A prospective study of health-related quality of life outcomes among men treated for intermediate- and high-risk prostate cancer: the impact of primary and secondary therapies

Mazen Alsinnawi, MD,[1] Jennifer Cullen, PhD,[2,3,4] Lauren M. Hurwitz, MHS,[2,3] Katherine E. Levie, CCRP,[2,3] John F. Burns, MD,[1] Inger L. Rosner, MD,[2,5] Timothy C. Brand, MD,[2,6] Sean Stroup, MD,[2,7] Joseph R. Sterbis, MD,[2,8] Kevin Rice, MD,[2,5] Galen Conti, MPH,[2,3] Christopher R. Porter, MD[1,2]

[1]Virginia Mason Medical Center, Seattle, Washington, USA
[2]Department of Surgery, Center for Prostate Disease Research, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA
[3]Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, Maryland, USA
[4]Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA
[5]Walter Reed National Military Medical Center, Bethesda, Maryland, USA
[6]Madigan Army Medical Center, Tacoma, Washington, USA
[7]Naval Medical Center San Diego, San Diego, California, USA
[8]Tripler Army Medical Center, Honolulu, Hawaii, USA

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Introduction: *To assess the impact of primary and secondary therapies for high- and intermediate-risk prostate cancer on health-related quality of life (HRQoL).*
Materials and methods: *A prospective study was initiated in 2007 at Center for Prostate Disease Research Multicenter National Database sites. Longitudinal patterns in HRQoL from baseline (pre-treatment) to 5 years post-diagnosis were examined for patients with high- and intermediate-risk prostate cancer, treated by radical prostatectomy (RP) or external beam radiation therapy (EBRT). Change in HRQoL was modeled using linear regression models fit with generalized estimating equations. The probability of maintaining HRQoL was compared between patients receiving RP only versus RP with secondary treatment.*
Results: *Of 445 men with high- and intermediate-risk prostate cancer, 228 underwent RP and 143 had EBRT± androgen deprivation therapy (ADT). Fifty received secondary therapy (EBRT and/or ADT or chemotherapy) after RP. RP patients showed a greater decline over time in sexual function and bother and urinary function compared to EBRT±ADT patients. Patients who had secondary therapy after RP were less likely to maintain their HRQoL compared to those who had RP alone. These differences were most pronounced for sexual and hormonal function.*
Conclusions: *Prostate cancer patients experience significant declines in HRQoL after primary therapy. Additional secondary therapy after RP, in the form of EBRT and/or ADT, appears to be responsible for further deterioration in HRQoL outcomes.*

Key Words: prostate cancer, quality of life, radiation, radical prostatectomy, secondary therapy

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Address correspondence to Dr. Jennifer Cullen, The Henry M. Jackson Foundation for the Advancement of Military Medicine, 6720A Rockledge Drive, Suite 300, Bethesda, MD 20817 USA

Introduction

Approximately half of newly diagnosed prostate cancer patients in the U.S. have intermediate- or high-risk disease.[1] Recommended treatment for these patients is radical prostatectomy (RP) or external beam radiation therapy (EBRT), with or without concomitant androgen deprivation therapy (ADT).[2] While these therapies prolong survival,[3,4] they are also associated with short

and long term decrements in health-related quality of life (HRQoL) in patients with localized cancer.[5-7]

The impact of treatment for low-risk prostate cancer on HRQoL outcomes has been the topic of many studies;[5-7] however, less is known about the effect treatment has on the HRQoL in intermediate- and high-risk prostate cancer patients.[8] Moreover, some patients are advised to undergo multiple therapies being in higher risk categories, or advised to because of biochemical recurrence. The American Society for Radiation Oncology and the American Urological Association recommend that secondary EBRT only be offered to patients after counselling on the possible side effects and benefits, taking into consideration patient's values, preferences, HRQoL and functional status.[9-11] However, an informed decision will be easier to make if more is known regarding the impact of secondary treatment on HRQoL.

The primary aim of this study was to compare 5-year trends in HRQoL among intermediate- and high-risk prostate cancer patients enrolled in a multicenter, prospective cohort study and treated with primary RP or EBRT. A secondary aim was to compare changes in HRQoL among patients who received secondary therapy post-RP versus those who only received only primary RP. Our hypothesis was that treatment with RP and EBRT leads to significant declines in several domains of HRQoL, and that secondary therapy after primary RP negatively influences HRQoL outcomes beyond RP alone.

Materials and methods

Study subjects

This prospective study examined patients enrolled in the Center for Prostate Disease Research (CPDR) Multicenter National Database from 2007-2015. Participating medical centers included: Madigan Army Medical Center, Tacoma, WA; Naval Medical Center, San Diego, CA; Virginia Mason Medical Center, Seattle, WA; Tripler Army Medical Center, Honolulu, HI; and Walter Reed National Military Medical Center, Bethesda, MD. Patient enrolment and data collection activities were approved by each institutional IRB, with second-tier IRB approval by the Uniformed Services University of the Health Sciences.

Eligible patients included those diagnosed with National Comprehensive Cancer Network (NCCN)-defined intermediate- and high-risk prostate cancer[2] who completed a baseline HRQoL survey and at least one post-baseline survey. The study population was further restricted to patients diagnosed with nonmetastatic disease who were followed for ≥ 12 months and treated with RP or EBRT within 12 months of prostate cancer diagnosis.

Data collection

All subjects enrolled in the CPDR database have detailed demographic, clinical, treatment, and outcomes information. Information on the following comorbid conditions is also collected: lung disease/chronic obstructive pulmonary disease (COPD), heart disease/coronary artery disease (CAD), stroke, other cancers, type II diabetes, elevated cholesterol, prostatitis, hypertension, and renal insufficiency, with the first four counting as major comorbidities.

Self-reported HRQoL was captured using two metrics, administered prior to or following the diagnostic biopsy (baseline) and at 3, 6, 9, 12, 18, 24, 30, 36, 48, and 60 months post-baseline. These instruments include the Expanded Prostate Cancer Index Composite (EPIC), a prostate cancer-specific instrument, and RAND Medical Outcomes Study Short Form survey (SF-36), a general health assessment instrument.[12,13] Both data collection tools were provided by healthcare practitioners for the patients to answer on their own. The EPIC measures urinary, sexual, bowel, and hormonal function and bother. The SF-36 measures eight subscales that can be combined into physical component summary (PCS) and mental component summary (MCS) scores. For both instruments, subscale scores range from 0-100, with higher scores indicating better HRQoL. For the SF-36 summary measures, scores are standardized to the general US population to have a mean of 50 and standard deviation of 10.

Statistical analysis

Patient demographics, clinical characteristics, and baseline HRQoL scores were compared across primary treatment groups using Welch's t-tests for continuous variables, Chi-square tests for categorical variables, and Cochran-Armitage trend tests for ordinal variables. Change in HRQoL at each time point was calculated as the follow up score minus the baseline score. Only follow up scores reported post-primary treatment were included. For patients treated with primary RP or EBRT, adjusted mean change scores were estimated using linear regression fit with generalized estimating equations, assuming an autoregressive working correlation. Models were adjusted for age at diagnosis, race/ethnicity, number of comorbidities, site, NCCN risk stratum, and baseline HRQoL.

To describe the impact of secondary EBRT (±ADT) (adjuvant or salvage) after RP relative to the impact of only primary RP, the unadjusted mean differences in HRQoL from approximately 6 months before to

6 months after secondary EBRT were compared to changes 6 months before and 6 months after primary RP. The unadjusted change in HRQoL from baseline to 36 months was also compared between patients receiving RP only and patients receiving RP plus any secondary therapy. Finally, the adjusted probability of maintaining HRQoL, defined as not suffering a decline in HRQoL greater than the minimal clinically important difference (MCID) for each subscale, was compared between patients receiving RP only versus RP with secondary treatment. These regression models used a complementary log-log link to account for the interval censored data, with secondary treatment included as a time-updated covariate and the same adjustment variables as above. MCIDs for each subscale were calculated as one half of the standard deviation of the baseline scores.[14] All statistical tests were two-sided, and p values less than 0.05 were considered statistically significant. Analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

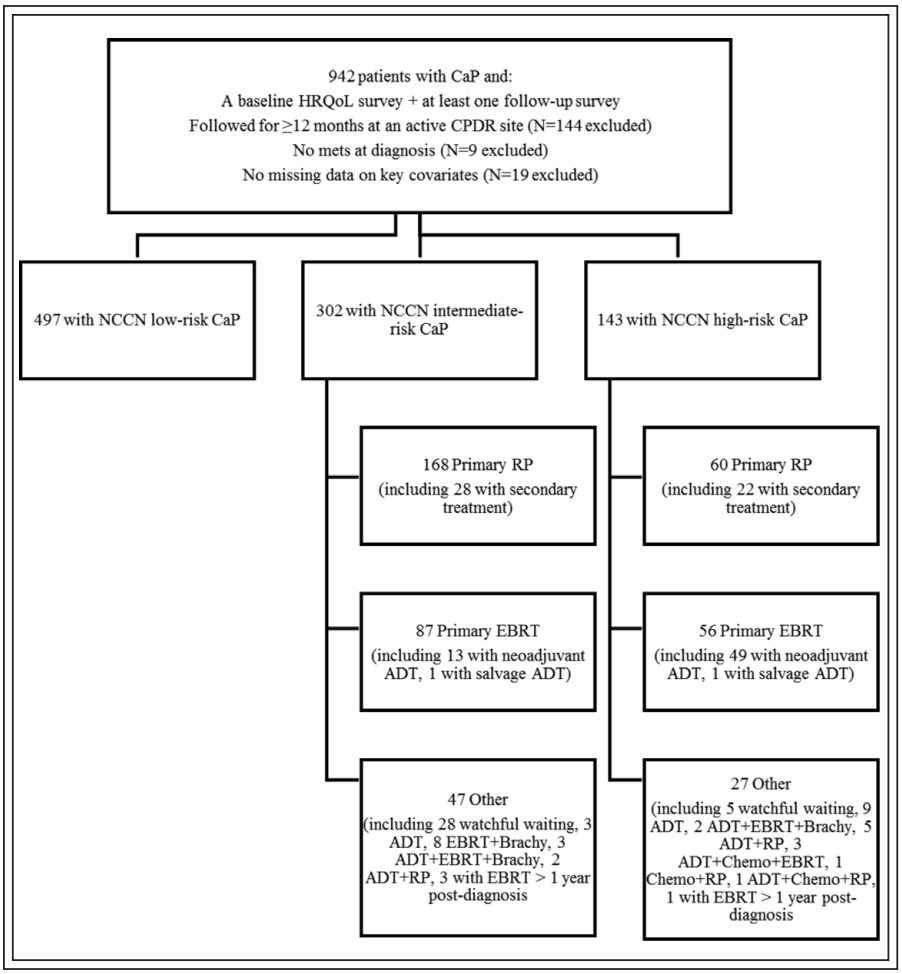

Figure 1. Inclusion criteria and sample size

Results

There were 445 patients with NCCN-defined high- or intermediate-risk disease who met initial study inclusion criteria. Among these subjects, 228 (51.2%) underwent primary RP, 143 (32.1%) received primary EBRT, while 74 (16.6%) had other treatment modalities, Figure 1. Among those who had primary RP, 50 (21.9%) received secondary therapy (adjuvant or salvage EBRT and/or ADT or chemotherapy) during the study period. Of the 143 primary EBRT patients, 62 received neoadjuvant ADT and 2 underwent salvage ADT, Table 1.

Patient demographic and clinical characteristics were compared across primary treatment type, Table 2. The mean age and PSA at diagnosis were significantly higher for EBRT versus RP patients. EBRT patients also had a greater comorbidity burden and were more likely to have high-risk disease. Treatment with EBRT was more common among African American patients than Caucasian American patients.

RP patients had better urinary, sexual, and physical function at baseline compared to the EBRT group, Table 3. Detailed treatment characteristics are shown in Table 1.

Changes in HRQoL after primary therapy

On average, RP patients showed a greater decline over time in sexual function and bother compared to EBRT (±ADT) patients after adjustment for key covariates, Figures 2a and 2b. Adjusted mean declines in sexual function were clinically meaningful (i.e. greater than the MCID of 14 for sexual function) for both groups, and maintained throughout the study period despite slight improvement over time. The RP group experienced clinically meaningful adjusted mean declines in urinary function across the study period; declines in urinary function were smaller for the EBRT (±ADT) group and only meaningful at 6, 48, and 60 months, Figures 2c, and 2d. After 6 months, urinary bother was not meaningfully

TABLE 1. **Treatment characteristics of patients receiving primary RP or EBRT**

	RP (n = 228)	EBRT (n = 143)
Neo-adjuvant ADT, n	0	62
Adjuvant treatment, n		
EBRT	15	0
ADT	9	2
EBRT+ADT	13	0
Salvage treatment, n		
EBRT	6	0
ADT	3	2
EBRT+ADT	6	0
Chemotherapy	1	0
Months from diagnosis to primary RP or EBRT		
Mean ± SD	2 ± 1	3 ± 2
Median (IQR)	2 (2, 3)	3 (2, 4)
Months from diagnosis to secondary treatment		
Mean ± SD	11 ± 10	21 ± 18
Median (IQR)	8 (5, 14)	21 (8, 34)
Duration of ADT		
Mean ± SD	10 ± 14	9 ± 10
Median (IQR)	5 (3, 16)	6 (3, 12)
Total dose for EBRT (cGy)		
Mean ± SD	6856 ± 1095	7962 ± 1660
Median (IQR)	6600 (6480, 6840)	7800 (7740, 7805)
Technique for primary/adjuvant EBRT		
4-field conformal	1	0
CT based/ 3D conformal	1	4
Cyberknife	0	3
IMRT/IGRT/SBRT	25	115
Laser beam	0	1
Proton beam	0	2
Rapid arc	2	0
SRS	0	1
Tomotherapy	0	1

RP = radical prostatectomy; EBRT = external beam radiation therapy; ADT = androgen deprivation therapy; SD = standard deviation; cGy = centigray

TABLE 2. **Baseline demographic and clinical characteristics by primary treatment type**

	RP/RP+Sec (n = 228)	EBRT (n = 143)	p value
Age at diagnosis			**< 0.0001**
Mean ± SD	62 ± 7	70 ± 8	
Median (IQR)	63 (57, 66)	71 (64, 76)	
PSA at diagnosis, ng/mL			**0.02**
Mean ± SD	7 ± 8	12 ± 29	
Median (IQR)	5 (4, 8)	7 (5,11)	
NCCN risk stratum			**0.009**
Intermediate	168 (74)	87 (61)	
High	60 (26)	56 (39)	
Clinical stage, n (%)			0.99
T1	139 (61)	88 (62)	
T2	84 (37)	51 (36)	
T3	5 (2)	4 (3)	
Clinical Gleason sum, n (%)			**0.02**
6	31 (14)	16 (11)	
7	145 (64)	76 (53)	
8-10	52 (23)	51 (36)	
Number of major comorbidities*, n (%)			**< 0.0001**
0	193 (85)	77 (54)	
1	32 (14)	48 (34)	
≥ 2	3 (1)	18 (12)	
Number of biopsies prior to baseline, n (%)			**0.0002**
0	205 (90)	108 (76)	
≥ 1	23 (10)	35 (24)	
Race/ethnicity, n (%)			**0.0008**
Caucasian	157 (69)	78 (55)	
African American	47 (21)	55 (38)	
Other	24 (11)	10 (7)	
Months of follow up			0.07
Mean ± SD	42 ± 17	39 ± 17	
Median (IQR)	48 (30, 60)	36 (24, 60)	

RP = radical prostatectomy; +Sec = plus secondary therapy; EBRT = external beam radiation therapy; SD = standard deviation; PSA = prostate specific antigen; NCCN = National Comprehensive Cancer Network

*major comorbidities include lung disease/chronic obstructive pulmonary disease (COPD), heart disease/coronary artery disease (CAD), stroke, other cancers

impacted in either group. For patients treated with EBRT (±ADT), declines in bowel function and bother were observed throughout the study period and were possibly clinically meaningful, Figures 2e and 2f. Patients treated with EBRT (±ADT) also experienced initial declines in hormonal function and bother, but scores improved steadily from 6-12 months onwards and returned to baseline values at 60 months, Figures 2g and 2h. Bowel and hormonal function and bother were not meaningfully impacted in the RP group, Figures 2e and 2h. Adjusted mean declines in general physical and mental health were similar in both treatment groups and not clinically meaningful, Figures 2i and 2j.

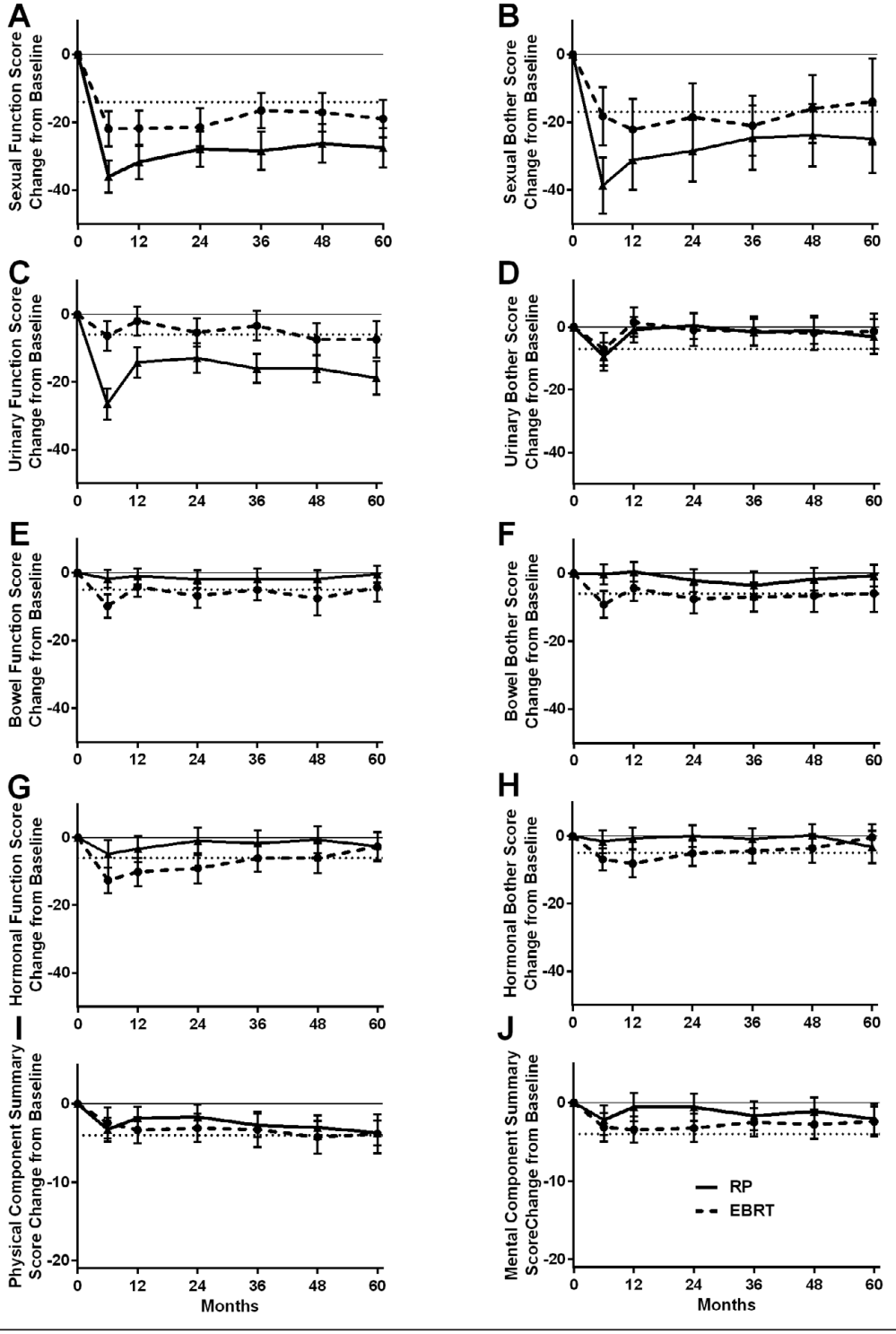

Figure 2. Adjusted mean change from baseline HRQoL scores for patients choosing primary RP or EBRT±ADT. The adjusted mean change scores and 95% confidence intervals for patients choosing primary RP and primary EBRT±ADT are shown for each subscale at each time point. Change score are adjusted for age at diagnosis, race/ethnicity, number of comorbidities, site, NCCN risk stratum, and baseline HRQoL. The dotted line indicates the minimal clinically important differences (MCIDs); changes from baseline that were greater than the MCID were considered clinically meaningful.

TABLE 3. **Baseline HRQoL among patients receiving primary RP or EBRT**

HRQoL domain	RP			EBRT			p value
	Median	Q1	Q3	Median	Q1	Q3	
EPIC							
Urinary function	100	88	100	95	87	100	**0.0497**
Urinary bother	89	79	96	86	71	93	**0.0109**
Sexual function	61	40	72	35	11	64	**< 0.0001**
Sexual bother	81	50	100	50	25	94	**< 0.0001**
Bowel function	96	89	100	96	89	100	0.5306
Bowel bother	100	93	100	100	93	100	0.9040
Hormonal function	90	80	100	90	80	100	0.5978
Hormonal bother	96	92	100	96	90	100	0.3311
SF-36							
Physical functioning	95	85	100	85	65	100	**< 0.0001**
Role-physical	100	81	100	88	63	100	**<0.0001**
Bodily pain	84	72	100	84	62	100	0.1159
General health	82	67	87	72	57	82	**< 0.0001**
Vitality	75	63	88	75	56	81	0.1353
Social functioning	100	88	100	100	75	100	0.6736
Role-emotional	100	83	100	100	75	100	0.0325
Mental health	85	75	90	85	75	90	0.2928
PCS	56	52	59	53	45	57	**<0.0001**
MCS	56	50	59	55	49	59	0.1425

HRQoL = health-related quality of life; RP = radical prostatectomy; EBRT = external beam radiation therapy; Q1 = 25th percentile; Q3 = 75th percentile; EPIC = Expanded Prostate Cancer Index Composite; SF-36 = RAND Medical Outcomes Study Short Form survey

Change in HRQoL after primary RP and secondary therapy

RP patients showed clinically meaningful declines in sexual and urinary function and bother in the 6 months following primary RP, Table 4. Further declines in sexual function and bother were noted in the short term (i.e. within a year) after secondary EBRT (±ADT) (mean declines of -12.14 and -13.89 respectively) and to a lesser extent in hormonal function and bother (-6.57, -4.01 respectively), compared to pre-EBRT baseline. With the exception of the decline in hormonal function, these declines were not greater than the MCID. Urinary function and bother, and physical and mental health did not decline meaningfully immediately after secondary EBRT.

From baseline to 36 months, patients who received RP plus secondary therapy showed greater declines in sexual, urinary, hormonal, and physical HRQoL, compared to patients who received RP only, Table 5.

Probability of maintaining HRQoL after secondary therapy post-RP compared to primary RP

Overall, patients who had secondary therapy after RP were less likely to maintain their HRQoL compared to those who had RP alone over the 5-year study period, Figure 3. Differences were not statistically significant, but the probability of maintaining HRQoL was consistently lower for patients receiving secondary therapy for all subscales examined. These differences were more pronounced for sexual and hormonal function and less apparent in urinary and bowel function.

Discussion

This study confirms the negative impact of primary prostate cancer therapy on HRQoL in high- and intermediate-risk prostate cancer patients and provides evidence of an association between secondary therapy following RP and additional deterioration in HRQoL.

TABLE 4. **Unadjusted mean HRQoL before and after primary RP and secondary EBRT**

	Primary RP (n = 102)[a]			Secondary EBRT (n = 28)[b]			MCID
	Before[c]	After[c]	Difference[d]	Before[e]	After[e]	Difference[d]	
Urinary function	92.53	65.57	**-26.96**	74.65	74.55	-0.18	6
Urinary bother	84.38	72.35	**-12.03**	77.04	77.04	0	7
Sexual function	52.13	16.50	**-35.63**	24.75	12.13	-12.14	14
Sexual bother	66.73	27.21	**-39.52**	42.82	27.90	-13.89	17
Bowel function	93.19	91.36	-1.83	89.29	92.18	3.11	5
Bowel bother	95.46	94.35	-1.11	91.07	90.71	-0.53	6
Hormonal function	88.62	84.49	-4.13	85.71	79.91	**-6.57**	6
Hormonal bother	92.81	89.65	-3.16	92.44	89.74	-4.01	5
Physical components summary	54.30	51.14	-3.16	52.72	51.16	-0.93	4
Mental components summary	53.63	51.72	-1.91	52.63	51.05	-0.91	4

HRQoL = health-related quality of life; RP = radical prostatectomy; EBRT = external beam radiation therapy; MCID = minimal clinically important difference
[a]includes all patients who underwent primary RP, completed baseline and 6-month questionnaires, and who did not receive secondary therapy within 6 months
[b]includes patients who underwent primary RP and secondary EBRT(± ADT), and with an HRQoL survey ≤ 1 year prior to and ≤ 1 year after secondary EBRT (17 secondary EBRT only and 11 secondary EBRT+ADT)
[c]for primary RP, before = baseline score, after = 6 month score
[d]bolded differences are clinically meaningful, i.e. greater than the MCID
[e]for secondary EBRT, scores were from the time points closest to receipt of secondary EBRT

TABLE 5. **Unadjusted mean HRQoL of patients receiving RP alone versus RP + secondary therapy**

	RP (n = 90)[a]			RP + secondary therapy (n = 28)[b]			MCID
	Baseline	36 mo.	Differenced	Baseline	36 mo.	Differenced	
Urinary function	93.10	78.48	**-14.62**	94.96	71.49	**-23.47**	6
Urinary bother	84.15	81.98	-2.17	87.70	73.70	**-14.00**	7
Sexual function	53.62	24.59	**-29.03**	55.04	13.99	**-41.05**	14
Sexual bother	67.30	43.24	**-24.06**	71.75	28.70	**-43.05**	17
Bowel function	91.45	91.57	0.12	95.63	92.53	-3.10	5
Bowel bother	92.75	91.65	-1.10	95.37	91.07	-4.30	6
Hormonal function	88.53	87.46	-1.07	90.56	79.12	**-11.44**	6
Hormonal bother	93.16	90.51	-2.65	95.74	86.02	**-9.72**	5
Physical components summary	54.31	51.47	-2.84	55.91	50.26	**-5.65**	4
Mental components summary	54.22	52.56	-1.66	55.55	51.64	-3.91	4

HRQoL = health-related quality of life; RP = radical prostatectomy; MCID = minimal clinically important difference
[a]includes patients who completed baseline and 36-month questionnaires and did not receive any secondary therapy
[b]includes patients who completed baseline and 36-month questionnaires and received secondary therapy within 36 months of diagnosis (12 secondary EBRT, 7 secondary HT, 8 secondary EBRT+ADT, and 1 secondary EBRT+ADT+chemotherapy)
[d]bolded differences are clinically meaningful, i.e. greater than the MCID

These results are important, given that few studies have focused on the HRQoL impact of secondary therapy in high- and intermediate-risk prostate cancer patients,[8] and may facilitate treatment decision-making for such patients.[10,11]

Studies that have addressed HRQoL for high-risk prostate cancer are rare and have primarily utilized cross-sectional study designs and highly-selected cohorts. These studies have also been limited by their small sample sizes,[15] focus on short term outcomes only,[16] use of a single clinical feature for inclusion criterion (e.g. cT3,[17,18] PSA > 40[19]), examination of functional outcomes without using a validated HRQoL questionnaire[18] (e.g. number of pads as a surrogate for incontinence[19,20]) and/or failure to assess multiple aspects of HRQoL.[21] Other studies have discussed the functional deterioration after active treatment for localized prostate cancer in general and have included considerable numbers of low-risk prostate cancer patients, who are currently often eligible for active surveillance.[7,22-24] In contrast to low-risk patients, patients in this study were high- and intermediate-risk, who are typically recommended to receive active treatment.

We modeled the probability of maintaining HRQoL after receiving secondary therapy, and found that patients with additional therapy had a lower probability of maintaining their HRQoL compared to those who had RP alone over the 5-year study period. These differences were most pronounced in sexual and urinary function. Secondary therapy also impacted hormonal function, but the impact was minimal at 5 years, possibly due to the withdrawal of ADT.

Few studies have focused on urinary, sexual, and bowel symptoms and overall HRQOL after secondary EBRT.[8] Moinpour et al,[25] using a dataset from SWOG 8794, reported more urinary frequency when adding adjuvant EBRT alone to RP. Furthermore, bowel function in their study was adversely impacted by secondary EBRT, but interestingly, sexual function was unaffected. The reason the report by Moinpour et al is in contradistinction to ours likely rests in the important methodological differences. For example, unlike our cohort they did not include men treated with ADT, which may be an important factor in sexual functional changes. Our study also observed a temporary impact of hormonal therapy on HRQoL in patients requiring additional therapy after RP, consistent with previous studies. Choo et al[26] and Pearce et al[27] showed that secondary EBRT plus 2 years of ADT did not result in any persistent, adverse effects on HRQoL.

Our finding that HRQoL is negatively impacted by secondary treatment with EBRT±ADT, is in accordance with the current literature. Patients who required

TABLE 6. **Demographic and pathological characteristics for RP group and RP group with secondary therapy**

	RP (n = 178)	**RP+Sec (n = 50)**
Age		
Mean ± SD	61.45 ± 7.52	62.47 ± 5.89
Median (IQR)	62 (57, 66)	63 (58, 65)
# of comorbidities, n (%)		
0	145 (81)	48 (9
1	30 (17)	2 (4)
≥ 2	3 (2)	0
Race		
White	126 (71)	31 (62)
Black	33 (19)	14 (28)
Other	19 (11)	5 (10)
Diagnostic PSA		
Mean ± SD	6.69 ± 5.34	8.84 ± 12.8
Median (IQR)	5.3 (4.2, 7.5)	5.9 (4.7, 7.4)
Path T stage		
T2	115 (65)	12 (24)
T3	53 (30)	37 (74)
Missing	10 (6)	1 (2)
Path Gleason sum		
6	41 (23)	2 (4)
7	110 (62)	27 (54)
8-10	17 (10)	20 (40)
Missing	10 (6)	1 (2)
Margin status		
Negative	127 (71)	24 (48)
Positive	35 (20)	23 (46)
Unknown	16 (9)	3 (6)
Capsule status		
Negative	112 (63)	12 (24)
Positive	48 (27)	34 (68)
Unknown	18 (10)	4 (8)
Seminal vesicle invasion		
Negative	150 (84)	33 (66)
Positive	10 (6)	15 (30)
Unknown	18 (10)	2 (4)
Any adverse pathology[a]		
No	113 (63)	11 (22)
Yes	65 (37)	39 (78)
Months of follow up		
Mean ± SD	50.03 ± 20.58	54.88 ± 22.24
Median (IQR)	51.3 (36.1, 62.7)	51.8 (36.6, 65.9)

RP = radical prostatectomy

[a]a patient was classified as having adverse pathology if he had positive surgical margins, extracapsular extension, or seminal vesicle invasion

TABLE 7. **Sample size at each time point**

Time point (months)	0	6	12	24	36	48	60
Primary RP[b]							
Eligible[a] (n)	228	207	192	167	149	123	98
Completed (n)	228	143	160	117	118	104	73
Capture rate (%)	100	69	83	70	79	85	74
Primary EBRT[c]							
Eligible[a] (n)	143	143	142	131	112	92	72
Completed (n)	143	91	94	69	59	51	37
Capture rate (%)	100	64	66	53	53	55	51

RP = radical prostatectomy; EBRT = external beam radiation therapy
[a]excludes patients who completed surveys before receiving primary treatment, patients who were deceased, patients censored for secondary treatment, and patients for whom not enough time had elapsed as of January 1, 2015 to reach the later time points
[b]includes RP with or without secondary treatment / [c]includes EBRT with or without neoadjuvant ADT

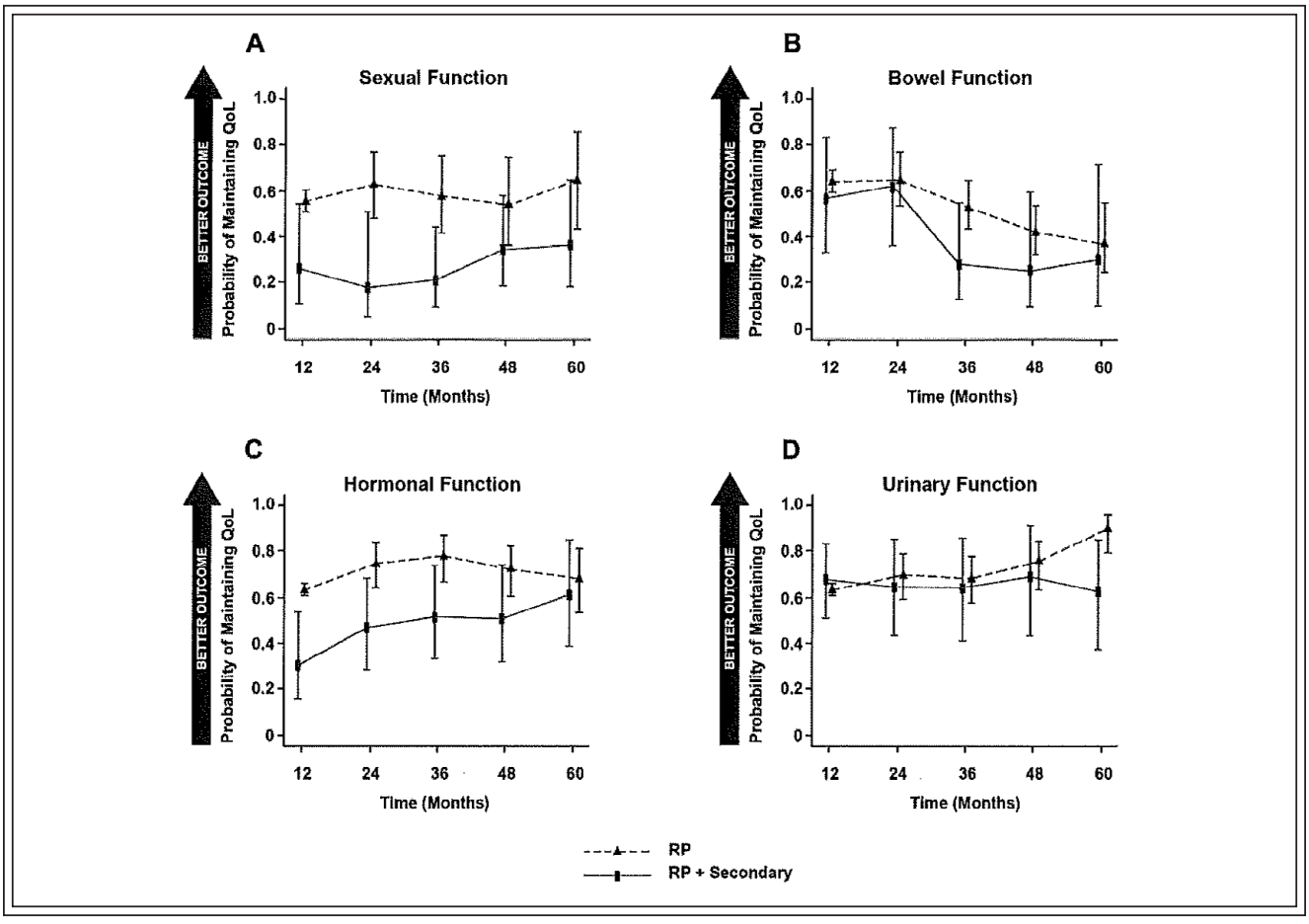

Figure 3. Adjusted probabilities of maintaining HRQoL. The probabilities of maintaining HRQoL, i.e. of not experiencing a decline greater than the subscale-specific MCID, are displayed above for patients undergoing primary RP, by receipt of secondary treatment. Secondary treatments could include adjuvant or salvage EBRT, ADT, and/or chemotherapy. Probabilities are adjusted for age at diagnosis, race/ethnicity, number of comorbidities, site, NCCN risk stratum, and baseline HRQoL.

secondary therapy after RP usually harbor higher risk disease and may have received less conservative surgical approach to better control their cancer, accounting for some of the deterioration in their HRQoL. In support of this, Namiki et al[17] showed that 44 % of pT3 prostate cancer patients failed to return to their urinary function baseline following RP, as compared to 20% of patients with early-stage prostate cancer, due to less use of nerve-sparing surgery. Carroll et al[28] noticed that men who required secondary treatment presented with more severe disease at baseline and were less likely to have nerve-sparing surgery compared to an RP only group, accounting for some of the group differences in urinary and sexual HRQoL. Similarly, in our cohort, patients who required secondary therapy had more adverse disease (i.e. high pathologic grade, positive surgical margins, extracapsular extension, or seminal vesicle invasion) compared to the RP only group, Table 6. Unfortunately, we were unable to determine the use of nerve-sparing surgery adequately in our cohort.

TABLE 8. **Demographic and clinical characteristics comparing patients who did versus did not complete at least half of all HRQoL surveys for which they were eligible, by treatment type[a]**

	RP/RP+Sec		EBRT	
	Completed ≤ 50% of eligible surveys (n = 97)	**Completed > 50% of eligible surveys (n = 131)**	**Completed ≤ 50% of eligible surveys (n = 71)**	**Completed > 50% of eligible surveys (n = 72)**
Age				
Mean ± SD	60.06 ± 7.32	62.86 ± 6.89	69.7 ± 8.66	71.17 ± 6.70
Median (IQR)	60.3 (55.5, 64.2)	64.1 (58.4, 67.6)	70.9 (62.7, 75.8)	72.0 (65.9, 76.4)
# of comorbidities, n (%)				
0	84 (87)	109 (83)	37 (52)	40 (56)
1	12 (12)	20 (15)	24 (34)	24 (33)
≥ 2	1 (1)	2 (2)	10 (14)	8 (11)
Race				
White	65 (67)	92 (70)	41 (58)	37 (51)
Black	25 (26)	22 (17)	28 (39)	27 (38)
Other	7 (7)	17 (13)	2 (3)	8 (11)
Diagnostic PSA				
Mean ± SD	7.28 ± 9.35	7.07 ± 6.11	14.77 ± 40.86	9.22 ± 6.23
Median (IQR)	5.5 (4.3, 7.3)	5.4 (4.2, 7.5)	7.3 (4.9, 11.0)	7.2 (5.0, 10.9)
Clinical T stage				
T1	61 (63)	78 (60)	44 (62)	44 (61)
T2	33 (34)	51 (39)	25 (35)	26 (36)
T3	3 (3)	2 (1)	2 (3)	2 (3)
Clinical Gleason sum				
6	13 (13)	18 (14)	7 (10)	9 (12)
7	65 (67)	80 (61)	38 (54)	38 (53)
8-10	19 (20)	33 (25)	26 (37)	25 (35)
NCCN risk stratum				
Intermediate	75 (77)	93 (71)	43 (61)	44 (61)
High	22 (23)	38 (29)	28 (39)	28 (39)
Baseline SF-36 PCS				
Mean ± SD	54.69 ± 6.19	54.31 ± 7.26	49.68 ± 8.71	51.41 ± 8.72
Baseline SF-36 MCS				
Mean ± SD	53.90 ± 7.19	54.25 ± 7.90	51.83 ± 7.42	54.32 ± 8.08

RP = radical prostatectomy; EBRT = external beam radiation therapy; SD = standard deviation; PSA = prostate specific antigen; NCCN = National Comprehensive Cancer Network

[a]patients were not eligible to complete HRQoL surveys at the earlier time points if they had not yet received primary treatment. Patients were not eligible to complete HRQoL survey at the later time points if not enough time had elapsed for them to reach the later time points (i.e. if they were enrolled < 5 years prior to the date of data analysis) or if they were deceased

Among key limitations of our study was the small number of patients who received secondary therapy after RP. However, patient recruitment is ongoing and future studies will be able to focus on the long term impact of secondary therapy in a growing cohort of intermediate- and high-risk prostate cancer patients. The primary EBRT group had significantly lower baseline HRQoL scores than the primary RP group, limiting the reserve for decline in scores. Despite statistical adjustment, our RP and EBRT patients may not be directly comparable given that primary EBRT patients were older and had worse comorbidity. In addition, the generalizability of the results may be limited since our cohort had subjects from military healthcare beneficiaries and private healthcare patients. Nevertheless, a focus on such patients allowed for examination of our study questions in a cohort with comparable access to health care services, follow up, and multidisciplinary clinics. Another limitation was that the ADT status of those receiving EBRT was not able to be separated due to small sample size in the secondary treatment group and therefore not separated in the primary group for comparison. It is expected that patients who receive ADT will have decrements in HRQoL compared to those who do not. Finally, not all patients completed surveys at all time points, Table 7, creating opportunity for bias due to missing data. Baseline characteristics were similar between patients who did and did not complete more than half of the follow up surveys for which they were eligible, Table 8 within each primary treatment group. Missing data may have still been dependent on unobserved characteristics, and results must be interpreted with this limitation in mind.

Our study has several strengths, including its prospective, longitudinal design. HRQoL outcomes were assessed relative to a baseline that was defined prior to any primary therapy, and patients were followed for several years after their prostate cancer diagnosis. Additional strengths include the use of validated HRQoL questionnaires and the racial diversity of the study population. As statistically significant differences in HRQoL scores may not always be clinically meaningful, MCIDs were calculated for each subscale, allowing for more practical interpretation of observed score differences.

Conclusions

Prostate cancer patients in our study showed significant declines in sexual and urinary function and failed to return to baseline HRQoL levels, regardless of their primary treatment modality; worse declines were observed in the primary RP group compared to primary EBRT group except for bowel function. Additional therapy after RP, in the form of EBRT±ADT, appears to be responsible for further deterioration in functional HRQoL outcomes for CaP patients. Providing patients with information on the probabilities of experiencing meaningful declines in HRQoL, in conjunction with information on how treatments may influence disease-free survival, may facilitate their ability to make decisions regarding additional therapy.

Disclaimers

The contents of this publication are the sole responsibility of the author(s) and do not necessarily reflect the views, opinions or policies of Uniformed Services University of the Health Sciences (USUHS), The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., the Department of Defense (DoD), the Departments of the Army, Navy, or Air Force, or (insert others as applicable). Mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. Government. □

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