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Original Research Article

Proton therapy toxicity outcomes for localized prostate cancer: Long-term results at a comprehensive cancer center

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A B S T R A C T

Background: Proton therapy (PT) has unique biologic properties with excellent clinical outcomes for the management of localized prostate cancer. Here, we aim to characterize the toxicity of PT for patients with localized prostate cancer and propose mitigation strategies using a large institutional database.

Methods: We reviewed medical records of 2772 patients with localized prostate cancer treated with definitive PT between May 2006 through January 2020. Disease risk was stratified according to National Comprehensive Cancer Network guidelines as low [LR, n = 640]; favorable-intermediate [F-IR, n = 849]; unfavorable-intermediate [U-IR, n = 851]; high [HR, n = 315]; or very high [VHR, n = 117]. Descriptive statistics and Kaplan-Meier estimates assessed toxicity and freedom from biochemical relapse (FFBR).

Results: Median follow-up was 7.0 years. The median dose was 78 Gy(RBE)(range: 72–79.2 Gy) in 2.0 Gy(RBE) fractions; 63 % of patients received 78 Gy(RBE) in 39 fractions, and 29 % received 76 Gy(RBE) in 38 fractions. Overall rates of late grade ≥3 GU and GI toxicity were 0.87 % and 1.01 %, respectively. Two patients developed grade 4 late GU toxicity and seven patients with grade 4 late GI toxicity. All patients experiencing severe late grade 4 toxicities were treated to 78 Gy(RBE) in 39 fractions with 80 Gy(RBE) dose to the anterior rectal wall and/or bladder neck. The 10-year FFBR rates for patients with LR to U-IR disease were compared between those treated with 76 and 78 Gy(RBE); the rates were 94.5 % (95 % confidence interval [CI] 92.4–96.0 %) and 93.2 % (95 % CI 91.3–95.7 %), respectively (log-rank p = 0.22).

Conclusions: Proton therapy is associated with low rates of late grade ≥3 GU and GI toxicity. While rare, late grade 4 toxicities occurred in nine (0.3 %) patients. De-escalation to a total dose of 76 Gy(RBE) yields excellent clinical outcomes for patients with LR to U-IR disease with the potential for significant reductions in grade ≥3 late toxicity.

Introduction

Proton therapy (PT) has unique biologic and physical properties with excellent clinical outcomes for the management of localized prostate cancer. Dose escalation with external beam radiation has been utilized to improve the rates of biochemical control in prostate cancer, although at the expense of increased toxicity [1–3]. However, advances in external beam radiotherapy, such as intensity-modulated radiotherapy

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(IMRT), have helped clinicians mitigate these radiation-related side effects [4–6]. Additionally, modalities like proton therapy (PT), with both passive and active scanning technologies, have been used to enhance the therapeutic ratio by leveraging the dosimetric advantages of protons [7,8].

Aside from standard dosimetry, other characteristics of the radiation beam can impact local control rates and toxicity. Linear Energy Transfer (LET) characterizes the ionization density of a beam, measuring the interactions between particles and the surrounding tissues. These interactions are closely associated with the number of DNA double-strand breaks, the underlying mechanism for cell killing in radiotherapy. Relative Radiobiologic Effectiveness (RBE) is a related term that quantifies the varied biologic effects of different types of radiation at the same dose. RBE can help estimate the proton dose that achieves an equivalent effect as conventional radiotherapy. Proton therapy holds promise to improve outcomes specifically in the context of prostate cancer through optimization of the therapeutic ratio. Not only is there decreased dose to surrounding tissues as a result of the Bragg peak, but prostate cancer cells also are generally considered to have low alpha/beta ratios (range 1.5–3), suggesting increased lethality following single hit DNA damage. This, in turn, may result in higher sensitivity to high LET radiotherapy beams including proton therapy.

We have previously described long-term clinical outcomes of patients with localized prostate cancer treated with PT at a comprehensive cancer center, demonstrating excellent disease control across low, intermediate, and high-risk disease [9]. The present study specifically focuses on treatment-related morbidity, predictors for toxicity, and proposed strategies to maintain the high control rates achieved with PT while minimizing toxicity.

Materials and methods

Patient eligibility

Patients participating in two prospective registry studies treated from May 2006 through January 2020 at a single comprehensive cancer center were included for analysis (Table 1). In order to be included, patients must have been adult men receiving proton therapy for the definitive management of prostate cancer. Individuals who had metastatic disease or those who were receiving concurrent therapy for other malignancies were excluded. There were no other specific exclusion criteria. Patients were stratified by National Comprehensive Cancer Network (NCCN) guidelines (version 1.2022), although a very low-risk group was not defined. Therefore, the five risk groups used in this analysis were low risk (LR), favorable-intermediate risk (F-IR), unfavorable-intermediate risk (U-IR), high risk (HR), and very high risk (VHR).

Treatment planning and delivery

The clinical target volume (CTV) included the prostate for the LR group, the prostate and the proximal seminal vesicles for F-IR and U-IR, and the prostate with entire seminal vesicles for HR and VHR. Pelvic lymph node treatment was optional and left to the physician's discretion. PT was delivered by either passive scatter or spot scanning techniques, with the latter reserved for those undergoing pelvic lymph node irradiation. All patients were treated to a total dose of 72–79.2 Gy(RBE) at 1.8–2.4 Gy(RBE) per fraction. Additionally, androgen deprivation therapy (ADT) was prescribed at the treating physician's discretion based on institutional guidelines.

Adverse events

Follow-up evaluations were performed every three months for the first year and every six months thereafter. Evaluations included an interim history and physical, PSA level, and testosterone measurement.

Table 1
Patient and treatment characteristics.

Characteristics	Count or Median (Q1-Q3) n = 2772	%			
Age	66 (60–71)				
Race					
Asian	56	2			
Black	178	6.4			
Hispanic	99	3.6			
White	2439	88			
Gleason Score					
6	712	25.7			
7 (3 + 4)	1146	41.3			
7 (4 + 3)	561	20.2			
8	214	7.7			
9 – 10	138	5			
Unknown	1	0			
PSA Level, ng/mL					
<10	2333	84.2			
10–20	352	12.7			
>20	86	3.1			
Unknown	1	0			
T Category					
Tx	3	0.1			
T1a	1	0			
T1b	8	0.3			
T1c	1730	62.4			
T2a	614	22.2			
T2b	234	8.4			
T2c	78	2.8			
T3a	68	2.4			
T3b	29	1			
T3c	0	0			
T4	7	0.3			
Risk Classification					
Low	640	23.1			
Favorable Intermediate	849	30.7			
Unfavorable Intermediate	851	30.7			
High	315	11.4			
Very High	117	4.2			
			Duration (mo)		
ADT Use per Risk Group			**Mean**	**Median**	**Range**
Low	71 of 640	11.1	6	6	4 – 12
Favorable Intermediate	361 of 849	42.5	5.99	6	4 – 12
Unfavorable Intermediate	699 of 851	82.1	6.63	6	4 – 24
High Risk	315 of 315	100	19.89	24	4 – 36
Very High Risk	117 of 117	100	24.16	24	18 – 36
Pelvic LN Irradiation by Risk Group					
Low	0 of 640	0			
Favorable Intermediate	0 of 849	0			
Unfavorable Intermediate	2 of 851	0.2			
High Risk	11 of 315	3.5			
Very High Risk	15 of 117	12.8			
Total PT Dose					
72 Gy(RBE) in 30 fx	30	1.1			
75.6 Gy(RBE) in 42 fx	187	6.7			
76 Gy(RBE) in 38 fx	801	28.9			
78 Gy(RBE) in 39 fx	1747	63			
77.4 Gy(RBE) in 43 fx	5	0.2			
79.2 Gy(RBE) in 44 fx	2	0			

Acute and late genitourinary (GU) and gastrointestinal (GI) toxicity were graded according to a modified toxicity scale based on criteria from the Radiotherapy Oncology Group (RTOG), the modified RTOG/EORTC morbidity scale, and Fox Chase Cancer Center (Supplementary Table 1) [10–12]. Acute toxicities were defined as any toxicities occurring within 90 days of the radiation start date; any toxicities after this time interval were considered late toxicities. The time to toxicity (acute and late) was calculated from the radiation start date. The total number of events was captured at each toxicity grade for each toxicity subtype. Some toxicities were counted multiple times if there was a toxicity-free interval between each episode. The number of unique events (for a particular toxicity subtype) was also counted separately. This unique count excludes multiple episodes of the same toxicity subtype (i.e., bleeding) and only captures the maximum grade if there was a progression of grade severity over time. Finally, the total number of patients experiencing toxicity at each grade level was also captured. For individuals with high-grade toxicity, we manually reviewed the final approved radiotherapy plans to assess potential relationships between delivered dose and subsequent toxicity.

Disease status at the time of a patient's death was individually reviewed; if the patient experienced a biochemical failure and their death could not be directly attributed to another disease process, they were categorized as having a prostate cancer-related death.

Statistical analyses

Descriptive statistics were calculated as frequencies for categorical variables and medians with ranges for continuous variables. Freedom from biochemical relapse (FFBR) rates were estimated with the Kaplan-Meier product-limited method. Rates of GU and GI toxicities were calculated as crude rates of cumulative incidence over time.

Univariate and multivariable binary logistic regression models were used to identify predictors of high-grade GU and GI toxicity, defined as grade 3 or higher. Factors with significant association on univariate comparison were selected for inclusion in the multivariable model. Given the low number of patients that did not receive either 76 Gy (RBE) or 78 Gy (RBE), those patients were excluded from the multivariable modelling. A P-value of < 0.05 was considered statistically significant. Statistical analyses were done with Stata (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP), R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria), GraphPad Prism (GraphPad Software, San Diego, CA, v9.0.0) and JMP Statistical Software, Version 15 (SAS Institute Inc., Cary, NC).

Results

A total of 2772 of the 3010 enrolled patients were eligible for this analysis. The median patient age was 66 years and median follow-up time was 7.0 years. A total of 150 patients experienced biochemical relapse (5.4 %) and 235 patients died of any cause (8.4 %) during study follow up; however, only 2 individuals died of prostate cancer (0.1 %). [9] Pelvic lymph node radiation was given to 28 patients (1 %) (2 [0.2 %] U-IR, 11 [3.5 %] HR, and 15 [12.9 %] VHR). All patients receiving pelvic nodal irradiation received 46 Gy(RBE) in 23 fractions to the pelvic nodes and received a total dose of 78 Gy(RBE) in 39 fractions to the prostate and seminal vescicles. The median PT dose was 78 Gy(RBE) at 2.0 Gy(RBE) per fraction; 63 % of patients received 78 Gy(RBE) in 39 fractions, and 29 % received 76 Gy(RBE) in 38 fractions. The relevant patient characteristics have been reproduced in Table 1. Characteristics of individuals receiving 76 Gy (RBE) vs 78 Gy (RBE) are compared in Table 2; overall, patients receiving 78 Gy (RBE) tended to have more aggressive or advanced disease than those receiving 76 Gy (RBE). ADT was used for 1562 patients (56.3 %) (71 [11.1 %] LR, 361 [42.5 %] F-IR, 699 [82.1 %] U-IR, 315 [100 %] HR, and 116 [100 %] VHR); median duration was six months for U-IR and 24 months for HR and VHR groups.

Table 2
Baseline and treatment characteristics of patients receiving 76 Gy/38 fractions and 78 Gy in 39 fractions.

Characteristics	Count (%) or Median (Q1-Q3)				P value
	78 Gy in 39 fractions n = 1747	%	76 Gy in 38 fractions n = 801	%	
Age	67 (61–71)		65 (59–70)		<0.001
Race					0.05
Asian	36	2.1	17	2.1	
Black	134	7.7	38	4.7	
Hispanic	66	3.8	27	3.4	
White	1511	86.5	719	89.8	
PSA Level, ng/mL					<0.001
<10	1404	80.4	728	90.9	
10–20	80	4.6	6	0.7	
>20	262	15.0	67	8.4	
Unknown	1	0.1	0	0.0	
T Category					<0.001
Tx	2	0.1	0	0.0	
T1	1001	57.3	558	69.7	
T2	644	36.9	230	28.7	
T3	93	5.3	3	0.4	
T4	7	0.4	0	0.0	
Risk Classification					<0.001
Low	268	15.3	295	36.8	
Favorable Intermediate	514	29.4	253	31.6	
Unfavorable Intermediate	561	32.1	229	28.6	
High	292	16.7	20	2.5	
Very High	112	6.4	4	0.5	
Hormone Therapy					<0.001
No	614	35.1	479	59.8	
Yes	1133	64.9	322	40.2	
Pelvic Nodal Irradiation					<0.001
No	1719	98	801	100	
Yes	28	2	0	0	

Other dose and fractionation regimens were excluded from this analysis due to low sample size.

Acute GU and GI toxicity

The incidence of acute GU and GI toxicities are summarized in Supplementary Table 2 and 3. The overall rates of acute grade ≥3 GU and GI toxicity were six of 2772 (0.22 %) GU and zero of 2772 (0 %) GI. There was one instance of acute grade 4 GU toxicity in a single patient that manifested as urinary retention approximately four weeks after the completion of PT. He was hospitalized due to acute renal failure and was found to have a urinary obstruction at the level of the urethra. After catheterization, his renal function returned to baseline, but he relied on intermittent catheterization until transurethral resection of the prostate (TURP) was performed approximately two months after hospitalization.

Late GU and GI toxicity

Fig. 1 depicts the distribution of toxicities at each grade for late GI and late GU toxicities according to total PT dose. The number and distribution of toxicities (all grades) between those treated to 76 and 78 Gy (RBE) were significantly different ($p < 0.001$ for GI, $p = 0.01$ for GU, respectively). 475 (17.1 %) and 449 (16.2 %) patients experienced grade 1 and grade 2 late GU toxicity, respectively, (Supplementary Table 2) while 760 (27.4 %) and 199 (3.6 %) patients experienced grade 1 and grade 2 late GI toxicity, respectively (Supplementary Table 3). The overall rates of late grade ≥3 toxicity were 24 of 2772 (0.87 %) GU and 28 of 2772 (1.01 %) GI. The grade 3 GU toxicities were mainly comprised of urinary stricture (64 %) followed by urinary retention (18 %). The grade 3 GI toxicities primarily consisted of rectal bleeding (62 %) and conservatively managed rectal ulcers (28 %).

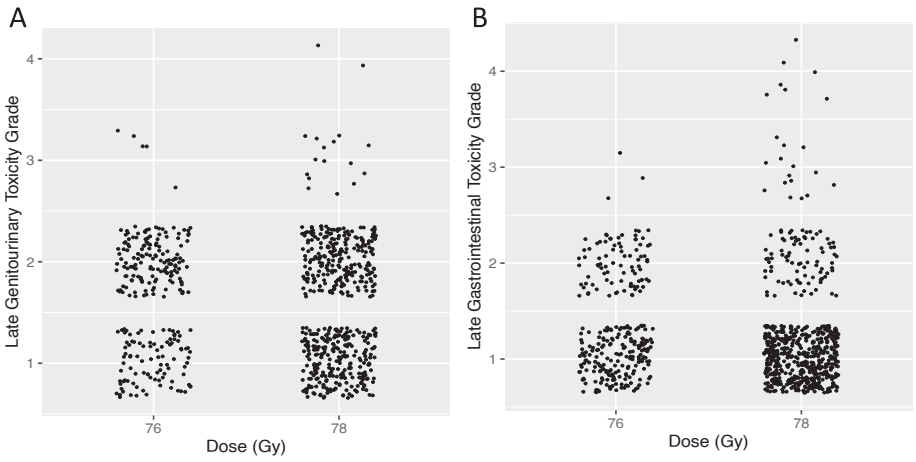

Fig. 1. Late genitourinary (A) and gastrointestinal (B) toxicity grade distributions according to total proton therapy (PT) dose Each black marker corresponds to a the maximum toxicity experienced per patient. Distributions of maximum toxicities were higher for those receiving 78 Gy compared to 76 Gy ($p < 0.001$ for GI, $p = 0.01$ for GU) by Chi-squared testing. Patients not experiencing any toxicity are not displayed as black dots but were included for Chi-squared testing.

The maximum toxicities experienced were grade 4 acute GU in one patient, grade 4 late GU in two patients, and grade 4 late GI in seven patients. The patient with the sole grade 4 acute GU toxicity later developed an anterior urethral fistula at the level of the prostate and was managed with hyperbaric oxygen. Another patient experienced grade 4 hemorrhagic cystitis approximately seven years after PT and two years after intravesicular chemotherapy. After completing PT, this patient was diagnosed with a renal pelvis malignancy and was treated with a nephroureterectomy and intravesicular gemcitabine. Severe late GI toxicities comprised five rectal fistulas and two rectal ulcers. These patients required surgical treatment that ranged from diverting colostomy to pelvic exenteration. The details regarding the type of grade 4 rectal and GU toxicities, interventions, and mitigating factors are summarized in Table 3. All patients experiencing severe late grade 4 toxicities were treated to a total dose of 78 Gy(RBE) in 39 fractions.

A hydrogel spacer (SpaceOAR, Boston Scientific) was placed in 56

Table 3
Summary of late grade 4 GU and GI toxicities and interventions.

GU/GI Toxicity	Age	TURP (pre-RT)	NCCN Risk Group	ADT (mo)	Dose /Frac	SpaceOAR	Mitigating Factor	Time to Toxicity	Grade 4 Type	Intervention
Acute GU **Late GU**	69		VHR	24	78/39	No		11 wks – 1.1 yrs	Urinary retention – Ant. urethral Fistula	Catheterization (11 wks) TURP (13 wks) – Hyperbaric O2 (1.6 yrs)
Late GU	68		U-IR	12	78/39	No	Intravesicular gemcitabine after RT for renal pelvis mass (4.2 yrs)	5.5 yrs	Hemorrhagic cystitis	Hyperbaric O2 (6.1 yrs) Rad. cystectomy (6.4 yrs) Prostatectomy + rectus flap (6.6 yrs)
Late GI	65		HR	24	78/39	No		5.2 yrs	Rectourethral fistula	Pelvic exenteration (5.4 yrs)
Late GI	52		LR	0	78/39	No		2.5 yrs	Rectourethral fistula	Hyperbaric O2 (2.5 yrs) LAR with coloanal anastomosis (3.8 yrs)
Late GI	63		U-IR	6	78/39	No		2.9 yrs	Rectoperineal fistula	End colostomy + I&D (3 yrs) Pelvic exenteration (3.3 yrs)
Late GI	71	14 wks	HR	24	78/39	No	Polymyalgia rheumatica	1.7 yrs	Rectal ulcer	Loop colostomy (1.7 yrs) Hyperbaric O2 (1.9 yrs) Revision end colostomy (3.3 yrs)
Late GI	78	≥ 8 wks	LR	0	78/39	No	Underwent rectal biopsy and repeat prostate Bx post RT (1.2 yrs, 1.2 yrs)	2.2 yrs	Rectoprostatic fistula	Diverting colostomy w/ SPT and perineal repair w/ flap (2.5 yrs) Long term SPT
Late GI	53		U-IR	6	78/39	No		1.3 yrs	Rectourethral fistula	End sigmoid colostomy with Hartmann stump (1.3 yrs) Pelvic Exenteration (1.6 yrs)
Late GI	75		HR	24	78/39	Yes	Patient underwent multiple colonoscopies and rectal wall biopsies after RT (0.8, 1.4 yrs) SLE	1.5 yrs	Perforated rectal ulcer	Loop colostomy (1.5 yrs) Hyperbaric O2 (1.9 yrs)

patients at the treating physician's discretion. Of these patients, four experienced a late toxicity, most of which were restricted to grade two or less. One patient with a SpaceOAR had a grade 4 perforated rectal ulcer. Of note, this patient had a history of systemic lupus erythematosus managed with hydroxychloroquine. SpaceOAR was not routinely used for proton patients until recently; the first proton patient with an implanted hydrogel was treated in April 2018. Therefore, patients with SpaceOAR have a much shorter median follow-up of 20.7 months.

Toxicity timing

Acute GU toxicities typically manifested within six weeks of treatment with some of the higher-grade ≥3 toxicities occurring later, centered around seven weeks after the start of radiation. Similarly, most acute GI toxicities occurred within six weeks of treatment (**Supplementary** Fig. 1).

The late GU toxicities typically occurred within two years of treatment; however, the grade 3 bleeding events tended to occur much later, centered at approximately 6.5 years post-treatment. Most of the late GI toxicities occurred within the first three years of treatment. The actuarial risk over time for late toxicities is depicted in **Supplementary** Fig. 2.

Biochemical failure

The FFBR for patients treated with PT across different risk levels was described in a prior manuscript.[9] The most common total doses used in this cohort were 76 Gy(RBE) in 29 % of patients and 78 Gy(RBE) in 63 % of patients. The distribution of the risk groups was not balanced across these dose levels; there was a higher proportion of higher-risk patients treated to 78 Gy(RBE) compared to 76 Gy(RBE) (Table 2). The biochemical control rates between the 76 and 78 Gy(RBE) dose levels were compared with HR and VHR patients excluded (Fig. 2). The 10-year FFBR rates were 94.5 % (95 confidence interval [CI] 92.4–96.0 %) and 93.2 % (95 % CI 91.3–95.7 %) for the 76 and 78 Gy(RBE) dose level, respectively (log-rank p = 0.22).

Clinical and treatment factors predicting late high-grade toxicity

Univariate and multivariable logistic regression models predicting grade 3 or higher GU and GI toxicities are summarized in Table 4 and Table 5, respectively. There were no significant predictors of high-grade late GU toxicity in this analysis. Only greater PT dose emerged as a significant predictor of development of late grade 3 or higher GI toxicity

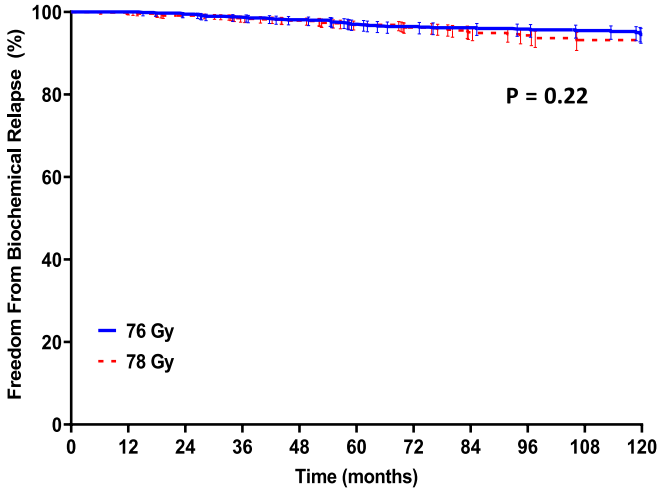

Fig. 2. Freedom from biochemical relapse for low risk to unfavorable intermediate risk patients treated with 76 vs 78 Gy(RBE).

Table 4
Univariate logistic regression model to predict G3 + late genitourinary toxicity.

	Univariate	
	OR (95 % CI)	p-value
Age	1.01 (0.96–1.07)	0.65
Race		
White	Ref	
Asian	NA*	
Black	2.07 (0.48–6.14)	0.25
Hispanic	NA*	
PSA Level, ng/mL		
<10	Ref	
10–20	6.46 (0.1–22.26)	0.56
>20	NA*	
T Category		
T1	Ref	
T2	0.90 (0.34–2.16)	0.82
T3	NA*	
T4	NA*	
Risk Classification		
Low	Ref	
Favorable Intermediate	3.33 (0.85–21.9)	0.12
Unfavorable Intermediate	3.6 (0.94–23.46)	0.1
High	NA	
Very High	2.44 (0.11–25.67)	0.47
Hormone Therapy		
No	Ref	
Yes	1.32 (0.56–3.31)	0.54
RT Dose		
76 Gy	Ref	
78 Gy	1.56 (0.62–4.78)	0.38

A multivariable model was not generated due to lack of significant association on univariate comparisons.

in a multivariable model (odds ratio 3.31 [95 % confidence interval 1.13–14.1] for 78 Gy (RBE) compared to 76 Gy (RBE), p = 0.04). On manual review of the delivered plans for which patients experienced grade 4 rectal toxicity, all patients had Dmax ≥ 80 Gy(RBE) to the anterior rectal wall. Although extremely rare, grade 4 toxicity was observed in both individuals receiving IMPT (2/1223, 0.2 %) and those receiving passive scattering proton therapy (7/1755, 0.4 %). Further, for individuals developing grade 4 toxicity, these toxicities generally manifested near the site of high dose in the rectal wall. Fig. 3 summarizes a representative case of an individual prescribed 78 Gy(RBE) with a hotspot of over 82 Gy(RBE) in the anterior rectal wall, correlating anatomically to a site of rectoperineal fistula that developed approximately three years after completion of PT.

Discussion

We have previously reported on the prospectively collected clinical outcomes for 2772 patients treated for localized prostate cancer with PT.[9] In the present report, we elaborate on the toxicity, the potential mechanisms of injury, and propose changes that may mitigate these higher-grade toxicities. To our knowledge, this is the most extensive toxicity analysis on dose-escalated PT to date. Biochemical outcomes were excellent and overall toxicity rates were low (late grade ≥ 3 GU [0.22 %] and GI toxicities [1.01 %]). However, nine patients (0.3 %) experienced severe late grade 4 toxicity. All these severe toxicities occurred in patients treated to 78 Gy(RBE); patients treated to 76 Gy (RBE) experienced no grade 4 toxicities and fewer grade 3 toxicities without any significant difference in biochemical control. A multivariable logistic regression model confirmed that RT dose was a significant predictor of late grade 3 or higher GI toxicity when controlling for other disease and treatment-related factors. Further, on manual review of plans, sites of hotspots correlated anatomically with subsequent regions of toxicity.

The total dose used for PT at our institution has evolved over time. Analysis of our patient outcomes and new data from the dose-escalation

Table 5
Univariate and multivariable model to predict G3 + late gastrointestinal toxicity.

	Univariate		Multivariable	
	OR (95 % CI)	p-value	OR (95 % CI)	p-value
Age	1.04 (0.99–1.10)	0.16		
Race				
White	Ref			
Asian	NA*			
Black	2.5 (0.72–6.7)	0.1		
Hispanic	NA*			
PSA Level, ng/mL				
<10	Ref			
10–20	0.56 (0.09–1.91)	0.98		
>20	NA*			
T Category				
T1	Ref		Ref	
T2	2.31 (1.04–5.21)	**0.04**	2.11 (0.95–4.79)	0.07
T3	NA*		NA*	
T4	NA*		NA*	
Risk Classification				
Low	Ref			
Favorable	0.92	0.9		
Intermediate	(0.24–3.72)			
Unfavorable	1.43	0.56		
Intermediate	(0.45–5.38)			
High	3.21 (0.96–12.33)	0.06		
Very High	1.21 (0.06–8.31)	0.86		
Hormone Therapy				
No	Ref			
Yes	1.6 (0.71–3.94)	0.27		
Pelvic Nodal Irradiation				
No	Ref			
Yes	3.85 (0.21–19.3)	0.194		
RT Dose				
76 Gy	Ref		Ref	
78 Gy	3.39 (1.17–14.36)	**0.04**	3.31 (1.13–14.1)	**0.04**

literature in the photon sector were the primary influencers on the PT dose and fractionation. One such study done in the 3-dimensional (3D) era examined the efficacy of dose escalation from 70 to 78 Gy(RBE) for prostate cancer.[1] The dose was prescribed to a reference point for these 3D conformal treatments. The transition to IMRT (and PT) required a change in dose specification from a point dose to volume-based specification. RT plans from the 3D era were examined and it was observed that a 78 Gy (RBE) delivered via 3D technique resulted in a CTV encompassed by the 75.6 Gy(RBE) isodose line. Therefore, for IMRT and PT, the target was prescribed a total dose of 75.6 Gy(RBE) and delivered at 1.8 Gy(RBE) (as opposed to 2 Gy(RBE)) per fraction for a more conservative approach. When the proton therapy center first became operational, only passive scattered proton therapy (PSPT) technology was available. Intensity modulated proton therapy (IMPT) later was later instituted, which offered further refinements to dose conformality and allowed further dose escalation to 78 Gy(RBE) with more conformal treatment of pelvic nodes when indicated. Additionally, in recent years active surveillance has emerged as the preferred strategy for the management of LR disease, and thus application of the results to this population may be limited.[13] Together, these changes in dose over time represent the careful transition from the historical 3D era with dose specified to a reference point to the modern, volume-based planning techniques of IMRT, PSPT, and IMPT.

PT is a particle-based therapy with interactions and dose deposition that differs from conventional x-rays. Protons are sparsely ionizing (low-LET) through most of the beam path, but the density of ionization increase within the Bragg peak at the distal end of the beam. The effective RBE for PT has been estimated to be 1.1, but recent data suggests that the RBE can be as high as 3–4 at the distal edge.[14–16] It should be noted that our treatment planning systems assume a constant RBE of 1.1; we have not evolved to change our prescription to a variable RBE to date. It is speculated that perhaps this variable RBE that is not accounted for by our modeling software contributes to both the increased biochemical control rates seen in our analysis and these infrequent late severe toxicities, but further analysis is needed to validate these claims.

The timing of acute side effects is well understood and is used to guide patients through the expected toxicities of treatment.[17,18] The timing of the late events was variable; some events, such as rectal bleeding, happened much later at around 6.5 years which highlights the need for close long-term follow-up for these patients even after the 5-year mark, which usually constitutes "survivorship." Furthermore, the development of rectal fistulas was noted to have a relatively wide range but could be seen in patients up to 5.2 years after RT. These results are particularly important to improve patient education and counseling for individuals considering proton therapy for definitive management of prostate cancer. Consistent follow-up and close surveillance of toxicity are critical for early management in the rare occasions where severe toxicities occur several years out from treatment.

Overall, in this cohort we observed had late grade ≥3 GU and GI toxicity rates of 0.87 % and 1.01 %. Notably, all severe grade 4 toxicity events were isolated to patients treated with a total dose of 78 Gy(RBE). These grade 4 events were observed for individuals receiving both passive scatter proton therapy and IMPT (0.4 % vs 0.2 %, respectively). Furthermore, patients receiving a total dose of 76 Gy(RBE) or less experienced no grade 4 GU and GI events and fewer grade 3 events,

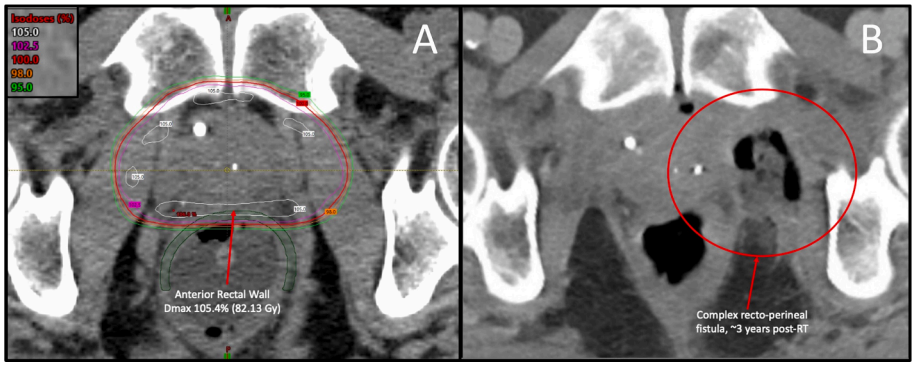

Fig. 3. Representative patient showing relationship between high Dmax to the anterior rectal wall (A) and subsequent long-term grade 4 rectal toxicity (B) Isodose lines are expressed as a percentage of the prescription dose (78 Gy(RBE)). The Dmax to the anterior rectal wall was 105.4 %, representing an absolute dose of 82.13 Gy(RBE), correlating anatomically to the subsequent site of recto-perineal fistula.

results that were corroborated in a multivariable model. These data, despite their retrospective nature, provide evidence that adding an additional fraction from 76 Gy(RBE) to 78 Gy(RBE) may add significant risk to development of late high-grade toxicity, even when accounting for other disease and treatment-related factors.

Further investigation into the biochemical control rates at these two dose levels revealed that the distribution of higher-risk patients was uneven and skewed towards the patients treated to 78 Gy(RBE). Therefore, the HR and VHR risk groups were excluded from the analysis to make a balanced comparison. Encouragingly, for individuals with LR to UF-IR disease, FFBR rates across these two dose levels exceeded 90 % at 10 years without any significant differences (log-rank $p = 0.22$). These data suggest that it is possible to maintain the biochemical control benefits of dose-escalated PT while potentially decreasing the risk of high-grade toxicity ($\geq$3) through the removal of one fraction (2 Gy (RBE)) from the treatment plan in select patients. This dose de-escalation strategy may be particularly important in patients at higher risk of experiencing treatment-related complications.

A hydrogel spacer (HS) is now increasingly used to artificially increase the separation between the rectum and the prostate, thereby decreasing radiation's impact on bowel toxicity and quality of life. [19–21] Only 56 patients had a HS placed in this cohort due to its relatively recent adoption into our practice. There was a smaller proportion of rectal toxicities experienced in this cohort, although more follow-up time is needed for HS patients for an adequate comparison. Nevertheless, one patient still experienced a grade 4 perforated rectal ulcer; although this patient had another predisposing factor (SLE), it suggests that HS can reduce but does not eliminate the risk of developing severe rectal toxicity.

Retrospective dosimetric comparisons between IMRT and PT have demonstrated that most of the OAR dose-sparing achieved with PT is in the low-to-moderate dose range (<50–60 Gy[RBE]) for both the rectum and bladder.[22] However, these PT dosimetric advantages have not yielded a well-defined benefit in reducing the potential for late toxicities or improved quality of life – at least for follow-up of up to 2 years. [23,24] These results suggest that either more time is needed before a difference can be appreciated or that most higher-grade late toxicities are driven by the dosimetry at the high-dose range.

Although this study draws strength from a large sample size of individuals treated consistently at a single institution, it does have several potential limitations and biases owing to its non-randomized design. Patients enrolled in prospective database studies may not always be representative of the general community population. Several aspects of treatment, including total PT dose, ADT use, and pelvic node RT depended on the treating physician's discretion based on our institutional guidelines. Therefore, although we attempted to account for confounding in a multivariable model, it is impossible to draw definitive conclusions regarding causal relationships between variables. Additionally, our center is a large tertiary referral center and some patients may obtain follow-up care at local facilities; therefore, it is possible that some toxicities were not captured in the electronic medical record and thus were under-reported in the present study. Last, when interpreting analyses of treatment-related toxicity, it is critical to consider the relationship between toxicities and deaths. Death not only acts a competing risk for toxicity but also can be a direct result of toxicity; however, attribution of toxicity-related deaths is subjective and thus difficult to assess robustly. These considerations are critical when interpreting these results. Fortunately, rates of severe toxicity and death were low in this population making significant impacts of overall conclusions unlikely.

In conclusion, this study reports on the toxicities encountered in our experience using proton therapy for the definitive treatment of prostate cancer. The occurrence of a grade 4 toxicity should be considered a "Zero Event"; de-escalation to a prescribed total dose of 76 Gy(RBE) with the anterior wall of the rectum Dmax < 80 Gy(RBE) offers excellent clinical outcomes for patients with LR or IR disease with the potential for significant reductions in grade $\geq$3 late GU and GI toxicity.

CRediT authorship contribution statement

Alan J. Sosa: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Michael K. Rooney:** Methodology, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Howard D. Thames:** Writing – review & editing. **Jeremiah W. Sanders:** Methodology, Writing – review & editing. **David M. Swanson:** Validation, Writing – review & editing. **Seungtaek L. Choi:** Writing – review & editing. **Quynh-Nhu Nguyen:** Writing – review & editing. **Henry Mok:** Writing – review & editing. **Deborah A. Kuban:** Writing – review & editing. **X. Ron Zhu:** Writing – review & editing. **Shalin Shah:** Writing – review & editing. **Lauren L. Mayo:** Writing – review & editing. **Karen E. Hoffman:** Writing – review & editing. **Chad Tang:** Writing – review & editing. **Sean E. McGuire:** Writing – review & editing. **Narayan Sahoo:** Writing – review & editing. **Xiaodong Zhang:** Writing – review & editing. **Andrew K. Lee:** Writing – review & editing. **Thomas J. Pugh:** Writing – review & editing. **Usama Mahmood:** Writing – review & editing. **John W. Davis:** Writing – review & editing. **Brian F. Chapin:** Writing – review & editing. **Paul Corn:** Writing – review & editing. **Reena Kudchadker:** Writing – review & editing. **Noveen Ausat:** Writing – review & editing. **Steven J. Frank:** Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2024.100822.

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