6, and 2.2 years, respectively. At last follow-up, the median PSA was 0.3 ng/mL (range, 0-800 ng/mL) for all patients. It was 0.2 ng/mL (range, 0.01-100 ng/mL) for patients who received ADT and 0.3 ng/mL (range, 0-800 ng/mL) for patients who did not receive ADT. Biochemical failure occurred in 94 patients (7.7%) at a median of 3.3 years (range, 0.3-7.1 years). The 5-year freedom from biochemical progression (FFBP) rates were 99% for low-risk, 94% for intermediate-risk, and 74% for high-risk patients (Fig. 1).

Patterns of failure

All patients with disease progression had biochemical progression. PSA progression was the sole indication of disease progression in 42 patients (3.5%) but was accompanied by isolated biopsy-proven local failure in 6 patients (0.5%), isolated pelvic nodal failure in 10 patients (0.8%), isolated distant metastases in 24 patients (2.0%), or a combination of clinical sites in 12 patients (1.0%), including local (n = 5), nodal (n = 7), and/or distant metastasis (n = 11). Freedom from distant metastasis at 5 years was 99% for low-risk, 99% for intermediate-risk, and 98% for high-risk patients. The median times to distant metastasis for each risk group were 3.6, 4.0, and 3.0 years, respectively. Freedom from nodal metastasis at 5 years was 99% for low-risk, 99% for

Table 2 Univariate and multivariate analysis for biochemical failure at 5 years

Factors	Univariate		Multivariate	
	5-year FFBP	*P* value	Hazard ratio (CI)	*P* value
Risk group				
Low	99%	<.01	-	-
Intermediate	94%		-	
High	75%		-	
Clinical T stage (T1-2 vs T3)	94% vs 42%	<.01	0.9 (0.3-2.6)	.81
Gleason score				
4-7	96%	<.01	-	.02
8	85%		1.7 (0.9-3.2)	
9	55%		4.2 (2.4-7.4)	
Percentage of zones undergoing biopsy and positive for cancer (<50% vs ≥ 50%)	97% vs 86%	<.01	1.8 (1.1-2.9)	.02
Maximum percentage of tumor involvement in each core (<50% vs ≥ 50%)	97% vs 89%	<.01	1.0 (0.6-21.6)	.81
Prostate-specific antigen (ng/mL)				
<10	96%	<.01	-	.02
10 to <20	87%		1.5 (0.9-2.5)	
≥20	58%		3.8 (2.0-7.3)	
Perineural invasion (yes vs no)	83% vs 96%	<.01	1.8 (1.2-2.9)	.01
Elective seminal vesicle radiation (yes vs no)	99% vs 89%	<.01	0.2 (0.1-0.5)	<.01
Receipt of androgen deprivation therapy (yes vs no)	84% vs 95%	<.01	0.9 (0.5-1.6)	.80
Elective pelvic nodal radiation therapy (yes vs no)	52% vs 94%	<.01	0.9 (0.4-2.2)	.98

Abbreviations: CI = confidence interval; FFBP = freedom from biochemical progression.

intermediate-risk, and 96% for high-risk patients. The median times to nodal metastasis were 4.4, 2.8, and 2.0 years, respectively.

Survival

Fifty-five deaths occurred, including 14 from intercurrent disease and 41 from prostate cancer. The 5-year rates of prostate cancer–specific survival and overall survival were 97% and 96%, respectively. Cause-specific survival rates at 5 years were 98% for low-risk, 97% for intermediate-risk, and 95% for high-risk patients.

Predictors of biochemical failure

The results from the univariate and multivariate analyses of factors potentially predictive of 5-year FFBP are shown in Table 2. On multivariate analysis, Gleason score (4-7 vs 8 vs ≥ 9-10; $P=.02$), PSA (0 to <10 vs10 to <20 vs ≥20; $P=.02$), perineural invasion (yes vs no; $P=.01$), and the percentage of positive zones on biopsy (<50% vs ≥50; $P=.02$) were significant predictors of biochemical failure. Seventy-eight percent (n=415) of intermediate-risk patients had only 1 intermediate risk factor (Gleason 7, PSA 10 to <20, or clinical stage T2b-c), and 22% (n=117) had 2 or more. Patients with 2 or more intermediate risk factors had a lower rate of FFBP than did patients with only 1 intermediate risk factor (90% vs 95%, $P=.03$). Similarly, those 19 (12%) high-risk patients with 2 or more high-risk factors (Gleason 8-10, PSA ≥20, or clinical stage T3-4) had a lower rate of FFBP compared with 149 patients (88%) with only 1 high-risk factor (32% vs 80%, $P<.01$). Patients with high-risk disease based solely on Gleason 8 histology (n=85) had a biochemical relapse-free survival rate of 87.5% at 5 years.

Toxicity

Seventy of the 1289 patients (5.4%) had at least 1 episode of a CTCAEv3 grade 3+ GU toxicity, including 9 patients with only acute events, 58 with only late events, and 3 with both acute and late events. One of the 70 events was scored as grade 4; there were no grade 5 events.

Eight of the 12 patients (67%) with acute grade 3 events had urinary obstructive symptoms requiring temporary catheterization. Three patients had bladder irritation treated with catheterization (n=2) and HBO (n=1); and 1 patient with hematuria required a blood transfusion. In 5 of the 12 cases, subsequent additional acute or late grade 3 interventions were required: 3 patients required temporary catheters for urinary obstruction, 1 patient required 2 TURP procedures 2.1 and 4.8 years after PT, and a fifth patient underwent 2 TURPs 2.7 and 2.9 years after PT and later experienced hematuria that was treated with cauterization and HBO.

Forty-nine (80%) of the 61 patients (4.7%) with late CTCAEv3 grade 3+ events experienced only 1 event, predominantly related to obstructive symptoms in 26, hematuria in 18, and irritative symptoms in 5 patients. Twelve (20%) patients had more than 1 late grade 3 event: 3 had only obstructive symptoms, 1 had only hematuria, and the remaining 8 had a combination of obstructive symptoms,

Table 3 Univariate and multivariate analyses of clinical and treatment factors potentially associated with late grade 3+ GU toxicities

	All patients with grade 3+ GU toxicity				Patients with grade 3+ GU toxicities without pretreatment TURP*			
	Univariate		Multivariate		Univariate		Multivariate	
Characteristics	*P*-value	HR (CI)	*P*-value	HR (CI)	*P*-value	HR (CI)	*P*-value	HR (CI)
Factors and co-morbidities								
Age (<60 vs ≥60)	.4437	0.8 (0.4-1.4)	NT	-	.8298	1.1 (0.5-2.1)	NT	-
Race (Non-African American vs African American)	.5341	0.6 (0.3-1.9)	NT	-	.6617	0.8 (0.3-3.4)	NT	-
Diabetes (no vs yes)	.0210	0.5 (0.3-0.9)	.0195	0.5 (0.3-0.9)	.0447	0.5 (0.3-1.1)	.0322	0.5 (0.2-0.9)
Aspirin (no vs yes)	.5369	0.9 (0.5-1.4)	NT	-	.7607	0.9 (0.5-1.7)	NT	-
Prescription anticoagulants (no vs yes)	.0316	0.5 (0.3-1.0)	.1848	0.6 (0.3-1.2)	.1992	0.6 (0.3-1.5)	.3685	0.6 (0.3-1.6)
Prostate factors								
Prostate volume Median = 36.3 cc (<36.3 vs ≥36.3)	.1734	0.7 (0.4-1.2)	NT	-	.3857	0.8 (0.4-1.4)	NT	-
Prostate volume (<40 vs 40-60 vs >60 cc)								
<40 vs >60	<.0001	0.3 (0.2-0.5)	.0085	0.4 (0.2-0.8)	.0001	0.3 (0.2-0.6)	.0268	0.5 (0.3-1.1)
40-60 vs >60		0.3 (0.1-0.5)		0.4 (0.2-0.8)		0.2 (0.1-0.6)		0.3 (0.1-0.7)
Disease factors								
T stage (T1 vs T2+)	.8241	1.1 (0.6-2.0)	NT	-	.9692	1.0 (0.5-2.0)	NT	-
T stage (T1-T2a vs T2b+)	.5614	1.4 (0.6-4.5)	NT	-	.4293	1.8 (0.5-10.8)	NT	-
Maximum Gleason score (4-6 vs 7 vs 8-10)	.8241	1.1 (0.6-2.0)	NT	-	.9692	1.0 (0.5-2.0)	NT	-
4-6 vs 8-10	.6477	0.8 (0.4-1.8)	NT	-	.4099	0.7 (0.3-1.8)	NT	-
7 vs 8-10		0.7 (0.3-1.6)		-	-	0.5 (0.2-1.4)	-	-
Risk group (low vs intermediate vs high)								
Low vs high	.844	0.9 (0.4-1.9)	NT	-	.4567	0.8 (0.4-1.9)	NT	-
Intermediate vs high	-	0.8 (0.4-1.8)	-	-	-	0.6 (0.3-1.5)	-	-
Pretreatment GU function								
α-blockers	<.0001	0.4 (0.2-0.6)	.0067	0.5 (0.3-0.8)	<.0001	0.3 (0.2-0.6)	.0008	0.3 (0.2-0.6)
α-reductase inhibitors	.1385	0.6 (0.3-1.3)	.89	1.0 (0.4-2.1)	.7361	0.8 (0.3-2.8)	.7302	1.3 (0.4-3.7)
Pretreatment TURP*	<.0001	0.2 (0.1-0.3)	<.0001	0.2 (0.1-0.3)	N/A	-	N/A	-
Any pretreatment GU symptom management†	<.0001	0.3 (0.2-0.4)	NT	-	.0019	0.4 (0.2-0.7)	NT	-
International Prostate Symptom Score	.1219	0.6 (0.3-1.0)	.4341	0.7 (0.4-1.3)	.0325	0.5 (0.3-1.0)	.3828	0.7 (0.4-1.4)
Treatment factors								
Hormone therapy	.0243	1.9 (1.0-3.2)	NT	-	.1048	1.7 (0.8-3.4)	NT	-
Chemotherapy	.6001	0.8 (0.3-2.5)	NT	-	.554	0.7 (0.3-2.9)	NT	-
Prescribed dose (<79 CGE vs ≥79 CGE)	.2208	1.6 (0.8-3.6)	NT	-	.1744	1.9 (0.8-5.5)	NT	-
Organs-at-risk dose-volume histogram factors								
Absolute bladder volume (cm^3)								
V30	<.0001	0.4 (0.2-0.6)	.0208	0.5 (0.3-0.9)	.0003	0.3 (0.2-0.6)	.0224	0.5 (0.2-0.9)
V39	.0022	0.5 (0.3-0.8)	.4029	0.8 (0.3-2.0)	.0148	0.5 (0.3-0.9)	.7378	1.0 (0.3-3.1)
V70	<.0001	0.4 (0.2-0.6)	.5139	0.8 (0.3-2.6)	.0004	0.4 (0.2-0.7)	.8468	1.0 (0.3-4.1)
V75	.0012	0.4 (0.2-0.7)	.4164	1.6 (0.4-5.7)	.0018	0.4 (0.2-0.7)	.8872	0.8 (0.2-3.3)
V80	.0077	0.5 (0.3-0.8)	NT	-	.0321	0.5 (0.3-0.9)	NT	-
V82	.1339	1.6 (0.9-3.3)	NT	-	.1063	1.9 (0.9-4.7)	NT	-
Absolute bladder wall volume (cm^3)								
V30	<.0001	0.3 (0.2-0.5)	.8871	1.3 (0.1-20.3)	.0008	0.3 (0.2-0.7)	.9108	1.3 (0.1-29.4)
V39	<.0001	0.3 (0.2-0.5)	.4614	0.5 (0.0-9.3)	.0007	0.3 (0.2-0.7)	.6192	0.7 (0.0-18.0)

(*continued on next page*)

Table 3 (*continued*)

Characteristics	All patients with grade 3+ GU toxicity				Patients with grade 3+ GU toxicities without pretreatment TURP*			
	Univariate		Multivariate		Univariate		Multivariate	
	P-value	HR (CI)	*P*-value	HR (CI)	*P*-value	HR (CI)	*P*-value	HR (CI)
V70	.0007	0.4 (0.3-0.7)	.4834	1.7 (0.4-6.6)	.0065	0.4 (0.2-0.8)	.7954	1.8 (0.4-7.4)
V75	.0006	0.4 (0.3-0.7)	.9696	0.6 (0.4-1.3)	.0023	0.4 (0.2-0.7)	.5155	0.6 (0.2-2.0)
V80	.0192	0.6 (0.3-0.9)	NT	-	.1244	0.6 (0.3-1.1)	NT	-
V82	.1785	1.6 (0.8-3.2)	NT	-	.1398	1.8 (0.9-4.5)	NT	-
% Bladder volume (cm^3)								
V30	.0047	0.5 (0.3-0.8)	NT	-	.0059	0.4 (0.2-0.8)	NT	-
V39	.0082	0.5 (0.3-0.8)	NT	-	.0118	0.4 (0.2-0.8)	NT	-
V70	.0069	0.5 (0.3-0.8)	NT	-	.0104	0.4 (0.2-0.8)	NT	-
V75	.0046	0.5 (0.3-0.8)	NT	-	.0079	0.4 (0.2-0.8)	NT	-
V80	.0063	0.5 (0.3-0.8)	NT	-	.0040	0.4 (0.2-0.8)	NT	-
V82	.2302	1.5 (0.8-3.0)	NT	-	.1712	1.8 (0.8-4.3)	NT	-
% Bladder wall volume (cm^3)								
V30	.0043	0.5 (0.3-0.8)	NT	-	.0688	0.6 (0.3-1.1)	NT	-
V39	.0032	0.5 (0.3-0.8)	NT	-	.0935	0.6 (0.3-1.1)	NT	-
V70	.0015	0.5 (0.3-0.8)	NT	-	.0471	0.5 (0.3-1.0)	NT	-
V75	.0028	0.5 (0.3-0.8)	NT	-	.0298	0.5 (0.3-1.0)	NT	-
V80	.0088	0.5 (0.3-0.9)	NT	-	.0091	0.4 (0.2-0.9)	NT	-
V82	.2202	1.5 (0.8-3.1)	NT	-	.1651	1.8 (0.8-4.3)	NT	-

Abbreviations: CI = confidence interval; GU = genitourinary; HR = hazard ratio; NA = not applicable; NT = not tested in multivariate analysis; TURP = transurethral resection of the prostate.

* Includes transurethral resection of the prostate and other prostate reductive procedure.

† Includes α-blockers, α-reductase inhibitors, and pretreatment TURP.

irritative symptoms, and hematuria. Twenty-two patients required TURP for a grade 3 urinary obstruction, including 20 for obstructive symptoms alone and 2 for either hematuria or incontinence associated with obstruction. Treatments for hematuria included blood transfusions (n=5), HBO (n=14), cauterization (n=11), catheterization (n=6), and TURP (n=1), with some patients requiring more than 1 treatment. Pain syndromes in 3 patients were treated with HBO (n=2) and catheterization (n=1). Two patients had a transurethral resection or biopsy specimen showing necrotic bladder tissue. The single grade 4 event was hematuria, which occurred in a patient living out of the country; no details regarding precipitating events and management decisions could be obtained. He had a 6-week hospitalization with multiple interventions, including blood transfusions, cauterizations, HBO, and catheterizations before the hematuria resolved.

Factors associated with grade 3+ GU toxicity

Univariate analyses of clinical and treatment factors potentially associated with late CTCAEv3 grade 3+ GU toxicities in all patients and in the subset of patients who did not have a pretreatment TURP are shown in Table 3. In the overall group, significant associations were found between late CTCAEv3 grade 3+ toxicities and the following variables: ADT ($P=.0243$), prescription anticoagulants ($P=.0316$), prostate volume <40 cm^3 versus 40-59 cm^3 versus ≥60 cm^3 ($P<.0001$), pretreatment use of α-blockers ($P<.0001$), diabetes ($P=.0210$), pretreatment TURP ($P<.0001$), any pretreatment urologic symptom management ($P<.0001$), and several dose–volume histogram (DVH) parameters for relative and absolute volumes of bladder and bladder wall exposed to various dose levels. In a univariate analysis restricted to patients without pretreatment TURP, factors significantly associated with CTCAEv3 grade 3+ toxicity included prostate volume <40 cm^3 versus 40-59 cm^3 versus ≥60 cm^3 ($P<.0001$), αblockers ($P<.0001$), any pretreatment urologic symptom management ($P=.0019$), diabetes ($P=.0447$), and bladder DVH parameters.

Multivariate analyses for GU toxicity

Multivariate analyses were performed in both the overall group and the group without pretreatment TURP to determine which factors were most predictive of late CTCAEv3 grade 3+ toxicity (Tables 3 and 4). Factors contributing to a predictive model for all grade 3+ events included pretreatment TURP, prostate volume, pretreatment α-blockers, and DVH parameters. As shown in Table 4, patients with no risk factors and 1, 2, and 3 or more risk factors had a 1.9%, 3.6%, 11.3%, and 17.8% estimated risk of grade 3+ toxicity at 5 years, respectively ($P<.0001$). In patients who did not have a pretreatment TURP, significant predictors for toxicity were prostate volume, pretreatment α-

Table 4 Factors associated with late grade 3+ genitourinary toxicity on multivariate analyses

No. of risk factors	Total with grade 3+ toxicity/no. of patients	5-year estimates of freedom from grade 3+ toxicity
0	14/720 (1.9%)	1.9%
1	13/355 (3.7%)	3.6%
2	26/174 (14.9%)	11.3%
3 or 4	8/40 (20.0%)	17.8%

Factors tested in this multivariate analysis included prostate volume, anticoagulation, pretreatment cytoreductive prostate procedures, pretreatment treatment with α-blockers, International Prostate Symptom Score, and 8 dose-volume histogram (DVH) parameters.

blockers, the absolute bladder volume receiving a dose of 30 Gy(RBE), and diabetes.

As shown in Table 5, patients in whom grade 3+ toxicity developed had a larger median prostate volume, more frequent pretreatment use of α-blockers, a higher incidence of pretreatment TURP, and a higher volume of bladder tissue receiving a dose of 30 Gy(RBE) than did the overall study group.

Impact of conversion from CTCAEv3 to CTCAEv4

When patient toxicities were retrospectively reassessed according to CTCAEv4, some grade 3+ events were downgraded. The overall and late actuarial 5-year grade 3+ GU toxicity rates changed from 5.4% and 4.7% with CTCAEv3 to 3.0% and 2.9% with CTCAEv4.

Late GI toxicity

Late CTCAEv3and v4 grade 3 GI symptoms occurred in 9 patients. Grade 3 events included 1 case of diarrhea, 7 cases of rectal bleeding requiring transfusion, and 1 case of rectal ulceration, which occurred after an endoscopic biopsy of inflamed rectal mucosa that required temporary colostomy for healing. The 5-year actuarial incidence of late grade 3 GI toxicity was 0.6%.

Patient-reported outcomes

As shown in Table 6, at 5 years of follow-up, the median baseline International Prostate Symptom Score remained unchanged at 7. Similarly, the median and mean EPIC summary scores for bowel, urinary irritative/obstructive, and urinary incontinence domains remained relatively stable. When mean differences were tested, only sexual function summary scores for patients not using ADT significantly declined from baseline to 5 years according to the minimal significant change test (15). Between baseline and 5 years, the mean scores in patients not receiving ADT declined from 67 to 53, and median sexual summary scores fell from 75 to 55.

Clinical trial versus outcome tracking protocol patients

A comparison of the patients enrolled on the clinical trials and those only on the OTP is provided in Tables E1 and E2 (available online at www.redjournal.org). Patients treated only on the OTP were less likely to receive radiation doses over 80 Gy(RBE) to the prostate and less likely to receive elective seminal vesicle radiation doses over 60 Gy(RBE) than were patients included in the clinical trials. Patients only on the OTP were also more likely to have >50% of positive results from zones undergoing biopsy than were patients treated on the clinical trials. Still, the multivariate analysis shown in Table E3 (available online at www.redjournal.org) examining risk factors for recurrence in the intermediate-risk patient population among the OTP patients failed to show a relationship between total dose, elective seminal vesicle radiation dose, or percentage of positive cancer results from zones undergoing biopsy and biochemical control at 5 years.

Discussion

This study represents the largest published series to date documenting the efficacy of dose-escalated PT for localized prostate cancer with prospectively collected patient-reported QOL and toxicity data. All patients were treated at a single institution with conventionally fractionated

Table 5 Factors associated with late grade 3+ genitourinary toxicity on multivariate analyses

Factors	No	Yes	*P*-value
Prostate volume ≥60 cm^3	38/1097 (3.5%)	23/188 (12.2%)	<.0001
α-blockers	37/1044 (3.5%)	24/245 (9.8%)	.0002
Pretreatment TURP*	44/1193 (3.7%)	17/96 (17.7%)	<.0001
Absolute bladder V30 ≥ 19.2 cm^3	34/989 (3.4%)	27/298 (9.1%)	.0002

Abbreviation: TURP = transurethral resection of the prostate.

Factors tested in this multivariate analysis included prostate volume, anticoagulation, pretreatment cytoreductive prostate procedures, pretreatment treatment with α-blockers, International Prostate Symptom Score, and 8 dose-volume histogram (DVH) parameters.

* Includes all prostate-reductive procedures.

Table 6 EPIC patient-reported quality of life

Factor	Baseline			4 years			5 years			6+ years		
	No. of patients	Median (range)	Mean (SD)	No. of patients	Median (range)	Mean (SD)	No. of patients	Median (range)	Mean (SD)	No. of patients	Median (range)	Mean (SD)
IPSS	1167	7 (0-34)	-	727	7 (0-30)	-	505	7 (0-34)	-	264	6 (0-35)	-
Urinary/obstructive summary	1122	88 (44-100)	87 (12)	701	93.75 (25-100)	89 (12)	575	94 (19-100)	88 (14)	373	94 (0-100)	89 (14)
Urinary incontinence summary	1139	100 (31-100)	95 (16)	704	100 (23-100)	89 (16)	582	100 (0-100)	90 (16)	371	100 (0-100)	89 (18)
Bowel summary	1158	100 (33-100)	87 (9)	715	95 (29-100)	91 (13)	589	96 (21-100)	92 (13)	381	96 (0-100)	92 (14)
Sexual summary without ADT	962	75 (0-75)	67 (29)	610	53 (0-100)	51 (32)	502	55 (0-100)	53 (33)	337	49 (0-100)	47 (33)
Sexual summary with ADT	169	17 (0-100)	34 (32)	81	26 (0-100)	41 (33)	69	32 (0-100)	37 (30)	34	26 (0-88)	37 (27)

Abbreviations: ADT = androgen deprivation therapy; EPIC = Expanded Prostate Cancer Index Composite; IPSS = International Prostate Symptom Score; SD = standard deviation.

image guided PT and had a median follow-up time of 5.5 years. The primary goal of the study was to determine whether the results of our first 3 benchmark prospective trials (7) using standard-dose fractionation could be replicated in a larger population of men treated in a similar fashion. In the benchmark clinical trials, the 5-year FFBP rates were 99% for low-risk, 99% for intermediate-risk, and 76% for high-risk prostate cancer. In the current larger study, the 5-year FFBR rates are the similar for low-risk and high-risk disease but slightly lower for intermediate-risk disease (94% vs 99%). The reason for the difference is unclear but may relate to a larger, broader sample of patients in the present study. A comparison of the patients enrolled on the benchmark prospective protocols and the remaining OTP patients is provided in Tables E1 and E2 (available online at www.redjournal.org). Although differences between the 2 groups of patients were seen with regard to disease characteristics and treatment, the differences did not appear to be significant predictors for biochemical failure on multivariate analysis. Consequently, the reasons for the small decline in biochemical control in the intermediate-risk patient population remains unclear.

Tumor control comparison with IMRT

Our study shows that PT is a highly effective treatment for low-risk, intermediate-risk, and high-risk prostate cancer. As Table 7 shows, PT provided comparable biochemical control rates to IMRT (6, 7, 16-19). For example, Spratt

Table 7 Literature review

Study	No. of patients	Therapy	Median RT dose Gy or CGE	Median F/U years	5-year BCR (%)	G3+ GI toxicity	G3+ GU toxicity
Mendenhall et al (7)	211	Proton therapy	78-82	5.2	LR, 99% IR, 99% HR, 76%	0.5%	1.0%
Slater et al, 2004 (6)	1255	Proton therapy	74	5.3	73%	1%	1%
Spratt et al, 2013 (16)	1002	IMRT	86.4	5.5	LR, 98.8%* IR, 85.6%* HR, 67.9%*	0.7%	2.2%
Vora et al, 2013 (17)	302	IMRT	75.6	7.6	LR, 77.4%† IR, 69.6%† HR, 53.3%†	0%	0.7%
Liauw et al, 2009 (18)	130	IMRT	76	4.4	LR, 97% IR, 94% HR, 87%	2%	2%
Pugh et al, 2013 (19)	291	Proton therapy	76	2.0	- - -	<0.3%	0%
Present study, 2015	1215	Proton therapy	78	5.5	LR, 99% IR, 94% HR, 74%	0.6%	2.9%

Abbreviations: BCR = biochemical control rate; CGE = cobalt-Gray equivalent; F/U = follow-up; GI = gastrointestinal; GU = genitourinary; HR = high risk; IMRT = intensity modulated radiation therapy; IR = intermediate risk; LR = low risk.

* 7-year results.

† 9-year results.

et al (16) published results from a series including 1002 men with localized prostate cancer treated with high-dose IMRT at Memorial Sloan-Kettering Cancer Center, New York, NY, between 1997 and 2008. The median dose delivered to the prostate was 86.4 Gy, and the 7-year biochemical relapse-free survival rate was 98.8% for low-risk, 85.6% for intermediate-risk, and 67.9% for high-risk patients (16). Additionally, a series of patients treated with high-dose photon radiation from the Mayo Clinic, Phoenix, AZ, showed somewhat lower rates of freedom from biochemical progression (17). Patients were treated to a median dose of 75.6 Gy, and 35.4% of patients received ADT. The median follow-up time was 7.6 years, and the 9-year freedom from biochemical relapse rates were 77.4% for low-risk, 69.6% for intermediate-risk, and 53.3% for high-risk prostate cancer. Although these 3 studies were stratified by risk category, risk category accounts for only some of the currently known prognostic factors for patients with prostate cancer (20). Consequently, our series may not be directly comparable with the other 2 series. A prospective comparative study, either randomized or large enough to account for the effects of heterogeneity, would be necessary to determine whether PT and IMRT provide equivalent biochemical control in localized prostate cancer.

Toxicity and quality of life compared with IMRT

According to CTCAEv4, the late grade 3+ GU and GI actuarial toxicity rates at 5 years in this study were 2.9% and 0.6%, respectively, which is similar to those in other retrospective series evaluating high-dose IMRT and 3-dimensional conformal radiation (3DCRT). As Table 7 shows, the risk of grade 3+ GU or GI toxicity is generally less than 3% after PT and IMRT (16). No prospective trials comparing toxicity and QOL rates between IMRT and PT have been reported thus far, but a few retrospective comparisons have been published. A comparative study by Gray et al (21) evaluating 3-dimensional conformal photon radiation (3DCRT), IMRT, and PT reported worse acute patient-reported QOL in the urinary irritative/obstruction and incontinence domains with 3DCRT and IMRT compared with PT but no differences between the 3 radiation modalities at 2 years. Hoppe et al (22) compared prospectively collected patient-reported QOL data for patients treated with PT for localized prostate cancer. The 2-year posttreatment results were compared with patient-reported QOL from the Prostate Cancer Outcomes and Satisfaction (PROSTQA) treatment assessment study, which included men with prostate cancer treated with high-dose photon radiation. At 2 years, there were no differences between treatment groups in terms of EPIC bowel summary, urinary irritative, urinary obstructive, or sexual summary scores. When confounding factors were considered, a statistically significant difference between modalities was found: patients treated with IMRT had more "moderate" or "big problems" with rectal urgency and bowel frequency than those treated with PT. Fang et al (23) published a case-matched study performed at the University of Pennsylvania comparing physician-reported toxicity for patients treated with IMRT or PT for prostate cancer. Patients in the study were retrospectively matched on the basis of age, prior GU and GI comorbidities, and risk group. At 2 years, there was no significant difference in physician-reported grade 2+ GU or GI toxicity between IMRT and PT. Finally, Yu et al (24) published a Medicare-based comparative study including patients treated with PT or IMRT for prostate cancer. Toxicities were compared between the 2 groups, and there was no significant difference in GI toxicity at 6 or 12 months. The risk for GU toxicity was significantly lower among patients treated with PT at 6 months compared with IMRT, but the difference disappeared by 12 months.

In each comparative study, the follow-up times were short. Also, patient-reported QOL data were not provided in the study from the University of Pennsylvania, and the authors did not report differences in bowel frequency, diarrhea, or erectile dysfunction between the 2 treatment groups. This is important because the benefits of PT over IMRT in reducing dose to the bladder, rectum, and penile bulb fall within the moderate-dose range of radiation (30-60 Gy) rather than the high-dose range (70-80 Gy) (23). The dosimetric improvements in the moderate-dose range with PT might be expected to result in less erectile dysfunction, diarrhea, and bowel urgency but not less rectal bleeding, urethritis, or urethral stricture (22). Additionally, some side effects, like long-term changes in bowel and bladder function and second malignancies, require longer observation times to enable the relative benefit of PT to be determined. Finally, the Yu et al (24) Medicare-based study's lack of treatment-related information (eg, radiation dose, field size), lack of toxicity grading, and reliance on the presence of codes to detect a toxicity limits the strength of its conclusions. Large prospective clinical comparative effectiveness studies with longer follow-up times will be necessary to clarify whether PT reduces the risk for side effects compared with IMRT, brachytherapy, stereotactic body radiation therapy or a combination of these treatments.

Study limitations and strengths

Our study has several limitations, including the potential for selection bias related to clinical factors and access to care. The patients who chose to be treated with PT may not have been directly comparable with patients who received IMRT, brachytherapy, or surgery in terms of risk factors for recurrence or toxicity after treatment. Although we are confident that PT was delivered in a consistent manner, ADT was provided heterogeneously and for varying durations, potentially obfuscating the impact of ADT on our population. Third, our reported local control rates may be

overestimates because a biopsy of the prostate was commonly not performed unless isolated local failure was suspected.

The strengths of this analysis are its large cohort size, short accrual times, and consistent patient treatment at a single institution with consistent guidelines for radiation delivery, follow-up, and toxicity management. Another important strength is the simultaneous and prospective assessment of outcomes such as disease control, patient-reported QOL, and physician-reported toxicity assessment.

It is concluded that image guided PT provides excellent biochemical control rates for patients with low-risk, intermediate-risk, and high-risk prostate cancer. The actuarial rates of CTCAEv4 grade 3+ GU and GI toxicity rates were low. Significant correlations were found between urologic toxicity and pretreatment use of α-blockers, diabetes, TURP, prostate volume, and volume of bladder receiving 30 Gy(RBE), with the risk of toxicity increasing with an increase in the number of predictive factors. From pretreatment to 5 years of follow-up, a significant decline was found in mean EPIC sexual summary for patients not receiving ADT. Prospective comparative studies are needed for a definitive comparison of PT with IMRT.

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