Early Versus Delayed Initiation of Salvage Androgen Deprivation Therapy and Risk of Prostate Cancer–Specific Mortality

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Abstract

Background: This study sought to ascertain whether there is an association between prostate cancer (PC)–specific mortality (PCSM) and timing of salvage androgen deprivation therapy (ADT) among men with short versus long prostate-specific antigen doubling times (PSA-DTs). **Methods:** The study cohort was selected from 206 men with localized unfavorable-risk PC randomized to radiation therapy (RT) or RT plus 6 months of ADT between 1995 and 2001. A total of 54 men who received salvage ADT for PSA failure after a median follow-up of 18.72 years following randomization defined the study cohort. The Fine-Gray competing risks regression model was used to analyze whether the timing of salvage ADT was associated with an increased risk of PCSM after adjusting for age, comorbidity, known PC prognostic factors, and previously identified interactions. **Results:** After a median follow-up of 5.68 years (interquartile range, 3.05–9.56) following salvage ADT, 49 of the 54 men (91%) died, of which 27 from PC (54% of deaths). Increasing PSA-DT as a continuous covariate (per month increase) was associated with a decreasing risk of PCSM (adjusted hazard ratio [HR], 0.33; 95% CI, 0.13–0.82; $P=.02$). Among men with a long PSA-DT (≥ 6 months), initiating salvage ADT later (PSA level >12 ng/mL, upper quartile) versus earlier was associated with an increased risk of PCSM (adjusted HR, 8.84; 95% CI, 1.99–39.27; $P=.004$), whereas for those with a short PSA-DT (<6 months; adjusted HR, 1.16; 95% CI, 0.38–3.54; $P=.79$) this was not true. **Conclusions:** Early initiation of salvage ADT for post-RT PSA failure in men with a PSA-DT of ≥ 6 months may reduce the risk of PCSM.

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Background

Prostate cancer (PC) is the most common noncutaneous malignancy in men, with 161,360 new cases and 26,730 deaths due to PC in 2017.¹ Although radical prostatectomy (RP) or radiation therapy (RT) with or without androgen deprivation therapy (ADT) are often curative treatments for localized disease,^{2–5} approximately one-quarter of patients will experience recurrence within 10 years after curative-intent therapy.^{6,7} An increasing prostate-specific antigen (PSA) level identifies men with biochemical recurrence defined as nadir +2 follow-

ing RT, or as detectable and increasing following RP.^{8,9} Although ADT has been standard treatment when combined with RT in men with unfavorable (intermediate or high)-risk localized PC,⁵ recent evidence shows that adding ADT to RT provides a progression-free and overall survival benefit in men with biochemically recurrent increasing PSA levels after RP.^{10,11} However, level 1 evidence is lacking to guide management for patients with a biochemical recurrence after definitive treatment with RT with or without ADT.

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Moreover, the optimal timing of ADT initiation after post-RT biochemical recurrence remains an open question given the lack of randomized data comparing this approach with surveillance, and therefore the unknown impact of salvage ADT use on survival. To help guide timing of ADT initiation after biochemical recurrence, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer recommend that patients with a short PSA doubling time (PSA-DT) and an otherwise long life expectancy be encouraged to consider earlier ADT.^{2,12–15} However, an alternative hypothesis is that patients with favorable risk factors such as long PSA-DT and interval to PSA recurrence and Gleason score ≤ 7 may be the ones who would have the potential for improved cancer-specific outcomes given that the recurrence may be less likely to be castration-resistant.

Therefore, the purpose of our study was to use data from a mature prospective randomized clinical trial that evaluated the use of RT versus RT and ADT as initial treatment in men with unfavorable-risk PC to ascertain whether a significant association existed between an increased risk of PC-specific mortality (PCSM) when salvage ADT was initiated at high versus lower PSA level among men with short versus long PSA-DTs after adjusting for age and known PC prognostic factors and previously identified interactions.¹²

Methods

Patient Population, Treatment, and Follow-Up

The study cohort was selected from 206 men with localized (1992 AJCC tumor category 1b to 2b) unfavorable (intermediate or high)-risk PC¹⁶ who underwent central pathology review and were enrolled in a randomized trial of RT or RT plus 6 months of ADT between December 1, 1995, and April 15, 2001. Information on eligibility criteria and patient characteristics stratified by randomized treatment arms was reported previously.⁵ 3D conformal RT was used to deliver 70.2 Gy in 39 fractions of 1.8 Gy per fraction to the prostate and seminal vesicles. Combined androgen blockade included 2 injections of a luteinizing hormone-releasing hormone (LHRH) agonist (leuprolide acetate, 22.5 mg every 3 months or goserelin, 10.8 mg every 3 months) and a non-steroidal antiandrogen (flutamide, 250 mg every 8

hours or bicalutamide, 50 mg every day, discontinued on day 85 after the second administration of the LHRH agonist). Baseline comorbidity at the time of study enrollment was characterized using the Adult Comorbidity Evaluation-27 (ACE-27) index.¹⁷

Prior to PSA failure, patients were followed with PSA testing, physical examination, and digital rectal examination every 3 months for 2 years, then every 6 months until 5 years, and annually thereafter.⁵ If PSA failure occurred, bone scan and pelvic CT or MRI were performed. A total of 108 patients developed biochemical failure, defined as 2 ng/mL elevation higher than the lowest PSA value achieved. The study protocol recommended lifelong salvage ADT or bilateral orchiectomy when PSA levels approached 10 ng/mL.¹⁸ Ultimately, 54 men (39 and 15 men randomized to RT vs RT + ADT, respectively) received salvage ADT (n=50) or orchiectomy (n=4) for PSA failure after a median follow-up of 18.72 years following randomization, and these men defined the study cohort as shown in the CONSORT diagram (Figure 1). The 54 remaining men with PSA failure were not treated with salvage ADT because their PSA levels remained < 10 ng/mL (n=48) due to significant comorbid illness (n=3) or because they had a PSA-DT > 2 years and advanced age of > 75 years (n=3).

Time zero for this study commenced at the time of salvage ADT initiation and concluded on the date of death or last follow-up through September 6, 2016, with no patients lost to follow-up. The Dana-Farber/Harvard Cancer Center Institutional Review Board granted permission to perform this study.

Cause of Death Determination

If a patient became refractory to first-line salvage ADT, second- and third-line ADT was used, usually followed by cytotoxic chemotherapy. Cause of death was determined by the treating oncologist who followed the patient from study entry until death. All cause-of-death determinations were reviewed and confirmed by the principal investigator of the study (A.V.D.).

Statistical Methods

Distribution and Comparison of Clinical Characteristics at Randomization: Descriptive statistics characterized the distribution of clinical characteristics for the 54 men in the study cohort, stratified by PSA-DT and PSA level at the time of salvage ADT. PSA-DT

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Figure 1. CONSORT diagram.

Abbreviations: 3D-CRT, 3D conformal radiation therapy; ADT, androgen deprivation therapy; LHRH, luteinizing hormone–releasing hormone; PSA, prostate-specific antigen; PSA-DT, prostate-specific antigen doubling time.

was stratified by ≥ 6 versus < 6 months because PSA-DT < 6 months is a well-established poor prognostic factor associated with a high risk of subsequent distant metastases and death due to PC.^{18–21} PSA level at salvage ADT was stratified by > 12 ng/mL versus ≤ 12 ng/mL because 12.05 ng/mL represented the upper quartile and we sought to determine whether a delay in the initiation of salvage ADT using PSA level as a surrogate for timing of ADT was associated with a higher risk of PCSM among men with short (< 6 months) or long (≥ 6 months) DTs. Wilcoxon rank sum²² and Fisher exact²³ tests were used to compare the distribution of the continuous covariates and categorical covariates, respectively. The log rank test²⁴ was used to compare the median survival times following salvage ADT in years. These comparisons were made across subgroups defined by the prespecified PSA-DT and PSA level cutpoints (ie, 6 months and 3rd quartile of 12 ng/mL, respectively; Table 1).

Univariable and Multivariable Competing Risks Regressions: Univariable and multivariable Fine-Gray competing risks regression analyses²⁵ were per-

formed to ascertain whether the timing of salvage ADT was significantly associated with an increased risk of PCSM adjusting for age, comorbidity, known PC prognostic factors, and previously identified interactions. Specifically, we included age, interval to PSA failure (continuous), PSA-DT (continuous), PSA level at time of salvage ADT (continuous), highest Gleason score (≤ 6 [referent] vs 7 vs 8–10), clinical tumor category (T1 [referent] vs T2), randomly assigned treatment arm (RT [referent] vs RT + ADT), and comorbidity status (no/minimal [referent] vs moderate/severe) in the primary model. The PSA-DT and PSA level were log transformed to ensure that the results followed a normal distribution. A “comorbidity x ADT” interaction term was also included because it was identified as a significant interaction in the randomized trial.⁵ In a second model, we categorized the PSA-DT split at 6 months and PSA level at time of salvage ADT split at 12 ng/mL in order to generate a testable hypothesis regarding the risk of PCSM and early versus delayed initiation of salvage ADT among men with short versus long PSA-DTs. We also included an interaction term

Table 1. Distribution and Comparison of Clinical Characteristics

Clinical Characteristics	PSA-DT ≥6 mo (n=37)			PSA-DT <6 mo (n=17)		
	PSA at Salvage		P Value	PSA at Salvage		P Value
	>12 ng/mL (N=5)	≤12 ng/mL (N=32)		>12 ng/mL (N=9)	≤12 ng/mL (N=8)	
Median age at salvage (IQR), y	83.26 (78.76–83.98)	76.61 (71.27–80.23)	.09	71.52 (69.49–73.77)	76.37 (75.22–80.03)	.09
Median interval to PSA failure (IQR), mo	43.89 (19.25–71.13)	37.75 (24.92–53.42)	.91	14.32 (8.71–21.52)	23.16 (19.37–58.78)	.11
Median survival after salvage ADT (IQR), y	4.94 (1.92–5.87)	6.78 (5.13–12.45)	.02 ^a	3.23 (2.07–5.20)	3.10 (2.87–7.29)	.29 ^a
AJCC clinical tumor category, n (%)						
T1	2 (40)	14 (43.75)	1.00	2 (22.22)	2 (25)	1.00
T2	3 (60)	18 (56.25)		7 (77.78)	6 (75)	
Highest Gleason score, n (%)						
≤6	2 (40)	9 (28.13)	.24	0 (0)	0 (0)	.62
7	1 (20)	18 (56.25)		5 (55.56)	6 (75)	
8–10	2 (40)	5 (15.63)		4 (44.44)	2 (25)	
Randomly assigned intervention, n (%)						
RT alone	4 (80)	24 (75)	1.00	7 (77.78)	4 (50)	.33
RT + ADT	1 (20)	8 (25)		2 (22.22)	4 (50)	
ACE-27–defined comorbidity						
No/Minimal	3 (60)	24 (75)	.60	9 (100)	7 (87.5)	.47
Moderate/Severe	2 (40)	8 (25)		0 (0)	1 (12.5)	

Abbreviations: ACE-27, Adult Comorbidity Evaluation-27; ADT, androgen deprivation therapy; IQR, interquartile range; PSA, prostate-specific antigen; PSA-DT, prostate-specific antigen doubling time; RT, radiation therapy.
^aLog-rank test *P* values.

between PSA-DT and PSA level at time of salvage ADT to ascertain whether an increase in PCSM risk could exist in men with long but not short PSA-DTs when salvage ADT was initiated at a higher versus lower PSA level. Unadjusted and adjusted hazard ratios (HRs) and associated 95% CIs with associated *P* values were calculated for each covariate.

Estimates of PCSM: For the purposes of illustration, cumulative incidence plots²⁶ for PCSM were generated stratified by PSA-DT (≥6 vs <6 months) and PSA level (>12 vs ≤12 ng/mL) at the time of salvage ADT. These estimates were compared across subgroups using Gray's K-mean *P* value.²⁵ The median follow-up for the study was 5.68 years and as such, 5-year point estimates of PCSM with associated 95% CIs were calculated and reported stratified by subgroup.

All *P* values were 2-sided, with *P*<.025 considered significant after Bonferroni corrections (n=2 PSA-DT groups) were made for multiple comparisons.²⁷ All analyses were performed using SAS 9.4 (SAS Institute), except for the PCSM estimates and

Gray's K-mean *P* value, which was calculated using R version 3.2.3 (R Foundation).

Results

Distribution and Comparison of Clinical Characteristics at Randomization

There was no significant difference in the distribution of patients, cancer, and treatment characteristics among men with a PSA-DT of <6 versus ≥6 months who started salvage ADT at a PSA level that exceeded the 3rd quartile (PSA level >12 ng/mL) versus those who did not (Table 1). However, a significantly shorter median survival (4.94 vs 6.78 years; *P*=.02) was seen in men with a long PSA-DT (≥6 months) and a PSA level >12 ng/mL at the time of salvage ADT compared with ≤12 ng/mL.

Univariable and Multivariable Competing Risks Regressions

After a median follow-up of 5.68 years (interquartile range, 3.05–9.56), 49 of 54 men died (91%), with 27 deaths due to PC (accounting for 54% of

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deaths). PSA-DT, when evaluated as a continuous covariate (per month increase), was significantly associated with a decreasing risk of PCSM as the value of PSA-DT increased (Table 2, footnote). Moreover, among men with a long PSA-DT (≥ 6 months), initiating salvage ADT later (at PSA level >12 ng/mL) as opposed to earlier was associated with an increased risk of PCSM (adjusted HR, 8.84; 95% CI, 1.99–39.27; $P=.004$). However, this was not seen for men with a short PSA-DT (<6 months; adjusted HR, 1.16; 95% CI, 0.38–3.54; $P=.79$). As a result, the interaction term between PSA-DT and PSA level at salvage was significant in the multivariable analysis ($P_{\text{interaction}}=.05$).

Estimates of PCSM

As shown in Figure 2A, cumulative incidence estimates of PCSM were significantly higher (K-mean

P value=.014) among men with a PSA-DT ≥ 6 months who started salvage ADT at PSA level >12 ng/mL as opposed to PSA level ≤ 12 ng/mL. However, these estimates were not significantly different (K-mean P value=.16) among men with a PSA-DT <6 months, as shown in Figure 2B. Specifically, among men with a PSA-DT ≥ 6 months, the 5-year cumulative incidence point estimates of PCSM were 40.0% (95% CI, 2.58–79.48) versus 6.25% (95% CI, 1.07–18.37) among men who started salvage ADT at PSA level >12 ng/mL as opposed to PSA level ≤ 12 ng/mL. In comparison, among men with a PSA-DT <6 months, the 5-year cumulative incidence point estimates of PCSM were 55.56% (95% CI, 17.47–82.03) versus 50.0% (95% CI, 12.05–79.69) when salvage ADT was initiated at PSA level >12 ng/mL as opposed to PSA level ≤ 12 ng/mL.

Table 2. Univariable and Multivariable Competing Risks Analyses—Defined HRs

Clinical Characteristics	Men, n	Deaths, n	Univariable Analysis		Multivariable Analysis	
			HR (95% CI)	P Value	AHR (95% CI)	P Value
PSA-DT x PSA level at salvage ADT	54	27	0.63 (0.10–3.84)	.62	0.13 (0.02–1.03)	.05
PSA-DT ≥ 6 mo ^a						
PSA ≤ 12 ng/mL	32	10	1.00 (Ref)		1.00 (Ref)	
PSA >12 ng/mL	5	3	4.26 (1.53–11.86)	.006	8.84 (1.99–39.27)	.004
PSA-DT <6 mo ^a						
PSA ≤ 12 ng/mL	8	6	1.00 (Ref)		1.00 (Ref)	
PSA >12 ng/mL	9	8	1.85 (0.57–6.01)	.30	1.16 (0.38–3.54)	.79
Age, y	54	27	0.95 (0.89–1.004)	.07	0.98 (0.90–1.07)	.65
Interval to PSA failure, mo	54	27	0.96 (0.94–0.99)	.003	0.97 (0.94–1.003)	.08
AJCC clinical tumor category						
T1	20	8	1.00 (Ref)		1.00 (Ref)	
T2	34	19	1.71 (0.77–3.80)	.19	1.33 (0.52–3.37)	.55
Highest Gleason score						
≤ 6	11	2	1.00 (Ref)		1.00 (Ref)	
7	30	17	4.03 (1.02–15.89)	.046	3.19 (0.84–12.12)	.09
8–10	13	8	5.43 (1.19–24.64)	.03	4.39 (0.83–23.34)	.08
ADT x comorbidity	54	27	2.21 (0.15–32.26)	.56	3.88 (0.24–63.20)	.34
No/Minimal ACE-27–defined comorbidity						
RT	31	19	1.00 (Ref)		1.00 (Ref)	
RT + ADT	12	4	0.48 (0.16–1.44)	.19	0.35 (0.06–1.97)	.24
Moderate/Severe ACE-27–defined comorbidity						
RT	8	3	1.00 (Ref)		1.00 (Ref)	
RT + ADT	3	1	1.05 (0.09–12.14)	.97	1.37 (0.19–9.88)	.75

Abbreviations: ACE-27, Adult Comorbidity Evaluation-27; ADT, androgen deprivation therapy; AHR, adjusted hazard ratio; HR, hazard ratio; IQR, interquartile range; PSA, prostate-specific antigen; PSA-DT, prostate-specific antigen doubling time; RT, radiation therapy.

^aWhen PSA-DT and level (both after log transformation) at time of salvage ADT were treated as continuous covariates and without an interaction term, the AHRs are 0.33 (95% CI, 0.13–0.82; $P=.02$) and 1.27 (95% CI, 0.69–2.32; $P=.44$), respectively.

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Figure 2. PSCM plots for PSA-DT of (A) ≥ 6 months and (B) < 6 months, stratified by PSA at time of initiation of salvage ADT (PSA > 12 ng/mL vs PSA ≤ 12 ng/mL). Abbreviations: ADT, androgen deprivation therapy; PSCM, prostate cancer-specific mortality; PSA, prostate-specific antigen; PSA-DT, prostate-specific antigen doubling time.

Discussion

Among men with long PSA-DTs (≥ 6 months), the risk of dying from PC was found to be significantly greater with initiation of salvage ADT at a PSA level that exceeded the 3rd quartile (PSA level > 12 ng/mL) compared with salvage ADT initiation at a lower PSA level (≤ 12 ng/mL). In contrast, we found that PSA level at the time of salvage ADT initiation did not significantly impact the risk of PSCM among men with short PSA-DTs (< 6 months).

The clinical significance of these observations is that they provide evidence to argue against the unproven assumption that patients with a short PSA-DT are those most likely to benefit from early initiation of salvage ADT. As such, our results raise a question

regarding the current NCCN Guideline recommendations encouraging earlier salvage ADT initiation specifically in men with short PSA-DTs.^{2,15,28–30} Instead, consideration of earlier initiation of salvage ADT in men with a long PSA-DT may be appropriate for some. Moreover, for a subgroup of these men with additional favorable prognostic factors (long interval to PSA failure and favorable risk disease), a reduction in the risk of PSCM from salvage local therapy alone may be possible.³¹ Conversely, men with short PSA-DTs may be optimal candidates for enrollment in randomized controlled trials evaluating the impact on time to metastasis and survival from adding drugs such as enzalutamide, docetaxel, and/or abiraterone, which have been shown to improve survival in men with recurrent, metastatic, and castration-resistant PC previously treated with a standard LHRH agonist.^{32–35}

Several points require further discussion. First, our results show an association and not causality between a lower risk of PSCM and initiation of salvage ADT at lower PSA levels in men with long PSA-DTs. To date, only a single randomized trial shows a survival benefit with early versus delayed salvage ADT (HR, 0.55; 95% CI, 0.30–1.00; $P = .05$) in a group of diverse patients who experienced PSA relapse after surgery or RT as initial definitive therapy, or who were medically unfit for definitive therapy.¹⁵ Although that study was stratified by a PSA-DT of 10 months,¹⁵ there was no report of these results stratified by PSA-DT in the post-RT cohort. Remaining evidence is level 2, including data from an observational follow-up study and a systematic review suggesting that the benefit of early salvage ADT is limited to men with short PSA-DTs,^{12,13} whereas data from the CaPSURE study suggested similar outcomes between early and delayed salvage ADT approaches.¹⁴ Therefore, proof that the association we observed in the significantly shorter median survival in men with a PSA-DT of ≥ 6 months who started salvage ADT later versus earlier is causal requires prospective validation in a larger study than ours, wherein only 17 and 37 men were in the short versus long PSA-DT subgroups, respectively.

Second, although men with short PSA-DTs did not appear to have an increased risk of PSCM despite whether salvage ADT was started at high versus low PSA levels, this may be a result of the fact that all PSA levels at which salvage ADT was initiated

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were high. This stems from a fact that a PSA level of 10 ng/mL was used in our prospective study to define when salvage ADT should be initiated, which was common practice in the late 1990s into early 2000s when we conducted this study. It is possible that salvage ADT initiation at lower PSA levels, as commonly practiced today, could lead to a reduced risk of PCSM even in men with short PSA-DTs. However, given that short PSA-DTs have been shown to place men at a higher risk for, and in some studies have been used as a surrogate end point for, PCSM and all-cause mortality,^{19,20,36} it is likely that such men may already have metastatic castration-resistant PC for whom conventional salvage ADT with an LHRH agonist may not be effective. This supports our pro-

posal to enroll such men onto randomized trials in which drugs capable of overcoming castration resistance,^{34,35,37} such as abiraterone, enzalutamide, and docetaxel, are added to the LHRH agonist and the impact on time to metastasis and death is evaluated.

Conclusions

The results of this small cohort of patients sets the stage for further investigation in larger studies to determine whether early initiation of salvage ADT at lower absolute PSA levels for biochemical recurrence in the setting of long PSA-DT (≥ 6 months) reduces the risk of PCSM.

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