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Mortality and Androgen-Deprivation Therapy as Salvage Treatment for Biochemical Recurrence after Primary Therapy for Clinically Localized Prostate Cancer

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Abstract

Purpose—Androgen-deprivation therapy is often used as salvage treatment (SADT) for men with rising prostate-specific antigen (PSA) after initial radical prostatectomy or radiotherapy for clinically localized prostate cancer. Given the lack of evidence from general practice, we examined the association of SADT with mortality in an observational cohort study.

Materials and Methods—Among three managed care organizations, we assembled a retrospective cohort of all men with newly diagnosed localized prostate cancer (1995-2009) who had a PSA rise (biochemical recurrence) after primary radical prostatectomy or radiotherapy (n=5,804). Main outcomes were all-cause and prostate-cancer specific mortality. We used Cox proportional hazards models to estimate mortality, with SADT as a time-dependent predictor.

Results—Overall, SADT was associated with neither all-cause nor prostate-cancer specific mortality within the prostatectomy cohort (hazard ratio [HR]=0.97, 95% CI: 0.70-1.35 or HR=1.18, 95% CI: 0.68-2.07) or the radiotherapy cohort (HR=0.84, 95% CI: 0.70-1.01 or HR=1.06, 95% CI: 0.80-1.40). Among men with PSA doubling time <9 months after their PSA rise, SADT was statistically significantly associated with decreased risk of all-cause and prostate-cancer specific mortality within the prostatectomy cohort (HR=0.35, 95% CI: 0.20-0.63 and HR=0.43, 95% CI: 0.21-0.91) and the radiotherapy cohort (HR=0.62, 95% CI: 0.48-0.80 and HR=0.65, 95% CI: 0.47-0.90).

Conclusions—We found no association of SADT with all-cause or cause-specific mortality in most men with biochemical recurrence after primary radical prostatectomy or radiotherapy for clinically localized prostate cancer. Men with quickly progressed disease may derive a clinical benefit from SADT.

Keywords

androgen deprivation therapy; localized prostate cancer; mortality; salvage treatment

Introduction

Prostate cancer is the most common non-skin cancer in men, with approximately 2.5 million survivors currently alive in the United States.¹ Approximately 35% of men experience biochemical recurrence as indicated by a rising serum prostate-specific antigen (PSA) within 10 years following initial prostatectomy or radiotherapy.²⁻⁴ For such men, androgen deprivation therapy (ADT) is frequently prescribed for salvage therapy.⁵⁻⁷ Some evidence suggests that in men who undergo post-prostatectomy radiotherapy for a rising PSA, salvage ADT (SADT) with radiotherapy may improve progression-free survival compared with radiation alone, especially in high-risk patients.⁸ There is also conflicting data in the literature on clinical benefits of early SADT use in men with biochemical recurrence after radical prostatectomy.^{9;10} Importantly, a recently published randomized clinical trial (TOAD study) from multiple centers in Australia, New Zealand, and Canada showed that immediate use of SADT improved overall survival compared with delayed SADT in men with biochemical recurrence after primary treatment of surgery with or without radiotherapy, or curative radiotherapy alone.¹¹ Nonetheless, this trial excluded patients with substantial

medical comorbidities,¹¹ results of which may not be generalizable to those typically seen in general practice.

The prolonged natural history of localized disease and the potential risks of adverse events associated with ADT use,¹²⁻¹⁴ add to the uncertainty of SADT's effectiveness in men experiencing a biochemical recurrence. Therefore, we assessed the association of SADT with all-cause and prostate-cancer specific mortality in a population-based cohort of men who experienced a biochemical recurrence after undergoing initial curative localized therapies within the US general practice.

Material and Methods

Data sources

All study data were obtained for men with newly diagnosed clinically localized prostate cancer in three integrated health systems that participate in the Health Care System Research Network (HCSRN): Kaiser Permanente Northern California, Kaiser Permanente Southern California, and Henry Ford Health System in Detroit, Michigan.¹⁵ These three health care systems possess electronic health records that incorporate comprehensive information from all inpatient and outpatient clinical encounters, laboratory test values, pharmacy data, and cancer registry data.

Cohort Selection

We identified all men aged ≥ 35 years diagnosed with clinically localized prostate cancer (T1-T2, N0, M0) between 1/1/1995 through 1/1/2009 ($n=51,511$; Figure 1). We included men with node negative disease who received primary therapy with radical prostatectomy or radiotherapy within 12 months after their initial prostate cancer diagnosis. We excluded men who received primary ADT, orchiectomy, or chemotherapy as part of initial therapy due to indication of metastatic disease, and those with <2 years of follow-up to ensure sufficient time to identify SADT exposure (Figure 1). From this group we identified 5,804 men with evidence of post-primary therapy PSA rise (biochemical recurrence). For men who had a prostatectomy, we defined PSA rise as PSA ≥ 0.2 ng/mL [$n=2,676$];^{8;11;16;17} for men who had primary radiotherapy (external beam or brachytherapy), we defined PSA rise as ≥ 2.0 ng/mL above the PSA nadir (the lowest PSA observed) or ≥ 10.0 ng/mL [$n=3,128$].^{11;18} We used the *date of the PSA rise* as “time zero” for the survival analysis.

Salvage Androgen Deprivation Therapy

We captured ADT use, gonadotropin releasing hormones (GnRH) analog or GnRH antagonists, from pharmacy records. SADT was defined as the ADT that commenced on the date after the first post-primary therapy PSA rise. We considered ADT as adjuvant rather than salvage therapy if it was given before any observed PSA rise following primary therapy.

Mortality outcomes

We captured all-cause and prostate-cancer specific mortality (C619, C61, 185) based on International Classification of Disease 10th revision (ICD-10) codes. Date and cause of death information was derived from a combination of clinical datasets, probabilistic linkage with

death certificate records from California or Michigan, and linkage with Social Security Administration data to ascertain deaths that occurred outside of California or Michigan. Each man was followed through date of death or end of study period (12/31/2010), whichever occurred first (median follow-up 8 years, range 2-15 years).

Baseline and post-primary therapy characteristics

We obtained from each of the health plans' cancer registries and electronic health records the following variables: age at PSA rise, racial/ethnic group, year of diagnosis, and diagnosis of prior or subsequent primary cancers other than prostate cancer (tumor sequence). The American Urological Association (AUA) risk group at baseline was assessed based on PSA, Gleason score, and clinical T stage,^{17;19} with low risk defined as PSA ≤ 10 , Gleason score ≤ 6 , and stages T1c-T2a; intermediate risk defined as PSA 11-20 or Gleason score = 7 or stage T2b; and high risk as PSA > 20 or Gleason score ≥ 8 , or stages T2c-3a. We computed the Elixhauser comorbidity index by assessing the presence of 30 individual health conditions diagnosed between two years before the prostate cancer diagnosis date up to three months after diagnosis.²⁰

We included time from primary therapy to PSA rise as a covariate in multivariate analysis. We calculated PSA doubling time based on PSA values after primary therapy until receipt of SADT, or to the end of follow-up for men without SADT (see Appendix).^{21;22} If men had primary prostatectomy, we adjusted for the receipt of radiotherapy for recurrence or progression.

Statistical Analysis

We analyzed mortality outcomes separately for men initially treated with primary radical prostatectomy or radiotherapy because we used different PSA-rise definitions and because some baseline characteristics varied by primary treatment group.¹⁸ We calculated the person-year mortality rates according to SADT use, for descriptive purpose only.

Due to varying timing of SADT initiation, we treated SADT as a time-dependent variable in the Cox proportional hazards model to estimate the hazard ratio (HR) for each mortality outcome. In each model, the follow-up started with date of PSA rise and ended with death as the outcome event or end of follow-up. We adjusted for multiple patient clinical and sociodemographic characteristics. Methods for assessing proportional hazards assumption and handling missing data are described in the Appendix.

To assess for effect modification by timing of SADT initiation, we conducted sensitivity analyses categorizing the SADT into three levels: SADT initiated within twelve months, beyond twelve months, and no SADT after the PSA rise. We also conducted subgroup analyses according to age at PSA rise, race/ethnicity, comorbidity, baseline AUA risk group, and PSA doubling time. This study was approved by Kaiser Permanente, Henry Ford, and the MedStar Health Research Institute-Georgetown University Institutional Review Board #2009-662.

Results

Patient Characteristics

We observed 2,676 (16.3%) men with a rising PSA after their primary prostatectomy. The mean ($\pm$ SD) age at the time of PSA rise was 66 ($\pm$ 7.8) years. Overall, patients had a PSA rise after a median 2.3 years after prostatectomy. There were 844 men who received SADT with 7,070 person-years of follow up; 1,832 men without SADT had 14,582 person-years of follow up.

There were 3,128 (16.0%) men with a rising PSA after their primary radiotherapy. The mean ($\pm$ SD) age at the time of PSA rise was 72 ($\pm$ 7.8) years. Overall, patients had a PSA rise after a median 3.9 years post-primary radiotherapy. Patient baseline demographic and clinical characteristics, as well as post-primary therapy characteristics are shown by their primary therapies (web-link).

Mortality Outcomes

In unadjusted comparisons, SADT (vs. no SADT) was associated with higher all-cause mortality (14.4 versus 9.8 deaths per 1000 person-years) and prostate-cancer specific mortality (6.8 vs. 2.4 per 1000 person-years) in prostatectomy patients. However, after adjusting for all covariates, we found no association of SADT use with all-cause mortality (HR=0.97, 95% CI: 0.70-1.35) or prostate-cancer specific mortality (HR=1.18, 95% CI: 0.68-2.07) (Table 1). Similarly, there was no statistically significant association of SADT with the risk of all-cause mortality (HR=0.84, 95% CI: 0.70-1.01) or prostate-cancer specific mortality (HR=1.06, 95% CI: 0.80-1.40) after adjustment in radiotherapy patients (Table 1).

Sensitivity Analysis for Timing of SADT

We next conducted sensitivity analyses assessing the timing of SADT initiation observed in our cohort (Table 2). We observed larger HRs for all-cause mortality (2.27, 95% CI: 1.51-3.41) and prostate-cancer specific mortality (2.43, 95% CI: 1.21-4.86) in prostatectomy patients who had no SADT compared with those who had SADT within 12 months after their PSA rise, after adjustment. Similarly, in patients receiving primary radiotherapy, men having no SADT were associated with higher risk of all-cause mortality (2.41, 95% CI: 1.96-2.96) and prostate-cancer specific mortality (2.25, 95% CI: 1.67-3.05) compared with patients who had SADT within 12 months after their PSA rise.

Subgroup Analyses

Among men with PSA doubling time <9.0 months, we observed that SADT was associated with a decreased risk of all-cause mortality (HR=0.35, 95% CI: 0.20-0.63) and prostate-cancer specific mortality (HR=0.43, 95% CI: 0.21-0.91) for those who initially treated with prostatectomy (Table 3). Similar findings were identified for men who initially treated with radiotherapy and with PSA doubling time <9.0 months, with a significant association between SADT and a decreased risk of all-cause mortality (HR=0.62, 95% CI: 0.48-0.80) and prostate-cancer specific mortality (HR=0.65, 95% CI: 0.47-0.90). No significant associations were observed for men with slower PSA doubling time, except for all-cause

mortality among men initially treated with prostatectomy and with PSA doubling time 9.0-
<15.0 months (HR=0.32, 95% CI: 0.11-0.92).

We observed, in the radiotherapy group, that SADT was associated with a decreased risk of
all-cause mortality in men aged 75 and over (HR=0.71, 95% CI: 0.55-0.93) and white men
(HR=0.75, 95% CI: 0.61-0.92), but not with prostate-cancer specific mortality.

Discussion

ADT has been increasingly used as salvage therapy for men experiencing biochemical
recurrence following primary therapy with prostatectomy or radiotherapy,^{2;4-6} despite
limited evidence for a survival benefit in general practice.¹¹ Overall, our findings of no
association of SADT with mortality do not support SADT as an effective treatment in most
men who had clinically localized prostate cancer and experienced biochemical recurrence.
However, we identified significant benefits on all-cause and prostate-cancer specific
mortality associated with SADT use in the subgroup of men with PSA doubling time smaller
than nine months after their primary therapy. Such findings help inform and guide current
practice in the general population. Additionally, any survival benefits of SADT must be
carefully weighed against quality-of-life and the potentially serious adverse effects of ADT
including cardiovascular disease, bone fractures, and diabetes mellitus,^{12;13;23} as well as
metabolic syndrome, sarcopenia, and psychosocial impacts.^{14;24-26}

We observed a lower rate (16%) of PSA rise than the literature,²⁻⁴ due to a younger study
population, more restrictive definition for PSA rise using electronic health records, and a
lack of mandated PSA testing. Our sensitivity analysis on timing of SADT after a rising PSA
implied a decreased risk of all-cause and prostate-cancer specific mortality among men
received SADT within 12 months after their PSA rise. This is consistent with the TOAD trial
that supports an immediate, rather than delayed, receipt of ADT in men with biochemical
recurrence after primary therapies.¹¹ However, we only identified significant differences
between men who received SADT within 12 months and men who had no SADT observed
after their PSA rise, the latter group could be a mixed one with varying follow-up time
(possibly also less than 12 months due to censoring). Additionally, we detected no mortality
differences between SADT initiation within 12 months and beyond 12 months after the PSA
rise. Therefore, the timing effect of SADT use cannot be fully confirmed based on our
results.

Notably, our subgroup analysis revealed associations between SADT and both all-cause
mortality and prostate-cancer specific mortality in men with PSA doubling time <9 months.
Such results suggest a clinical benefit from SADT for men whose disease quickly progress
with rapid PSA doubling time, which confirmed a recently published systemic review.²⁷
Similarly, the TOAD trial was stratified by PSA doubling time,¹¹ suggesting it a predictive
factor for implementing earlier ADT. Additionally, our results suggested a decreased risk of
all-cause mortality among men who underwent primary prostatectomy and with PSA
doubling time between 9.0 and 15.0 months. However, since we did not detect an association
of SADT with cause-specific mortality, it is possible that this finding for all-cause mortality
may be partly due to selection bias; i.e., healthier men at the time of a rising PSA were more

likely to receive SADT than those with lower life expectancies. Our statistical adjustments for observed differences in age and comorbidity are not likely to fully account for differences in patients' baseline health status.

Further, our subgroup analysis detected associations between SADT and all-cause mortality in non-Hispanic white men and in men aged 75-90 receiving primary radiotherapy. This finding may also be due partly to selection bias, and the observed benefits were small. Thus, use of SADT in older men after primary radiotherapy should be carefully weighed against its possible risks in terms of side effects.

The present study has several strengths. We studied a large, heterogeneous population-based sample of 36,000 men with localized prostate cancer treated with primary prostatectomy or radiotherapy, including approximately 6,000 men with evidence of PSA rise and 926 deaths. We accounted for baseline prognostic factors and considered longitudinal PSA values, which are critical to determine biochemical recurrence. Further, our results are more applicable to patients in the general practice compared to the TOAD trial.¹¹ With a median follow-up of 5 years in the trial, only 40% of men in the delayed arm avoided SADT,¹¹ compared to 60% in our study with a median follow-up of 8-years, suggesting a lower risk group. Thus, advising the patient on risks and benefits of starting SADT must be based on their risk factors for progression.

Our findings are subject to limitations. First, we lacked information on bone metastasis and imaging results, so we cannot be certain that the rise in PSA is truly a biochemical-only recurrence. However, rising PSA often occurs many years before metastases develop,⁷ so the majority of men in our sample with rising PSA are unlikely to have bone metastasis. Second, we could not address unobserved confounders from the electronic health records such as reasons for SADT initiation, physicians' or patients' preferences, health status and behaviors. Third, it is possible that certain patients may have received SADT after the end of the follow-up, but were classified as "no SADT" based on our definition. Fourth, effects based on duration of ADT exposure or differentiation of intermittent vs. continuous ADT was not addressed in this paper. However, in light of findings of equivocal mortality comparing intermittent vs. continuous ADT for a rising PSA,²⁸ the specific type of ADT administration is not likely to influence the outcomes we observed for salvage ADT. Fifth, our cut-off points for PSA doubling time were based on our data distribution and previous studies,^{17;29} but are still arbitrary. Finally, our cohort consisted of members of integrated managed care plans. This may potentially limit the generalizability of our findings to men treated in fee-for-service settings, for example. However, the populations covered by the three health plans are sociodemographically diverse, and the plans include Medicare and Medicaid patients.

Conclusions

We found that treatment of rising PSA with SADT after primary prostatectomy or radiotherapy for clinically localized prostate cancer was not associated with all-cause or prostate cancer-specific mortality for most men. Nonetheless, we did identify statistically significant benefits on mortality associated with SADT use in subgroup analysis. Given the

study limitations, any true benefit of SADT should be carefully weighed against the known side effects of ADT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

PSA Doubling Time Following Primary Therapy

We estimated the PSA trajectory by calculating the PSA doubling time^{21;22} from the time of nadir after radiotherapy or undetectable PSA after prostatectomy to 1) the first SADT use, or 2) to the end of follow-up for patients without SADT use. The PSA doubling time was the natural log of 2 (=0.693) divided by the slope of a linear regression of the log(PSA) over time. The PSA slope was estimated with the use of linear least squares when three or more

PSA values were available, or by calculation using the formula $\frac{\log 2 * (T2 - T1)}{\log PSA2 - \log PSA1}$ when only two PSA values were available, where PSA1 and PSA2 were obtained at times T1 and T2, respectively.²¹ The PSA doubling time was finally categorized into 4 levels (in months): <9.0, 9.0–<15.0, 15.0–<36.0, and ≥36.0 (indicating no PSA rise) in multivariate analysis.^{17;29}

Assessing proportional hazards assumption

We assessed departures from the proportional hazards assumption by adding a time-varying covariate to the model in the form of the product of the specific variable and a function of time. The proportional hazards assumption for each covariate was tested individually. If the assumption was violated, we performed stratified analysis on that variable to adjust for differences.

Handling of missing data

A substantial proportion of cases (20%) had at least one or more of the key clinical prognostic variables (clinical stage, Gleason score, or baseline PSA) missing. We performed multiple imputations using all other covariates to predict values for these variables. We constructed five imputed datasets, each having estimates for the missing values for PSA, Gleason score, and T-stage. We then pooled the estimates and corresponding SEs across the five imputations using Rubin's method. All model results used these imputed datasets; multivariate models using only the complete cases did not show any significant deviations from the results shown.

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Key of Definitions for Abbreviations

ADT	androgen deprivation therapy
SADT	salvage androgen deprivation therapy
PSA	prostate-specific antigen
ICD	International Classification of Disease
AUA	American Urological Association
HR	hazard ratio
CI	confidence interval

Figure 1. Study Cohort

SADT: salvage androgen deprivation therapy; RP: radical prostatectomy; RT: radiotherapy

Mortality risk of salvage ADT after PSA rise among men with newly diagnosed localized prostate cancer who had primary prostatectomy or radiotherapy

Table 1

Prostatectomy	Total (Rate is number of death per 1000 person-years)		Death according to initiation of salvage ADT						Unadjusted Risk Estimates			Adjusted Risk Estimates [^]		
			Yes (n = 844)		No (n = 1,832)									
			No. of Death	Rate	No. of Death	Rate	No. of Death	Rate	HR	95% CI	P	HR	95% CI	P
All-cause mortality	245	11.3	102	14.4	143	9.8	1.71	1.31, 2.22	<0.001	0.97	0.70, 1.35	0.857		
Prostate-cancer specific mortality	83	3.8	48	6.8	35	2.4	3.20	2.05, 5.00	<0.001	1.18	0.68, 2.07	0.555		
Radiotherapy			Yes (n = 1,421)		No (n = 1,707)									
All-cause mortality	681	27.4	357	30.1	324	25.0	1.60	1.36, 1.88	<0.001	0.84	0.70, 1.01	0.068		
Prostate-cancer specific mortality	303	12.2	191	16.1	112	8.6	2.49	1.94, 3.19	<0.001	1.06	0.80, 1.40	0.699		

Notes: HR: hazard ratio; CI: confidence interval; ADT: androgen deprivation therapy.

[^] Multivariate analysis using a Cox proportional hazards model adjusted for age, race/ethnicity, AUA risk group, tumor sequence, Elixhauser score, PSA doubling time, post-surgical radiotherapy (prostatectomy group only), adjuvant ADT, time from primary therapy to PSA rise, diagnosis year, and health plan.

Table 2
Mortality risk of salvage ADT after PSA rise (sensitivity analysis on pre-specified time from PSA rise to salvage ADT)

	All-cause mortality			Prostate-cancer specific mortality		
	HR	95% CI	p-value	HR	95% CI	p-value
Prostatectomy						
SADT within 12 months of PSA rise (ref)	1.00			1.00		
SADT after 12 months of PSA rise	1.12	0.73, 1.72	0.59	2.00	0.99, 4.03	0.054
No SADT observed	2.27	1.51, 3.41	<0.0001	2.43	1.21, 4.86	0.012
Radiotherapy						
SADT within 12 months of PSA rise (ref)	1.00			1.00		
SADT after 12 months of PSA rise	0.83	0.59, 1.12	0.36	1.00	0.74, 1.36	0.98
No SADT observed	2.41	1.96, 2.96	<0.0001	2.25	1.67, 3.05	<0.0001

Notes: HR: hazard ratio; CI: confidence interval; ADT: androgen deprivation therapy.

Multivariate analysis using a Cox proportional hazards model adjusted for age, race/ethnicity, AUA risk group, tumor sequence, Elixhauser score, PSA doubling time, post-surgical radiotherapy (prostatectomy group only), adjuvant ADT, time from primary therapy to PSA rise, diagnosis year, and health plan.

Table 3
Subgroup analyses of all-cause and prostate-cancer specific mortality risk of salvage ADT

	All-cause mortality		Prostate-cancer specific mortality	
	Prostatectomy	Radiotherapy	Prostatectomy	Radiotherapy
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age at PSA rise (years)				
<=64	1.66 (0.85,3.22)	1.10 (0.67,1.81)	1.24 (0.45,3.41)	1.30 (0.62,2.75)
65-74	0.72 (0.41,1.28)	1.03 (0.76,1.39)	0.72 (0.26,1.98)	1.00 (0.66,1.52)
>=75	0.72 (0.39,1.34)	0.70 (0.54,0.92) *	1.21 (0.36,4.06)	1.04 (0.66,1.63)
Race				
White	0.97 (0.65,1.45)	0.74 (0.60,0.91) **	1.08 (0.57,2.07)	0.94 (0.68,1.28)
Black	0.65 (0.31,1.35)	1.10 (0.65,1.86)	1.58 (0.27,9.17)	1.87 (0.78,4.46)
Hispanic	3.13 (0.61,16.15)	1.64 (0.70,3.85)	#	1.29 (0.21,7.79)
Elixhauser score				
0	1.31 (0.74,2.34)	0.88 (0.63,1.22)	0.97 (0.39,2.39)	0.91 (0.56,1.49)
1	1.02 (0.53,1.95)	0.74 (0.53,1.04)	1.08 (0.33,3.54)	0.94 (0.57,1.55)
2+	0.68 (0.38,1.21)	0.97 (0.71,1.33)	1.29 (0.41,4.00)	1.51 (0.93,2.46)
Risk group				
Low	0.26 (0.06,1.21)	0.89 (0.45,1.78)	#	#
Intermediate	1.34 (0.82,2.20)	0.76 (0.57,1.00)	3.29 (1.29,8.36) *	1.37 (0.86,2.17)
High	0.87 (0.53,1.43)	0.89 (0.69,1.17)	0.52 (0.23,1.21)	0.78 (0.55,1.12)
PSA doubling time (months)				
0.0-<9.0	0.35 (0.20,0.63) **	0.62 (0.48,0.80) **	0.43 (0.21,0.91) *	0.65 (0.47,0.90) **
9.0-<15.0	0.32 (0.11,0.92) *	0.91 (0.59,1.42)	#	1.25 (0.54,2.89)
15.0-<36.0	1.74 (0.72,4.23)	1.19 (0.79,1.77)	#	#
36.0+ (no rise)	0.78 (0.21,2.90)	1.08 (0.24,4.82)	#	#

Each cell represents result from a separate Cox proportional hazards model adjusted for age, race/ethnicity, AUA risk group, tumor sequence, Elixhauser score, PSA doubling time, post-surgical radiotherapy (prostatectomy group only), adjuvant ADT, time from primary therapy to PSA rise, diagnosis year, and health plan; ADT: androgen deprivation therapy; PSA: prostate-specific antigen;

* p<0.05,

** P<0.01,

model cannot converge due to limited cases in the subgroup.