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European Association of Urology

Prostate Cancer

Patient-reported Outcomes and Late Toxicity After Postprostatectomy Intensity-modulated Radiation Therapy

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Article info

Article history:
Accepted May 7, 2019

Associate Editor:
Todd Morgan

Keywords:
Adjuvant or salvage
Intensity-modulated radiation therapy
Late toxicity
Long term
Postprostatectomy
Postoperative
Prostate cancer
Patient-reported outcomes
Quality of life
Radiation therapy

Abstract

Background: Limited long-term data characterize patient-reported quality of life (QOL) following postprostatectomy intensity-modulated radiation therapy (PPRT), and predictors of decline are poorly defined.
Objective: To identify modifiable dosimetric and clinical risk factors impacting QOL and late toxicity following PPRT.
Design, setting, and participants: A prospective cohort study of consecutive men with prostate cancer who received PPRT between 2007 and 2015 at a single academic institution.
Intervention: Patients were prospectively evaluated using the Expanded Prostate Cancer Index Composite (EPIC-26) QOL instrument. Radiation Therapy Oncology Group/Common Toxicity Criteria for Adverse Events toxicity grades were assigned at every follow-up visit. Treatment was delivered to the prostate bed (median 68 Gy) ± pelvic lymphatics (65%, median 50.4 Gy) with daily image guidance. Androgen deprivation therapy was concomitantly administered to 132 (66%) men for a median of 4 mo.
Outcome measurements and statistical analysis: Changes were deemed relevant if they exceeded the minimally clinically important difference (MCID), as calculated by a distribution-based method. Generalized estimating equation models and Cox regression were used for QOL and late toxicity univariate and multivariable analysis.
Results and limitations: Overall, 199 men were identified with a median follow-up of 33 mo. Overall urinary function (UF), bowel function (BF), sexual function (SF), and urinary irritation/obstruction (UI/UO) scores were never lower than the MCID. Between 8% and 18% of men experienced a small multidomain (1× MCID) decline, and 0–8% experienced a moderate multidomain decline (2× MCID) at a given time point up to 84 mo after PPRT. The rates of freedom from grade 2 or higher (Gr2+) genitourinary (GU) and gastrointestinal (GI) toxicity were 94% and 95%, respectively, at 4 yr. Factors associated with worse QOL or toxicity included longer time to PPRT (UC and UF), higher BMI (UF, BF, and late GI toxicity), older age (BF, SF, and late GU toxicity); hormone therapy (SF), total dose (late GI toxicity), tobacco history (BF), and higher bladder V70 Gy (UC, UF, and late GU toxicity).
Conclusions: Long-term QOL and late toxicity are favorable following postprostatectomy radiation therapy. Identifiable clinical and dosimetric risk factors may guide decision making to optimize urinary, sexual, and bowel function.
Patient summary: The following study provides a detailed report of favorable patient-reported quality of life and late side-effect profiles of radiation therapy following surgery for localized prostate cancer. Our findings provide patients guidance on what symptoms to expect if they are planning to undergo radiation therapy in this setting. It also allows physicians to counsel patients appropriately, and modify certain clinical and radiation-related risk factors to optimize quality of life.

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https://doi.org/10.1016/j.eururo.2019.05.011
0302-2838/

1. Introduction

Prostate cancer is estimated to be diagnosed in 170 000 men in the USA in 2018 [1]. Approximately one-third of men undergoing radical prostatectomy (RP) as a primary treatment modality for localized prostate cancer develop biochemical recurrence within 10 yr, with higher rates reported in men with adverse pathologic features [2,3]. Despite these findings, use of immediate or delayed postoperative prostate radiation therapy (PPRT) in high-risk men is <10% after RP [4]. The low rate of PPRT utilization may reflect potential concerns for declining quality of life (QOL) and late toxicity.

Modern series utilizing intensity-modulated radiation therapy (IMRT) have reported approximately 80–90% of men receiving PPRT to be free from grade 2 or higher (G2+) gastrointestinal (GI) and genitourinary (GU) toxicity up to 5 yr following PPRT [5–9]. However, limited patient-reported outcomes and QOL data exist to guide patient expectations and physician counseling. Furthermore, modifiable dosimetric and clinical predictors for change in these outcomes are not well characterized.

Our group previously published QOL results following PPRT and found only temporary declines, with no impact of whole pelvic radiotherapy (RT) on either QOL or late toxicity [10]. The goal of the current study was to analyze a larger cohort of patients with longer follow-up to better define outcomes and characterize predictors for QOL and late toxicity.

2. Patients and methods

A consecutive cohort of men with prostate cancer who received PPRT for curative intent between 2007 and 2015 was identified from a prospectively collected database, with approval by the University of Chicago Institutional Review Board. All men underwent computed tomography (CT)-based simulation for radiation planning in the supine position with custom immobilization.

IMRT was given with adjuvant (8%) or salvage (92%) intent, with or without androgen deprivation therapy (ADT) typically consisting of gonadotropin-releasing hormone agonist and nonsteroidal antiandrogen started 2 mo prior to RT. Radiation was delivered to the prostate bed (median dose 68 Gy) with or without pelvic lymphatics (65%, median 50.4 Gy). Of 129 men treated with pelvic nodal RT, 128 (99%) were given ADT for high-risk features such as Gleason 8+, pT3b, or node-positive disease. Prostate bed volumes were contoured according to anatomy-based interdisciplinary consensus guidelines [11], with a 0.6–0.9 cm anisotropic margin [12]. Daily image-guided RT typically consisted of orthogonal kilovoltage radiographs and twice-weekly cone beam CT to verify soft tissue alignment. Institutional treatment planning goals have been described previously [10].

Patients were seen during follow-up at 2 mo and subsequently every 6–12 mo. Prior to treatment (including neoadjuvant ADT) and at each follow-up visit, patient QOL was prospectively evaluated using the Expanded Prostate Cancer Index Composite (EPIC-26) instrument. Five QOL domains were assessed, including urinary irritation or urinary obstruction (UI/UO), urinary continence (UC), and overall urinary (UF), bowel (BF), and sexual (SF) function. Radiation Therapy Oncology Group (RTOG)/Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0 late toxicity grades were assigned by a board-certified radiation oncologist. Late toxicity occurred ≥90 d following PPRT.

Clinical risk factors analyzed included age, race, tobacco use, diabetes, body mass index (BMI), highest prostate-specific antigen (PSA) before the start of radiation, Gleason score, pathologic T stage, time from RP to PPRT, hormone therapy use, anticoagulation, and pelvic versus prostate bed RT. Dosimetric data analyzed included the V70 Gy, V65 Gy, and V40 Gy for the bladder and rectum, mean penile bulb dose, total radiation dose, and radiation dose to initial treatment volume.

Changes were deemed to be clinically relevant if they exceeded the minimally clinically important difference (MCID), as calculated by a distribution-based method [13]. Men with a decline exceeding the MCID in four out of five QOL domains were categorized as having multidomain decline with small effect (1× MCID) versus moderate effect (2× MCID) [14]. Generalized estimating equation (GEE) models were used for univariate (UVA) and multivariable (MVA) analysis to identify risk factors impacting each QOL domain. Cox regression models were used for UVA and MVA of late G2+ toxicity, respectively. Continuous variables were analyzed both continuously and as binary variables dichotomized at the median. Generally, potential risk variables with a p value of ≤0.15 on UVA were tested on MVA. Only the highest dose metric for the bladder or rectum was tested on MVA if multiple dose metrics were significant on UVA to avoid multicollinearity between independent variables. Baseline QOL for each domain was adjusted for in the GEE models. Given low event rates of late Gr 2+ GU and GI toxicity, only three covariates were included in the GU toxicity model, while two covariates were included in the GI toxicity model. For these toxicity analyses, in the event that multiple covariates were associated with UVA, we selected covariates that had the strongest rationale to be associated with the outcome, especially if prior data or mechanism could support an association. Gonen and Heller's K concordance statistic was used to assess the final Cox regression models. All statistical tests were performed using STATA/SE software, version 15.1 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Baseline characteristics

A total of 199 men met the inclusion criteria. Mean age was 63 yr. The majority of men were Caucasian (65%), median BMI was 29 (interquartile range [IQR] 26–33), 11% had diabetes, and 56% were current or former smokers (Table 1). Gleason ≥7 was present in 93% of men, T3a was present in 42%, pathologically positive lymph nodes were present in 21%, median preradiation PSA was 0.29 ng/ml (IQR 0.17–0.57), and median time from RP to radiation was 19 mo (IQR 8.9–47.3). ADT was concomitantly given in 132 (66%) men for a median of 4 mo (range 3–48). Fifteen (8%) men were treated with adjuvant intent, to a median dose of 64.8 Gy. Median V70/65/40 Gy to the bladder and rectum was approximately 18%/45%/76% and 6%/21%/54%, respectively. Median penile bulb dose was 25.77 Gy.

3.2. QOL and late toxicity

Median follow-up was 33 mo (IQR 19–59) with 27% of patients providing patient-reported outcomes at 5 yr and 10% of patients providing outcomes at 7 yr. The percentages of patients lost to follow-up were 0% at 2 mo, 59% by 3 yr, and 82% by 6 yr. QOL remained stable over time in all five QOL domains, with no decline at any time point exceeding the MCID (Fig. 1 and the Supplementary material). Between 8% and 18% of men experienced a small effect in multi-

Table 1 – Baseline characteristics (*n* = 199)

Patient characteristics	
Median age, yr (IQR)	64 (58–69)
Race, no. (%)	
Caucasian	130 (65)
African American	57 (29)
Other	12 (6)
Median BMI, kg/m^2 (IQR)	29 (26–33)
Diabetes mellitus, no. (%)	21 (11)
Current or former smoker, no. (%)	112 (56)
Tumor characteristics	
Gleason score, no. (%)	
6	15 (7)
7	121 (61)
8	22 (11)
9	41 (21)
Pathologic T stage, no. (%)	
pT2	60 (31)
pT3a	82 (42)
pT3b	53 (27)
Pathologic lymph node positive, no. (%)	41 (21)
Median pre-RT PSA, ng/ml (IQR)	0.29 (0.17–0.57)
Median time from RP to RT, mo (IQR)	19 (8.9–47.3)
Treatment characteristics	
Median follow up, mo (IQR)	33 (19–59)
ADT received, no. (%)	132 (66)
Median ADT duration, mo (range)	4 (3–48)
Median RT dose, Gy (IQR)	68.4 (68–68.4)
Pelvic nodal RT, no. (%)	129 (65)
Salvage (vs adjuvant), no. (%)	184 (92)
Median rectum V70 Gy, % (IQR)	5.63 (1.63–9.07)
Median rectum V65 Gy, % (IQR)	21.45 (16.24–28.27)
Median rectum V40 Gy, % (IQR)	54.44 (42.78–67.19)
Median bladder V70 Gy, % (IQR)	17.98 (5.5–25.48)
Median bladder V65 Gy, % (IQR)	45.30 (35.23–53.36)
Median bladder V40 Gy, % (IQR)	75.92 (60.74–80.91)
Median penile bulb dose, Gy (IQR)	25.77 (15.01–37.64)

ADT = androgen deprivation therapy; BMI = body mass index; IQR = interquartile range; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy.

domain decline up to 84 mo following PPRT, whereas 0–8% experienced a moderate effect in multidomain decline (Supplementary material). The percent of patients reporting moderate to severe levels of dysfunction or distress for each QOL domain as captured by EPIC-26 is shown in the Supplementary material. The most common baseline symptoms in each QOL domain included nocturia for UI/UO (10%), leaking one or more time per day for UC (46%), overall urinary problem (UF) in 10%, loose stools greater than or equal to half the time for BF (11%), and poor erection for SF (66%). The incidence of these symptoms was relatively stable up to 7 yr following PPRT.

The Supplementary material demonstrates the percentage of highest GU and GI toxicity rate at each follow-up interval. The rates of freedom from G2+ GU and GI toxicity at 4 yr were 94% and 95%, respectively. This remained <10% up to 7 yr following PPRT. Freedom from any GU or GI toxicity (G1+) at 4 yr was 78% or 89%, respectively.

3.3. *Use of sexual aids*

Use of sexual aids at baseline in order of descending frequency included a phosphodiesterase (PDE) inhibitor (75%), penile injection therapy (15%), vacuum erection device (8%), and urethral suppository (5%; (Fig. 2 and the Supplementary material). The highest percentage of men gained benefit from the use of penile injection therapy (79%). These values were relatively stable up to 7 yr following PPRT. While functional erections at baseline initially declined following PPRT, 59% (95% confidence interval 40–79%) of men recovered at month 36 and recovery continued to increase over time (Supplementary material).

3.4. *Pad usage*

Patients were categorized into groups with stable, increased, or decreased pad use compared with baseline for urinary incontinence, with 80–94% of patients reporting stable/decreased pad use up to 7 yr following PPRT (Table 2). To determine the impact of baseline pad use on future urinary QOL, patients were categorized into three groups for comparison at each time point: 0 pad/d, 1 pad/d, and ≥2

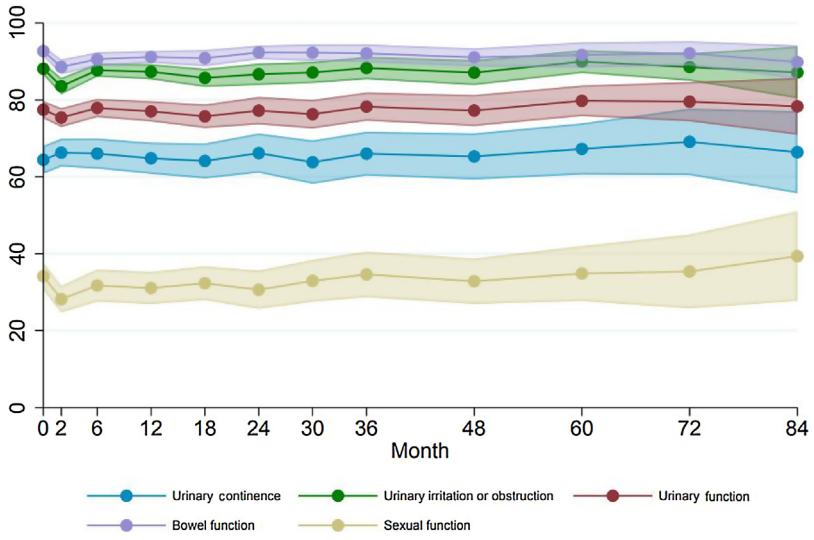

Fig. 1 – Patient-reported quality of life over time for major quality-of-life domains.

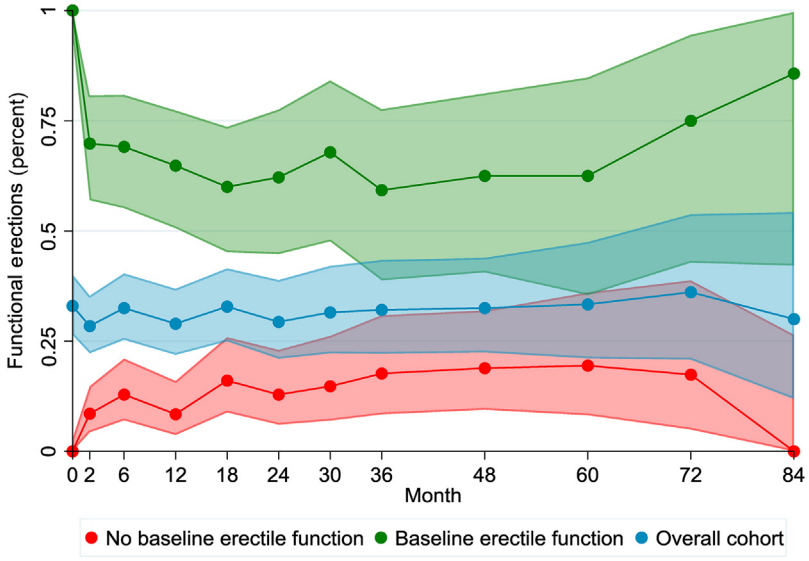

Fig. 2 – Changes in erectile function over time stratified by those with baseline function versus no baseline function.

Table 2 – Change in pad usage (percentage) at each time interval compared with baseline

Time (mo)	N[b]	Stable pad usage (%)[a]	Increased pad usage (%)	Decreased pad usage (%)
2	188	82	6	12
6	148	78	9	13
12	146	77	9	14
18	130	75	11	14
24	106	72	11	17
30	92	71	14	15
36	81	70	16	14
48	78	68	18	14
60	53	68	15	17
72	36	61	17	22
84	20	50	20	30

[a] Compared with baseline of zero, one, or two or more pads per day.
[b] Patients who were present at a given time point and baseline.

pads/d (Fig. 3). Statistically significant differences in UC and UF domains among these groups were no longer present 4 yr following treatment.

3.5. *Clinical and dosimetric predictors*

On MVA by GEE model and Cox regression, longer time to RT and bladder V70 Gy > median (18%) were associated with worse UC QOL (Table 3). Variables impacting UF QOL included BMI, time to RT, and bladder V70 Gy > median. When these risk factors were further analyzed by stratifying into quartiles, higher quartiles did not appear to reduce the QOL score more than lower quartiles (Supplementary material). To analyze the effect of time between RP and RT on urinary QOL, the top quartile of <9 mo was chosen as a stratification point to evaluate patients treated with early postop RT who may be subject to the ongoing recovery of continence after RP. Variables associated with BF included age > median, BMI > median, and current tobacco use, whereas variables associated with SF included hormone therapy use and age > median. BMI and total dose were associated with late Gr2+ GI toxicity, and age and bladder V70 Gy with Gr 2+ GU toxicity.

4. Discussion

We report favorable long-term QOL and late toxicity following PPRT. QOL in all five domains (UI/UO, UC, UF, BF, and SF) showed transient declines at 2 and 18 mo, similar to prior investigations by our research group and others [8,10,15–17]. PPRT studies utilizing QOL assessment tools other than EPIC such as EORTC QLQ-C30 and PR-25 have yielded similar results [18–20]. Gr 2+ GU and GI toxicity was <10% up to 7 yr PPRT, similar to previous studies [5–9]. To our knowledge, this represents one of the few reports detailing QOL outcomes, including urinary pad and sexual aid usage, and identifying clinical and dosimetric predictors of decline in a large prospectively evaluated cohort receiving intensity-modulated PPRT.

A notable finding was no statistically significant differences in UC QOL beyond 4 yr between patients who used 0 pad/d, 1 pad/d, and ≥2 pads/d at baseline. This suggests

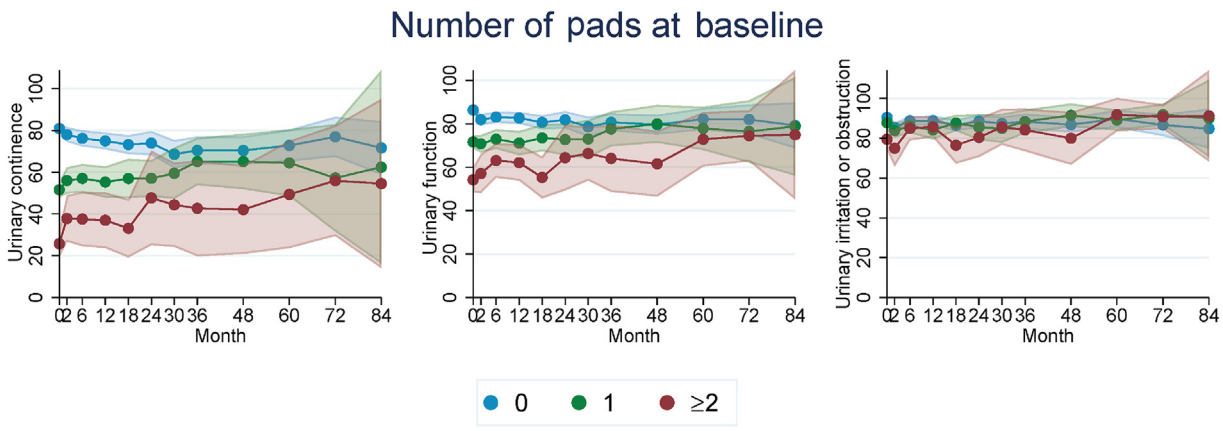

Fig. 3 – Urinary quality of life (normalized to 0–100, with 100 being the best health) comparing pad usage at baseline prior to postoperative radiation therapy.

that recovery of UF following surgery continues to occur during and after PPRT. Further supporting this hypothesis was shorter time between RP and PPRT resulting in improvement of UC and UF scores, likely driven by ongoing urinary recovery following surgery. Future studies with a control group may help clarify whether a compromise in completeness of recovery occurs with the use of PPRT.

Several studies have shown transient or no declines in urinary QOL with PPRT [8,10,15–17], while others have shown a detriment to urinary QOL. Comparisons are challenging due to heterogeneity of design, patient inclusion, radiation techniques, variable follow-up, and QOL assessment methods. The largest series of 2000 RP, RP + PPRT, or RP + PPRT + ADT patients reported a 4% higher overall incontinence rate (91% vs 87%) 3 yr after surgery in RP + PPRT patients compared with matched RP-only patients [21]. These results may differ from the current study in part due to the use of three-dimensional conformal RT, matched cohort design, large sample size allowing for the detection of small absolute differences, and different QOL assessment tools. Other studies suggesting a decline in urinary QOL with PPRT report mixed results regarding the impact of PPRT timing. Two retrospective studies and one randomized study suggesting that early PPRT is detrimental to urinary QOL are limited by premature assessments in the PPRT group [22,23] or no incorporation of baseline UC [24]. In contrast, one randomized study of continence recovery in men who were treated with RP alone versus RP + RT within 4 mo showed no difference in continence at 1 yr [25]. Finally, a retrospective study reported worsening of objective stress UC following PPRT regardless of timing. Notably, a subset of men who received adjuvant RT within 4 mo of RP showed ongoing recovery of continence over time [26]. Collectively, these data support the concept of ongoing recovery from surgery during and after PPRT.

To our knowledge, the current study is the first to detail long-term trends of sexual aid usage in the PPRT setting, although we have previously reported such findings in the intact setting [27]. Overall patterns of sexual aid usage remain similar up to 7 yr following PPRT. Most men (75%) have attempted the use of a PDE inhibitor at baseline. Approximately 50% of men continue to benefit from PDE inhibitors, and higher percentages benefit from other modalities such as penile injection. While therapeutic efficacy of sexual aids is not optimal, some men with sexual dysfunction adapt to their decline in sexual health; despite stable percentages of patient-reported sexual problems over time, the proportion of men citing overall SF as a "medium or big" problem decreased with time.

An important secondary goal was to identify modifiable predictors of declines in QOL and late toxicity. Similar to prior investigations by our group, bladder V70 was an impactful dosimetric variable, whereas no rectal or penile bulb dose metrics correlated with QOL or late toxicity [5,28]. While the association between V70 bladder dose and QOL is not uniformly supported by other data [26], it is possible this dose represents a tipping point for urethral or bladder neck toxicity, so that hot spots should be minimized with a dose prescription of 68–68.4 Gy to the prostate bed. The total dose was also shown to have an impact on late GI toxicity.

A number of clinical variables were associated with QOL on MVA, including time to PPRT for UC and UF; BMI for UF, BF and Gr2+ GI toxicity; age for BF, SF, and Gr2+ GU toxicity; current tobacco use for BF; and hormone therapy use for SF. BMI has previously been correlated with both incontinence [29] and worse BF [30] following RP, perhaps secondary to its adverse effects on pelvic floor musculature. Older age has also been shown to increase late GU toxicity in a large single-institution analysis of PPRT patients [31].

The strengths of our study include a prospective evaluation of detailed QOL and toxicity in a large PPRT cohort. Limitations include patients lost to follow-up over time and a relatively low event rate, which suggest that a larger cohort may be needed to adequately study predictors of decline. However, GEE analysis including only men with 3 yr of follow-up showed no differences in covariates significantly associated with the full data presented (data not shown). Nevertheless, this study remains one of the few published series examining QOL in detail following PPRT.

At our institution, patients are commonly provided a handout of these patient-reported outcomes (e.g. the table

Table 3 – Clinical and dosimetric predictors of patient-reported quality of life and physician-assigned late toxicity for urinary and gastrointestinal domains

	Multivariable analysis		
	Coefficient	95% CI	*p* value
Urinary Continence (UC)			
Age (yr)	−0.20	−0.56, 0.16	0.269
BMI (kg/m^2)	−0.39	−0.80, 0.02	0.065
Race (other)	6.91	−3.76, 17.59	0.204
Time to RT (mo)*	−0.08	−0.16, −0.01	0.018
Bladder V70 Gy (>median)*	−6.75	−11.54, −1.97	0.006
Urinary irritation or urinary obstruction (UI/UO)			
Age (yr)	−0.18	−0.39, 0.02	0.084
BMI (kg/m^2)	−0.16	−0.39, 0.08	0.196
Race (Caucasian)	2.81	−0.33, 5.96	0.080
Time to RT (mo)	−0.02	0.06, 0.02	0.324
Tobacco history (never)	4.05	−0.33, 8.42	0.070
Bladder V70 Gy (>median)	−2.46	−5.21, 0.29	0.079
Urinary Function (UF)			
Age (yr)	−0.23	−0.47, 0.01	0.061
BMI (kg/m^2)*	−0.30	−0.58, −0.02	0.036
Time to RT (mo)*	−0.05	−0.10, −0.003	0.038
Bladder V70 Gy (>median)*	−4.01	−7.28, −0.75	0.016
Bladder V65 Gy (>median)	–	–	–
Bowel Function (BF)			
Age (>median)*	−2.04	−4.08, −0.004	0.050
BMI (>median)*	−2.30	−4.25, −0.34	0.021
Tobacco history (previous vs current)*	3.38	0.24, 6.52	0.035
Race (African American)*	2.24	−0.02, 4.51	0.052
Pelvic nodal RT	−1.10	−3.24, 1.03	0.311
Total dose (Gy)	0.004	−0.001, 0.01	0.137
Sexual Function (SF)			
Age (>median)*	−5.59	−10.23, −0.94	0.018
Hormone therapy*	−6.38	−11.32, −1.45	0.011
Total dose (Gy)	−0.007	−0.02, 0.01	0.294
Diabetes	−5.11	−12.48, 2.26	0.174

	Multivariable analysis		
	Hazard ratio	95% CI	*p* value
Grade 2+ late GI toxicity			
BMI (kg/m^2)*	1.10	1.04, 1.17	0.002
Total dose (Gy)*	0.998	0.995, 0.999	0.025
Grade 2+ late GU toxicity			
Age (yr)*	1.06	1.01, 1.12	0.022
Bladder V70 Gy (%)*	1.05	1.02, 1.08	0.001
Diabetes	2.22	0.96, 5.13	0.062

BMI = body mass index; CI = confidence interval; GI = gastrointestinal; GU = genitourinary; RT = radiotherapy; * p < = 0.05

in supplement 3) to help weigh the risks versus benefits of PPRT and guide expectations following treatment. Our results provide reassurance that PPRT does not dramatically or routinely impact QOL and rarely leads to severe late toxicity. With ongoing advances in image guidance and intrafractional motion management, ideally QOL and late toxicity profiles will continue to improve and allow for further optimization of PPRT's therapeutic ratio.

5. Conclusions

Long-term QOL and late toxicity are favorable following post-prostatectomy IMRT. Certain clinical and dosimetric risk factors may help guide decision making in consideration of preserving QOL and limiting late toxicity.

Author contributions: Stanley L. Liauw had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Liauw.
Acquisition of data: Liauw, Akthar.
Analysis and interpretation of data: Liauw, Akthar, Eggener, Liao.
Drafting of the manuscript: Akthar, Liauw.
Critical revision of the manuscript for important intellectual content: Liauw, Eggener, Liao, Akthar.
Statistical analysis: Liao.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Liauw.
Other: None.

Financial disclosures: Stanley L. Liauw certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Acknowledgments: The authors thank Dr. Ping Liu for contributing to the statistical analysis in this manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2019.05.011.

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