VOLUME 34 · NUMBER 32 · NOVEMBER 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Improved Metastasis-Free and Survival Outcomes With Early Salvage Radiotherapy in Men With Detectable Prostate-Specific Antigen After Prostatectomy for Prostate Cancer

Bradley J. Stish, Thomas M. Pisansky, William S. Harmsen, Brian J. Davis, Katherine S. Tzou, Richard Choo, and Steven J. Buskirk

See accompanying article on page 3829

Bradley J. Stish, Thomas M. Pisansky, William S. Harmsen, Brian J. Davis, and Richard Choo, Mayo Clinic, Rochester MN; and Katherine S. Tzou and Steven J. Buskirk, Mayo Clinic, Jacksonville FL.

Published online ahead of print at www.jco.org on August 1, 2016.

The contents of the manuscript are solely the responsibility of the authors.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding author: Thomas M. Pisansky, MD, Department of Radiation Oncology, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: pisansky.thomas@mayo.edu.

0732-183X/16/3432w-3864w/$20.00

DOI: 10.1200/JCO.2016.68.3425

ABSTRACT

Purpose
To describe outcomes of salvage radiotherapy (SRT) for men with detectable prostate-specific antigen (PSA) after radical prostatectomy for prostate cancer and identify associations with outcomes.

Patients and Methods
A total of 1,106 patients received SRT between January 1987 and July 2013, with median follow-up 8.9 years. Outcomes were estimated using Kaplan-Meier for overall survival (OS) and cumulative incidence for biochemical recurrence (BcR), distant metastases (DM), and cause-specific mortality (CSM). Variable associations with outcomes used Cox or Fine-Gray methods, as appropriate. Multiple variable analyses used backward selection with $P < .05$ for retention.

Results
In multiple variable analyses, pathologic tumor stage, Gleason score, and pre-SRT PSA were associated with BcR, DM, CSM, and OS; androgen suppression and SRT doses > 68 Gy were associated with BcR; and age was associated with OS. Each pre-SRT PSA doubling increased significantly the relative risk of BcR (hazard ratio [HR], 1.30; $P < .001$), DM (HR, 1.32; $P < .001$), CSM (HR, 1.40; $P < .001$), and all-cause mortality (HR, 1.12; $P = .02$). Using a pre-SRT PSA cutoff ≤ 0.5 versus > 0.5 ng/mL, 5-year and 10-year cumulative incidences for BcR were 42% versus 56% and 60% versus 68% ($P < .001$), DM 7% versus 14% and 13% versus 25% ($P < .001$), CSM 1% versus 4% and 6% versus 13% ($P < .001$), and OS of 94% versus 92% and 83% versus 73% ($P > .05$).

Conclusion
SRT outcomes are in part affected by factors associated with prostatectomy findings but may be positively affected by using SRT at lower PSA levels, including reductions in BcR, DM, CSM, and all-cause mortality. These findings argue against prolonged monitoring of detectable postprostatectomy PSA levels that delay initiation of SRT.

J Clin Oncol 34:3864-3871. © 2016 by American Society of Clinical Oncology

INTRODUCTION

Salvage radiotherapy (SRT) to the pelvis is a potentially curative treatment for some men with a detectable prostate-specific antigen (PSA), a state termed biochemical recurrence (BcR), after radical prostatectomy (RP) for prostate cancer. Post-RP radiotherapy has been studied in randomized clinical trials, and subset analysis of participants with measurable PSA demonstrated that SRT reduced progression of BcR and improved metastasis-free survival.[1,2] Single-institution observational studies found also that SRT is associated with reduced cause-specific mortality (CSM) and all-cause mortality (ACM) compared with observation after RP.[3,4] These and other supporting observations led to endorsement of SRT in consensus guidelines.[5]

The prognostic significance of PSA level at SRT initiation is well established for freedom from subsequent BcR as a therapeutic end point.[6,7] However, data regarding an association between pre-SRT PSA and distant metastasis (DM) or CSM are currently limited, potentially because prior studies lack sufficient sample sizes and follow-up duration of patients. We conducted, and herein

report, the largest single-institution patient sample study to our knowledge with the hypothesis that initiating SRT at a lower PSA level is associated with a reduced long-term incidence of DM and CSM in men with prostate cancer.

PATIENTS AND METHODS

Patients and Eligibility

Between January 1987 and July 2013, 1,427 consecutive patients with surgically staged prostate cancer received SRT at Mayo Clinic Rochester or Jacksonville after RP. Patients were excluded if there was not a documented PSA of ≥ 0.1 ng/mL before SRT (126 patients), or there was insufficient clinical follow-up (148 patients), metastatic disease at SRT initiation (three patients), or androgen suppression (AS) that overlapped with SRT for > 3 years' treatment duration (44 patients). These exclusions yielded 1,106 patients in the study cohort.

Research activities complied with Standards for Privacy of Individually Identifiable Health Information issued under the Health Insurance Portability and Accountability Act of 1996 and the American Recovery and Reinvestment and the Health Information Technology for Economic and Clinical Health Acts of 2009 after approval by the Mayo Clinic Institutional Review Board. Analysis and reporting were guided by Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[8]

Treatments

All patients had documented RP for a histologic diagnosis of prostatic adenocarcinoma, with surgical lymph node sampling in all but 11 patients. Staging was assigned on post-RP pathologic findings in accordance with the American Joint Committee on Cancer 7th Edition Staging Manual.[9] Pre-SRT radiographic evaluation, AS use, and SRT dose and treatment volumes were at the discretion of the radiation oncologist. Radiation dose was prescribed to the prostatic bed planning target volume as specified by International Commission on Radiation Units and Measurement Reports 50 and 62 for three-dimensional conformal and intensity-modulated treatments[10] and at the International Commission on Radiation Units and Measurement Reports isocenter reference point for two-dimensional custom-blocked SRT. The SRT treatment planning, target localization, and delivery methods evolved over the study. SRT included pelvic lymphatics in 41 patients (4%). Post-SRT event monitoring was conducted primarily with serial PSA determinations and clinical examination. Additional testing was done to pursue elevations of PSA or clinical findings. Salvage AS for rising PSA or for clinical progression after SRT was initiated at clinician discretion and with patient informed consent.

End Points

Prespecified end points for reporting included BcR, DM, CSM, and ACM/overall survival (OS). The time to all end points was calculated from the date of SRT completion. DM, CSM, and ACM/OS were also calculated from the date of RP for all patients, as a secondary analysis. In addition, salvage AS was recorded as a secondary outcome. BcR was defined by either a post-SRT PSA > 0.2 ng/mL with a second confirmatory value or a single PSA of > 0.4 ng/mL, initiation of salvage AS, or clinical evidence of DM before achieving the specified PSA thresholds. Patients without documented BcR were censored at the date of last recorded PSA. DM was defined as radiographic or histologic evidence of prostate cancer involving distant sites (eg, bone), including nonregional lymph nodes.[9] CSM events were any deaths occurring with progressive disease on secondary therapies (eg, AS), as a result of adverse effects from prostate cancer–directed therapy or with documented death attribution to prostate cancer.

Statistical Methods

BcR, DM, CSM, and salvage AS use are reported as cumulative incidence estimates from the Fine-Gray method[11] to account for competing risks, including ACM for BcR and DM and nonprostate cancer–related death for CSM. The Kaplan-Meier method estimated OS.[12] The hazard ratio (HR) and corresponding 95% CI for single variable associations with outcomes were calculated using either the Cox proportional hazards[13] or Fine-Gray competing risks hazard regression,[14] as appropriate.

Multiple variable analyses (MVA) for association with all end points were performed analyzing all variables that reached statistical significance ($P < .05$) on single variable analysis. Only patients with known values for all variables analyzed were included in MVA. A backward selection model for MVA with a P value < .05 was used for retention in the final model. The pre-SRT PSA variable was assessed in separate MVA models as either a log-base-2 transformed continuous variable or as a prespecified categorical variable (≤ 0.5 *v* > 0.5 ng/mL). The HRs for variables other than pre-SRT PSA obtained on MVA are calculations using pre-SRT PSA as a continuous variable.

RESULTS

Patient Characteristics

The characteristics of the study cohort are provided in Table 1. The median age of patients was 66.7 years (range, 44.1 to 85.4 years), with 683 (62%) age 65 years or older when SRT was given.

Table 1. Characteristics of 1,106 Study Patients

Characteristic	Patients (No.)	%
Pathologic tumor stage		
T2	621	56.2
T3a	303	27.4
T3b	167	15.1
T4	7	0.6
Missing	8	0.7
Pathologic nodal stage		
0	1,087	98.3
1	11	1.0
Missing	8	0.7
Gleason score		
≤ 6	330	29.8
7	550	49.7
8	82	7.4
9-10	97	8.8
Missing	47	4.3
Pre-RP PSA, ng/mL		
< 10	695	62.8
10-20	231	20.9
> 20	120	10.9
Missing	60	5.4
Surgical margins		
Negative	539	48.7
Positive	537	48.6
Missing	30	2.7
Pre-SRT PSA, ng/mL		
Median (range)	0.6 (0.1-37.5)	
≤ 0.5	501	45.3
> 0.5	605	54.7
Androgen suppression duration, years		
None	926	83.7
≤ 1.0*	108	9.8
> 1.0	72	6.5
SRT dose, Gy		
< 66	339	30.7
66-67.99	197	17.8
68-71.99	384	34.7
≥ 72	186	16.8

Abbreviations: SRT, salvage radiotherapy; PSA, prostate-specific antigen; RP, radical prostatectomy.
*Three patients ≤ 3-month duration.

The median interval from RP to SRT was 2.8 years (interquartile range [IQR], 1.2 to 5.7 years). Median SRT dose was 68 Gy (IQR, 64.8 to 70.2) delivered in 1.8 Gy or 2 Gy once per day fractions with intensity modulation (40%), three-dimensional conformal (21%), or two-dimensional custom-blocked (39%) external beam techniques. Neoadjuvant/concurrent and/or adjuvant AS was administered in 180 patients (16%).

Outcomes

The median follow-up duration was 8.9 years (IQR, 4.9 to 13.7 years), with ≥ 2.5 years' follow-up for 90% of patients. Six hundred patients (54%) experienced BcR, with 5- and 10-year cumulative incidence of 49.9% (95% CI, 46.6% to 53.0%) and 64.3% (95% CI, 60.5% to 67.8%), respectively. Variables and their associations with BcR are shown in Table 2. Surgical margin status, SRT technique, and year of RP were not associated with BcR in single variable analysis ($P > .05$). The MVA demonstrated that increasing tumor stage, Gleason score (GS), and pre-SRT PSA levels retained strong association with an increased risk of BcR, and SRT doses ≥ 68 Gy and use of AS were associated with reduced risk of BcR.

A total of 208 patients developed DM (before salvage AS in 89 patients), with associations shown in Table 3. The 5- and 10-year cumulative incidence estimates were 10.9% (95% CI, 9.0% to 12.9%) and 19.9% (95% CI, 17.1% to 22.7%), respectively. Age, pre-RP PSA, receipt of AS, and SRT dose were not associated with DM ($P > .05$). In MVA, pathologic T3b and GS ≥ 7 were associated significantly with greater DM risk. Each doubling of pre-SRT PSA (eg, 0.8 ng/mL *v* 0.4 ng/mL) was associated with a 32% increase in the relative risk of DM ($P < .001$), adjusting simultaneously for the effect of other significant variables.

The association of study variables with CSM and ACM/OS is shown in Table 4. Among the study population, 280 patients died during follow-up, with 110 deaths (39%) attributed to prostate cancer. OS at 5 years and at 10 years for the entire cohort was 92.9% (95% CI, 91.3% to 94.5%) and 77.3% (95% CI, 74.2% to 80.5%), respectively. The CSM incidence rates were 3.0% (95% CI, 1.9% to 4.0%) at 5 years and 10.4% (95% CI, 8.0% to 12.6%) at 10 years, with an increased risk in MVA of CSM associated with pathologic T3b, GS ≥ 7 and higher pre-SRT PSA level. The relative risk of CSM increased 40% for each doubling of PSA. Increasing pre-SRT PSA was further associated with an increased

Table 2. Cumulative Incidence of Biochemical Recurrence According to Exploratory Patient Subsets

Characteristic	Events (No.)*	5-Year (%)	10-Year (%)	Single Variable HR (95% CI)	*P*	Multiple Variable HR (95% CI)†	*P*
Pathologic tumor stage							
T2	287	41	57	1.0 (Ref)	—	1.0 (Ref)	—
T3a	175	54	67	1.37 (1.14 to 1.65)	.001	1.27 (1.04 to 1.55)	.02
T3b	128	72	83	2.29 (1.86 to 2.82)	<.001	2.05 (1.64 to 2.56)	< .001
T4	7	71	100	2.03 (0.84 to 4.93)	.12	1.15 (0.42 to 3.15)	.78
Pathologic nodal stage							
N0	584	49	64	1.0 (Ref)		1.0 (Ref)	—
N1	10	82	82	2.11 (1.13 to 3.94)	.02	1.48 (0.75 to 2.95)	.26
Gleason score							
≤ 6	136	35	52	1.0 (Ref)	—	1.0 (Ref)	—
7	301	51	66	1.63 (1.33 to 2.00)	<.001	1.7 (1.38 to 2.09)	< .001
8	59	70	80	2.44 (1.80 to 3.32)	<.001	2.67 (1.95 to 3.65)	< .001
9-10	71	71	81	2.85 (2.14 to 3.80)	<.001	3.34 (2.47 to 4.52)	< .001
Pre-RP PSA, ng/mL							
< 10	345	46	62	1.0 (Ref)	—	1.0 (Ref)	—
10-20	136	51	68	1.18 (0.97 to 1.44)	.11	1.01 (0.81 to 1.26)	.91
> 20	84	66	71	1.55 (1.22 to 1.97)	<.001	1.11 (0.84 to 1.47)	.46
RP to detectable PSA							
< 1.0 year	255	56	66	1.0 (Ref)	—	1.0 (Ref)	—
≥ 1.0 years	310	45	62	0.77 (0.65 to 0.91)	.002	0.86 (0.72 to 1.03)	.10
Pre-SRT PSA (per doubling)				1.18 (1.11 to 1.25)	<.001	1.30 (1.21 to 1.39)	< .001
Androgen suppression							
None	527	51	66	1.0 (Ref)	—	1.0 (Ref)	—
≤ 1.0 year	51	48	62	0.81 (0.61 to 1.08)	.14	0.59 (0.43 to 0.81)	< .001
> 1.0 years	22	35	50	0.52 (0.34 to 0.79)	.002	0.26 (0.16 to 0.41)	< .001
SRT dose (Gy)							
< 66	224	54	70	1.0 (Ref)	—	1.0 (Ref)	—
66-67.99	119	56	66	1.03 (0.82 to 1.29)	.80	1.09 (0.86 to 1.38)	.50
68-71.99	187	47	59	0.80 (0.65 to 0.97)	.021	0.77 (0.60 to 0.98)	.04
≥ 72	70	39	70	0.68 (0.52 to 0.89)	.005	0.60 (0.43 to 0.86)	.005
SRT year							
1987-2002	253	57	70	1.0 (Ref)	—	1.0 (Ref)	—
2003-2007	203	44	61	0.76 (0.63 to 0.92)	.004	1.08 (0.86 to 1.35)	.52
2008-2013	144	48	—	0.79 (0.64 to 0.98)	.03	1.49 (1.10 to 2.01)	.009

Abbreviations: HR, hazard ratio; PSA, prostate-specific antigen; Ref, referent; RP, radical prostatectomy; SRT, salvage radiotherapy.
*Six hundred events total; number of events not shown for patients with missing variables.
†Multiple variable analyses limited to patients in whom all characteristics are known.

Table 3. Cumulative Incidence of Distant Metastases According to Exploratory Patient Subsets

Characteristic	Events (No.)*	5-Year (%)	10-Year (%)	Single Variable HR (95% CI)	*P*	Multiple Variable HR (95% CI)†	*P*
Pathologic tumor stage							
T2	85	7	15	1.0 (Ref)	—	1.0 (Ref)	—
T3a	64	13	22	1.46 (1.06 to 2.03)	.02	1.25 (0.88 to 1.78)	.21
T3b	54	21	33	2.39 (1.69 to 3.38)	< .001	1.81 (1.23 to 2.66)	.003
T4	2	14	14	2.18 (0.57 to 8.27)	.25	1.43 (0.32 to 6.41)	.64
Pathologic nodal stage							
N0	202	11	20	1.0 (Ref)	—	1.0 (Ref)	—
N1	5	28	57	3.46 (1.40 to 8.54)	.007	1.04 (0.40 to 2.74)	.93
Gleason score							
≤ 6	36	5	9	1.0 (Ref)	—	1.0 (Ref)	—
7	103	11	23	2.16 (1.49 to 3.13)	< .001	2.41 (1.59 to 3.64)	< .001
8	24	17	28	3.36 (2.02 to 5.57)	< .001	4.05 (2.31 to 7.11)	< .001
9-10	37	31	43	5.45 (3.39 to 8.75)	< .001	6.15 (3.63 to 10.43)	< .001
RP to detectable PSA							
< 1 year	96	14	23	1.0 (Ref)	—	1.0 (Ref)	
≥ 1 years	97	8	17	0.71 (0.54 to 0.95)	.02	0.95 (0.70 to 1.28)	.71
Pre-SRT PSA (per doubling)				1.33 (1.21 to 1.46)	< .001	1.32 (1.19 to 1.46)	< .001

Abbreviations: HR, hazard ratio; PSA, prostate-specific antigen; Ref, referent; RP, radical prostatectomy; SRT, salvage radiotherapy.
*Two hundred eight events total; number of events not shown for patients with missing variables.
†Multiple variable analyses limited to patients in whom all characteristics are known.

risk of ACM in MVA, as were age at SRT, pathologic T3b, and GS ≥ 8.

Secondary analyses were conducted to test for associations of pre-SRT PSA as a categorical variable (≤ 0.5 *v* > 0.5 ng/mL),[7] with the prespecified end points. Figure 1 shows the cumulative incidence (BcR, DM, and CSM) and Kaplan-Meier (OS) estimate plots according to pre-SRT PSA category. In MVA, BcR, DM, and CSM were significantly increased for patients with pre-SRT > 0.5 ng/mL compared with ≤ 0.5 ng/mL ($P < .05$ for all end points; Appendix Table A1, online only). There was no difference in OS when comparing pre-SRT PSA ≤ 0.5 versus > 0.5 ng/mL ($P > 0.05$). Salvage AS was used more commonly in patients with a pre-SRT PSA of > 0.5 versus ≤ 0.5 ng/mL (HR, 1.7; $P < .001$), with 10-year cumulative incidence estimates of 45.0% (95% CI, 40.5% to 49.4%) versus 31.0% (95% CI, 25.6% to 35.3%).

An additional secondary analysis was performed to explore associations between variables and DM, CSM, and ACM/OS when outcomes were indexed from the date of RP instead of the date of SRT completion. In MVA, each doubling of pre-SRT PSA continued to show significant association with an increased risk of DM (Appendix Table A2) and CSM but not with OS (Appendix Table A3).

DISCUSSION

Approximately one-third of men undergoing RP for prostate cancer have disease recurrence, often first evidenced by a detectable serum PSA.[15-17] Compared with observation, SRT reduces the risk of prostate cancer progression by significantly reducing the incidence of DM, CSM, and ACM.[3,4,18] The use of SRT at lower PSA levels and delivery of higher doses are each strongly associated with a reduced incidence of further BcR.[6,19,20] Our study furthers understanding about the clinical implications of BcR after RP and the treatment effect of SRT. These findings are unique and strengthened by a large sample size and long-term follow-up. It provides confirmation of antecedent research that found early intervention with SRT, higher SRT dose, and use of AS reduces subsequent secondary BcR.[1-4,6,19-24]

We observed also that pre-SRT PSA level is independently associated with the risk of DM in long-term patient follow-up, and (for the first time to our knowledge) worsening CSM and ACM with higher PSA levels. When adjusting in MVA for well-validated risk factors, such as GS and pathologic T stage, each doubling of pre-SRT PSA resulted in a significant 32% increase in the relative risk of DM. This finding translated also into an increased risk for CSM (40% relative risk) and ACM (12% relative risk). Outcomes on the basis of the prespecified pre-SRT PSA cutoff point of 0.5 ng/mL, a precedent in the literature used to define early SRT,[7,25] provided similar results. Patients who received SRT when PSA was ≤ 0.5 ng/mL had a significantly lower incidence of BcR, DM, and CSM. When taken together, these findings provide strong evidence supporting the clinical benefits attributable to early SRT in men with detectable PSA after RP.

Serum PSA is a biomarker with no natural cutoff points to characterize unfavorable from favorable test findings, other than undetectability when BcR has not occurred. As such, its level exerts a predictive effect along a continuum, without a known threshold effect. Each doubling of pre-SRT PSA in our study cohort had a significant association with increasing risk of disease progression in MVA. This observation suggests that SRT at the lowest PSA level is most beneficial for long-term therapeutic efficacy. It is not clear presently if certain patient subsets should not receive SRT and whether such patients reside at the lower or the higher end of the PSA spectrum.

Randomized clinical trials have shown that immediate RT after RP results in significantly lower group rates of disease progression and possibly improved survival compared with initial observation in patients with adverse pathologic features (eg, extraprostatic tumor extension).[1,2,26] However, BcR does not occur in all such men, and clinicians have been hesitant to proceed with RT when post-RP PSA levels are undetectable.[27,28] As an

Table 4. Survival Estimates According to Exploratory Patient Subsets

Characteristic	Cause-Specific Mortality							Overall Survival						
	Events (No.)*	5-Year (%)	10-Year (%)	Single Variable HR (95% CI)	*P*	Multiple Variable HR (95% CI)†	*P*	Events (No.)*	5-Year (%)	10-Year (%)	Single Variable HR (95% CI)	*P*	Multiple Variable HR (95% CI)†	*P*
Age at SRT, years														
< 65	35	3	9	1.0 (Ref)	—	—	—	72	95	85	1.0 (Ref)	—	—	—
≥ 65	75	3	11	1.25 (0.83 to 1.86)	.28	—	—	208	92	73	1.94 (1.48 to 2.55)	< .001	—	—
Age (per 10 years)	—		—	1.22 (0.95 to 1.56)	.12	—	—	—	—	—	1.86 (1.56 to 2.24)	< .001	1.79 (1.48 to 2.17)	< .001
Pathologic tumor stage														
T2	40	1	7	1.0 (Ref)	—	1.0 (Ref)	—	115	96	83	1.0 (Ref)	—	1.0 (Ref)	—
T3a	33	4	11	1.46 (0.92 to 2.33)	.11	1.40 (0.85 to 2.29)	.18	95	91	73	1.50 (1.14 to 1.97)	.004	1.41 (1.06 to 1.88)	.017
T3b	34	8	20	2.87 (1.81 to 4.55)	< .001	2.10 (1.23 to 3.50)	.006	66	84	66	1.85 (1.36 to 2.51)	< .001	1.65 (1.20 to 2.28)	.002
T4	2	17	17	4.46 (1.15 to 17.30)	.03	2.70 (0.58 to 12.51)	.20	4	83	56	2.50 (0.79 to 7.87)	.118	1.33 (0.41 to 4.36)	.64
Pathologic nodal stage														
N0	106	3	10	1.0 (Ref)	—	1.0 (Ref)	—	274	93	78	1.0 (Ref)	—	—	—
N1	4	19	46	5.35 (1.92 to 14.90)	.001	1.43 (0.42 to 4.83)	.32	4	81	54	2.06 (0.77 to 5.54)	.15	1.45 (0.51 to 4.15)	.49
Gleason score														
≤ 6	20	1	5	1.0 (Ref)	—	1.0 (Ref)	—	82	94	79	1.0 (Ref)	—	1.0 (Ref)	—
7	52	3	11	2.00 (1.21 to 3.33)	.007	2.48 (1.36 to 4.50)	.003	118	94	79	1.12 (0.84 to 1.49)	.44	1.08 (0.81 to 1.43)	.61
8	14	4	17	3.31 (1.7 to 6.47)	< .001	4.48 (2.10 to 9.56)	< .001	31	86	67	1.98 (1.31 to 3.00)	.001	1.68 (1.09 to 2.57)	.018
9-10	18	12	23	4.51 (2.38 to 8.57)	< .001	6.20 (3.00 to 12.80)	< .001	30	85	67	1.87 (1.23 to 2.85)	.003	1.86 (1.22 to 2.85)	.004
RP to detectable PSA, years														
< 1	53	5	13	1.0 (Ref)	—	1.0 (Ref)	—	118	92	77	1.0 (Ref)	—	—	—
≥ 1	45	2	8	0.45 (0.43 to 0.96)	.03	0.90 (0.59 to 1.38)	.63	131	94	78	0.93 (0.72 to 1.20)	.59	—	—
Pre-SRT PSA (per doubling)	—	—	—	1.40 (1.23 to 1.60)	< .001	1.40 (1.21 to 1.63)	< .001	—	—	—	1.18 (1.08 to 1.29)	< .001	1.12 (1.02 to 1.23)	.02

Abbreviations: HR, hazard ratio; PSA, prostate-specific antigen; Ref, referent; RP, radical prostatectomy; SRT, salvage radiotherapy.
*One hundred ten events (cause-specific mortality) and 280 events (overall survival) total; number of events not shown for patients with missing variables.
†Multiple variable analyses limited to patients in whom all characteristics are known.

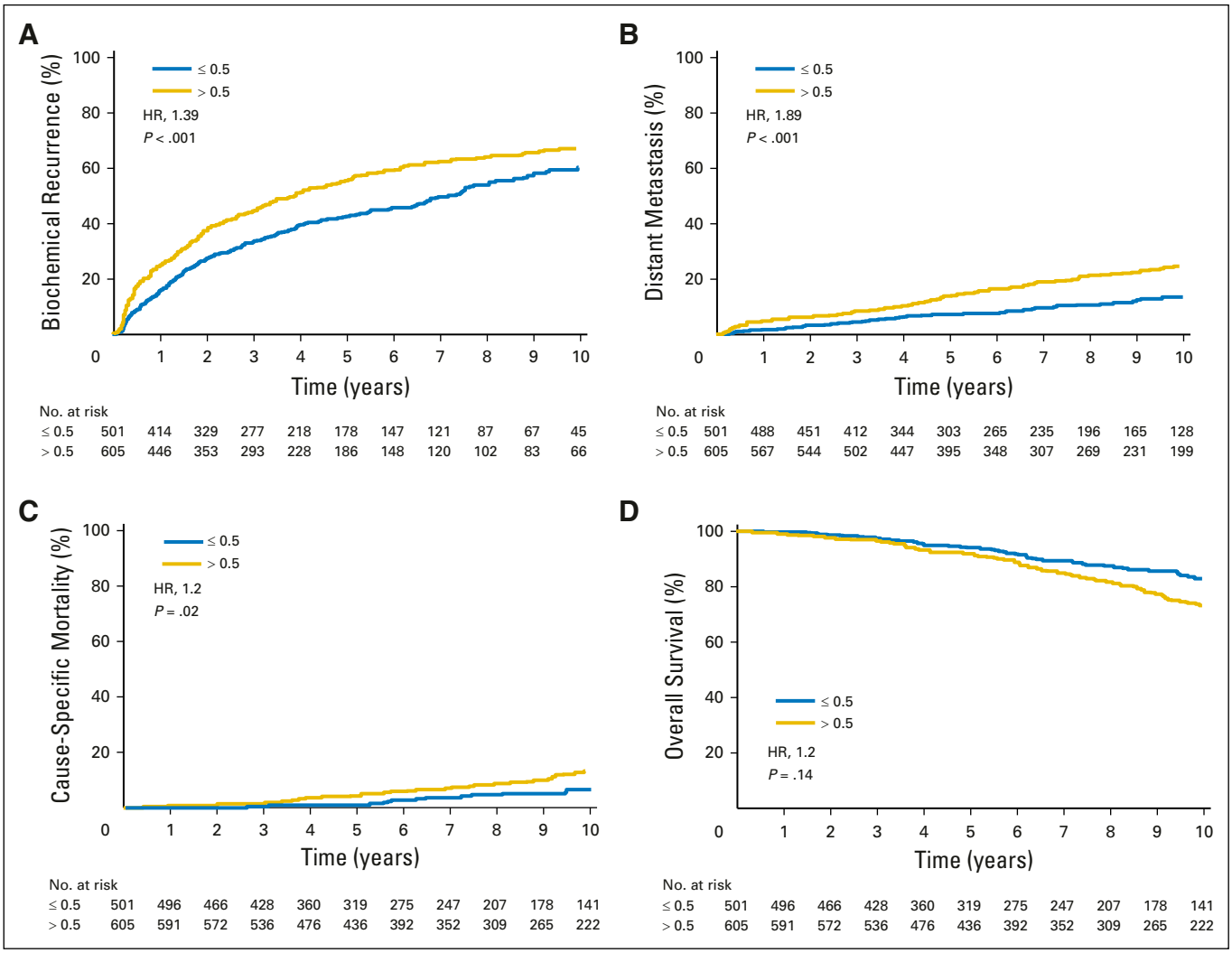

Fig 1. Outcomes of salvage radiotherapy stratified by pre-radiotherapy prostate-specific antigen. Cumulative incidences of (A) biochemical recurrence, (B) distant metastasis, and (C) cause-specific mortality, and (D) estimate of overall survival according to pre–salvage radiotherapy prostate-specific antigen level (ng/mL). HR, hazard ratio.

alternative, PSA monitoring and selective use of SRT for BcR is a common management strategy, given the variability in the natural history of disease progression.[29] The findings of our research are thus germane to a common management strategy used in clinical practice and can be applied presently to general medical care settings.

Current consensus guidelines recommend offering SRT to all men with BcR and no evidence of metastatic disease and that patients should be informed of the improved efficacy of treatment initiated at lower PSA levels.[5] This recommendation is based largely on an extensive review of prior publications in which increasing pre-SRT PSA levels were associated with a greater risk for further BcR,[6,7,30] without evidence for improved DM, CSM, or ACM outcomes. Our study affirms the widely held view that pre-SRT PSA is a strong prognostic factor for secondary BcR, a finding that extends to the meaningful clinical outcomes of DM, CSM, and ACM. These findings add information to the health care discussion and shared decision-making with the patient, further substantiating the claim that SRT at lower PSA levels has greater efficacy.

In addition to when SRT is started (that is, at what PSA level), prescribed SRT dose is another potentially modifiable factor associated with subsequent risk of BcR. Consensus guidelines suggest that a minimum dose of 64 to 65 Gy should be used,[5] but this is an evolving area, where some research suggests thresholds of at least 66.6 or 70 Gy are associated with improved outcome[20,21]—a finding affirmed in systematic reviews.[19,24] Patients treated to doses of 68 Gy or greater in our study had a significantly lower incidence of BcR. The randomized clinical trial (64 Gy *v* 70 Gy) of the Swiss Group for Clinical Cancer Research (NCT01272050) showed no between-group difference in early adverse events, and among patient-reported quality of life measures, only urinary symptoms were modestly worsened in the high-dose group.[31] Although we did not find improved cancer control in our analysis with more conformal intensity modulation, previous research demonstrated significant reduction in moderate to severe gastrointestinal and genitourinary adverse events with its use.[32] Image guidance with linear accelerator-based volumetric (eg, computed tomographic) methods offers further opportunity to improve the therapeutic

ratio by ensuring target coverage and avoidance of surrounding normal organs.[33]

Observational studies suggested that some patients with high-risk factors benefit from AS, but sound conclusions may be confounded by selection bias.[22,23] Radiation Therapy Oncology Group (RTOG) trial 9601 (NCT00002874) randomly assigned men with post-RP BcR to SRT (with placebo) or SRT with 2 years of bicalutamide (150 mg once per day), with improved freedom from progression and survival attributed to bicalutamide.[34] The Groupe d'Etude des Tumeurs Uro-Génitales (GETUG) randomized trial (NCT00423475) demonstrated reduced BcR with 6-month luteinizing-hormone releasing-hormone analog AS and SRT,[35] but no difference in other end points noted to date. AS use in our study was not given in a controlled manner, but we observed a significant reduction in BcR, an association that was greater with a treatment duration longer than 1 year; an effect on DM, CSM, or ACM was not seen in MVA. More detailed reporting of RTOG 9601 and of ongoing similar research will clarify the role of AS with SRT in the future.

The greatest limitation of our study is its observational case series nature, rather than a construct that would provide level I evidence. This reporting method may contain unrecognized selection bias and confounding by intention, leading to outcome measures that lack precision. However, this limitation applies to the preexisting literature that addresses the natural history and therapeutic effects relating to post-RP BcR.[3,6,7,18,20,21,25,27,31-33] Patients were also treated over more than 25 years, a period over which substantial changes occurred in SRT delivery, surgical techniques, and radiologic imaging. Although patients with a shorter PSA doubling time have a greater risk of disease progression and CSM,[6,36] we did not evaluate post-RP PSA kinetics because of limitations in the frequency of PSA testing in some patients and early SRT (sometimes with a single pre-SRT PSA only), limiting the ability to calculate this parameter.[37]

Lead-time bias may be introduced with an early detection method (eg, PSA monitoring), and we cannot fully exclude its intrusion into OS estimates in our study cohort or in other research studies similar to our own.[3,6,7,18,20,21,25] Patients with a higher PSA level at SRT may be reasonably assumed to have had a lesser level at an earlier post-RP time point. Thus, calculating the interval from SRT completion to death, as in our primary analysis, may yield a reduced survival duration compared with a theoretical construct of earlier SRT administration. Although it may be possible to mathematically estimate the lead-time (sojourn) interval, we conducted a secondary analysis of all end points indexed from the RP date (Appendix Tables A2-A3), when cancer burden was least. Pathologic tumor stage, GS, and pre-SRT PSA level retained significant association with DM and CSM. Similar findings were noted for pathologic tumor stage and GS in ACM/OS.

Secondary analyses of randomized trials may someday influence clinical practice further in men with BcR after RP, but this study provides important data presently about patients receiving SRT. Although outcomes for patients receiving SRT are partially determined by factors intrinsic to RP finding, this study identified modifiable treatment parameters that affect outcomes. Initiation of SRT at a lower PSA level was strongly associated with significant improvements in subsequent BcR, DM, CSM, and ACM. These observations reaffirm findings of previous studies[6,7] but also demonstrate for the first time to our knowledge the benefit of early SRT related to survival outcomes. Furthermore, higher SRT dose levels ($\geq$ 68 Gy) and AS were identified as additional modifiable treatment factors that may reduce the risk of post-SRT BcR. Taken together, these findings argue against prolonged monitoring of detectable post-RP PSA levels that delays initiation of SRT and serve as an important component of shared decision making between patient and physician.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Bradley J. Stish, Thomas M. Pisansky
Provision of study materials or patients: Thomas M. Pisansky, Brian J. Davis, Katherine S. Tzou, Richard Choo, Steven J. Buskirk
Collection and assembly of data: Bradley J. Stish, Thomas M. Pisansky, Katherine S. Tzou, Steven J. Buskirk
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Bolla M, van Poppel H, Tombal B, et al: Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: Long-term results of a randomised controlled trial (EORTC trial 22911). Lancet 380:2018-2027, 2012
2. Thompson IM, Tangen CM, Paradelo J, et al: Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: Long-term followup of a randomized clinical trial. J Urol 181:956-962, 2009
3. Trock BJ, Han M, Freedland SJ, et al: Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. JAMA 299: 2760-2769, 2008
4. Cotter SE, Chen MH, Moul JW, et al: Salvage radiation in men after prostate-specific antigen failure and the risk of death. Cancer 117:3925-3932, 2011
5. Valicenti RK, Thompson I, Jr., Albertsen P, et al: Adjuvant and salvage radiation therapy after prostatectomy: American Society for Radiation Oncology/American Urological Association guidelines. Int J Radiat Oncol Biol Phys 86:822-828, 2013
6. Stephenson AJ, Scardino PT, Kattan MW, et al: Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol 25:2035-2041, 2007
7. Briganti A, Karnes RJ, Joniau S, et al: Prediction of outcome following early salvage radiotherapy among patients with biochemical recurrence after radical prostatectomy. Eur Urol 66:479-486, 2014
8. Vandenbroucke JP, von Elm E, Altman DG, et al: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. Epidemiology 18:805-835, 2007
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 17:1471-1474, 2010
10. International Commission on Radiation Units and Measurements. Prescribing, Recording, and Reporting Photon Beam Therapy. Bethesda, MD, International Commission on Radiation Units and Measurements, 1999

11. Gray RJ: A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 16:1141-1154, 1988

12. Kaplan EL MP: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53: 457-481, 1958

13. Cox DR: Regression models and life tables. J R Stat Soc B 34:187-220, 1972

14. Fine JP, Gray RJ: A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94:496-509, 1999

15. Agarwal PK, Sadetsky N, Konety BR, et al: Treatment failure after primary and salvage therapy for prostate cancer: Likelihood, patterns of care, and outcomes. Cancer 112:307-314, 2008

16. Mullins JK, Feng Z, Trock BJ, et al: The impact of anatomical radical retropubic prostatectomy on cancer control: The 30-year anniversary. J Urol 188: 2219-2224, 2012

17. Toussi A, Stewart-Merrill SB, Boorjian SA, et al: Standardizing the definition of biochemical recurrence after radical prostatectomy-what prostate specific antigen cut point best predicts a durable increase and subsequent systemic progression? J Urol 195:1754-1759, 2016

18. Boorjian SA, Karnes RJ, Crispen PL, et al: Radiation therapy after radical prostatectomy: Impact on metastasis and survival. J Urol 182:2708-2714, 2009

19. King CR: The timing of salvage radiotherapy after radical prostatectomy: A systematic review. Int J Radiat Oncol Biol Phys 84:104-111, 2012

20. Bernard JR, Jr., Buskirk SJ, Heckman MG, et al: Salvage radiotherapy for rising prostate-specific antigen levels after radical prostatectomy for prostate cancer: Dose-response analysis. Int J Radiat Oncol Biol Phys 76:735-740, 2010

21. Cozzarini C, Montorsi F, Fiorino C, et al: Need for high radiation dose (≥ 70 Gy) in early postoperative irradiation after radical prostatectomy: A single-institution analysis of 334 high-risk, node-negative patients. Int J Radiat Oncol Biol Phys 75: 966-974, 2009

22. Jackson WC, Schipper MJ, Johnson SB, et al: Duration of androgen deprivation therapy influences outcomes for patients receiving radiation therapy following radical prostatectomy. Eur Urol 69:50-57, 2016

23. Katz MS, Zelefsky MJ, Venkatraman ES, et al: Predictors of biochemical outcome with salvage conformal radiotherapy after radical prostatectomy for prostate cancer. J Clin Oncol 21:483-489, 2003

24. Ohri N, Dicker AP, Trabulsi EJ, et al: Can early implementation of salvage radiotherapy for prostate cancer improve the therapeutic ratio? A systematic review and regression meta-analysis with radiobiological modelling. Eur J Cancer 48:837-844, 2012

25. Pfister D, Bolla M, Briganti A, et al: Early salvage radiotherapy following radical prostatectomy. Eur Urol 65:1034-1043, 2014

26. Wiegel T, Bartkowiak D, Bottke D, et al: Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. Eur Urol 66:243-250, 2014

27. Sheets NC, Hendrix LH, Allen IM, et al: Trends in the use of postprostatectomy therapies for patients with prostate cancer: A surveillance, epidemiology, and end results Medicare analysis. Cancer 119:3295-3301, 2013

28. Maurice MJ, Zhu H, Abouassaly R: Low use of immediate and delayed postoperative radiation for prostate cancer with adverse pathological features. J Urol 194:972-976, 2015

29. Freedland SJ, Humphreys EB, Mangold LA, et al: Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA 294:433-439, 2005

30. Fossati N, Karnes RJ, Cozzarini C, et al: Assessing the optimal timing for early salvage radiation therapy in patients with prostate-specific antigen rise after radical prostatectomy. Eur Urol 69: 728-733, 2016

31. Ghadjar P, Hayoz S, Bernhard J, et al: Acute toxicity and quality of life after dose-intensified salvage radiation therapy for biochemically recurrent prostate cancer after prostatectomy: First results of the randomized trial SAKK 09/10. J Clin Oncol 33: 4158-4166, 2015

32. Goenka A, Magsanoc JM, Pei X, et al: Improved toxicity profile following high-dose post-prostatectomy salvage radiation therapy with intensity-modulated radiation therapy. Eur Urol 60:1142-1148, 2011

33. Berlin A, Cho E, Kong V, et al: Phase 2 trial of guideline-based postoperative image guided intensity modulated radiation therapy for prostate cancer: Toxicity, biochemical, and patient-reported health-related quality-of-life outcomes. Pract Radiat Oncol 5:e473-e482, 2015

34. Shipley WU, Seiferheld W, Lukka H, et al: Report of NRG Oncology/RTOG 9601, a phase 3 trial in prostate cancer: Anti-androgen therapy (AAT) with bicalutamide during and after radiation therapy (RT) in patients following radical prostatectomy (RP) with pT2-3pN0 disease and an elevated PSA. Int J Radiat Oncol Biol Phys 94:3, 2016

35. Carrie C, Hasbini A, de Laroche G, et al: Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): A randomised, multicentre, open-label phase 3 trial. Lancet Oncol 17:747-756, 2016

36. Zhou P, Chen MH, McLeod D, et al: Predictors of prostate cancer-specific mortality after radical prostatectomy or radiation therapy. J Clin Oncol 23:6992-6998, 2005

37. Maffezzini M, Bossi A, Collette L: Implications of prostate-specific antigen doubling time as indicator of failure after surgery or radiation therapy for prostate cancer. Eur Urol 51:605-613, 2007; discussion 613

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Improved Metastasis-Free and Survival Outcomes with Early Salvage Radiotherapy in Men With Detectable Prostate-Specific Antigen After Prostatectomy for Prostate Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Bradley J. Stish
No relationship to disclose

Thomas M. Pisansky
No relationship to disclose

William S. Harmsen
No relationship to disclose

Brian J. Davis
Stock or Other Ownership: Pfizer

Katherine S. Tzou
No relationship to disclose

Richard Choo
No relationship to disclose

Steven J. Buskirk
No relationship to disclose

Appendix

Table A1. Multiple Variable Regression Analysis of Outcomes with Pre-SRT PSA as a Categorical Variable

	Pre-SRT PSA ≤ 0.5 ng/mL			Pre-SRT PSA > 0.5 ng/mL				
Outcomes*	Events (No.)	5-year % (95% CI)	10-year % (95% CI)	Events (No.)	5-year % (95% CI)	10-year % (95% CI)	Multiple Variable HR (95% CI)†	*P*
Biochemical recurrence	237	43 (38 to 47)	60 (54 to 66)	363	56 (51 to 60)	68 (63 to 72)	1.49 (1.25 to 1.77)	< .001
Distant metastases	59	7 (5 to 10)	13 (10 to 17)	149	14 (11 to 17)	25 (21 to 28)	1.97 (1.43 to 2.72)	< .001
Cause-specific mortality	32	1 (0 to 2)	6 (3 to 9)	78	4 (3 to 6)	13 (10 to 16)	1.61 (1.03 to 2.54)	.04
Overall survival	96	94 (92 to 96)	83 (79 to 88)	184	92 (90 to 94)	73 (69 to 78)	1.11 (0.86 to 1.43)	.44

Abbreviations: HR, hazard ratio; PSA, prostate-specific antigen; SRT, salvage radiotherapy.
*Overall survival estimates from Kaplan-Meier, others from Fine-Gray cumulative incidence estimator.
†Pre-SRT PSA ≤ 0.5 ng/mL as referent group.

Table A2. Cumulative Incidence of Distant Metastases from Date of RP According to Exploratory Patient Subsets

Characteristic	Single Variable HR (95% CI)	*P*	Multiple Variable HR (95% CI)	*P*
Pathologic tumor stage				
T2	1.0 (Ref)	—	1.0 (Ref)	—
T3a	1.39 (1.01 to 1.93)	.05	1.23 (0.87 to 1.75)	.25
T3b	2.11 (1.50 to 2.98)	< .001	1.70 (1.15 to 2.50)	.007
T4	1.90 (0.49 to 7.39)	.36	1.54 (0.35 to 6.84)	.57
Pathologic nodal stage				
N0	1.0 (Ref)	—	1.0 (Ref)	—
N1	3.09 (1.23 to 7.75)	.02	1.02 (0.39 to 2.72)	.96
Gleason score				
≤ 6	1.0 (Ref)	—	1.0 (Ref)	—
7	2.08 (1.43 to 3.04)	< .001	2.37 (1.57 to 3.59)	< .001
8	3.10 (1.87 to 5.16)	< .001	3.77 (2.15 to 6.58)	< .001
9-10	4.83 (2.99 to 7.78)	< .001	5.68 (3.34 to 9.67)	< .001
RP to detectable PSA, years				
< 1	1.0 (Ref)	—	1.0 (Ref)	
≥ 1	0.89 (0.66 to 1.22)	.47	1.14 (0.82 to 1.61)	.44
Pre-SRT PSA (per doubling)	1.36 (1.24 to 1.49)	<.001	1.32 (1.18 to 1.46)	< .001

Abbreviations: HR, hazard ratio; PSA, prostate-specific antigen; Ref, referent; RP, radical prostatectomy; SRT, salvage radiotherapy.

Table A3. Survival Estimates from Date of RP for Exploratory Patient Subsets

Characteristic	Cause-Specific Mortality				Overall Survival			
	Single Variable HR (95% CI)	*P*	Multiple Variable HR (95% CI)	*P*	Single Variable HR (95% CI)	*P*	Multiple Variable HR (95% CI)	*P*
Age at SRT, years								
<65	1.0 (Ref)	—	—	—	1.0 (Ref)	—	—	—
≥65	1.21 (0.81 to 1.81)	.34	—	—	1.57 (1.20 to 2.06)	.001	—	—
Age (per 10 years)	1.19 (0.93 to 1.52)	.17	—	—	1.45 (1.22 to 1.73)	< .001	1.43 (1.18 to 1.72)	< .001
Pathologic tumor stage								
T2	1.0 (Ref)	—	1.0 (Ref)	—	1.0 (Ref)	—	1.0 (Ref)	—
T3a	1.52 (0.96 to 2.41)	.08	1.40 (0.85 to 2.29)	.18	1.54 (1.17 to 2.02)	.002	1.44 (1.19 to 1.73)	.01
T3b	3.01 (1.91 to 4.73)	< .001	2.15 (1.27 to 3.62)	.004	2.14 (1.58 to 2.90)	< .001	1.90 (1.38 to 2.62)	< .001
T4	4.85 (1.29 to 18.20)	.02	2.96 (0.75 to 11.77)	.12	3.13 (0.99 to 9.89)	.05	2.16 (0.67 to 6.97)	.20
Pathologic nodal stage								
N0	1.0 (Ref)	—	1.0 (Ref)	—	1.0 (Ref)	—	—	—
N1	4.85 (1.89 to 12.42)	.001	1.41 (0.47 to 4.25)	.54	1.63 (0.61 to 4.38)	.33	—	—
Gleason score								
≤ 6	1.0 (Ref)	—	1.0 (Ref)	—	1.0 (Ref)	—	1.0 (Ref)	—
7	2.01 (1.20 to 3.35)	.007	2.47 (1.35 to 4.49)	.003	1.21 (0.91 to 1.61)	.18	1.16 (0.87 to 1.55)	.31
8	3.40 (1.75 to 6.63)	< .001	4.56 (2.15 to 9.69)	< .001	2.26 (1.49 to 3.43)	< .001	1.91 (1.25 to 2.92)	.003
9-10	4.73 (2.51 to 8.88)	< .001	6.08 (2.93 to 12.63)	< .001	2.44 (1.59 to 3.74)	< .001	2.26 (1.46 to 3.48)	< .001
RP to detectable PSA, years								
< 1	1.0 (Ref)	—	1.0 (Ref)	—	1.0 (Ref)	—	—	—
≥ 1	0.55 (0.37 to 0.81)	.003	0.71 (0.47 to 1.08)	.11	0.89 (0.56 to 1.42)	.62	—	—
Pre-SRT PSA (per doubling)	1.39 (1.23 to 1.58)	< .001	1.37 (1.19 to 1.58)	< .001	1.12 (1.02 to 1.23)	.01	1.09 (0.99 to 1.20)	.09

Abbreviations: HR, hazard ratio; PSA, prostate-specific antigen; Ref, referent; RP, radical prostatectomy; SRT, salvage radiotherapy.