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Long-term complications and health-related quality of life outcomes after radical prostatectomy with or without subsequent radiation treatment for prostate cancer

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Abstract

Background: To report objective long-term complications and health related quality of life (HRQOL) outcomes after radical prostatectomy (RP) with and without radiation therapy (RT) for prostate cancer (CaP).

Methods: We analyzed patients diagnosed with CaP who underwent RP from the UCSF Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry between 1995 and 2020. Cox proportional hazards were used to assess risk of postoperative complications which included cystitis, gastrointestinal (GI) toxicity, incontinence requiring a surgical procedure, ureteral injury and urinary stricture. Repeated measures mixed models were used to assess the effects of radiation and complications on patient-reported urinary, bowel, and sexual function after surgery.

Results: Of 6,258 men who underwent RP, cumulative incidence of EBRT was 9.1% at 5 years after surgery. Patients who received post-operative radiation were at increased risk for onset of cystitis (HR 5.60, 95% CI 3.40–9.22, $P < 0.01$). Receipt of RT was not associated with other complications. In repeated measures analysis, postoperative RT was associated with worsening general health scores, adjusting for complications of incontinence, urinary stricture, GI toxicity or ureteral injury, independent of whether patients had those complications.

Conclusions: RT after RP was associated with an increase in the risk of cystitis and worse general health in the long term. Other complications and HRQOL outcomes did not demonstrate differences by whether patients had RT or not. While post-operative RT is the only curative option for CaP after RP, patients and providers should be aware of the increased risks when making treatment decisions.

Keywords: Prostate cancer; Radiotherapy; Quality of life; Complications

1. Introduction

Treatment-related side effects are important considerations in the decision making process for patients with prostate cancer (CaP) [1]. Currently, the ASTRO/AUA guidelines advocate offering adjuvant radiation therapy (ART) for patients with adverse pathological findings at

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time of radical prostatectomy (RP) [2]. However, based on recent results from the RADICAL, RAVES and GETUG-AFU 17 prospective randomized controlled trials, salvage radiation therapy (SRT) offers similar outcomes to ART with better complication profiles [3−6].

Decision making for both patients and providers at this time is complicated by both evolving data on cancer control and adverse effects. Radiation therapy (RT) has the biological potential to cause complications years past treatment [7]. Long term complications after ART/SRT remain underreported [2]. In addition, the most recent ASTRO/AUA guideline on ART/SRT calls for studies validating the long-term health-related quality of life (HRQOL) outcomes for ART and SRT patients [2]. We aimed to document the long-term complications and HRQOL outcomes of patients who undergo RP. We hypothesize that postoperative complication rates will be nominal and subsequent RT after RP will be a risk factor for increased complications and worse HRQOL outcomes than those who had RP alone.

2. Materials and methods

2.1. Patient selection

Participants were enrolled in the Cancer of Prostate Strategic Urologic Research Endeavor (CaPSURE), a longitudinal observational registry of over 15,000 men with all stages of biopsy-proven CaP at 43 centers nationwide since 1995 [8]. At CaPSURE sites, clinical and demographic data were collected at enrollment and at each patient visit. Patients were treated per individual clinicians' standard of care, completed questionnaires at yearly intervals after treatment, and were followed until death or study withdrawal. Participants in the current analysis underwent RP within 1 year of diagnosis. All patients provided written informed consent for research under institutional review board approval.

2.2. Independent variables

Independent variables included patient characteristics (age, race/ethnicity, body mass index (BMI), number of comorbid conditions), clinical *characteristics* at diagnosis (year, PSA (ng/ml), T-stage, biopsy Gleason grade group (GG1, GG2, GG3, GG≥4), NCCN clinical risk group), surgical features at RP (open vs. laparoscopic/robotic approach, complete bilateral nerve sparing, Gleason grade, staging per UICC TNM classification, surgical margin status, Cancer of the Prostate Risk Assessment post-Surgical (CAPRA-S) score, community vs. academic center), and receipt of postoperative radiation. Radiation occurred prior to onset of complication, if any, and was defined as external beam radiation (EBRT) with or without androgen deprivation therapy (ADT) delivered as ART for adverse pathologic features at RP or SRT for biochemical recurrence [9,10]. Concurrent ADT receipt was not hypothesized as a predictor for the selected complications. Variables were described with frequency tables for categorical values and medians with interquartile range for continuous values. Missing values were represented by a separate category for variables with incomplete data. There was a 75% response rate for self-reported HRQOL and complication questionnaries' from CaPSURE during the study period.

2.3. Complications

Complications included in this analysis focused on late-developing, postsurgical complications out to 15 years after RP. Participants were followed for post treatment cystitis, gastrointestinal (GI) toxicity, *surgery* for urinary incontinence, ureteral injury and urinary stricture. Complications were selected based on clinical experience and identified by inpatient/outpatient visits (ICD-9/ICD-10 and CPT procedure codes), or medication use. (Supplementary Tables 1−5). Cystitis included exudative, hemorrhagic, septic or suppurative etiologies of bladder infection/inflammation; it was diagnosed predominately during outpatient visits (47%) or procedure (49%) followed by medication use (4%) limiting inclusion of incidental infections. For GI toxicity, ICD 9/10 and CPT codes included diagnoses (ex: fistula, proctitis) and procedures (ex: urethorrhaphy, fistula closure) representative of chronic and/or severe sequalae. Mild to moderate and/or transient GI distress did not meet the GI toxicity threshold but likely were reflected by with patient reported HRQOL assessments. We also reported the patient-reported or physician-reported use of urinary pads or overactive bladder medications in the peri- and postoperative periods.

2.4. Health related quality of life assessment

Patient-reported QOL outcomes were measured with SF-36 General Health score (GH) and the University of California, Los Angeles (UCLA) prostate cancer index (CaPI) urinary function (UF), bowel function (BF), and sexual function (SF) scores, all ranging from 0 (worse) to 100 (best QOL) [11,12]. Post-RP changes in QOL were tracked with respect to time from surgery to onset of treatment-related toxicity.

2.5. Statistical analysis

Life tables for cumulative incidence and Cox proportional hazards regression were used to assess risk of post-treatment complications after prostatectomy. Follow up for time-dependent analyses began at date of RP. Censoring was determined by last follow up date (visit, treatment, evaluation, patient-reported questionnaire, hospital audit, death certificate) for patients who did not have onset of complication. Cox model covariates were selected *a priori* based upon clinical experience and included patient, clinical, surgical, and radiation characteristics as described above. Postoperative radiation was treated as a time-varying covariate in relation to each individual QOL assessment for mixed modeling to account for different start dates for adjuvant and

salvage radiotherapy in individual patients. Repeated measures mixed models were used to assess the association of each complication with QOL outcomes of UF, BF, SF, and GH scores up to 10 years after prostatectomy. Individual models were adjusted for baseline HRQOL score, years since RP, and the same covariates as the Cox models.

All analysis was done in SAS 9.4 (Cary, NC). Repeated measures mixed models were performed using SAS PROC mixed with patient identifier as random effect. Multiple imputation of missing BMI, comorbid conditions and CAPRA-S was performed prior to each statistical model with the recommended 3-step SAS programming process [13]. A two-sided *P*-value <0.01 with 99% confidence interval was considered significant given multiple comparisons in the analysis.

3. Results

From a total of 15,332 men enrolled in CaPSURE between 1995 and 2020, 6,258 underwent RP and met the study criteria. Of these men, cumulative incidence of EBRT was 9.1% at 5 years after surgery. Median (IQR) duration on EBRT was 1.7 years (1.4−1.8) with over half (52%) of EBRT recipients receiving ADT. Table 1 shows the characteristics of the study participants. Urinary pad use and overactive bladder medication use through 60 months after RP were reported for a subset of 2,860 patients regardless of RT receipt. At 1 year, 876 (30%) of patients did not use pads and by 5 years, 2,462 (86%) of these patients did not use pads. About 188 (7%) patients began using overactive bladder medication in the perioperative period, 107 (4%) from 6 to 24 months, and 77 (3%) from 24 to 60 months after RP. The median follow-up after RP for all patients was 86 months (IQR 44−156).

Table 1
Characteristics of 6,258 patients who underwent radical prostatectomy in the cancer of the prostate strategic urologic research endeavor (CaPSURE).

Patient characteristics	Units/Category	Value	
Age at diagnosis, median (IQR)	Years	62	(57, 67)
Race/ethnicity, n (%)	Native American	14	(<1)
	Asian/Pacific Islander	25	(<1)
	Latino	65	(1)
	Black/African American	343	(5)
	White	4,463	(71)
	Mixed	19	(<1)
	Unknown	1,329	(21)
Body mass Index, median (IQR)	kg/m^2	27	(25−30)
Number of comorbidities, median (IQR)	Count	1	(1, 2)
PSA at diagnosis, median (IQR)	ng/ml	5.8	(4.5−8.6)
Biopsy Gleason grade, n (%)	GG1	3,963	(64)
	GG2	1,236	(20)
	GG3	539	(9)
	GG≥4	453	(7)
	Missing	67	(10
Clinical T-stage, n (%)	T1	3,272	(53)
	T2	2,785	(45)
	T3	95	(2)
	T4	2	(<1)
	Missing	104	(2)
NCCN risk category, n (%)	Low	2,611	(42)
	Intermediate	2,857	(46)
	High	790	(13)
Surgical approach, n (%)	Open	5,398	(86)
	Laparoscopic/robotic	860	(14)
Complete bilateral nerve-sparing, n (%)	Yes	2,679	(43)
Prostatectomy Gleason grade group, n (%)	GG1	2,760	(48)
	GG2	1,893	(33)
	GG3	570	(10)
	GG≥4	519	(9)
	Missing	516	(8)
Pathologic T-stage, n (%)	T2	4,515	(79)
	T3	775	(14)
	T4	412	(7)
	Missing	556	(9)
Pathologic N-stage, n (%)	NX	1,117	(20)
	N0	4,497	(79)
	N1	113	(2)
	Missing	531	(8)
Surgical margin status, n (%)	Positive	1,643	(29)
	Missing	680	(11)
CAPRA-S, n (%)	Low (0−2)	3,303	(58)
	Intermediate (3−5)	1,737	(30)
	High (≥6)	702	(12)
	Missing	516	(8)
Type of clinical site, n (%)	Academic	601	(10)
	Community	5,657	(90)

RP = radical prostatectomy; EBRT = external beam radiation; GG = Gleason grade group; NCCN = National Comprehensive Cancer Network; CAPRA = Cancer of the Prostate Risk Assessment score; IQR = interquartile range.

Estimates are given as median (quartile 1, quartile 3) or frequency (with percentage).

3.1. Rate of complications

Complication rates were <1% before RP. By 15 years after RP the cumulative incidence of any complication was 9.3%, with urinary stricture (4.9%) the most common complication. Cumulative incidence rates were lower for the other conditions of cystitis (2.3%), GI toxicity (2.1%), incontinence procedures (1.5%) and ureter injury (0.3%). Table 2 shows unadjusted life table estimates for complications. Cox proportional hazard models found that patients who received postoperative radiation were at risk for the complication of cystitis compared to those who did not (HR 5.60, 95% CI 3.40−9.22, $P < 0.01$). Postoperative radiation

Table 2
Unadjusted cumulative incidence of postsurgical complications of 6,258 patients who underwent Radical Prostatectomy in the cancer of prostate strategic urologic research endeavor (CaPSURE).

Complication by treatment group	Event within 15 y N	Event at 1 y %	2 y %	3 y %	4 y %	5 y %	6 y %	7 y %	8 y %	9 y %	10 y %	11 y %	12 y %	13 y %	14 y %	15 y %
Cystitis	76	0.2	0.3	0.4	0.6	0.8	1.0	1.1	1.2	1.4	1.4	1.7	1.9	2.0	2.2	2.3
Number at risk	6,258	6,013	5,504	5,063	4,661	4,004	3,577	3,224	2,810	2,561	2,516	2,072	1,858	1,582	1,312	1,113
GI toxicity	64	0.1	0.2	0.3	0.5	0.6	0.7	0.8	0.9	1.0	1.3	1.3	1.6	1.7	2.0	2.1
Number at risk	6,258	6,001	5,519	5,031	4,547	4,020	3,759	3,181	2,823	2,717	2,296	2,101	1,804	1,524	1,236	1,166
Incontinence requiring a procedure	63	0.3	0.4	0.6	0.7	0.9	0.9	1.0	1.2	1.2	1.3	1.4	1.4	1.5	1.5	1.5
Number at risk	6,258	5,959	5,556	5,027	4,541	4,069	3,599	3,181	2,845	2,573	2,352	2,092	1,959	1,509	1,509	1,509
Ureteral Injury	8	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.3	0.3	0.3
Number at risk	6,258	6,127	6,127	6,127	4,811	4,179	4,179	3,563	3,057	3,057	2,521	2,521	2,521	1,633	1,633	1,633
Urinary stricture	208	1.6	2.1	2.3	2.5	2.7	2.9	3.0	3.2	3.5	3.8	4.1	4.5	4.7	4.9	4.9
Number at risk	6,258	5,888	5,402	5,001	4,463	3,958	3,492	3,128	2,773	2,495	2,247	2,026	1,725	1,570	1,249	1,249
Any Complication	357	1.9	2.6	3.2	3.8	4.4	4.7	5.1	5.7	6.2	6.8	7.4	8.0	8.6	9.1	9.3
Number at risk	6,258	5,861	5,367	4,882	4,395	3,859	3,423	3,045	2,679	2,418	2,167	1,947	1,680	1,396	1,141	1,075

Table 3
Cox proportional hazard regression models for risk of complications in 6,258 patients with prostate cancer.

Complication	HR (95% CI)	*P*-value
Cystitis		
Postsurgical radiation Yes vs. No	5.60 (3.40−9.22)	<0.01
GI Toxicity		
Postsurgical radiation Yes vs. No	1.69 (0.86−3.34)	0.13
Incontinence requiring a procedure		
Postsurgical radiation Yes vs. No	1.67 (0.81−3.46)	0.17
Ureteral Injury		
Postsurgical radiation Yes vs. No	1.56 (0.16−15.2)	0.7
Urinary Stricture		
Postsurgical radiation Yes vs. No	1.16 (0.74−1.80)	0.52
Any Complication		
Postsurgical radiation Yes vs. No	1.93 (1.45−2.57)	<0.01

CI = confidence interval; HR = hazard ratio.
All models adjusted for year of diagnosis, age at diagnosis, race, NCCN clinical risk score, body mass index at diagnosis, comorbidities at diagnosis, Cancer of the Prostate Risk Assessment, Surgical approach (open vs. robotic), nerve sparing, clinical site (academic vs. community).

was not an independent risk factor for any other complication. Table 3 shows the Cox proportional hazard models for all complications examined.

3.2. *Quality of life*

Adjusted postsurgical SF-36 GH scores ranged from 77 at 1 to 2 years to 71 at 9−10 years. PCI UF fluctuated from 73 up to 78 and back down to 75 by 9−10 years. Likewise, SF varied from 27 to 34 to 30 over time. PCI BF scores were stable over time (88−89). Repeated mixed measures models were used to assess long-term trends in UF, BF, SF and GH scores up to 10 years after prostatectomy. Cystitis, GI toxicity, and urinary stricture were associated with poorer GH, all $P < 0.01$. Incontinence procedure and urinary stricture were associated with better postsurgical UF scores, both $P < 0.01$. Postoperative radiation was associated with lower GH scores over time independent of onset or type of complication, $P < 0.01$. Supplementary Tables 6−11 show parameter estimates from the repeated mixed measures models.

4. Discussion

The aim of this study was to investigate long-term complications and HRQOL outcomes in patients who underwent RP with or without postoperative RT. We hypothesized that although rates of complications would be low, subsequent RT after RP would be a risk factor for increased complications and worse HRQOL outcomes, compared to RP alone. We report 2 principal findings. First, the cumulative incidence of cystitis after RP was 2.3% over 15 years and after controlling for covariates in Cox proportional hazards model, postoperative RT was associated with an increased risk of cystitis compared to patients who

underwent RP alone (HR 5.60, 95% CI 3.40−9.22). Multiple studies report a steady cumulative increase in late toxicities several years post RT. Ost et al. [14] noted after SRT the rate of grade 2 to 3 genitourinary complications rose from 12% at 24 months to 22% at 60 months. Pearse et al. [15] reported an increase of 13% at 12 months post-SRT to 28% at 60 months post-SRT. We did not find that postoperative RT was a risk factor for development of urinary strictures, risk of having a procedure for urinary incontinence, GI toxicity or ureteral injury.

Our second principal finding is that postoperative RT was an independent risk factor for worsening GH scores when examining the complications of cystitis, GI toxicity, incontinence procedures, ureteral injury, or urinary stricture, independent of whether patients had those complications. Receiving postoperative RT was not associated with any differences in UF, SF and BF scores in our models. Southwest Oncology Group (SWOG) 8794, which randomly assigned patents to RP and observation vs. RP+RT, found that after 5 years patients who received RT reported worse urinary function than those who had RP alone [16]. Bowel function was initially worse for the RP+RT group for approximately 2 years but there was no difference at the end of the 5-year period. They also found no differences in erectile function. Similarly, we found no statistically significant difference in sexual function in CaPSURE patients who received postoperative radiation. We did not find evidence that RT after RP affected urinary function in the long term, unlike results from SWOG 8794; *this difference may be explained in part due to the composition of the CaPSURE registry representing a large proportion of younger, healthier men with lower-risk disease (cT1-T2, GG1 disease).* Our study is similar to a report from Hu et al. [17] who found men that underwent SRT had decreases in sexual and bowel function compared to RP alone with no changes in urinary function. Prior work by our group indicates that most clinically meaningful HRQOL changes are experienced in the first 2 years after treatment [18]. Jenkins et al. [19] report in a cohort of 106 patients who received postprostatectomy RT that a decline in continence was the main driver of worsening urinary HRQOL scores. A study with a median follow up time of 10 years from surgery found men who underwent SRT were more likely to report urinary symptoms than those who underwent RP (16% vs. 9%, respectively) [20].

Our study has several limitations. We adjusted for multiple comparisons by using $P < 0.01$ and 99% confidence intervals for the repeated measures mixed models, rather than using Bonferroni corrections. Using procedure codes to detect complications may also potentially underestimate the incidence given not all patients undergo procedures. We did not assess minor complications such as pad use or cystoscopy/endoscopy alone. Additionally, we did not have data on the specific dose and field of radiation for patients undergoing postoperative RT and most of the participants were treated using nonconformal radiation techniques, unlike current radiation standards. Half (52%) of patients in our cohort were diagnosed with GG1 on biopsy and most (87%) were treated with open prostatectomy. *Both a cohort of men with lower-risk disease and recipients of a surgical approach that is no longer the gold standard* could potentially limit the application of this study to contemporary surgical practice. Additionally, it is possible that patients who undergo RT do so because they have more extensive disease which could inherently increase the risk of complications in this group. We attempted to control for these features by adjusting multivariate models using year of diagnosis, NCCN risk group, comorbidities, clinical site, CAPRA-S, surgical approach, and degree of nerve sparing.

A strength of the CaPSURE registry is that over 80% of patients were managed at community sites, with the remainder from academic and VA networks, making these results more generalizable for men being treated with localized CaP in community practices in the United States. In addition, our study has one of the longest reported follow up periods for patients who underwent RP with subsequent radiation and provides patient reported HRQOL measures using validated questionnaires.

5. Conclusion

The aim of our study was to evaluate long term complications and HRQOL after RP and specifically investigate if RT after RP was associated with increased rates of complications and decreased HRQOL. RT after RP was associated with a significant increase in the likelihood of cystitis in the follow up period compared to RP alone. There was no demonstrated increased risk of other complications between the RT after RP and RP alone groups. General Health was the only significant HRQOL metric that was negatively affected in patients who had RT and RP compared to RP alone — regardless of whether they had complications. While postoperative RT is the only curative option after RP at this time, patients and providers should be aware of the increased risk of cystitis and worsening overall health when making treatment decisions.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, PRC, upon reasonable request.

Ethical approval statement

CHR approval 95982 CapSURE, IRB# 10-00881.

Declaration of Competing Interest

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

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2023.06.003.

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