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Authors

Tallman, Jacob
Wallis, Christopher
Zhao, Zhiguo
et al.

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Prostate volume, baseline urinary function, and their association with treatment choice and post-treatment urinary function in men treated for localized prostate cancer

Jacob E. Tallman, MD[1], **Christopher J.D. Wallis, MD, PhD, FRCSC**[1], **Zhiguo Zhao, MS**[2], **Li-Ching Huang, PhD**[2], **David F. Penson, MD, MPH**[1], **Tatsuki Koyama, PhD**[2], **Michael Goodman, MD, MPH**[3], **Ann S. Hamilton, PhD, MA**[4], **Xiao-Cheng Wu, MD, MPH**[5], **Lisa E. Paddock, PhD, MPH**[6], **Antoinette Stroup, PhD**[6], **Matthew R. Cooperberg, MD, MPH**[7], **Mia Hashibe, PhD**[8], **Brock B. O'Neil, MD**[9], **Sherrie H. Kaplan, PhD, MS, MPH**[10], **Sheldon Greenfield, MD**[10], **Karen E. Hoffman, MD, MHSc, MPH**[11], **Daniel A. Barocas, MD, MPH**[1]

[1]Department of Urology, Vanderbilt University Medical Center, Nashville, TN

[2]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN

[3]Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA

[4]Department of Preventive Medicine, Keck School of Medicine at the University of Southern California, Los Angeles, CA

[5]Department of Epidemiology, Louisiana State University New Orleans School of Public Health, New Orleans, LA

[6]Department of Epidemiology, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

Corresponding Author: Jacob E Tallman, MD, Department of Urologic Surgery, Vanderbilt University Medical Center, A1302 Medical Center North, Nashville, TN 37232-2765, Phone: (615) 322-2101, Fax: (615) 322-8990.

Author Contributions

Jacob E. Tallman, MD: 1,3,4,5,6
Christopher J.D. Wallis, MD, PhD, FRCSC: 1,3,4,5,6
Zhiguo Zhao, MS: 1,3,5,6
Li-Ching Huang, PhD: 1,3,5,6
David F. Penson, MD, MPH: 1,2,5,6
Tatsuki Koyama, PhD: 1,3,5,6
Michael Goodman, MD, MPH: 1,2,5,6
Ann S. Hamilton, PhD, MA: 1,2,5,6
Xiao-Cheng Wu, MD, MPH: 1,2,5,6
Lisa E. Paddock, PhD, MPH: 1,2,5,6
Antoinette Stroup, PhD: 1,2,5,6
Matthew R. Cooperberg, MD, MPH: 1,2,5,6
Mia Hashibe, PhD: 1,2,5,6
Brock B. O'Neil, MD: 1,2,5,6
Sherrie H. Kaplan, PhD, MS, MPH: 1,2,5,6
Sheldon Greenfield, MD: 1,2,5,6
Karen E. Hoffman, MD, MHSc, MPH: 1,2,5,6
Daniel A. Barocas, MD, MPH: 1,2,3,4,5,6
1) Conception or design of the work
2) Data collection
3) Data analysis and interpretation
4) Drafting the article
5) Critical revision of the article
6) Final approval of the version to be published

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[7]Department of Urology, University of California, San Francisco, CA

[8]Department of Family and Preventive Medicine, University of Utah School of Medicine, Salt Lake City, UT

[9]Department of Urology, University of Utah Health, Salt Lake City, UT

[10]Department of Medicine, University of California Irvine, Irvine, CA

[11]Department of Radiation Oncology, University of Texas M. D. Anderson Center, Houston, TX

Abstract

Background: Benign prostatic hyperplasia, lower urinary tract symptoms, and prostate cancer often co-occur. Their effect on urinary function is an important consideration regarding prostate cancer treatment choices. While prostate volume (PV) and urinary symptoms are commonly used in treatment choice decision making, their association with post-treatment urinary function is unknown. We evaluated the associations between PV and baseline urinary function with treatment choice and post-treatment urinary function among men with localized prostate cancer.

Methods: We identified 1647 patients from CEASAR, a multicenter population-based, prospective cohort study of men with localized prostate cancer, for analysis. Primary outcomes were treatment choice and health-related quality of life (HRQOL) assessed by the 26-item Expanded Prostate Index Composite (EPIC-26) at pre-specified intervals up to 5 years. Multivariable analysis was performed, controlling for demographic and clinicopathologic features.

Results: Median baseline PV was 36 mL (IQR 27–48), and baseline urinary irritative/obstructive domain score was 87 (IQR 75–100). There was no observed clinically meaningful association between PV and treatment choice or post-treatment urinary function. Among patients with poor baseline urinary function, treatment with radiation or surgery was associated with statistically and clinically significant improvement in urinary function at 6 months which was durable through 5 years (improvement from baseline at 5 years: radiation 20.4 points, surgery 24.5 points).

Conclusions: PV was not found to be associated with treatment modality or post-treatment urinary irritative/obstructive function among men treated for localized prostate cancer. Men with poor baseline urinary irritative/obstructive function improve after treatment with surgery or radiation therapy.

Keywords

Prostatic neoplasms; prospective studies; patient reported outcome measures; survey and questionnaires; cohort studies

Introduction

Benign prostatic hyperplasia (BPH), lower urinary tract symptoms (LUTS), and prostate cancer often co-occur[1]. Current management options for localized prostate cancer include radical prostatectomy, radiation therapy, and active surveillance. It is recognized that baseline function is one of the strongest predictors of functional outcomes after treatment for prostate cancer, and surgery and radiation are both known to be associated with

changes in urinary function. Furthermore, there is a long-standing belief that radiation may exacerbate baseline urinary symptoms. Indeed, until recently, the AUA guidelines recommended surgical approaches for men with obstructive, non-cancer-related LUTS, though the recent update stops short of recommending one treatment modality over another for these patients[2,3]. Radical prostatectomy has itself been associated risk of urinary incontinence, but potential improvement in urinary irritative symptoms while radiation therapy has been associated with a deterioration in those symptoms[4].

Contemporary surveys of patients with prostate cancer indicate that avoidance of urinary adverse effects is an important factor in deciding on treatment choice[5]. While a patient's PV and baseline LUTS may be used by clinicians to aid treatment decision-making in men with localized prostate cancer, it is unknown if they are associated with treatment choice or post-treatment patient-reported urinary function. Furthermore, the previously noted AUA guideline recommendations for men with baseline urinary symptoms are based on limited evidence (grade C).

We utilized data from the Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) cohort to examine whether pre-treatment PV and baseline patient-reported urinary function were associated with (1) treatment choice for patients newly diagnosed with localized prostate cancer and (2) post-treatment patient-reported urinary function. We hypothesized that men with larger PV and worse baseline urinary function would be more likely to choose surgery over radiation therapy due to a perceived potential improvement in urinary function with surgery and potential deterioration with radiation. We also hypothesized that men with larger PV and worse baseline urinary function who chose surgery would experience a significant improvement in urinary function after treatment while men who chose radiation would experience worse urinary function after treatment.

Methods

The CEASAR study design has been described previously[6]. Briefly, CEASAR is a multicenter population-based, prospective cohort study that enrolled 3709 men with clinically localized prostate cancer from January 2011 to February 2012. Patients were accrued from five population-based Surveillance, Epidemiology and End Results (SEER) registry catchment areas (Atlanta, Los Angeles, Louisiana, New Jersey, and Utah), as well as an additional prostate cancer patient registry (Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE™)). Patients were excluded if they received primary treatment other than surgery, radiation, or active surveillance (e.g. thermal ablation, primary androgen deprivation therapy), were missing PV or baseline urinary irritative/obstructive domain score data, or did not complete a post-treatment survey. Patient-reported HRQOL outcomes were collected via mail surveys at enrollment (baseline) and 6, 12, 36, and 60 months after the initial pathology-confirmed diagnosis. Institutional review board approval was obtained from Vanderbilt University Medical Center (coordinating center) and from each site. Informed consent was obtained from each participant.

Exposures and Outcomes: Prostate Volume and Urinary Function

Baseline PV was evaluated using transrectal ultrasound (TRUS) at the initial diagnostic biopsy. These data were included as an *a priori* variable of interest for abstraction at the time of medical chart review, obtained around 12 months of the diagnosis by trained medical chart abstractors. PV was stratified into 4 groups: ≤ 30 mL, 31–50 mL, 51–70 mL, and > 70 mL. As there are no generally accepted PV groupings in the literature and prior studies vary widely in prostate size stratification, our stratification schema was selected based on prior literature[7–9] and to provide balanced group size and clinically meaningful groups in this cohort.

Baseline and post-treatment urinary irritative/obstructive function were evaluated using the validated 26-item Expanded Prostate Index Composite (EPIC-26)[10]. The EPIC-26 survey characterizes HRQOL outcomes in several prostate cancer-specific domains (sexual function, urinary incontinence, urinary irritation/obstruction, bowel function, and hormone therapy-related symptoms) scored from 0–100, with 100 being the best HRQOL. Minimum clinically important difference (MCID) in the urinary irritative/obstructive domain sub-scale score has been quantified as 5–7 points, in the urinary incontinence sub-scale the MCID is 6–9 points, and in the sexual function sub-scale it is 10–12 points[11]. Baseline urinary function was grouped into four categories based on scaled urinary irritative/obstructive domain scores: 0–74, 75–84, 85–94, and 95–100. These score cutoffs were selected based on the distribution of data to provide balanced group size. The primary outcomes were treatment choice and post-treatment EPIC-26 urinary irritative/obstructive domain score. Secondary outcomes include post-treatment EPIC-26 urinary incontinence and sexual function domain score.

Baseline Characteristics

Clinically important covariates collected from self-report and medical records included age, race, educational attainment, marital status, household income, health insurance, employment, D'Amico disease risk classification, serum PSA at diagnosis (continuous), clinical tumor stage, biopsy Gleason score, use of androgen deprivation therapy, and accrual site. Comorbidity was measured using the Total Illness Burden Index (TIBI)[12]. The CEASAR survey questionnaires included multiple related validated HRQOL surveys including Short Form (SF-36) general HRQOL and social support survey scores[13], Center for Epidemiologic Studies Depression (CESD) scale score[14], and participatory decision making (PDM) scale[15].

Statistical Analysis

Patients' demographic and clinical characteristics were summarized using medians (quartiles) for continuous variables and frequencies (proportions) for categorical variables. Differences in demographic and clinical characteristics across PV strata and baseline urinary irritative/obstructive domain score categories were assessed using Kruskal-Wallis (continuous variables) and Pearson χ^2 tests (categorical variables). To evaluate the associations of PV and baseline urinary irritative/obstructive domain scores with treatment modality, two-way contingency tables were constructed and Pearson χ^2 tests were used.

We then assessed the correlation between PV and baseline urinary function using Pearson correlation coefficient.

To evaluate the associations of PV and baseline urinary irritative/obstructive domain with post-treatment urinary and sexual function, multivariable longitudinal linear regression models were used. All previously mentioned potential confounders were included in the models as covariates. The mean differences in post-treatment domain scores comparing PV strata and baseline urinary irritative/obstructive domain score strata were reported as the effect measurements along with the 95% confidence intervals (CIs) from each domain specific model. To account for the potential serial correlation between the multiple records collected for each patient at different follow-up, the Huber-White method[16,17] was used to estimate robust covariance matrix. Missing values in the regression variables were imputed using the multiple imputation using chained equations procedure[18,19]. No outcome variables were imputed. Two-sided p-values < 0.05 were used to define statistically significant results. To account for multiple simultaneous comparisons, clinical significance was also evaluated based on previously identified MCID for each EPIC-26 domain as noted previously[11]. All analyses were conducted using R version 4.1.

Results

From the CEASAR cohort, we identified 1647 men who completed at least one HRQOL survey and had complete data for critical variables including TRUS PV and PSA level at diagnosis (Supplementary Figure 1). Median age was 64 years (IQR: 59–69) (Table 1). With respect to race/ethnicity, 77% of the cohort were non-Hispanic white, 12% black, 8% Hispanic, and 3% Asian. D'Amico low-, intermediate and high-risk disease was observed in 45%, 39% and 16% of study participants, respectively. Response rates for the follow up surveys were 98% for the 6-month survey, 95% at 1 year, 85% at 3 years, and 77% at 5 years. 926 (56%) patients were treated with surgery, 387 (23%) with EBRT, 78 (5%) with brachytherapy, and 256 (16%) were put on active surveillance. 195 of 465 (42%) patients receiving radiation therapy (EBRT or brachytherapy) received any androgen deprivation therapy.

Median baseline TRUS PV was 36 mL (IQR 27–48) (Table 2). Median EPIC-26 irritative/obstructive domain score at baseline as 87 (IQR 75–100). There was a statistically significant association between PV and treatment choice, but this association was small and likely not clinically significant (median volume for surgery 35mL, radiation 37mL, active surveillance 40mL, $p<0.001$). Similarly, there was a statistically significant association between PV and urinary irritative/obstructive domain score at baseline with larger PV being associated with worse urinary function, but the association was weak and most of the variation in urinary irritative/obstructive function was not explained by PV ($R = -0.175$, $p<0.001$, Supplementary Figure 2).

Prostate size and urinary irritative/obstructive symptom outcomes

Multivariable longitudinal regression evaluating the association between PV, baseline urinary function, and post-treatment urinary function is shown in Table 3. When comparing patients with the largest baseline PV (> 70 mL) vs. those with the smallest PV (< 30

mL), there were no statistically or clinically significant associations between PV and post-treatment urinary function.

Baseline urinary irritative obstructive function and post-treatment urinary irritative/obstructive function outcomes

We identified both statistically and clinically significant associations between urinary irritative/obstructive domain score at baseline and at each post-treatment time point (Figure 1, Table 3). Among patients undergoing either surgery or EBRT, we identified statistically and clinically significant improvement in urinary function after treatment (Figure 2). The difference between patients with the best baseline function (baseline domain score 95–100, “high baseline” group) and worst baseline function (baseline domain score 0–75, “low baseline” group) diminished over time after treatment with EBRT but remained clinically significant at 5 year follow up (mean baseline difference 37.5 points, mean 5-year survey difference 10.3 points; MCID 7 points). Patients in the low baseline group receiving brachytherapy had similar improvement to those receiving EBRT with persistent clinically significant difference between the low and high baseline groups at 5 years (mean baseline difference 40.6 points, mean 5-year survey difference 12.5 points). Among patients treated with surgery, the difference diminished further and was no longer clinically significant at 5 year follow up (mean baseline difference 37.5 points, mean 5 year survey difference 6 points). For both EBRT and surgery patients, the attenuated difference between the low baseline and high baseline groups was driven largely by improvement in symptom scores in the low baseline group, more than it was driven by decline in scores in the high baseline group. Patients on active surveillance showed no clinically significant improvement in urinary function over time, with a stable 15–20 point difference between patients in the high and low baseline groups at each survey time point.

Multivariable analysis was also performed to assess the associations between PV and other EPIC-26 HRQOL domains, including urinary incontinence and sexual function. There were few statistically significant, and no clinically meaningful associations found (Supplementary Table 1). Similar results were found when comparing baseline urinary irritative/obstructive domain score with post-treatment urinary incontinence and sexual function, with no clinically significant associations identified. The use of androgen deprivation therapy by patients receiving radiation therapy was not statistically significantly associated with post-treatment urinary irritative/obstructive scores at any time points (all $p > 0.05$).

Discussion

In this large, population-based, prospective cohort study of men with localized prostate cancer, we found no clinically meaningful associations of PV or baseline urinary irritative/obstructive function with treatment choice. Furthermore, PV was not associated with urinary function outcomes through 5 years of follow up. Among men with poor baseline urinary function, we found that treatment with surgery as well as EBRT was associated with clinically significant improvement in urinary function. Men receiving surgery with poor irritative/obstructive LUTS had sufficient improvement that the differences between the low and high baseline groups were no longer clinically significant at 5 years. Among patients

who underwent EBRT, brachytherapy, or active surveillance, there were persistent, clinically meaningful differences in irritative/obstructive LUTS between the low and high baseline groups at 5 years.

Results of studies evaluating the association between PV and LUTS are varied. Analyses of large randomized trial data have shown that larger PV is associated with increased incidence of LUTS[20] as well as increased risk of clinical progression of BPH[21]. However, studies of men with BPH have found that prostate enlargement itself is not necessarily predictive of LUTS severity[22] and most urologists recognize that PV alone is a poor predictor of incidence and severity of LUTS. Among patients with prostate cancer specifically, irritative LUTS are a commonly reported adverse effect of treatment with radiation therapy but have been reported to improve after radical prostatectomy[23–26]. Indeed, recent iterations of the AUA guideline on the treatment of localized prostate cancer recommended surgical treatment over radiation therapy among men with baseline urinary irritative or obstructive symptoms based on grade C evidence, while the current revision makes no recommendation for one treatment modality over another in these patients[2,3].

Despite the known adverse short- and long-term impact of radiation therapy on urinary function, we surprisingly found that patient-reported irritative/obstructive urinary function among men treated with radiation therapy for prostate cancer improved overall, though less so than among men treated with surgery. Our study contrasts with recently published data in both EBRT[27,28] and BT cohorts[29] which each show short-term (1–3 month) decrements in irritative/obstructive urinary function with long-term return to baseline. This perhaps reflects improvements in radiation therapy techniques over recent years, including the adoption of stereotactic body radiation therapy, intensity-modulated radiation therapy, and image-guided radiation therapy. We did not find androgen deprivation therapy use to be associated with urinary irritative/obstructive function after treatment with radiation therapy.

Our study has some important limitations. The data are nonrandomized and subject to the risk of confounding by indication, though we controlled for demographic and clinicopathologic variables expected to have a potential association with the outcomes of interest. A significant proportion of patients in the CEASAR cohort were missing data on PV, but there is no reason to believe there is systematic bias due to missing data. Information regarding the use of medications for the treatment of LUTS (including alpha-blockers, 5-alpha reductase inhibitors, and phosphodiesterase-5 inhbitors) as well as surgical treatment of BPH and LUTS (such as transurethral resection of the prostate) were unavailable in this dataset and is therefore not included in our analysis. Use of these treatments may in part explain some of the observed improvements in post-treatment urinary function, though they should have no significant influence on irritative LUTS which is a major component of the EPIC-26 urinary function questions. The EPIC-26 instrument is specifically built to measure prostate cancer treatment-related symptoms and provides less granularity than other surveys designed to measure changes in LUTS like the AUA Symptom Index, which may influence the generalizability of our results. Our results should be interpreted in the context of the multiple *a priori* tests performed and we minimize the risk of type I error by interpreting our results based on clinical significance via the MCID rather than solely statistical significance. Strengths of our study include the prospectively collected, population-based cohort from

which the data are derived, granular demographic and clinicopathologic data to control for potential biases, and excellent follow up through 5 years which we expect to be adequate to detect changes in lower urinary tract function.

Despite these limitations, our findings provide physicians with important data to guide treatment choice and expectations of patient-reported urinary function after treatment for prostate cancer. Recognizing that our results run counter to AUA guidelines and conventional wisdom favoring radical prostatectomy over radiation therapy among men with enlarged prostates and/or significant baseline urinary symptoms, our results indicate that men with poor baseline urinary function can expect to see significant improvement in their irritative/obstructive symptoms after treatment with both EBRT and surgery, irrespective of their baseline PV, with surgery likely to have a greater improvement.

Conclusions

In a prospective cohort study of men with localized prostate cancer, we found that neither PV nor baseline urinary function were associated with treatment choice, while treatment with surgery or radiation therapy was associated with improvement in urinary function among men with poor baseline urinary function, regardless of baseline PV. Clinicians should consider patients' urinary function when counseling men on treatment options for prostate cancer and can utilize these data to inform potential response of LUTS to prostate cancer treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability:

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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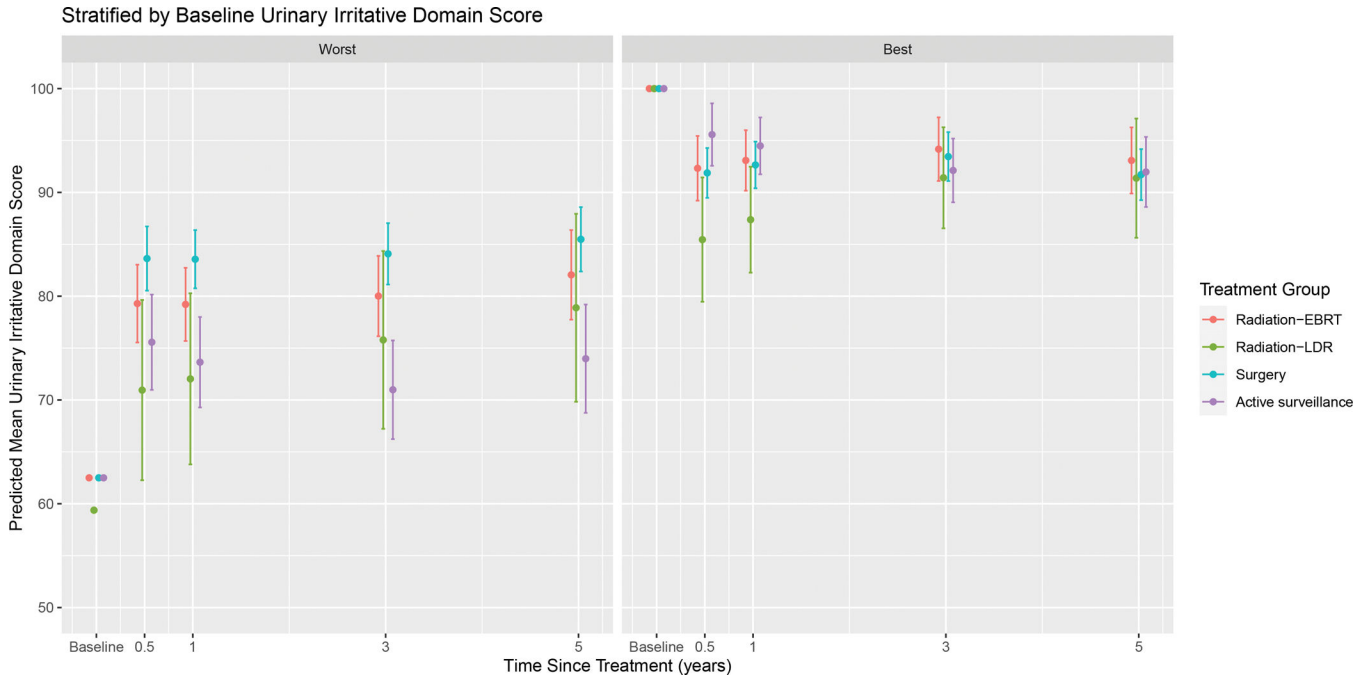

Figure 1: Multivariable Model Predicted Urinary Irritative/Obstructive Domain Score Stratified by Baseline Urinary Irritative/Obstructive Function and Treatment Choice

a. Baseline scores shown are observed median values at baseline

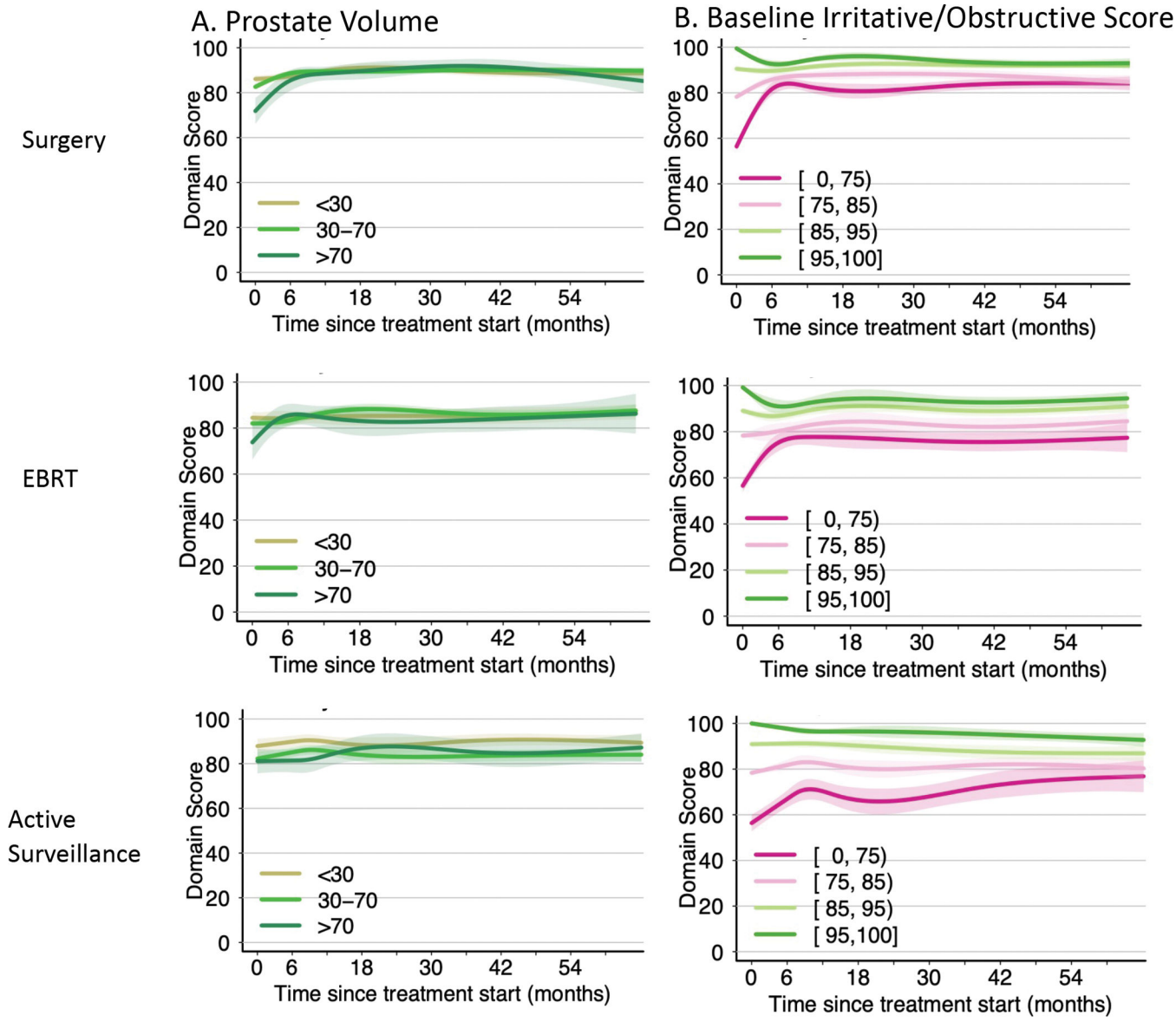

Figure 2.

Unadjusted urinary irritative/obstructive scores over time, stratified by treatment choice, and by prostate volume (column A) and baseline urinary irritative/obstructive score (column B). Brachytherapy cohort not displayed due to small group size.

Table 1:

Baseline demographic and clinicopathology characteristics by baseline EPIC-26 irritative/obstructive domain score

		[0, 75) (N=338)	[75, 85) (N=353)	[85, 95) (N=535)	[95,100] (N=421)	Combined (N=1647)	p-value[a]
TRUS prostate volume	≤30	99 (29%)	107 (30%)	201 (38%)	191 (45%)	598 (36%)	<0.001
	31–50	134 (40%)	153 (43%)	241 (45%)	172 (41%)	700 (43%)	
	51–70	62 (18%)	65 (18%)	62 (12%)	38 (9%)	227 (14%)	
	>70	43 (13%)	28 (8%)	31 (6%)	20 (5%)	122 (7%)	
Age at diagnosis		65 (59 – 70)	65 (60 –71)	64 (59 – 69)	62 (56 – 67)	64 (59 – 69)	<0.01
Race	White	238 (72%)	273 (78%)	429 (81%)	317 (76%)	1257 (77%)	0.1
	Black	45 (13%)	35 (10%)	53 (10%)	55 (13%)	188 (12%)	
	Hispanic	36 (11%)	27 (8%)	28 (5%)	34 (8%)	125 (8%)	
	Asian	10 (3.0%)	13 (4%)	13 (2%)	7 (2%)	43 (3%)	
	Other	4 (1%)	4 (1%)	9 (2%)	3 (1%)	20 (1%)	
Education	Less than high school	45 (14%)	30 (9%)	26 (5%)	35 (9%)	136 (9%)	0.001
	High school graduate	74 (23%)	59 (17%)	113 (22%)	77 (19%)	323 (20%)	
	Some college	77 (24%)	77 (22%)	119 (23%)	96 (23%)	369 (23%)	
	College graduate	69 (21%)	92 (27%)	132 (25%)	91 (22%)	384 (24%)	
	Graduate/ professional	59 (18%)	86 (25%)	134 (26%)	112 (27%)	391 (24%)	
Marital status	Not married	74 (23%)	57 (16%)	103 (20%)	83 (20%)	317 (20%)	0.4
	Married	250 (77%)	288 (84%)	417 (80%)	328 (80%)	1283 (80%)	
Income	Less than $30,000	90 (30%)	66 (21%)	83 (17%)	68 (18%)	307 (20%)	<0.001
	$30,001 – $50,000	69 (23%)	68 (21%)	94 (19%)	56 (14%)	287 (19%)	
	$50,001 – $100,000	79 (26%)	97 (30%)	166 (33%)	133 (35%)	475 (32%)	
	More than $100,000	65 (21%)	91 (28%)	154 (31%)	129 (33%)	439 (29%)	
Health insurance type	Medicare	166 (49%)	175 (50%)	237 (44%)	154 (37%)	732 (45%)	<0.001
	Private / HMO	148 (44%)	159 (45%)	276 (52%)	243 (58%)	826 (50%)	
	VA/Military/ Medicaid /Other/ None	23 (7%)	19 (5%)	22 (4%)	24 (6%)	88 (5%)	
Employment	Full/Part time	151 (45%)	156 (44%)	270 (51%)	242 (57%)	819 (50%)	<0.001
	Retired/ Unemployed	187 (55%)	197 (56%)	265 (49%)	179 (43%)	828 (50%)	
TIBI	0--2	50 (15%)	79 (23%)	165 (31%)	158 (38%)	452 (28.1%)	<0.001
	3--4	128 (39%)	148 (43%)	222 (42%)	178 (43%)	676 (42%)	
	5 or more	148 (45%)	119 (34%)	138 (26%)	77 (19%)	482 (30%)	
D'Amico risk group	Low Risk	151 (45%)	156 (44%)	249 (47%)	190 (45%)	746 (45%)	0.8

		[0, 75) (N=338)	[75, 85) (N=353)	[85, 95) (N=535)	[95,100] (N=421)	Combined (N=1647)	p-value[a]
	Intermediate Risk	124 (37%)	141 (40%)	209 (39%)	163 (39%)	637 (39%)	
	High Risk	62 (18%)	56 (16%)	77 (14%)	68 (16%)	263 (16%)	
PSA at diagnosis, corrected		5.7 (4.2, 8.0)	5.5 (4.4, 7.6)	5.3 (4.1, 7.2)	5.2 (4.2, 6.9)	5.4 (4.2, 7.3)	0.05
Biopsy Gleason score	6 or less	180 (53%)	184 (52%)	283 (53%)	219 (52%)	866 (53%)	0.8
	3 + 4	90 (27%)	99 (28%)	142 (27%)	120 (29%)	451 (27%)	
	4 + 3	29 (9%)	43 (12%)	61 (11%)	42 (10.0%)	175 (11%)	
	8,9,10	38 (11%)	27 (8%)	49 (9%)	40 (9%)	154 (9%)	
Any ADT in year 1	No	279 (84%)	291 (83%)	428 (82%)	371 (89%)	1369 (84%)	0.003
	Yes	54 (16%)	58 (17%)	95 (18%)	46 (11%)	253 (16%)	
EPIC-26 urinary irritative/obstructive domain score at baseline		62 (50, 69)	81 (75, 81)	94 (87, 94)	100 (100, 100)	87 (75, 100)	<0.001
EPIC-26 urinary incontinence domain score at baseline		79 (54, 100)	100 (79, 100)	100 (92, 100)	100 (100, 100)	100 (81, 100)	<0.001
EPIC-26 bowel function score at baseline		92 (79, 100)	100 (92, 100)	100 (96, 100)	100 (100, 100)	100 (92, 100)	<0.001
EPIC-26 sexual function score at baseline		50 (15, 80)	65 (27, 85)	75 (42, 90)	85 (65, 100)	75 (38, 90)	<0.001
EPIC-26 hormonal domain score at baseline		85 (70, 95)	90 (81, 100)	95 (90, 100)	100 (90, 100)	95 (85, 100)	<0.001

[a]Kruskal-wallis and Pearson tests were used

Values are N (%) or median (IQR)

Table 2:

TRUS Prostate Volume and Baseline Urinary Irritative/Obstructive Function by Treatment Modality

			Surgery (N=926)	EBRT (N=387)	BT (N=78)	Active Surveillance (N=256)	Combined (N=1647)	p-value
Prostate Volume	**Combined**	Median (IQR)	35 (27, 45)	38 (27, 51)	33 (26, 40)	40 (30, 57)	36 (27, 48)	<0.01[1]
	≤ 30	N (%)	366 (40%)	124 (32%)	34 (44%)	74 (29%)	598 (36%)	<0.01[2]
	31–50		408 (44%)	159 (41%)	37 (47%)	96 (38%)	700 (43%)	
	51–70		105 (11%)	66 (17%)	6 (8%)	50 (20%)	227 (14%)	
	> 70		47 (5%)	38 (10%)	1 (1%)	36 (14%)	122 (7%)	
EPIC-26 Urinary Irritative/Obstructive Domain Score	**Combined**	Median (IQR)	87 (75, 100)	87 (75, 94)	91 (77, 100)	87 (75, 94)	87 (75, 100)	0.2[1]
	0–74	N (%)	195 (21%)	81 (21%)	12 (15%)	50 (20%)	338 (21%)	0.3[2]
	75–84		186 (20%)	95 (25%)	15 (19%)	57 (22%)	353 (21%)	
	85–94		289 (31%)	130 (34%)	28 (36%)	88 (34%)	535 (32%)	
	95–100		256 (28%)	81 (21%)	23 (29%)	61 (24%)	421 (26%)	

Tests used:

[1]Kruskal-Wallis test

[2]Pearson test

EBRT = external beam radiotherapy, BT = brachytherapy

Table 3 –

Unadjusted and multivariable adjusted analysis of association of prostate volume and baseline urinary irritative/obstructive domain score on post-treatment urinary irritative/obstructive domain score

			Unadjusted				Multivariable Adjusted Difference		
			Prostate Volume < 30 cc		Prostate Volume > 70 cc		Prostate Volume > 70 cc vs. < 30 cc		
	Treatment	Time	Mean	95% CI	Mean	95% CI	Effect	95% CI	p-value
EPIC-26 Urinary Irritative / Obstructive Domain Score	Surgery (n=926)	Baseline	93.7		75.0				
		6 month	88.1	85.5–90.7	87.7	83.8–91.6	−0.39	−3.9, 3.2	0.8
		1 year	89.1	86.6–91.6	89.9	86.5–93.2	0.76	−2.1, 3.6	0.6
		3 year	90.7	88.1–93.2	93.2	89.9–96.5	2.52	−0.2, 5.3	0.07
		5 year	89.5	86.8–92.1	90.6	86.7–94.5	1.09	−2.5, 4.7	0.5
	EBRT (n=387)	Baseline	87.5		81.3				
		6 month	88.3	85.1–91.5	87.9	83.1–92.7	−0.44	−4.8, 3.9	0.8
		1 year	89.3	86.2–92.4	90.0	85.5–94.5	0.71	−3.3, 4.8	0.7
		3 year	91.2	87.9–94.4	93.6	88.8–98.4	2.46	−1.9, 6.8	0.3
		5 year	90.6	87.2–94.0	91.6	86.4–96.9	1.04	−3.8, 5.9	0.7
	BT (n=78)	Baseline	93.7		56.3				
		6 month	78.2	72.2–84.1	18.5	9.2–27.7			
		1 year	80.3	74.8–85.9	21.8	12.4–31.2			
		3 year	85.1	79.3–91.0	28.3	17.6–39.1			
		5 year	85.6	79.6–91.6	27.4	16.6–38.2			
	AS (n=256)	Baseline	93.7		87.5				
		6 month	90.5	87.5–93.4	87.6	83.4–91.9	−2.82	−6.7, 1.0	0.2
		1 year	89.6	86.8–92.4	87.9	84.2–91.7	−1.67	−5.1, 1.8	0.3
		3 year	88.0	84.9–91.1	88.1	84.1–92.1	0.09	−3.6, 3.8	0.9
		5 year	88.4	85.3–91.5	87.1	82.7–91.4	−1.34	−5.4, 2.7	0.5
			Baseline Irritative/Obstructive Domain Score 0–75		Baseline Irritative/Obstructive Domain Score 95–100		Baseline Irritative/Obstructive Domain Score0–75 vs. 95–100		

		Unadjusted				Multivariable Adjusted Difference		
		Prostate Volume < 30 cc		Prostate Volume > 70 cc		Prostate Volume > 70 cc vs. < 30 cc		
Treatment	Time	Mean	95% CI	Mean	95% CI	Effect	95% CI	p-value
		Mean	95% CI	Mean	95% CI	Effect	95% CI	p-value
Surgery (n=926)	Baseline	62.5		100				
	6 month	83.6	80.5–86.7	91.9	89.5–94.3	−8.25	−10.8, −5.7	<0.001
	1 year	83.6	80.8–86.4	92.6	90.4–94.9	−9.08	−11.2, −6.9	<0.001
	3 year	84.1	81.1–87.0	93.5	91.1–95.8	−9.37	−11.8, −7.0	<0.001
	5 year	85.5	82.4–88.6	91.7	89.3–94.2	−6.23	−8.9, −3.6	<0.001
EBRT (n=387)	Baseline	62.5		100				
	6 month	79.3	75.5–83.0	92.3	89.2–95.4	−13.03	−16.5, −9.6	<0.001
	1 year	79.2	75.7–82.7	93.1	90.2–96.0	−13.87	−17.1, −10.6	<0.001
	3 year	80.0	76.1–83.9	94.2	91.1–97.2	−14.16	−17.7, −10.6	<0.001
	5 year	82.1	77.7–86.4	93.1	89.9–96.3	−11.02	−14.7, −7.3	<0.001
BT (n=78)	Baseline	59.4		100				
	6 month	70.9	62.3–79.6	85.5	79.5–91.4	−14.50	−23.6, −5.5	0.002
	1 year	72.0	63.8–80.3	87.4	82.3–92.5	−15.34	−24.3, −6.4	<0.001
	3 year	75.8	67.2–84.3	91.4	86.5–96.3	−15.62	−24.6, −6.6	<0.001
	5 year	78.9	69.8–87.9	91.4	85.6–97.1	−12.49	−21.5, −3.5	0.007
AS (n=256)	Baseline	62.5		100				
	6 month	75.6	71.0–80.2	95.6	92.6–98.6	−20.01	−24.2, −15.8	<0.001
	1 year	73.6	69.3–78.0	94.5	91.7–97.2	−20.84	−24.8, −16.9	<0.001
	3 year	71.0	66.2–75.7	92.1	89.0–95.2	−21.13	−25.3, −17.0	<0.001
	5 year	74.0	68.8–79.2	92.0	88.6–95.3	−17.99	−22.4, −13.5	<0.001

- EBRT = External beam radiotherapy, BT = brachytherapy, AS = active surveillance

- Missing values of regression model covariates were imputed using the multiple imputation by chained equations procedure

- Models controlled for demographic variables including age, race, education, marital status, health insurance type; as well as clinicopathologic variables such as comorbidity score, PSA at diagnosis, clinical tumor stage, and biopsy Gleason score

- Minimum clinically important difference in the EPIC-26 urinary irritative/obstructive domain is 7 points

- Effect size listed is the point difference between groups

- Multivariable modeling was not performed for brachytherapy group stratified by prostate volume due to sample size constraints