Survival and secondary interventions following treatment for locally-advanced prostate cancer

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Introduction: *The utility of radical prostatectomy (RP) for locally-advanced prostate cancer remains unknown. Retrospective data has shown equivalent oncologic outcomes compared to radiation therapy (RT). RP may provide local tumor control and prevent secondary interventions from local invasion, and may decrease costs.*
Materials and methods: *Using SEER-Medicare data from 1995-2011 we identified men with locally-advanced prostate cancer undergoing RP or RT. Rates of post-treatment diagnoses and interventions were identified using ICD-9 and CPT codes. Skeletal related events (SRE), androgen deprivation therapy (ADT) utilization, all-cause mortality, prostate cancer-specific mortality, and costs were compared.*
Results: *A total of 8367 men with locally-advanced prostate cancer were identified (6200 RP, 2167 RT). RT was associated with increased urinary obstruction, hematuria, infection, and cystoscopic intervention while RP was associated with increased urethral stricture intervention and erectile dysfunction. Compared to RT, RP was associated with decreased all-cause mortality (3.1 versus 5.2 deaths/100-person-years, $p < 0.001$), prostate cancer-specific mortality (0.8 versus 2.0 deaths/100-person-years, $p < 0.001$), SREs (2.0 versus 3.4 events/100 person-years, $p < 0.001$), and ADT utilization overall (7.4 versus 33.8 doses/100-person-years, $p < 0.001$) and > 3 years after treatment (3.6 versus 4.6 doses/100-person-years, $p < 0.001$). Overall and cancer specific costs were significantly lower for RP versus RT.*
Conclusions: *RT for locally-advanced prostate cancer has a higher incidence of mortality, secondary diagnoses and interventions, SRE, and ADT utilization compared to RP. This may lead to increased costs and have implications for quality of life. Our findings support the utility of RP in appropriately selected men with locally-advanced prostate cancer given the possible decreased morbidity and survival benefit.*

Key Words: prostate cancer, radiation therapy, radical prostatectomy, SEER-Medicare

Introduction

Optimal treatment for locally advanced (≥ pT3) prostate cancer remains elusive; retrospective analyses have supported the use of radical prostatectomy (RP)[1] while others advocate radiation therapy (RT)[2] or report equivalent outcomes.[3] RP, RT and primary androgen deprivation therapy (ADT) have all had varying degrees of success. Given the increasing incidence of high-risk prostate cancer[4] urologists may soon be faced with treating more men with locally-advanced prostate cancer.

Few studies have assessed post-treatment quality of life (QOL) and need for subsequent interventions in men with locally-advanced prostate cancer. Moreover, limited population-based studies have assessed use of

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secondary therapies according to primary treatment. There are few studies analyzing post-treatment QOL and need for secondary interventions in men with locally-advanced prostate cancer. One prospective trial comparing post-treatment QOL outcomes for RT versus RP in high-risk prostate cancer reported increased incontinence for RP versus RT, while RT was associated with higher incidence of pain, hematuria, and difficulty with urination.[5] However, this only reported short term outcomes, and RT may be associated with long term morbidity to the urinary and gastrointestinal system.[6] Additionally, radiation-induced lower urinary tract symptoms (LUTS) and lack of local tumor control may lead to increased use of secondary interventions to prevent urinary obstruction and therefore may diminish QOL.

We sought to perform a population-based study in order to analyze the frequency of secondary morbidity and subsequent use of secondary interventions, related costs, and mortality outcomes for men treated for locally-advanced prostate cancer.

Materials and methods

Data source

We used the Surveillance, Epidemiology, and End Results (SEER) – Medicare database, comprised of a linkage of population based cancer registries from 20 SEER areas covering approximately 28% of the U.S. population. Medicare provides healthcare benefits to most Americans aged 65 years or older. SEER-Medicare captures approximately 97% of incident cancer cases and collects data such as patient demographics, tumor characteristics, and initial course of treatment.[7]

Study cohort

We identified 19425 men aged ≥ 65 years diagnosed with ≥ T3 locally-advanced prostate cancer (ICD-9 Code 185.0) between 1995-2011. Subjects were excluded if diagnosed at autopsy or death, were not enrolled continuously in both Medicare A and B, had less than one full year enrollment after diagnosis, watchful waiting or underwent treatment with primary ADT reducing the sample size to 10414. After excluding men with unknown demographic data, the final number of subjects was 8367. We also identified a sub-cohort of men aged 65-69 (n = 4228), as men in this cohort are more likely to undergo RP than RT.

Using Current Procedural Terminology, Fourth Edition (CPT-4) codes, we identified 6200 men undergoing RP and 2167 men undergoing RT, Table 1. Pathologic staging was used for RP while clinical staging was used for RT.

Independent variables

Age was obtained from the Medicare denominator file while race, US Census region, education level, household income, population density of residence, and marital status were obtained from SEER. Comorbidity was assessed using the Klabunde modification of the Charlson index based inpatient, outpatient and physician services for the year before prostate cancer diagnosis.[8] Tumor grade and stage were obtained from SEER. Stage was defined using the American Joint Committee on Cancer Staging (AJCC) Manual, 7th edition[9].

Dependent variables

Under the SEER grading system "Well Differentiated" corresponds with Gleason scores 2-4, "Moderately Differentiated" corresponds with Gleason scores 5-7, and "Poorly Differentiated" corresponds with Gleason scores 8-10. Gleason score 7 was moved from "Moderately Differentiated" to "Poorly Differentiated" with cases diagnosed after January 1, 2003. For this analysis, tumor grade was categorized into two groups based on the SEER grading system: well/moderately differentiated and poorly differentiated/unknown, similar to prior studies utilizing SEER.[10] PSA was excluded from analysis given unreliability of PSA values using SEER-Medicare data.[11]

Procedures and diagnoses related to primary therapy were identified according to the CPT and ICD-9 codes, Table 1. We did not assess for erectile or urinary function as we do not have access to validated questionnaires and this is often a very subjective outcome that cannot be captured with administrative data. Prostate cancer-specific mortality (PCSM) and overall mortality (OM) were defined by cause of death listed as prostate cancer and other, respectively. Skeletal-related events (SRE) were defined as bone fractures identified utilizing ICD-9 codes as defined in prior studies.[12] ADT use following treatment was evaluated both overall and also at any time > 3 years following treatment date to avoid capturing adjuvant ADT.

To determine overall costs, Medicare healthcare expenditures from inpatient, outpatient, and physician services from cancer diagnosis throughout the study period were summed. This sum was divided by the number of months of follow up to obtain monthly costs. To determine overall prostate cancer associated costs, all expenditures with prostate cancer listed as primary diagnosis were summed and divided by number of months of follow up to obtain monthly costs. Costs were adjusted to 2010 dollars using the 2007 Annual Report of the Boards of Trustees of the Federal Hospital Insurance and Federal Supplementary Medical Insurance Trust Fund.[13]

TABLE 1. **CPT and ICD-9 codes used to identify primary treatments and secondary interventions**

Procedures for primary treatment of prostate cancer	
Procedure	**CPT Codes Used**
Radical prostatectomy	55810, 55812, 55815, 55840, 55842, 55845, 55866
Radiation therapy	9227, 4604, 4610, 55859, 55860, 55862, 55865, 76873, 76968, 77326, 77327, 77328, 77761, 77762, 77763, 77776, 77777, 77778, 77781, 77782, 77783, 77784, 77790, 77799, C1164, C1174, C1325, C1350, C1700, C1701, C1702, C1703, C1704, C1705, C1706, C1707, C1708, C1709, C1710, C1711, C1712, C1715, C1716, C1717, C1718, C1719, C1720, C1728, C1790, C1791, C1792, C1793, C1794, C1795, C1796, C1797, C1798, C1799, C1800, C1801, C1802, C1803, C1804, C1805, C1806, G0256, G0261, Q3001, 77785, 77786, 77787, 55875, C2638, C2639, C2640, C2641, 9226, 77520, 77522, 77523, 77525, 77380, 77381

	Secondary interventions	
Description	**CPT Code**	**ICD-9 Codes**
Ureteral stent placement	52332, 52334	59.8
Nephrostomy	50382, 50384, 50385, 50386, 50387, 50389, 50390, 50392, 50393, 50394, 50395, 50396, 50398	55.02, 55.93
Incision of ureter	50600, 50605	56.2
Urinary diversion	50800, 50810,50815, 50820, 50825, 50840, 50845, 50860, 50780, 50770	56.71, 56.51, 57.87, 56.61, 56.74, 56.75
Suprapubic tube	51040, 51045, 51705, 51710	57.1, 57.17, 57.18, 59.94
Infection	51080, 50020, 50021, 50040, 50045	59.92
Bladder catheterization	51701, 51702, 51703	57.94, 57.95
Cystoscopy/ureteroscopy	52000, 52351	57.3, 57.32, 56.31
Clot evacuation/hematuria	51700, 52001	57.0
Retrograde pyelogram	52005	87.74
Bladder biopsy	52204, 52214, 52224,52234, 52235, 52240	57.33, 57.93, 57.49
Transurethral prostate surgery	52450, 52500, 52601, 52630, 52647, 52648	60.29, 60.0, 60.21
Urethral stricture	52276, 52281, 52282, 52283, 53600, 53601, 53605, 53620, 53621,52640, 53855	57.91, 57.92, 58.3 58.39, 58.5, 58.6
Ureteral stricture	52344, 52351,52354, 52355, 52341	56.33
Erectile dysfunction	55400, 55401, 55402, 55405, 55407	64.94, 64.95, 64.96, 64.97
Incontinence	53440, 53447, 53440	58.93, 58.99, 59.4, 59.5

Statistical analysis

Baseline demographic and clinical characteristics were compared using χ^2 tests and adjusted utilizing propensity scoring, to control for observed confounding factors that may influence both group assignment and outcome using a single composite.[14] We used a logistic regression model to calculate the propensity of men undergoing each treatment modality based on all covariates described above and weighted each subject's data based on the inverse propensity of being in one of the two treatment groups.[15] Covariate balance was checked after adjustment to ensure that there were no statistically significant differences.

As the primary outcomes analyzed do not have an upper time limit and length of follow up varied, we compared number of events per 100 person-years of follow up after propensity-weighting. Because costs were not normally distributed, median costs were compared by treatment type. Adjusted analyses were performed to assess determinants of overall costs, adjusting for demographic and clinical characteristics. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). All p values were considered significant at ≤ 0.05.

Results

Trends in primary treatment for locally-advanced prostate cancer over time are presented in Figure 1. Over the study period, RP utilization increased steadily, while RT utilization remained stable. Demographic and clinical data is presented in Table 2. In unadjusted analysis, men undergoing RP versus RT had fewer comorbidities (Charlson = 0 in 80.6% versus 73.3%, $p < 0.001$), were younger (58.5% versus 27.8% aged 65-69, $p < 0.001$), and married (82.2% versus 74.5%, $p < 0.001$). Additionally, men undergoing RP tended to have higher education levels (42.7 versus 36.9% residing in census region with > 90% high school graduation rate $p < 0.001$) and income (24.7% versus 18.3% residing in census region with ≥ $60,000 median income level, $p < 0.001$).

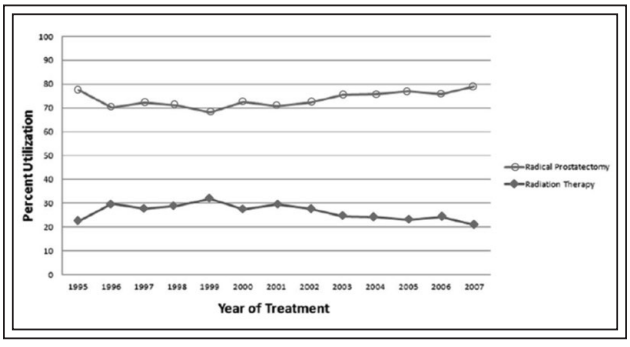

Figure 1. Trends in the utilization of radical prostatectomy and radiation therapy for locally-advanced prostate cancer from 1995-2007.

Table 3 summarizes the incidence of prostate cancer-related complications and interventions following primary treatment. Genitourinary obstruction overall was significantly higher following RT versus RP (36.0% versus 29.9%, respectively; $p < 0.0001$), with urinary retention more likely to occur following RT versus RP (27.6% versus 19.8%, respectively; $p < 0.001$). Following RT, there was increased utilization of bladder biopsy (7.5% versus 5.9%, $p = 0.03$) and transurethral surgery (5.4% versus 3.2%, $p < 0.05$). However, interventions for urethral stricture (10.9% versus 16.3% in RT versus RP, respectively; $p < 0.001$) and ED (2.2% versus 8.9%, respectively; $p < 0.001$) were less likely in the RT group compared to RP. Infection was more frequent in RT versus RP, with inflammatory disease of the prostate (17.6% versus 12.3%, respectively; $p < 0.001$) and dysuria (14.1% versus 8.6%, respectively; $p < 0.001$) being the most common. Hematuria was also more common for RT versus RP (36.8% versus 27.1%, respectively). In contrast, RP had significantly higher incidence of incontinence (36.4% versus 17.9% in RT, $p < 0.001$) and impotence (41.0% versus 22.8% in RT, $p < 0.001$).

Table 4 displays rates of mortality, SRE, and ADT utilization per 100-person years. RP was associated with lowest OM (3.1 versus 5.2 deaths per 100 person-years, $p < 0.001$), lowest PCSM (0.8 versus 2.0 deaths per 100 person-years, $p < 0.001$), lowest incidence of SREs (20 versus 3.4 events per 100 person-years, $p < 0.001$), and lowest ADT utilization overall (7.4 versus 33.8, $p < 0.001$) and > 3 years post-treatment (3.6 versus 4.6, $p < 0.001$).

Median overall and monthly costs were lower in the RP group when compared to RT ($53094 and $783 versus $62894 and $1,024 respectively, $p < 0.001$). Median cancer-specific costs were also lower both overall and monthly in the RP group versus RT ($17882 and $283 versus $23429 and $379, respectively, $p < 0.001$), Table 5. All trends in demographics, secondary diagnoses and interventions, mortality, SRE, ADT use, and costs remained unchanged in men aged 65-69.

Discussion

Significant uncertainty exists regarding the management of locally-advanced prostate cancer.[16] While prospective studies are lacking and the SPCG-15 trial is underway which will likely shed light on PCSM differences between RP and RT,[17] there are several published retrospective studies. Zelefsky found similar 8-year

TABLE 2. Baseline clinicopathologic and demographic data

		Unadjusted			Propensity score weighted		
Variable		**RP (n = 6200)**	**RT (n = 2167)**	**p value**	**RP**	**RT**	**p value**
Year of diagnosis				< 0.0001			0.999
1995		396 (6.39%)	115 (5.31%)		376 (6.1%)	133 (6.1%)	
1996		302 (4.87%)	128 (5.91%)		327 (5.3%)	118 (5.4%)	
1997		311 (5.02%)	119 (5.49%)		320 (5.2%)	113 (5.2%)	
1998		302 (4.87%)	123 (5.68%)		310 (5%)	105 (4.8%)	
1999		266 (4.29%)	125 (5.77%)		284 (4.6%)	96 (4.4%)	
2000		531 (8.56%)	202 (9.32%)		543 (8.8%)	192 (8.8%)	
2001		551 (8.89%)	229 (10.57%)		583 (9.4%)	208 (9.5%)	
2002		578 (9.32%)	223 (10.29%)		588 (9.5%)	208 (9.5%)	
2003		571 (9.21%)	186 (8.58%)		560 (9.1%)	206 (9.4%)	
2004		577 (9.31%)	185 (8.54%)		554 (9%)	190 (8.7%)	
2005		572 (9.23%)	172 (7.94%)		553 (8.9%)	190 (8.7%)	
2006		577 (9.31%)	183 (8.44%)		559 (9%)	195 (8.9%)	
2007		666 (10.74%)	177 (8.17%)		623 (10.1%)	232 (10.6%)	
Age at diagnosis				< 0.0001			0.924
65-69		3626 (58.48%)	602 (27.78%)		3134 (50.7%)	1119 (51.2%)	
70-74		2056 (33.16%)	744 (34.33%)		2073 (33.5%)	723 (33.1%)	
75+		518 (8.35%)	821 (37.89%)		974 (15.8%)	345 (15.8%)	
Charlson	0	4998 (80.61%)	1589 (73.33%)	< 0.0001	4878 (78.9%)	1734 (79.3%)	0.880
score	1	964 (15.55%)	384 (17.72%)		994 (16.1%)	341 (15.6%)	
	2+	238 (3.84%)	194 (8.95%)		309 (5%)	111 (5.1%)	
Race				0.430			0.911
1-White/non-h		5093 (82.15%)	1748 (80.66%)		5049 (81.7%)	1769 (80.9%)	
2-Black/non-h		433 (6.98%)	168 (7.75%)		438 (7.1%)	161 (7.4%)	
3-Hispanic		418 (6.74%)	151 (6.97%)		425 (6.9%)	154 (7%)	
4-Asian/non-h		256 (4.13%)	100 (4.61%)		269 (4.4%)	102 (4.7%)	
Marital status				< 0.0001			0.950
0:Not married		920 (14.84%)	457 (21.09%)		1002 (16.2%)	348 (15.9%)	
1:Married		5099 (82.24%)	1614 (74.48%)		4971 (80.4%)	1762 (80.6%)	
9:Unknown		181 (2.92%)	96 (4.43%)		208 (3.4%)	75 (3.5%)	
Education*	1:<75	1098 (17.71%)	437 (20.17%)	< 0.0001	1122 (18.2%)	390 (17.8%)	0.978
	2:75-84.99	1271 (20.50%)	478 (22.06%)		1295 (21%)	460 (21%)	
	3:85-89.99	1184 (19.10%)	453 (20.90%)		1195 (19.3%)	416 (19%)	
	4:90+	2647 (42.69%)	799 (36.87%)		2569 (41.6%)	920 (42.1%)	
Income**				<0.0001			0.944
1: <$35,000		1829 (29.50%)	749 (34.56%)		1893 (30.6%)	663 (30.3%)	
2: $35,000-44		1381 (22.27%)	551 (25.43%)		1430 (23.1%)	507 (23.2%)	
3: $45,000-59		1461 (23.56%)	471 (21.74%)		1417 (22.9%)	491 (22.5%)	
4: >=$60,000		1529 (24.66%)	396 (18.27%)		1441 (23.3%)	525 (24%)	
Population density				0.913			0.866
Metropolitan		5597 (90.27%)	1958 (90.36%)		5581 (90.3%)	1977 (90.4%)	
Non-metropolitan		603 (9.73%)	209 (9.64%)		600 (9.7%)	209 (9.6%)	
Prostate cancer grade				0.063			0.786
Poorly		3754 (60.55%)	1361 (62.81%)		3775 (61.1%)	1344 (61.5%)	
Well		2446 (39.45%)	806 (37.19%)		2406 (38.9%)	843 (38.5%)	
Prostate cancer stage				< 0.0001			0.730
T3		5785 (93.31%)	1935 (89.29%)		5710 (92.4%)	2025 (92.6%)	
T4		415 (6.69%)	232 (10.71%)		471 (7.6%)	161 (7.4%)	

*percent of high school graduates in census region; **median income level in census region

TABLE 3. **Secondary diagnoses and interventions related to prostate cancer treatment**

Intervention/ complication	Unadjusted RP (n = 6200) n (%)	Unadjusted RT (n = 2167) n (%)	Unadjusted p value	Propensity score weighted RP %	Propensity score weighted RT %	Propensity score weighted p value
GU obstruction diagnosis	1793 (28.92%)	830 (38.30%)	< 0.001	29.92	36.04	< 0.0001
Hydronephrosis	376 (6.06%)	205 (9.46%)	< 0.001	6.35	8.22	0.011
Ureteral obstruction	208 (3.35%)	97 (4.48%)	0.013	3.55	4.64	0.069
Urinary obstruction	288 (4.65%)	184 (8.49%)	< 0.001	4.93	7.89	< 0.0001
Bladder obstruction	6 (0.10%)	1 (0.05%)	0.312	0.10	0.02	0.085
Urinary retention	1180 (19.03%)	638 (29.44%)	< 0.001	19.81	27.56	< 0.0001
GU obstruction intervention	281 (4.53%)	136 (6.28%)	< 0.001	4.82	5.88	0.107
Ureteral stent placement	190 (3.06%)	86 (3.97%)	0.086	3.21	3.88	0.216
Nephrostomy	75 (1.21%)	32 (1.48%)	< 0.001	1.30	1.43	0.696
Incision of ureter	5 (0.08%)	2 (0.09%)	0.866	0.07	0.04	0.418
Urinary diversion	24 (0.39%)	8 (0.37%)	0.253	0.43	0.42	0.966
SP tube	49 (0.79%)	41 (1.89%)	< 0.001	0.93	1.65	0.041
Bladder catheterization	615 (9.92%)	279 (12.87%)	< 0.001	10.34	11.87	0.087
Urethral stricture	685 (11.05%)	223 (10.29%)	< 0.001	11.46	10.14	0.130
Urethral stricture intervention	975 (15.73%)	235 (10.84%)	< 0.001	16.31	10.87	< 0.0001
Cystoscopic intervention	1602 (25.84%)	642 (29.63%)	< 0.001	26.40	28.25	0.148
Cystoscopy/ureteroscopy	1370 (22.10%)	531 (24.50%)	< 0.001	22.52	23.70	0.328
Clot evacuation	209 (3.37%)	120 (5.54%)	< 0.001	3.43	4.42	0.056
Retrograde pyelogram	179 (2.89%)	86 (3.97%)	0.019	3.05	3.72	0.218
Bladder biopsy	345 (5.56%)	176 (8.12%)	< 0.001	5.86	7.47	0.026
Transurethral surgery	192 (3.10%)	131 (6.05%)	< 0.001	3.24	5.39	0.0003
Erectile dysfunction	2639 (42.56%)	409 (18.87%)	< 0.001	41.00	22.82	< 0.0001
Erectile dysfunction intervention	587 (9.47%)	37 (1.71%)	< 0.001	8.92	2.16	<0.0001
Incontinence intervention	1539 (24.82%)	546 (25.20%)	< 0.001	25.05	24.84	0.863
GU infectious diagnoses	2922 (47.13%)	1179 (54.41%)	< 0.001	48.11	51.40	0.023
Pyelonephritis	128 (2.06%)	59 (2.72%)	0.014	2.38	2.57	0.671
UTI	2398 (38.68%)	961 (44.35%)	< 0.001	39.72	40.27	0.696
Prostatitis	731 (11.79%)	386 (17.81%)	< 0.001	12.28	17.63	< 0.0001
Orchitis	138 (2.23%)	51 (2.35%)	0.355	2.15	2.14	0.985
Dysuria	524 (8.45%)	310 (14.31%)	< 0.001	8.59	14.11	< 0.0001
Fistula disease	41 (0.66%)	18 (0.83%)	0.715	0.66	1.03	0.203
Lower urinary tract symptoms	3129 (50.47%)	948 (43.75%)	< 0.001	50.86	42.45	< 0.0001
Incontinence	2220 (35.81%)	411 (18.97%)	< 0.001	36.38	17.86	< 0.0001
Frequency	1880 (30.32%)	799 (36.87%)	< 0.001	30.77	35.91	0.0002
Urgency	239 (3.85%)	117 (5.40%)	0.001	3.83	5.15	0.027
Hesitancy	13 (0.21%)	12 (0.55%)	0.034	0.23	0.72	0.058
Straining	7 (0.11%)	1 (0.05%)	0.537	0.10	0.03	0.184
Hematuria	1642 (26.48%)	805 (37.15%)	< 0.001	26.77	36.25	< 0.0001

cancer-specific survival for T1c-T3b prostate cancer patients undergoing RP versus RT (98.6% versus 95.3%, respectively); however cancer-related mortality in high-risk patients was significantly higher following RT (9.5% versus 3.8%, respectively).[18] Finally, a large retrospective study by Yamamoto showed a 10-year prostate cancer-specific survival of 93.7% in RP versus 85.1% in RT, although not statistically significant.[19] We sought to clarify questions surrounding treatment of locally-advanced prostate cancer utilizing a population-based

TABLE 4. **Rates of mortality, skeletal related events, and ADT use following local treatment for locally advanced prostate**

Outcome	Unadjusted			Propensity score weighted		
	RP (n = 6200)	RT (n = 2167)	p value	RP	RT	p value
Overall mortality (death per100person-years)[1]	2.89	6.24	< 0.001	3.14	5.23	< 0.001
Cancer-specific mortality (death per100person-years)[1]	0.73	2.13	< 0.001	0.77	2.01	< 0.001
Skeletal related events[2]	1.91	3.50	< 0.001	1.97	3.37	< 0.001
Use of androgen deprivation therapy - overall[2]	7.15	34.03	< 0.001	7.43	33.82	< 0.001
Use of androgen deprivation therapy – overall > 3 years after treatment[3]	3.44	4.55	< 0.001	3.58	4.62	< 0.001

[1]any outcomes after cancer diagnosed date; [2]any outcomes after first treatment date; [3]any ADT after 3 years of first treatment date

TABLE 5a. **Overall cost after primary treatment of locally-advanced prostate cancer**

Outcome	Unadjusted			Propensity score weighted		
	RP (n = 5775)	RT (n = 2061)	p value	RP	RT	p value
Follow up time (months) Median (IQR)	72 (44-107)	66 (41-99)	< 0.0001	73 (44-106)	66 (40-99)	< 0.0001
Overall cost ($) Median (IQR)	51172 (28627-94747)	68598 (38801-118852)	< 0.0001	53094 (29605-98449)	62894 (36336-111085)	<0.0001
Monthly overall cost ($) Median (IQR)	757 (448-1332)	1093 (644-1937)	< 0.0001	783 (460-1380)	1024 (611-1786)	<0.0001

IQR = interquartile range

TABLE 5b. **Overall cost after primary treatment of locally-advanced prostate cancer**

Outcome	Unadjusted			Propensity score weighted		
	RP (n = 5843)	RT (n = 2087)	p value	RP	RT	p value
Follow up time (months) Median (IQR)	72 (44-107)	67 (41-99)	< 0.0001	73 (44-106)	66 (40-99)	<0.0001
Cancer specific cost ($) Median (IQR)	17623 (12477-30294)	23399 (14171-35715)	< 0.0001	17882 (12633-30746)	23429 (14432-35730)	< 0.0001
Monthly cancer ($) specific cost Median (IQR)	283 (170-489)	369 (189-676)	< 0.0001	283 (171-490)	379 (192-705)	<0.0001

IQR = interquartile range

approach to not only assess oncologic outcomes, but also rate of secondary interventions and diagnosis following each treatment which may significantly hamper QOL.

Our study has several important findings. First, RT for locally-advanced prostate cancer was associated with increased utilization of secondary procedures compared to RP. Men undergoing RT most commonly had obstructive complications and need for post-treatment transurethral surgery compared to RP. While there is an increased incidence of LUTS in the RP cohort, this is likely due to inclusion of urinary incontinence in the definition of LUTS, and not obstruction. Sanda found patients undergoing brachytherapy and RT had early increase in obstructive and irritative symptoms with an eventual return to baseline, while those undergoing RP reported gradual improvement in obstructive symptoms.[20] These findings are replicated in other studies.[21,22]

We also found that RT was associated with increased incidence of gross hematuria. This is likely due to radiation cystitis, which is unique to RT.[23] Though rare, this can be cumbersome and require multiple interventions,[24] which could potentially drive up cost. RT was also associated with increased cystoscopy and bladder biopsy which may reflect a higher risk of bladder cancer. Boorjian retrospectively analyzed the CAPSURE database and found men undergoing RT were twice as likely to be diagnosed with bladder cancer compared to men undergoing RP, which increased to almost 4-fold among smokers.[25] A more recent meta- analysis of 21 studies found RT for prostate cancer to be associated with higher risk of secondary malignancies of the bladder, colon and rectum when compared to those unexposed, but the absolute rates were low.[26] Finally, in our study genitourinary infections were higher in the RT group which may reflect impaired emptying related to bladder outlet obstruction.

Second, a significant decrease in overall and cancer-specific mortality was noted for men undergoing RP versus RT, even after controlling for baseline differences. In addition, SREs were more common in men undergoing RT. While the difference in OM may be due to variables that we are unable to control for, the difference in PCSM is more striking. Boorjian showed similar PCSM between patients undergoing RT and RP, with a slight improvement in overall survival in the RP cohort. However, in contrast to the present study, these patients were not stratified based on pre-treatment risk category.[26] Other studies have had similar findings. As previously mentioned, Zelefsky found that men with high-risk prostate cancer undergoing RP had lower cancer-specific mortality (3.8% versus 9.5% in RT, respectively).[18] Similarly, Kubelian found that 5-year biochemical recurrence free survival was improved in high-risk patients undergoing RP with negative margins (37% versus 26% in RT).[27] These combined with findings of the present study suggest that there may be survival benefit following RP in high-risk locally-advanced prostate cancer. However, this question cannot be answered definitively without prospective trials.

Third, significantly fewer African-American men and men with low income received treatment for locally-advanced prostate cancer. This reflects disparities in access to treatment among racial and socioeconomic classes in the US. This is especially concerning given the higher incidence of high-risk prostate cancer in African-American men. Other studies have confirmed this disparity.[28]

Finally, costs following RT for locally-advanced prostate cancer were significantly higher than RP. One possible explanation may be due to higher rates of secondary diagnoses and interventions related to treatment and local tumor progression, particularly those related to the increased risk of bladder cancer. The cancer-specific costs may be higher in patients undergoing RT due to the high volume of outpatient visits required during therapy. Cooperberg similarly found that RT of any type was consistently more expensive than surgery across multiple risk categories utilizing Markov models.[29]

Our study had several limitations and must be interpreted in the context of the study design. First, the retrospective nature of a database review allows for significant selection bias. Worse outcomes in the RT group may reflect advanced age and comorbidities, which is commonly observed among patients who may have been deemed inappropriate surgical candidates. However, it is important to note that statistically significant trends remained after propensity-scoring, which is designed to mitigate this bias. Second, we are unable to utilize PSA values and pathologic tumor stage was used in RP group versus clinical tumor stage in radiation therapy group, which may skew results and contribute to a significant type I error. However, we were able to stratify based on Gleason score, therefore accounting for overall stage and grade. Additionally, metastatic disease was excluded, likely excluding men with highest PSA. Because pathologic staging was used for RP and clinical staging for RT, it is possible that many men with clinical stage T2 who were upgraded to pT3 disease after surgery were selectively captured in the RP cohort. The selection bias from this discrepancy in staging may skew results in favor of better outcomes for RP. Finally, our cohort only applies to men >65 thus excluding younger men, who may see the most benefit of aggressive treatment.

Conclusion

RT is associated with increased secondary diagnosis and interventions related to primary treatment of locally-advanced prostate cancer compared to RP, which may have QOL implications. In addition, mortality rates and SREs were more common in men following RT versus RP. Finally, costs following RT for locally-advanced prostate cancer were significantly higher than RP. Our findings support the utility of RP in appropriately selected men with locally-advanced prostate cancer given the possible lower risk of long term morbidity and survival benefit. □

References

1. Tewari A, Divine G, Chang P et al. Long-term survival in men with high grade prostate cancer: a comparison between conservative treatment, radiation therapy and radical prostatectomy--a propensity scoring approach. *J Urol* 2007;177(3):911-915.
2. Fletcher SG, Mills SE, Smolkin ME, Theodorescu D. Case-matched comparison of contemporary radiation therapy to surgery in patients with locally advanced prostate cancer. *Int J Radiat Oncol Biol Phys* 2006;66(4):1092-1099.
3. D'Amico AV, Whittington R, Kaplan I et al. Equivalent biochemical failure-free survival after external beam radiation therapy or radical prostatectomy in patients with a pretreatment prostate specific antigen of > 4-20 ng/ml. *Int J Radiat Oncol Biol Phys* 1997;37(5):1053-1058.
4. Weiner AB, Matulewicz RS, Eggener SE, Schaffer EM. Increasing incidence of metastatic prostate cancer in the United States (2004-2013). *Prostate Cancer Prostatic Dis* 2016;19(4):395-397.
5. Akakura K, Suzuki H, Ichikawa T et al. A randomized trial comparing radical prostatectomy plus endocrine therapy versus external beam radiotherapy plus endocrine therapy for locally advanced prostate cancer: results at median follow-up of 102 months. *Jpn J Clin Oncol* 2006;36(12):789-793.
6. Budaus L, Bolla M, Bossi A et al. Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. *Eur Urol* 2012;61(1):112-127.
7. Zippin C, Lum D, Hankey BF. Completeness of hospital cancer case reporting from the SEER Program of the National Cancer Institute. *Cancer* 1995;76(11):2343-2350.
8. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. *J Clin Epidemiol* 2000;53(12):1258-1267.
9. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010;17(6):1471-1474.
10. Wright JL, Dalkin BL, True LD et al. Positive surgical margins at radical prostatectomy predict prostate cancer specific mortality. *J Urol* 2010;183(6):2213-2218.
11. Sun M, Trinh QD. A Surveillance, Epidemiology and End Results (SEER) database malfunction: perceptions, pitfalls and verities. *BJU Int* 2016;117(4):551-552.
12. Krupski TL, Smith MR, Lee WC et al. Natural history of bone complications in men with prostate carcinoma initiating androgen deprivation therapy. *Cancer* 2004;101(3):541-549.
13. The Board of Trustees, Federal Hospital Insurance and federal Supplementary Medical Insurance Trust Funds. 2007 Annual Report of the Boards of Trustees of the Federal Hospital Insurance and federal Supplementary Medical Insurance Trust Funds. April 23, 2007 via Centers for Medicare & Medicaid Services.
14. Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med* 1997;127(8 Pt 2):757-763.
15. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11(5):550-560.
16. Chang AJ, Autio KA, Roach M 3rd, Scher HI. High-risk prostate cancer-classification and therapy. *Nat Rev Clin Oncol* 2014;11(6):308-323.
17. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2017 July. Identifier NCT02102477, Surgery Versus Radiotherapy for Locally Advanced Prostate Cancer (SPCG-15) Available from: https://clinicaltrials.gov/ct2/show/NCT02102477.
18. Zelefsky MJ, Eastham JA, Cronin AM et al. Metastasis after radical prostatectomy or external beam radiotherapy for patients with clinically localized prostate cancer: a comparison of clinical cohorts adjusted for case mix. *J Clin Oncol* 2010;28(9):1508-1513.
19. Yamamoto S, Kawakami S, Yonese J et al. Long-term oncological outcome in men with T3 prostate cancer: radical prostatectomy versus external-beam radiation therapy at a single institution. *Int J Clin Oncol* 2014;19(6):1085-1091.
20. Sanda MG, Dunn RL, Michalski J et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* 2008;358(12):1250-1261.
21. Litwin MS, Gore JL, Kwan L et al. Quality of life after surgery, external beam irradiation, or brachytherapy for early-stage prostate cancer. *Cancer* 2007;109(11):2239-2247.
22. Budaus L, Bolla M, Bossi A et al. Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. *Eur Urol* 2012;61(1):112-127.
23. Crew JP, Jephcott CR, Reynard JM. Radiation-induced haemorrhagic cystitis. *Eur Urol* 2001;40(2):111-123.
24. Smart D, Wallington M. A cost-analysis case study of radiation cystitis treatment including hyperbaric oxygen therapy. *Diving Hyperb Med* 2012;42(2):92-97.
25. Boorjian S, Cowan JE, Konety BR et al. Bladder cancer incidence and risk factors in men with prostate cancer: results from Cancer of the Prostate Strategic Urologic Research Endeavor. *J Urol* 2007;177(3):883-887; discussion 7-8.
26. Boorjian SA, Karnes RJ, Viterbo , et al. Long-term survival after radical prostatectomy versus external-beam radiotherapy for patients with high-risk prostate cancer. *Cancer* 2011;117(13):2883-2891.
27. Wallis CJ, Mahar AL, Choo R, et al. Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis. *BMJ* 2016;352:i851.
28. Kupelian P, Katcher J, Levin H et al. External beam radiotherapy versus radical prostatectomy for clinical stage T1-2 prostate cancer: therapeutic implications of stratification by pretreatment PSA levels and biopsy Gleason scores. *Cancer J Sci Am* 1997;3(2):78-87.
29. He T, Mullins CD. Age-related racial disparities in prostate cancer patients: A systemic review. *Ethn Health* 2017;22(2):184-195.
30. Cooperberg MR, Ramakrishna NR, Duff SB et al. Primary treatments for clinically localised prostate cancer: a comprehensive lifetime cost-utility analysis. *BJU Int* 2013;111(3):437-450.