ELSEVIER

Urologic Oncology: Seminars and Original Investigations 38 (2020) 930.e23–930.e32

UROLOGIC ONCOLOGY

Clinical-Prostate cancer

Radiotherapy after radical prostatectomy: Effect of timing of postprostatectomy radiation on functional outcomes

Heather L. Huelster, M.D.[a], Aaron A. Laviana, M.D.[a], Daniel D. Joyce, M.D.[a], Li-Ching Huang, Ph.D.[b], Zhiguo Zhao, M.S.[b], Tatsuki Koyama, Ph.D.[b], Karen E. Hoffman, M.D., M.H.Sc., M.P.H.[c], Ralph Conwill, B.S.[d], Michael Goodman, M.D., M.P.H.[e], Ann S. Hamilton, Ph.D.[f], Xiao-Cheng Wu, M.D., M.P.H.[g], Lisa E. Paddock[h,i,j], Antoinette Stroup, Ph.D.[h,i,j], Matthew Cooperberg, M.D., M.P.H.[k], Mia Hashibe, Ph.D.[l], Brock B. O'Neil, M.D.[m], Sherrie H. Kaplan, Ph.D., M.P.H.[n], Sheldon Greenfield, M.D.[n], David F. Penson, M.D., M.P.H.[a], Daniel A. Barocas, M.D., M.P.H.[a,*]

[a] *Department of Urology, Vanderbilt University Medical Center, Nashville, TN*
[b] *Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN*
[c] *Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX*
[d] *Office of Patient and Community Education, Patient Advocacy Program, Vanderbilt Ingram Cancer Center, Nashville, TN*
[e] *Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA*
[f] *Department of Preventive Medicine, Keck School of Medicine at the University of Southern California, Los Angeles, CA*
[g] *Department of Epidemiology, Louisiana State University New Orleans School of Public Health, New Orleans, LA*
[h] *Department of Biostatistics and Epidemiology, Rutgers School of Public Health, Piscataway, NJ*
[i] *Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*
[j] *New Jersey State Cancer Registry, New Jersey Department of Health, Trenton, NJ*
[k] *Department of Urology, University of California, San Francisco, CA*
[l] *Department of Family and Preventative Medicine, University of Utah School of Medicine, Salt Lake City, UT*
[m] *Department of Urology, University of Utah Health, Salt Lake City, UT*
[n] *Department of Medicine, University of California Irvine, Irvine, CA*

Received 3 April 2020; received in revised form 11 June 2020; accepted 19 June 2020

Abstract

Introduction and objective: The timing of radiotherapy (RT) after prostatectomy is controversial, and its effect on sexual, urinary, and bowel function is unknown. This study seeks to compare patient-reported functional outcomes after radical prostatectomy (RP) and post-prostatectomy radiation as well as elucidate the timing of radiation to allow optimal recovery of function.

Methods: The Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) study is a prospective, population-based, observational study of men with localized prostate cancer. Patient-reported sexual, urinary, and bowel functional outcomes were measured using the 26-item Expanded Prostate Index Composite at baseline and at 6, 12, 36, and 60 months after enrollment. Functional outcomes were compared among men undergoing RP alone, post-RP adjuvant radiation (RP + aRT), and post-RP salvage radiation (RP + sRT) using multivariable models controlling for baseline clinical, demographic, and functional characteristics.

Results: Among 1,482 CEASAR participants initially treated with RP for clinically localized prostate cancer, 11.5% ($N = 170$) received adjuvant (aRT, $N = 57$) or salvage (sRT, $N = 113$) radiation. Men who received post-RP RT had worse scores in all domains (sexual function

Funding: CEASAR is supported by the National Cancer Institute, Agency for Healthcare Research and Quality (1R01HS019356, 1R01HS022640) and the Patient-Centered Outcomes Research Institute (CE-12-11-4667). Data management was facilitated by Vanderbilt University's REDCap system, supported by the Vanderbilt Institute for Clinical and Translational Research grant (UL1TR000011 from NCATS/NIH).

Author responsible for statistical analyses: Zighuo Zhao, Ph.D., Vanderbilt University Medical Center, Department of Biostatistics 2525 West End Ave #1100, Nashville, TN 37203.

*Corresponding author.
E-mail address: dan.barocas@vumc.org (D.A. Barocas).

https://doi.org/10.1016/j.urolonc.2020.06.022

[−9.0, 95% confidence interval {−14.5, −3.6}, $P < 0.001$], incontinence [−8.8, {−14.0, −3.6}, $P < 0.001$], irritative voiding [−5.9, {−9.0, −2.8}, $P < 0.001$], bowel irritative [−3.5, {-5.8, −1.2}, $P = 0.002$], and hormonal function [−4.5, {−7.2, −1.7}, $P = 0.001$]) compared to RP alone at 5 years of follow-up. Compared to men treated with RP alone in an adjusted linear model, sRT was associated with significantly worse scores in all functional domains. aRT was associated with significantly worse incontinence, urinary irritation, and hormonal function domain scores compared to RP alone at 5 years of follow-up. On multivariable modeling, RT administered approximately 24 months after RP was associated with the smallest decline in sexual domain score, with an adjusted mean decrease of 8.85 points (95% confidence interval [−19.8, 2.1]) from post-RP, pre-RT baseline.

Conclusions: In men with localized prostate cancer, post-RP RT was associated with significantly worse sexual, urinary, and bowel function domain scores at 5 years compared to RP alone. Radiation delayed for approximately 24 months after RP may be optimal for preserving erectile function compared to radiation administered closer to the time of RP.

Keywords: Prostate cancer; Outcomes; Prostatectomy; Radiation; Erectile function

1. Introduction

Radical prostatectomy (RP) is the most commonly utilized treatment option for men with intermediate- or high-risk clinically localized prostate cancer [1,2]. Despite refinements in preoperative risk stratification, patient selection, and surgical technique, approximately 25% to 41% of men will develop local recurrence with prostate-specific antigen (PSA) elevation in the absence of radiographic distant disease within 10 years after surgery [3-6] prompting evaluation for salvage therapy. Additionally, 4 randomized trials have demonstrated reduction in the risk of biochemical recurrence (BCR), local recurrence, and clinical progression of cancer with adjuvant radiotherapy (RT) in men with adverse features at prostatectomy such as positive margins, seminal vesical invasion, and/or extraprostatic extension [7-10]. Despite broad recommendations for consideration of adjuvant RT in these men in both the American Urological Association and European Association of Urology guidelines, adjuvant therapy is utilized in only 6% to 51% of men and is declining over time [11,12].

Variations in adjuvant (aRT, administered within 1 year of RP) and salvage RT (sRT, administered greater than 1 year after RP) patterns worldwide for localized prostate cancer managed with initial RP stem from multiple factors. Studies in aRT vs. early sRT differ regarding freedom from BCR, freedom from androgen deprivation therapy (ADT), and freedom from distant metastases but are largely concordant in demonstrating no change in overall survival (OS) [13-16]. As a result, patients and providers may delay post-RP radiation due to uncertainty regarding the survival benefit and concern about the adverse functional effects of post-RP radiation.

Despite current prospective investigations into the timing of post-RP radiation with regard to BCR, cancer-specific survival, and OS, there remains a paucity of prospective data on the functional outcomes of men undergoing post-RP radiation and the association between the timing of radiation with functional outcomes. Anecdotally, urologists often counsel patients that longer duration between prostatectomy and radiation improves the chance of recovery of continence and erectile function. However, data to support this are scarce. This study aims to examine the effect of post-RP radiation on patient-reported functional outcomes as well as the timing of aRT or sRT to allow optimal recovery of continence, sexual function, and bowel function after RP using data from the prospective, population-based Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) cohort.

2. Methods

2.1. Study population

The CEASAR study is a prospective, population-based observational cohort designed to measure the effectiveness and harms of contemporary management strategies for men diagnosed with localized prostate cancer (NCT 0136286). Patients were accrued from 5 Surveillance Epidemiology, and End Results registry catchment areas (Louisiana, New Jersey, Utah, Atlanta, and Los Angeles) augmented with a sample of men enrolled in Cancer of the Prostate Strategic Urologic Research Endeavor [17]. The CEASAR methodology has previously been described [18]. Briefly, a total of 3,709 participants were enrolled in CEASAR between 2011 and 2012 and completed at least one follow-up survey, of which, 3,277 men met inclusion criteria: age ≤80 years old, clinical stage cT1 or cT2 disease, PSA <50 ng/dl, English- or Spanish-speaking, able to give consent, and enrolled within 6 months after pathologically diagnosed localized adenocarcinoma of the prostate.

Among 3,277 eligible men, 1,482 who underwent RP as initial treatment were analyzed. Men excluded from this study were those who had missing treatment dates, reported both RP and RT on the same date, or underwent ablation before RP or between RP and RT (Supplemental Fig. 1). aRT was defined as RT administered within 1 year after RP regardless of pathologic risk factors or intent of treatment, and sRT was defined as RT administered greater than 1 year after RP regardless of known recurrence or progression of disease.

The coordinating site at Vanderbilt, Surveillance Epidemiology, and End Results sites, and Cancer of the Prostate Strategic Urologic Research Endeavor each obtained approval from the corresponding local Institutional Review Board.

2.2. Survey instruments and medical chart abstraction [19]

Surveys were completed at baseline (time of study enrollment within 6 months of diagnosis) and at 6, 12, 36, and 60 months after enrollment. The validated 26-item Expanded Prostate Index Composite (EPIC-26) was used to evaluate patient-reported disease-specific function with summary scores calculated for urinary irritative, urinary incontinence, bowel, sexual, and hormonal domains ranging from 0 to 100, with higher scores representing better function. Surveys captured patient-reported race, age, income, education, marital status, and insurance. Validated instruments assessing general health and function, emotional health, cancer-related anxiety, and illness management style were previously described [18]. Total Illness Burden Index for Prostate Cancer measured comorbidity, with higher scores corresponding to greater severity [20]. Tumor characteristics, treatment, and treatment dates were obtained from medical charts by participating registries 1 year after enrollment. For patients without available chart information, treatment was determined from self-reported surveys and data from cancer registries.

2.3. Statistical analysis

Patients' demographic and baseline characteristics were summarized by treatment groups (RP-alone vs. RP + aRT or RP + sRT). Differences among groups were compared with the Kruskal-Wallis or Wilcoxon rank-sum test for continuous variables and the Pearson χ^2 test for categorical variables.

The primary outcomes measured at baseline and each follow-up included the 5 EPIC-26 domain scores: sexual function, urinary incontinence, urinary irritative, bowel irritative, and hormonal function. Among the men who underwent RP and any type of radiation, we defined the secondary outcomes as the changes in the 5 domain scores from the post-RP-baseline to the last follow-up.

In the primary analyses, we first evaluated the overall effects of RT on outcomes by comparing patients who underwent RP-only with those who underwent any radiation following RP. The effect of timing of radiation was investigated by comparing men who underwent RP + aRT or RP + sRT separately. Linear regression models were used, and mean differences in domain scores among groups was reported along with 95% confidence intervals. Models adjusted for age (continuous), race (white, nonwhite), Total Illness Burden Index for Prostate Cancer comorbidity score (≤4, >5), D'Amico risk (low, intermediate, high), bilateral nerve-sparing prostatectomy technique (yes, no), use of ADT (yes, no), margin status (positive, negative), and corresponding baseline domain scores (continuous). Restricted cubic spline terms were included for age to allow for flexible association with the outcomes. To account for potential correlations among multiple records collected from the same individual at different follow-ups, robust covariance matrix estimates by the Huber-White method was used [21,22].

For the secondary analysis, with the goal of identifying the optimal timing for post-RP radiation for functional recovery, we used linear regressions to model the association between time from RP to post-RP radiation (RP-RT-interval) and changes in domain scores from the post-RP, pre-RT baseline to last follow-up. Restricted cubic splines for RP-RT-interval were included in these models. The time from radiation to last follow-up and covariates included in the primary analysis were included in this model. Mean changes in domain scores were estimated as a function of RP-RT-interval.

Results were interpreted in light of both statistical and clinical significance according to previously published minimally clinically important differences (4−6 points for bowel and hormonal, 5−7 for urinary irritation, 6−9 for urinary incontinence, and 10−12 points for sexual function domains) [28]. Statistical significance was considered for all 2-sided P values ≤5%. All analyses were conducted using R software version 3.5 [23].

3. Results

There were 1,482 men in the CEASAR cohort with clinically localized prostate cancer who underwent initial treatment with RP. Of those, 170 men (11%) underwent post-RP RT within 5 years, including 57 men (34%) who received aRT and 113 men (66%) who received sRT. The median time from RP to aRT was 7.3 months, and median time from RP to sRT was 28.5 months. Age at prostate cancer diagnosis, race, education, marital status, comorbidities, clinical tumor stage, and preprostatectomy baseline EPIC-26 domain scores were similar among treatment groups (Table 1). There were expected statistically significant differences in the RP-alone vs. RP + aRT vs. RP + sRT groups with regard to PSA at diagnosis, Gleason score, D'Amico risk, clinical and pathologic stages, margin status, and exposure to ADT as these covariates are related to the indications for subsequent radiation exposure after RP.

Unadjusted comparisons between RP-alone, RP + aRT, and RP + sRT demonstrated that each group had distinct functional recovery trajectories following RP, depending on whether and when they received radiation (Fig. 1). For example, men who underwent aRT had lower hormonal domain scores in the first 2 years after RP compared to men who underwent RP-alone or RP + sRT (Fig. 1E).

3.1. Comparison between RP alone and any additional RT

Compared to men who underwent RP alone, men who received post-RP RT had worse scores in all domains

Table 1
Demographics and baseline characteristics

	RP only ($n = 1,312$)	RP + aRT ($n = 57$)	RP + sRT ($n = 113$)	P value
Median age at diagnosis (IQR), years	62 (57, 66)	62 (56, 65)	63 (58, 66)	0.23[a]
Race, *N* (%)				0.35[c]
White	996 (77)	37 (65)	84 (75)	
Black	152 (12)	12 (21)	11 (10)	
Hispanic	98 (8)	5 (9)	10 (9)	
Asian	38 (3)	1 (2)	5 (4)	
Other	17 (1)	2 (4)	2 (2)	
Education, *N* (%)				0.14[c]
Less than high school	91 (7)	7 (13)	12 (11)	
High school graduate	257 (21)	9 (16)	15 (14)	
Some college	276 (22)	13 (24)	21 (19)	
College graduate	310 (25)	10 (18)	24 (22)	
Graduate/professional school	297 (24)	16 (29)	37 (34)	
Marital status, *N* (%)				0.49[c]
Not married	198 (16)	10 (18)	22 (20)	
Married	1031 (84)	45 (82)	86 (80)	
Comorbidity score, *N* (%)				0.44[c]
0–2	422 (34)	19 (35)	29 (27)	
3–4	530 (43)	21 (38)	55 (50)	
>5	286 (23)	15 (27)	25 (23)	
PSA at diagnosis, median (IQR), ng/ml	5 (4, 7)	7 (5, 12)	6 (4, 8)	<0.001[a]
Biopsy Gleason score, *N* (%)				<0.001[c]
6 or less	718 (55)	13 (23)	23 (20)	
3 + 4	380 (29)	13 (23)	43 (38)	
4 + 3	127 (10)	9 (16)	20 (18)	
8, 9, 10	82 (6)	22 (39)	27 (24)	
D'Amico prostate cancer risk, *N* (%)				<0.001[c]
Low	628 (48)	8 (14)	17 (15)	
Intermediate	518 (40)	22 (39)	59 (52)	
High	163 (12)	27 (47)	37 (33)	
Clinical stage, *N* (%)				0.013[c]
cT1	1007 (77)	42 (74)	73 (65)	
cT2	303 (23)	15 (26)	40 (35)	
Pathologic pT stage, *N* (%)				<0.001[c]
pT0	1 (0)	0 (0)	0 (0)	
pT2 (NOS)	44 (4)	2 (4)	2 (2)	
pT2a	125 (12)	3 (6)	5 (5)	
pT2b	24 (2)	0 (0)	0 (0)	
pT2c	736 (70)	16 (31)	46 (48)	
pT3 (NOS)	5 (0)	2 (4)	2 (2)	
pT3a	96 (9)	15 (29)	30 (31)	
pT3b	18 (2)	13 (25)	11 (11)	
pT4	1 (0)	0 (0)	0 (0)	
Margin status, *N* (%)				<0.001[c]
Negative	865 (8%)	19 (40)	62 (65)	
Positive	212 (20)	29 (60)	33 (35)	
Any hormone therapy, *N* (%)				<0.001[c]
Yes	83 (6)	28 (49)	39 (35)	
No	1229 (94)	29 (51)	74 (65)	
Nerve-sparing surgery, *N* (%)				<0.001[c]
Nerve-sparing	759 (82)	25 (61)	53 (68)	
Nonnerve-sparing or unilateral nerve-sparing	165 (18)	16 (39)	25 (32)	
Time from radiation to final survey, median (IQR), months		51 (41, 55)	25 (11, 39)	<0.001[b]
Time from surgery to radiation, median (IQR), months		7 (5, 9)	29 (20, 40)	<0.001[b]
Pre-RP baseline EPIC-26 score (IQR)				
Sexual function	80 (40, 95)	69 (48, 99)	75 (44, 90)	0.84[a]
Urinary incontinence	100 (79, 100)	100 (73, 100)	100 (79, 100)	0.85[a]

(*continued*)

Table 1 (***Continued***)

	RP only ($n = 1,312$)	RP + aRT ($n = 57$)	RP + sRT ($n = 113$)	P value
Urinary irritative	88 (75, 100)	88 (69, 100)	88 (75, 100)	0.97[a]
Bowel function	100 (96, 100)	100 (96, 100)	100 (92, 100)	0.78[a]
Hormonal	95 (85, 100)	90 (80, 100)	95 (81, 100)	0.16[a]
Baseline EPIC-26 score between RP and RT (IQR)				
Sexual function	80 (40, 95)	43 (5, 65)	22 (0, 50)	<0.001[a]
Urinary incontinence	100 (79, 100)	76 (51, 100)	76 (54, 98)	<0.001[a]
Urinary irritative	88 (75, 100)	88 (80, 100)	94 (81, 100)	0.003[a]
Bowel function	100 (96, 100)	100 (100, 100)	100 (92, 100)	0.053[a]
Hormonal	95 (85, 100)	90 (80, 100)	90 (80, 100)	0.007[a]

Tests used:
[a] Kruskal-Wallis test.
[b] Wilcoxon test.
[c] Pearson test.

regardless of the timing of receiving RT (sexual function [−9.0 point difference in EPIC-26 score, 95% confidence interval {−14.5, −3.6}, $P < 0.001$], incontinence [−8.8, {−14.0, −3.6}, $P < 0.001$], irritative voiding [−5.9, {−9.0, −2.8}, $P < 0.001$], bowel irritative [−3.5, {−5.8, −1.2}, $P = 0.002$], and hormonal function [−4.5, {−7.2, −1.7}, $P = 0.001$]) at 5 years of follow-up (Supplemental Table 1 and Supplemental Fig. 2).

3.2. Comparisons between RP alone, aRT, and sRT

When taking the timing of RT into consideration, RP + aRT was associated with significant decrements in incontinence (−11.9 [−20.7, −3.1], $P = 0.008$), urinary irritation (−5.9 [−11.2, −0.6], $P = 0.030$), and hormonal function (−7.3 [−13.6, −1.0], $P = 0.023$) at 5 years of follow-up vs. RP alone. RP + sRT was also associated with a significant decline in sexual function (−11.1 [−17.0, −5.3], $P < 0.001$), incontinence (−7.6 [−13.6, −1.6], $P = 0.014$), urinary irritative (−6.1 [−9.7, −2.4], $P = 0.001$), bowel irritative (−4.5 [−7.4, −1.7], $P = 0.002$), and hormonal function (−3.3 [−6.0, −0.6], $P = 0.017$) domain scores vs. RP alone at 5 years of follow-up (Table 2). Irritative voiding and hormonal function scores were affected by aRT in the first year after RP; however, no statistically significant differences were found between RP + aRT and RP + sRT with regard to any functional domain scores beyond 1 year.

3.3. Multivariable modeling of change from baseline domain score over time from RP

We modeled the change in domain score from post-RP, pre-RT baseline to the longest follow-up outcome in order to identify the optimal timing for post-RP radiation for functional recovery (Fig. 2). The smallest decline in sexual function score occurred when RT was administered approximately 24 months after RP (mean 8.9 point decline on EPIC-26 sexual domain, $P = 0.016$). RT administered before 19 months or after 29 months from RP was associated with a mean decline of at least 10 points, which meets the threshold for minimally clinically important difference. These models did not identify optimal timing of radiation to preserve urinary incontinence, urinary irritative, bowel, or hormonal function.

4. Discussion

In this study, both adjuvant and salvage radiation were associated with worse EPIC-26 incontinence, urinary irritative, and hormonal function; with sRT also affecting sexual function and bowel irritative domain scores compared to RP alone at 5 years of follow-up. Furthermore, an interval of approximately 24 months between RP and RT was associated with the least pronounced decline in sexual function associated with post-RP radiation when compared to RT administration at other time points.

This prospective analysis is consistent with reports of lower long-term continence rates in men who undergo radiation at any time point after prostatectomy in retrospective analyses [24-28]. However, retrospective data assessing the impact of post-RP RT on sexual function are more varied. Zaffuto et al. observed a significantly decreased 3-year erectile function recovery rate of 11.6% after aRT vs. 29.0% after sRT compared to 35.0% after RP suggesting that time from surgery to radiation administration does play a role in recovery [25]. Adam et al. also demonstrated that post-RP RT was associated with an 18% lower potency rate compared to RP alone, with aRT significantly lowering potency compared to sRT (37% vs. 45%) [26]. This is in contrast to studies by Hegarty et al. and Showalter et al. that showed no difference in rates of erectile dysfunction after RP vs. post-RP RT with subgroup analysis demonstrating no increased rate of erectile dysfunction between aRT and sRT [27,28]. Differences between our findings and those studies may reflect the fact that we were able to adjust

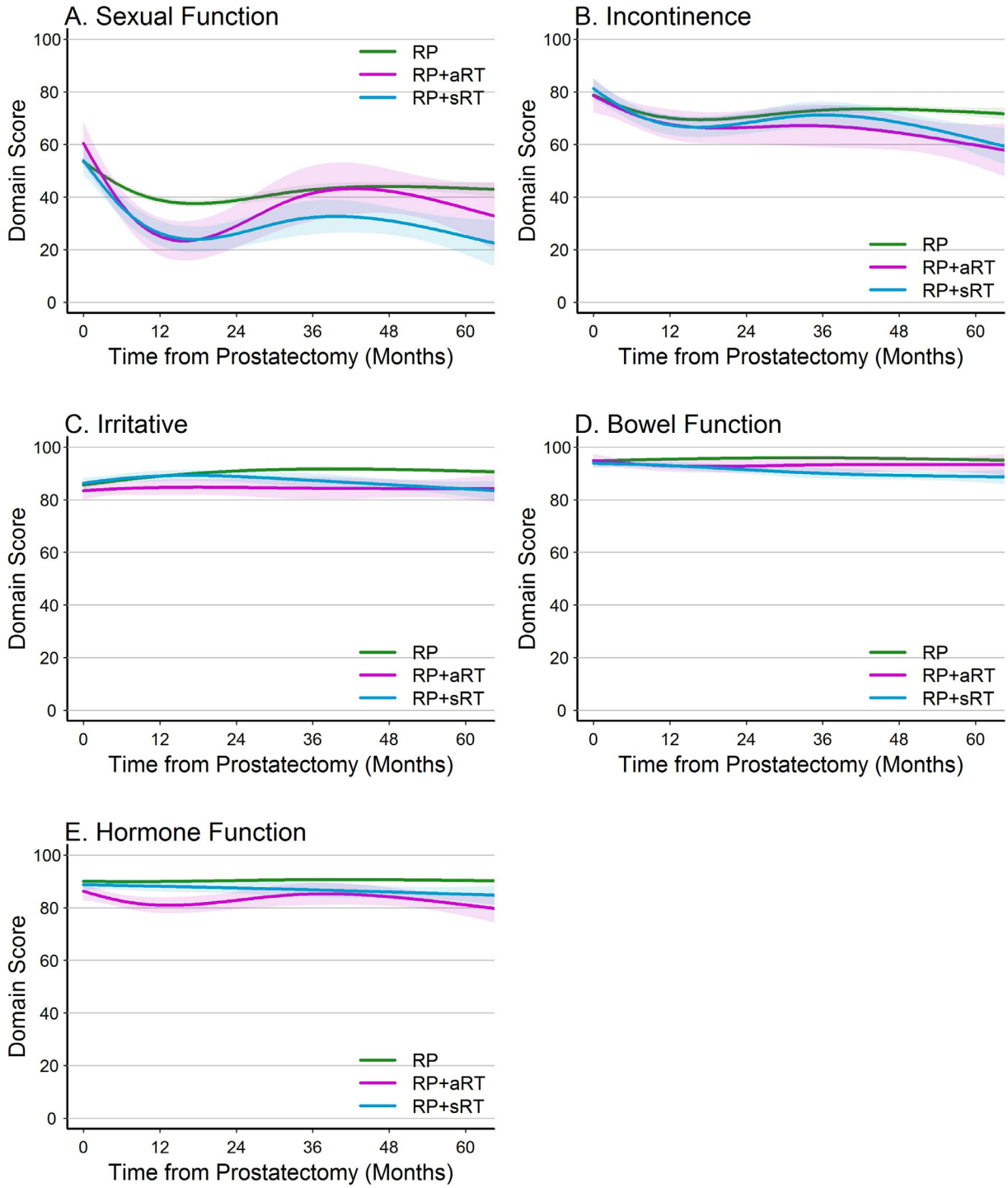

Fig. 1. Unadjusted trajectory plot of EPIC-26 scores for (A) sexual function, (B) incontinence, (C) urinary irritative, (D) bowel function, (E) hormonal function domains for men undergoing RP, RP + aRT, and RP + sRT over time from RP (median time from RP to aRT 7.3 months; median time from RP to sRT 28.5 months).

for baseline function and disease severity, which substantially influence outcomes [29].

While the EPIC-26 domain scores employed in our study are increasingly being utilized for patient-reported functional outcomes among prostate cancer survivors, consideration should be given to the clinical implication of these findings. The 10 to 12 point minimally important difference previously established by Skolarus et al. [31] for erectile function is observed when RT is administered before 19.0 months and after 29.0 months after RP.

Time from RP to radiation was associated with a significant change in sexual domain score from baseline with the

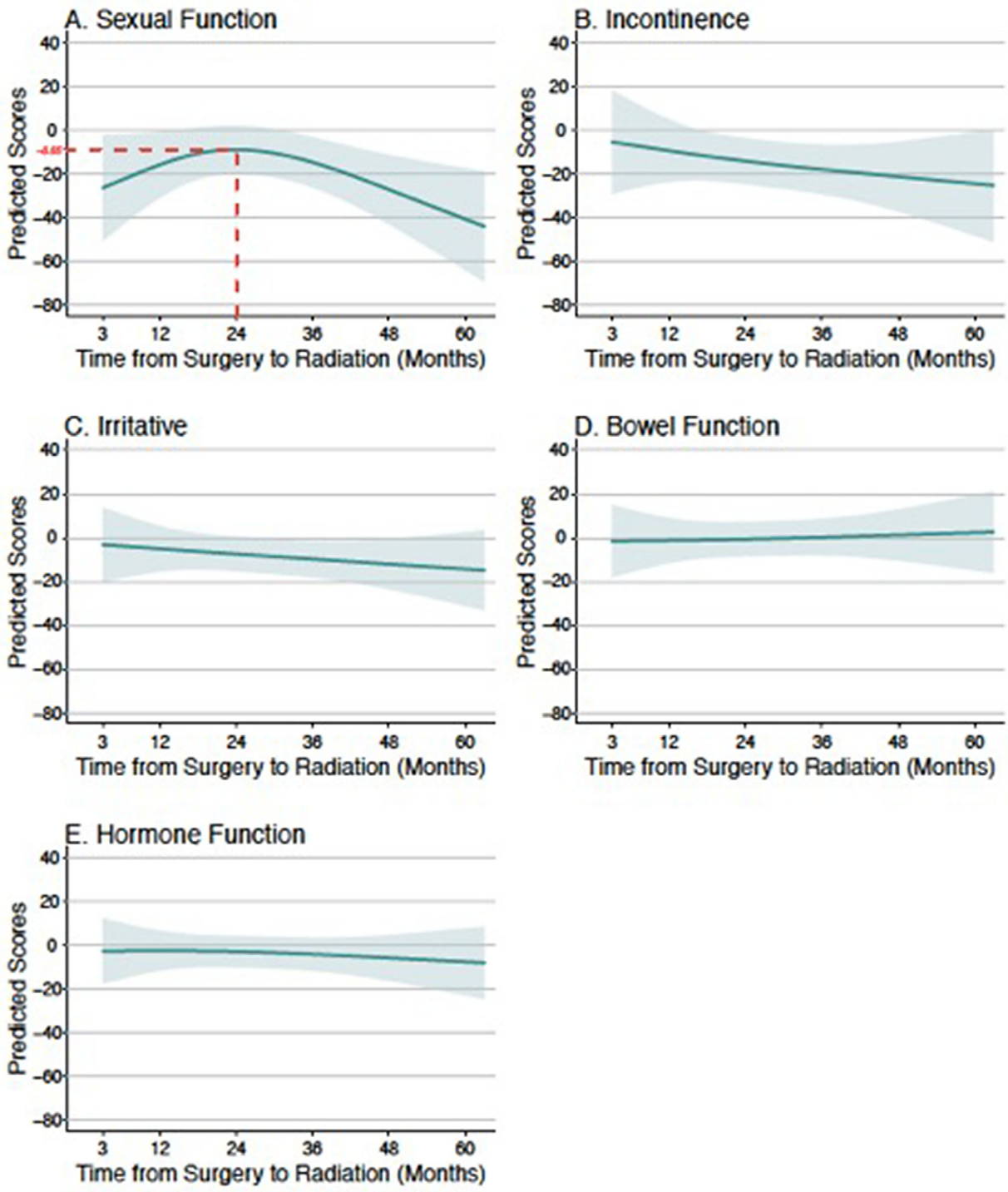

Fig. 2. Predicted changes in EPIC-26 domain scores from post-RP, pre-RT baselines to the longest follow-up outcome [for (A) sexual function, (B) incontinence, (C) urinary irritative, (D) bowel function, (E) hormonal function] as functions of time interval from RP to administration of post-RP radiation. (Red dotted line denotes smallest decrease {mean −8.85 points, 95% CI [−19.8, 2.1]} in sexual function domain score was achieved when the post-RP radiation was administered approximately 24 months after RP.) (Color version of figure is available online.)

least decline in erectile function achieved at approximately 24 months. This suggests that an approximately 2-year recovery period after surgery may be optimal for erectile function preservation, and, therefore, sRT would be preferred if there is no compromise in oncologic control. Whereas older studies have demonstrated differences in progression-free survival between aRT and sRT, interim analysis of the ongoing RADICALS − RT trial did not show a benefit for aRT vs. early sRT with regard to biochemical progression-free survival [30]. Patient-reported urinary incontinence for the aRT group was worse at 1 year, but other functional measures of the RADICALS-

Table 2
Unadjusted and adjusted linear regression model comparing sexual function, incontinence, urinary irritative, bowel irritative, and hormonal function EPIC-26 domain scores over time for RP-alone vs. RP + aRT vs. RP + sRT

Time from prostatectomy (months)	Unadjusted[a]				Adjusted[b]							
	N	RP (*n* = 1,265)	RP + aRT (*n* = 57)	RP + sRT (*n* = 112)	RP vs. RP + aRT			RP vs. RP + sRT			RP + aRT vs. RP + sRT	
						95% CI	*P* value		95% CI	*P* value	95% CI	*P* value
Sexual function												
12	1315	33 (10, 65)	15 (0, 58)	17 (5, 43)	-3.5	[-10.9, 3.9]	0.356	-4.5	[-10.2, 1.2]	0.121	-1 [-9.5, 7.5]	0.817
36	1202	38 (12, 73)	24 (0, 70)	27 (0, 49)	-2.2	[-12.5, 8.2]	0.68	-5.1	[-10.4, 0.2]	0.057	-2.9 [-13.9, 8.0]	0.598
60	1100	39 (10, 75)	20 (0, 75)	12 (0, 49)	-4.2	[-14.4, 6.0]	0.417	-11.1	[-17.0, -5.3]	**<0.001**	-6.9 [-18.0, 4.1]	0.219
Incontinence												
12	1289	75 (52, 100)	79 (46, 100)	73 (52, 100)	1.4	[-6.2, 9.1]	0.714	-0.7	[-6.3, 4.8]	0.796	-2.2 [-11.1, 6.7]	0.635
36	1208	79 (54, 100)	71 (46, 88)	76 (58, 98)	-7	[-16.6, 2.5]	0.149	-1	[-6.5, 4.5]	0.724	6 [-4.5, 16.6]	0.259
60	1106	75 (58, 100)	66 (38, 86)	67 (46, 85)	-11.9	[-20.7, -3.1]	**0.008**	-7.6	[-13.6, -1.6]	**0.014**	4.3 [-5.9, 14.5]	0.407
Irritative												
12	1312	94 (88, 100)	88 (77, 94)	94 (88, 100)	-5.1	[-8.7, -1.6]	**0.005**	-0.3	[-2.5, 1.8]	0.759	4.8 [0.9, 8.7]	**0.015**
36	1208	94 (88, 100)	88 (75, 100)	94 (81, 100)	-5.7	[-10.9, -0.4]	**0.035**	-3	[-6.2, 0.2]	0.07	2.7 [-3.3, 8.6]	0.38
60	1102	94 (88, 100)	88 (75, 100)	88 (75, 100)	-5.9	[-11.2, -0.6]	**0.03**	-6.1	[-9.7, -2.4]	**0.001**	-0.2 [-6.4, 6.0]	0.947
Bowel irritative												
12	1328	100 (96, 100)	96 (88, 100)	100 (92, 100)	-3	[-5.4, -0.5]	**0.016**	-1.3	[-3.8, 1.2]	0.306	1.6 [-1.6, 4.9]	0.323
36	1224	100 (96, 100)	100 (92, 100)	100 (83, 100)	-1.3	[-4.3, 1.6]	0.382	-4.6	[-8.1, -1.2]	**0.008**	-3.3 [-7.8, 1.1]	0.144
60	1117	100 (96, 100)	100 (88, 100)	96 (83, 100)	-1.1	[-4.1, 1.8]	0.46	-4.5	[-7.4, -1.7]	**0.002**	-3.4 [-7.4, 0.5]	0.088
Hormonal function												
12	1314	95 (85, 100)	90 (66, 99)	90 (80, 100)	-7.2	[-12.1, -2.2]	**0.005**	-0.4	[-3.0, 2.1]	0.747	6.7 [1.3, 12.1]	**0.014**
36	1209	95 (85, 100)	95 (75, 100)	92 (79, 100)	-2.8	[-8.1, 2.6]	0.312	-2	[-5.0, 1.1]	0.208	0.8 [-5.3, 6.9]	0.796
60	1108	95 (85, 100)	90 (70, 100)	90 (75, 100)	-7.3	[-13.6, -1.0]	**0.023**	-3.3	[-6.0, -0.6]	**0.017**	4 [-2.8, 10.8]	0.247

Bold values indicate statistically significant results.
[a] Omitted 48 patients who had surgery after 1 year.
[b] Covariates included age, race, TIBICAP, D'Amico risk, use of ADT, bilateral nerve-sparing technique, time from RT administration to final survey completion, and corresponding baseline domain scores.

RT trial have not yet been reported. Taken together with the current study, this suggests that men considering selective sRT may preserve function compared to aRT without compromising oncologic outcomes. Final results of RADICALS- RT and the ongoing RAVES and GETUG-17 trials comparing aRT and sRT will help to better understand the impact of delayed RT on survival outcomes.

There are several limitations of this study, including confounding to indication inherent to this type of nonrandomized study which may limit outcome comparisons between RP, aRT, and sRT groups in the CEASAR cohort. Nevertheless, we controlled for prostate cancer risk group, Gleason score, PSA at diagnosis, pathologic stage, margin status, and ADT exposure, which are related to the indications for subsequent radiation exposure. The knowledge of additional radiation treatment could influence patient assessment and reporting of symptoms, and utilization of interventions for symptomatic management of erectile dysfunction and bladder symptoms in the time period after prostate cancer treatment were not reported. Given the relatively small sample size of 170 men undergoing post-RP RT in our study, negative results for the other domains may be a reflection of being underpowered to discern statistical significance.

These findings help describe the potential harms of post-prostatectomy radiation on sexual, urinary, and bowel function, and the differential outcomes based on the timing of radiation. This information may assist physicians in counseling men with localized prostate cancer with high-risk features, PSA persistence, or BCR after RP, particularly when used in conjunction with emerging data on comparative oncologic effectiveness of aRT and sRT. Balancing the effect of the timing of radiation on both the optimization of functional outcomes and maintenance of disease-specific and OS will be of critical value to prostate cancer survivors participating in shared decision making regarding future treatments.

5. Conclusions

In men with localized prostate cancer, postprostatectomy radiation was associated with worse erectile function, incontinence, urinary irritative, bowel function, and hormonal function domain scores at 5 years compared to RP alone. RT delayed for approximately 24 months after RP was associated with a smaller decline in sexual function than radiation administered closer to the time of RP, suggesting that an approximately 2-year recovery period after surgery may be optimal for erectile function preservation if there is no compromise in oncologic control.

Conflicts of interest

None.

Acknowledgments

We thank the CEASAR study staff for their efforts in data collection and study coordination. Most importantly, we thank the men who participated in CEASAR and shared their experience with prostate cancer.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2020.06.022.

References

[1] Moul JW, Wu H, Sun L, et al. Epidemiology of radical prostatectomy for localized prostate cancer in the era of prostate-specific antigen: an overview of the Department of Defense Center for Prostate Disease Research national database. Surgery 2002;132:213–9.

[2] Chen J, Oromendia C, Halpern JA, Ballman KV. National trends in management of localized prostate cancer: a population based analysis 2004-2013. Prostate 2018;78:512–20.

[3] Roehl KA, Han M, Ramos CG, Antenor JA, Catalona WJ. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. J Urol 2004;172:910–4.

[4] Hull GW, Rabbani F, Abbas F, Wheeler TM, Kattan MW, Scardino PT. Cancer control with radical prostatectomy alone in 1,000 consecutive patients. J Urol 2002;167:528–34.

[5] Amling CL, Blute ML, Bergstralh EJ, Seay TM, Slezak J, Zincke H. Long-term hazard of progression after radical prostatectomy for clinically localized prostate cancer: continued risk of biochemical failure after 5 years. J Urol 2000;164:101–5.

[6] Lu-Yao GL, Potosky AL, Albertsen PC, Wasson JH, Barry MJ, Wennberg JE. Follow-up prostate cancer treatments after radical prostatectomy: a population-based study. J Natl Cancer Inst 1996;88:166–73.

[7] Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol 2009;181:956–62.

[8] Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet 2012;380:2018–27.

[9] Wiegel T, Bartkowiak D, Bottke D, et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. Eur Urol 2014;66:243–50.

[10] Hackman G, Taari K, Tammela TL, et al. Randomised trial of adjuvant radiotherapy following radical prostatectomy versus radical prostatectomy alone in prostate cancer patients with positive margins or extracapsular extension. Eur Urol 2019;76:586–95.

[11] Balakrishnan AS, Zhao S, Cowan JE, Broering JM, Cooperberg MR, Carroll PR. Trends and predictors of adjuvant therapy for adverse features following radical prostatectomy: an analysis from Cancer of the Prostate Strategic Urologic Research Endeavor. Urology 2019;131:157–65.

[12] Jin CJ, Hanna TP, Cook EF, Miao Q, Brundage MD. Variation in radiotherapy referral and treatment for high-risk pathological features after radical prostatectomy: results from a population-based study. Clin Oncol (R Coll Radiol) 2018;30:47–56.

[13] Fossati N, Karnes RJ, Boorjian SA, et al. Long-term impact of adjuvant versus early salvage radiation therapy in pT3N0 prostate cancer patients treated with radical prostatectomy: results from a multi-institutional series. Eur Urol 2017;71:886–93.

[14] Buscariollo DL, Drumm M, Niemierko A, et al. Long-term results of adjuvant versus early salvage postprostatectomy radiation: a large single-institutional experience. Pract Radiat Oncol 2017;7:e125–e33.
[15] Briganti A, Wiegel T, Joniau S, et al. Early salvage radiation therapy does not compromise cancer control in patients with pT3N0 prostate cancer after radical prostatectomy: results of a match-controlled multi-institutional analysis. Eur Urol 2012;62:472–87.
[16] Casas F, Valduvieco I, Oses G, et al. Postoperative adjuvant and very early salvage radiotherapy after prostatectomy in high-risk prostate cancer patients can improve specific and overall survival. Clin Transl Oncol 2019;21:355–62.
[17] Lubeck DP, Litwin MS, Henning JM, et al. The CaPSURE database: a methodology for clinical practice and research in prostate cancer. CaPSURE Research Panel. Cancer of the Prostate Strategic Urologic Research Endeavor. Urology 1996;48:773–7.
[18] Barocas DA, Chen V, Cooperberg M, et al. Using a population-based observational cohort study to address difficult comparative effectiveness research questions: the CEASAR study. J Comp Eff Res 2013;2:445–60.
[19] Lee DJ, Barocas DA, Zhao Z, et al. Comparison of patient-reported outcomes after external beam radiation therapy and combined external beam with low-dose-rate brachytherapy boost in men with localized prostate cancer. Int J Radiat Oncol Biol Phys 2018;102:116–26.
[20] Litwin MS, Greenfield S, Elkin EP, Lubeck DP, Broering JM, Kaplan SH. Assessment of prognosis with the Total Illness Burden Index for Prostate Cancer: aiding clinicians in treatment choice. Cancer 2007;109:1777–83.
[21] Huber P. The behavior of maximum likelihood estimates under nonstandard conditions. Proc Fifth Berkeley Symp Math Stat Probab 1967;1:221–33.
[22] White H. Maximum likelihood estimation of misspecified models. Econometrica 1982;50:1–25.
[23] Core Team R. R: a language and environment for statistical computing. Austria: R Foundation for Statistical Computing V; 2019 https://www.R-project.org/.
[24] Nyarangi-Dix JN, Steimer J, Bruckner T, et al. Post-prostatectomy radiotherapy adversely affects urinary continence irrespective of radiotherapy regime. World J Urol 2017;35:1841–7.
[25] Zaffuto E, Gandaglia G, Fossati N, et al. Early postoperative radiotherapy is associated with worse functional outcomes in patients with prostate cancer. J Urol 2017;197:669–75.
[26] Adam M, Tennstedt P, Lanwehr D, et al. Functional outcomes and quality of life after radical prostatectomy only versus a combination of prostatectomy with radiation and hormonal therapy. Eur Urol 2017;71:330–6.
[27] Hegarty SE, Hyslop T, Dicker AP, Showalter TN. Radiation therapy after radical prostatectomy for prostate cancer: evaluation of complications and influence of radiation timing on outcomes in a large, population-based cohort. PloS One 2015;10:e0118430.
[28] Showalter TN, Hegarty SE, Rabinowitz C, et al. Assessing adverse events of postprostatectomy radiation therapy for prostate cancer: evaluation of outcomes in the Regione Emilia-Romagna, Italy. Int J Radiat Oncol Biol Phys 2015;91:752–9.
[29] Resnick MJ, Barocas DA, Morgans AK, et al. Contemporary prevalence of pretreatment urinary, sexual, hormonal, and bowel dysfunction: defining the population at risk for harms of prostate cancer treatment. Cancer 2014;120:1263–71.
[30] Parker CC, Clarke NW, Cook A, Kynaston HG, Meidahl Petersen P, Cross W, et al. Timing of radiotherapy (RT) after radical prostatectomy (RP): first results from the RADICALS RT randomised controlled trial (RCT). Ann Oncol 2019;30:v883-4.
[31] Skolarus TA, Dunn RL, Sanda MG, et al. Minimally important difference for the Expanded Prostate Cancer Index composite short form. Urology 2015;85:101–5.