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PSA Doubling Time Predicts for the Development of Distant Metastases for Patients Who Fail 3DCRT Or IMRT Using the Phoenix Definition

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Abstract

Purpose—PSA doubling time (PSADT) is commonly used as an indication for salvage androgen deprivation therapy (ADT) for PSA failure following RT. Previously, we had shown that PSADT of <12 months is an important predictor of distant metastasis following 3DCRT using the ASTRO definition of BF. We sought to determine if this approach is still valid using the Phoenix definition.

Methods—Eligible patients included 432 men with T1-3N0M0 prostate cancer who demonstrated PSA failure after completing definitive 3DCRT or IMRT from 1989–2005. Endpoints included freedom from distant metastasis (FDM), cause-specific survival (CSS) and overall survival (OS). PSADT was stratified by 0–6, 6–12, 12–18, 18–24, and >24 months. The median follow-up was 95 months (6–207 months).

Results—The 7 year FDM, CSS, and OS rates for the entire group were 73%, 77% and 52%, respectively. 7 year FDM was 50% for PSADT <6 months vs. 83% for PSADT >6 months ($p=0.0001$). 7 year CSS was 61% for PSADT <6 and 85% for PSADT >6 ($p=0.0001$). 7 year OS was 47% for PSADT <6 and 53% for PSADT >6 ($p=0.04$). The proportion of men with BF receiving salvage ADT with a PSADT <6 months was 59%, 6–12 was 45%, 12–18 was 42%, 18–24 was 36%, >24 was 28%. ADT was associated with improved 7 year CSS (68% vs. 46%, $p=0.015$). Of the 314 men with PSADT >6 months, 124 received ADT and 190 were observed. With a median follow-up of 38 months from BF, there was no demonstrable benefit to ADT in the 7 year CSS (87% vs. 79%, respectively; $p=0.758$). Independent predictors of FDM were PSADT ($p<0.0001$), GS ($p=0.011$), and the use of initial ADT ($p=0.005$).

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Conclusion—PSADT remains a significant predictor of clinical failure and CSS for men treated with 3DCRT or IMRT who fail according to the Phoenix definition. Immediate use of ADT in patients with PSADT <6 months is significantly associated with improved CSS, although the benefit is less apparent in patients with longer PSADT. These results further refine the role of PSADT in predicting which patients may benefit from salvage ADT and those who may be observed expectantly.

Keywords

Prostate Cancer; Prostate Specific Antigen; IMRT; PSA Doubling Time; Biochemical Failure; Phoenix Definition

INTRODUCTION

Biochemical failure after external beam radiation therapy can present a management challenge to the clinician. Distinguishing which men are most likely to benefit from early androgen deprivation therapy (ADT) from those who are suitable for continued observation remains a topic of active investigation (1–4). Multiple authors have identified factors associated with clinical progression and prostate cancer specific mortality such as high Gleason score (4–7), PSA nadir (8–12), interval to biochemical failure (IBF) (1, 13), and pretreatment PSA. PSA doubling time (PSADT), described as a predictor for clinical failure at Fox Chase Cancer Center in 1993 (14), has been validated several times as an important predictor of clinical failure, both in the postoperative (6) and post definitive radiation setting (4, 7, 15, 16). Since 1989, it has been our institution's practice to closely observe patients with biochemical failure and PSADT greater than 12 months, while recommending early salvage to those with PSADT less than 12 months. Our institutional experience, published in 2003 (17), validated this practice, demonstrating that men with a PSADT greater than 12 months were unlikely to develop clinical progression, and can most likely be spared immediate androgen deprivation therapy.

Since that time, the accepted definition of biochemical failure has changed, reflecting the multiple studies that have identified the Phoenix definition (PSA nadir + 2 ng/mL) as superior to the ASTRO consensus definition (midpoint between nadir and the first of three consecutive rises) for identifying those patients who will progress to clinical failure (18–24). Other significant changes in the management of prostate cancer patients included the advent of dose-escalation and intensity modulated radiation therapy (IMRT). Therefore, we sought to determine if a PSADT <12 months still predicts clinical failure and benefit from ADT using the Phoenix definition for biochemical failure. In addition, we attempted to validate our previous results in patients treated with IMRT and longer follow up.

MATERIALS AND METHODS

Between May 1989 and August 2005, 2,608 men with T1-T3N0/XM0 adenocarcinoma of the prostate underwent definitive external beam 3-dimensional conformal radiation therapy (3DCRT) or IMRT at our institution and had complete baseline analysis data available in our prospectively collected prostate cancer database. Informed consent was obtained for inclusion in the IRB approved database. Of these, 435 experienced biochemical failure according to the Phoenix definition; three men were excluded who had only one eligible PSA after RT so doubling time could not be determined, leaving 432 men who comprised our study population. The median follow-up time was 95 months (range: 6–207) from the start of radiation, and 38 months (range: 0.1–161) from time of BF. Patient characteristics can be seen in Table 1. All patients had a complete staging workup, including a transrectal ultrasound-guided biopsy of the prostate gland with a central review by in-house

pathologists. T-stage was determined solely by the clinical digital rectal exam. No patient had evidence of distant metastases prior to treatment. Serum PSA was obtained prior to treatment and serially following completion of treatment. Risk group was assigned by the Fox Chase single factor model (25). All patients were treated definitively with 3DCRT or IMRT as described in our previous publications (26, 27). ADT, in the form of an LHRH agonist, was typically prescribed for at least 2 years for patients with high risk prostate cancer (pretreatment PSA >20 ng/mL, Gleason score >7, or T3-4 disease), although actual use and duration of ADT was dependent on physician-patient preference and patient tolerance.

After completion of radiation treatment, serum PSA was initially measured at 6 weeks to 4 months and then at six-month intervals thereafter, unless there was concern for disease progression. Biochemical failure was defined by a PSA increase of 2 ng/ml from the post RT nadir (Phoenix definition (23)), or at the start of salvage hormone therapy. In the study population, 23 of the 432 patients had BF declared by the start of salvage therapy. PSA doubling time (PSADT) was calculated for each patient using the log-slope method which uses a linear model to estimate the slope of the log transformed PSA levels and time; PSADT is calculated as $\ln(2)$ divided by this slope. PSA values included in the doubling time calculation included post-RT PSA nadir and subsequent PSA values up to biochemical failure.

Outcome events were measured from the time of biochemical failure, with distant metastases documented radiographically. For comparative analysis, we stratified the cohort by PSADT into 5 groups with 6 month intervals (0–6, 6–12, 12–18, 18–24, and >24 months). We used Kaplan Meier survival analysis to estimate FDM in these groups, and compared using the logrank test (28, 29). In addition, recursive partitioning for survival data was used to identify significant cut points in PSADT to predict for FDM (30). This method creates a classification tree for PSADT based on the survival times from BCF to DM. Kaplan Meier methodology was used to estimate FDM, CSS, and OS in the PSADT and salvage hormone subgroups. The log rank test was used to compare survival distributions for the FDM, CSS, and OS outcomes. Cox proportional hazards multivariable analysis (MVA) was used to identify independent predictors of distant metastases (31). The recursive partitioning analyses were done in R, version 2.5.1 (32), and other analyses were done using SAS/STAT software for Windows, version 9.1 (SAS Institute Inc, Cary, NC). Variables examined included PSADT, use of salvage ADT, initial PSA, age at start of treatment, radiation dose (ICRU dose for 3DCRT patients, mean prostate PTV dose for IMRT patients), Gleason score, T-stage, initial ADT, and IMRT vs. 3DCRT. A repeat MVA, substituting risk category in place of initial PSA, Gleason score, and T-stage, was performed.

RESULTS

Seven year OS was 47% (95% CI = 35%–59%) for men with PSADT <6 months and 53% (95% CI = 43%–62%) for men with PSADT >6 months (log rank test $p = 0.04$). Seven year CSS was 61% (95% CI = 47%–73%) for men with PSADT <6 months versus 85% (95% CI = 75%–91%) for men with PSADT >6 months ($p = 0.0001$). Distant metastases developed in 90 men. FDM at 7 years was 50% (95% CI = 38%–62%) for men with PSADT <6 months and 83% (95% CI = 77%–88%) for men with a PSADT >6 months ($p < 0.0001$). Figure 1 shows FDM stratified by PSADT. Figures 2 and 3 show CSS and OS, respectively. One-hundred thirty men have died, 49 of which were due to prostate cancer specific causes. Thirty-seven men are alive with disease.

Recursive partitioning analysis (RPA) for survival data and the logrank test identified PSADT of less than 6 months as the significant breakpoint for FDM. The logrank test was used to compare the five groups determined a priori ($p < 0.0001$). The four cutpoints between these groups were evaluated (PSADT of less than 6, 12, 18 and 24 months), and the 6 month cut points was most significant of the cutpoints ($p < 0.0001$). Further, the RPA identified the optimal PSADT cutpoint of 5.985 months ($p < 0.001$); there were no additional cut points identified, i.e. neither the < 6 month DT or > 6 month DT groups were further subdivided.

The proportion of men receiving salvage ADT was inversely related to longer PSADT. Fifty-nine percent of men with PSADT < 6 months received ADT, versus 46% of those with PSADT 6–12, 42% with PSADT 12–18, 36% with PSADT 18–24, and 28% with PSADT > 24 months. The relatively high percentage (41%) of men with PSADT < 6 months in the observation arm is due, in part, to the occurrence of DMs before salvage could be initiated (median time between BF and DM for these patients = 1.6 months), and patient refusal secondary to quality of life concerns. Use of ADT was associated with higher CSS in men with PSADT < 6 months (log rank test $p = 0.015$, 7-yr survival was 68% (95% CI = 51%–81%) vs. 46% (95% CI = 22%–66%)) but not for those with PSADT > 6 mo (log rank test $p = 0.758$, 7 yr survival was 87% (95% CI = 76%–94%) vs. 79% (95% CI = 57%–91%). These results are presented graphically in Figures 4 and 5. In the cohort of men with PSADT between 6 and 12 months, there was no difference in FDM between those receiving salvage ADT and those under observation ($p = 0.469$).

Multivariable analysis showed PSADT (HR = 5.31 for PSADT < 6 months vs. PSADT > 6 months, $p \leq 0.0001$), salvage ADT (HR = 0.43 for ADT vs. observed, $p = 0.0003$), Gleason score (HR = 1.85 for G7-10 vs G2-6, $p = 0.011$) and initial ADT (HR = 0.44 for initial ADT vs. no ADT, $p = 0.005$) to be independent predictors of distant metastases, as seen in Table 2a. Radiation dose or treatment technique was not significantly associated with the development of distant metastatic disease. When the MVA was repeated, substituting risk group for initial PSA, Gleason score and T-stage, only PSADT (HR = 5.89 for PSADT < 6 months vs. PSADT > 6 months, $p < 0.0001$), salvage ADT (HR = 0.42 for ADT vs. observed, $p = 0.0002$), and initial ADT (HR = 0.49 for initial ADT vs. no ADT, $p = 0.014$) were independent predictors of DMs (Table 2b).

DISCUSSION

This study confirms that PSADT remains a robust predictor of clinical outcomes following biochemical failure for men treated with definitive 3DCRT or IMRT. Using RPA, we have identified 6 months as a significant cut point of PSADT for the prediction of distant metastasis. We have also demonstrated a significant survival benefit associated with the use of salvage ADT for men with PSADT < 6 months. Men with PSADT > 6 months did not show any distant-metastases-free or cause-specific survival benefit when receiving salvage ADT. In addition to PSADT, we found Gleason score and omission of initial ADT to be significant predictors for distant metastases.

In 1993, Hanks et al. identified PSADT as a predictor of clinical progression in a group of 22 patients experiencing biochemical failure after definitive radiation, leading him to recommend immediate androgen suppression for patients with PSADT < 9 months (14). A subsequent study by Lee et al. (15) found PSADT and interval to biochemical failure to be independent predictors of distant metastases in a cohort of 151 prostate cancer patients with rising PSA after definitive radiation. In 2003, Pinover et al. published the results of a study examining 248 patients who experienced biochemical failure according to the original ASTRO definition after treatment with 3DCRT to the prostate at our institution (17). The use of ADT did not have a significant association with 5-year FDM for men with PSADT

>12 months (88% vs. 92%, $p = 0.74$), but did show a significant improvement in men with PSADT <12 months (78% vs. 57%, $p = 0.003$). The authors were unable to demonstrate a significant impact of ADT use on cause-specific or overall survival. Independent predictors of distant metastases included PSADT, early salvage ADT, high PSA nadir, and Gleason score. Based on these results, Pinover et al. developed an algorithm for the use of salvage ADT in patients with rising PSA based on PSADT, PSA nadir, and Gleason score in which we recommended immediate ADT if the PSADT was <12 months (17). The current study updates and confirms our earlier results with longer follow-up and a larger database reflecting more patients treated with dose-escalation and IMRT. The use of RPA for survival data has allowed us to show that PSADT <6 months is more significant than PSADT <12 for the prediction of clinical progression.

Dose escalation has become standard of care after a series of clinical trials demonstrated superior biochemical control with acceptable toxicity for patients receiving doses above 74–76 Gy (33–39). As our treatment planning and localization technology has improved, we have been able more precisely target the prostate while avoiding the surrounding tissues, allowing for higher prescription doses (40). At our institution, radiation dose has increased over time such that patients treated more recently have received higher radiation doses than those treated earlier (41). In this study population, the median radiation dose is 76 Gy (range: 66–84 Gy), up from the median of 74 Gy (range: 61–80 Gy) at the time of Pinover's publication (17). Like Pinover, we were unable to demonstrate a significant relationship between RT dose and FDM. Similarly, there was no relationship between treatment technique, with IMRT use indicative of escalated RT doses, and FDM. While the relationship between RT dose and FDM likely exists, it was probably not seen in this study due to small patient numbers.

Other institutions have published their experiences illustrating the predictive value of PSADT on clinical outcomes. Zelefsky et al. describes the outcomes of 381 patients who developed biochemical failure following definitive conformal radiation. PSADT and T-stage were the only independent predictors of distant metastases in both patients who received neoadjuvant ADT as well as those who did not (4). Patients with PSADT >12 months had a 3-year distant failure rate of 7%. Compared to these patients, the hazard ratios for the development of distant disease or death were 7.0, 6.6, and 2.8 (95% CI not reported) respectively for those patients with PSADT of 0–3, 3–6, and 6–12 months (4). The correlation between CSS and PSADT was also demonstrated in a British Columbian analysis of 465 patients with post-EBRT biochemical failure, with almost universal salvage treatment in patients with PSADT <6 months (3). Five-year CSS was 19%, 84%, 93%, and 98% ($p < 0.0001$) respectively for patients with PSADTs 0–3, 3–6, 6–12, and >12 months (3). The excellent CSS of patients with long PSADT, most of whom avoided salvage ADT (86% at 5 years for patients with PSADT >2 years), led to a departmental policy similar to our own, of observation for asymptomatic men with low PSA and long PSADT. In an update, no prostate-cancer specific deaths or symptomatic recurrences have been observed in 113 patients selected for observation with a median follow up of 43 months (2). A patterns-of-failure analysis from a randomized dose escalation trial found PSADT to be significantly related to prostate cancer specific mortality in patients experiencing a biochemical failure, with an odds ratio of 15 for patients with PSADT <3.6 months ($p < 0.0001$); median PSADT was 3 months in patients dying from prostate cancer, versus 12 months in those patients still living. Other significant predictors of prostate cancer specific mortality for patients with a BCF included TTBF <2.6 years (HR = 9, $p < 0.0001$), Gleason score 9–10 (HR = 6, $p = 0.032$), and pretreatment PSA >10.5 ng/mL (HR = 4, $p = 0.014$). Eighty percent of the patients who died from prostate cancer were treated on the low-dose (70 Gy) arm (5).

PSADT has been confirmed as an independent predictor of clinical recurrence in the setting of initial ADT. Lee and colleagues retrospectively examined the records of 65 patients experiencing PSA failure after definitive prostate radiation with ADT. Compared to those with PSADT >8 months, patients with a PSADT ≤8 months had a significantly higher rate of locoregional/distant recurrence (69% vs. 7% at 5 years after BF, $p < 0.001$) and death (70% vs. 21% at 6 years after BF, $p < 0.001$) (42).

Since the time of our original publication in 2003, the Phoenix definition has replaced the ASTRO consensus definition as the standard for defining biochemical failure (21). The ASTRO Consensus definition was dependent on multiple PSA measurements, with the time of biochemical failure backdated to the midpoint between PSA nadir and the first of three consecutive rises in PSA (23). This backdating, as demonstrated by Vicini and Horwitz, can result in an underreporting of biochemical failure that is dependent on follow-up length (43, 44). Bellera and colleagues, using statistical inference to generate continuous PSA profiles, demonstrated the higher specificity of the Phoenix definition over the ASTRO definition, in particular for patients with follow-up greater than 3 years (19). In 2008, Abramowitz et al. demonstrated the superiority of the Phoenix definition over the ASTRO Consensus definition for predicting distant metastases, cause-specific survival, and overall survival (18). Pickles et al have demonstrated the Phoenix definition as more appropriate in the setting of androgen deprivation; the ASTRO consensus definition has a higher likelihood of picking up a false positive biochemical failure during the PSA rebound after discontinuation of ADT (45, 46). These findings were confirmed by Buyyounouski et al in 2005 (24).

The strength of this study is limited by the retrospective nature of our data. Management decisions can be affected by selection bias, leading to unaccountable imbalances between groups. CSS, instead of overall survival, was chosen for the survival endpoint to reduce the impact of this potential confounding bias. Patients agreeing to salvage ADT had more frequent visits to the center for treatment compared to those patients who were being observed, which may account for the differences in follow-up times in the salvage ADT group as compared to the observation group. Men who developed early DMs before salvage ADT could be initiated are included in the observation arm, leading to a potential bias in favor of salvage ADT. Our statistical power was limited by small sample sizes, with endpoints for metastatic disease and PCSM respectively met by only 90 and 49 men. Follow-up, with a median of 38 months from BCF, may be inadequate to fully account for the incidence of metastatic disease and cause-specific survival, especially for patients with longer PSADT. The average time from post-RT BF to clinical failure has been estimated to be approximately 40 months (16). Patients with longer intervals to BF and PSADTs will experience correspondingly longer times to clinical failure (1, 5, 42).

Determining when to initiate salvage ADT in the setting of biochemical failure can be challenging for both clinicians and patients. The potential reduction in distant metastases and cause specific mortality must be weighed against the clinically significant complications of hormone treatment including hot flashes, sexual dysfunction, depression, impotence, gynecomastia, weight gain, osteoporosis, and increased risk of cardiac death (47). Without a prospective randomized trial we must rely upon retrospective patient outcome studies, such as this one, to guide our recommendations. Our results support the use of immediate salvage ADT in patients with rising PSA after definitive RT and PSADT <6 months, as it is associated with significantly higher cause specific survival. At our institution, it remains our policy to base the initiation of salvage ADT on PSADT. We continue to recommend immediate salvage ADT for patients with PSADT <6 months. For those patients with long PSADT (>12 months), we recommend close follow-up with serial PSA levels (typically every 6 months). We have previously recommended that salvage ADT be offered to all patients with PSADT <12 (17); however, in this study the addition of ADT was not

associated with a decreased incidence of distant metastases in patients with PSADT between 6–12 months. For these patients we base the start of ADT on a variety of factors including performance status, age, anxiety and comfort level, and recommend more frequent PSA levels and follow-up visits for those who do not begin ADT.

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Figure 1.

Freedom from distant metastases (FFDM) from the time of biochemical failure (BCF) for all study patients. BCF = biochemical failure; DT = doubling time

Figure 2.
Prostate cancer specific survival (CSS) from the time of biochemical failure (BCF) for all patients. BCF = biochemical failure; DT = doubling time

Figure 3.

Overall survival (OS) from the time of biochemical failure (BCF) for all patients. BCF = biochemical failure; DT = doubling time

Figure 4.
Cause specific survival (CSS) from the time of biochemical failure (BCF) in patients with PSADT < 6 months. BCF = biochemical failure; ADT = androgen deprivation therapy

Figure 5.
Cause specific survival (CSS) from the time of biochemical failure (BCF) in patients with PSADT > 6 months. BCF = biochemical failure; ADT = androgen deprivation therapy

Table 1

Characteristics of PSA Failure Patients with PSADT <6 and ≥6 Months

Variable	PSADT < 6 months			PSADT ≥ 6 months		
	Observe n=48	ADT n=70	p	Observe n=190	ADT n=124	p
Median Age (range)	70 (51–81)	67 (43–82)	0.471	70 (45–86)	68 (54–81)	0.111
T1–T2A	16 (33%)	23 (33%)	0.305	100 (53%)	61 (49%)	0.558
T2B–T2C	25 (52%)	29 (41%)		70 (37%)	45 (36%)	
T3	7 (15%)	18 (26%)		20 (10%)	18 (15%)	
Gleason score 2–6	14 (29%)	23 (33%)	0.539	119 (63%)	80 (65%)	0.865
Gleason score 7	26 (54%)	31 (44%)		61 (32%)	39 (31%)	
Gleason score 8–10	8 (17%)	16 (23%)		10 (5%)	5 (4%)	
Median PSA (range)	11.5 (4.1–136.9)	17.1 (3.3–98.6)	0.014	11.5 (2.8–123)	12.9 (1.7–191)	0.134
Risk group: Low	3 (6%)	4 (5%)	0.058	38 (20%)	18 (15%)	0.171
Risk group: Intermediate	26 (54%)	23 (33%)		95 (50%)	57 (46%)	
Risk group: High	19 (40%)	43 (61%)		57 (30%)	49 (40%)	
Median Radiation Dose (range)	76 (69–84)	76 (69–84)	0.821	76 (66–83)	75 (67–84)	0.191
3D CRT	42 (88%)	58 (83%)	0.491	175 (92%)	116 (94%)	0.631
IMRT	6 (12%)	12 (17%)		15 (8%)	8 (6%)	
Received initial ADT	13 (27%)	38 (54%)	0.003	26 (14%)	20 (16%)	0.549
Median duration of initial ADT, months	18.9	6.7	0.266	2.9	3.0	0.523
Median PSA nadir	0.8	0.5	0.049	0.7	0.8	0.131
Median PSADT, months	3.8	3.8	0.459	14.6	13.3	0.035
Median IBF, months	24	23	0.783	52	62	<.0001
Median Follow-Up from start of RT, months	44	80	<.0001	99	113	.0064
Median Follow-up from BF, months (range)	18 (0.3–152)	55 (1.4–161)	<.0001	29 (0.1–148)	53 (0.1–158)	<.0001

Abbreviations: PSADT = PSA Doubling Time; ADT = Androgen Deprivation Therapy; IBF = Interval to Biochemical Failure

Table 2

a: Multivariable Analysis for Freedom From Distant Metastases				
Variable	Coding	Hazard Ratio (HR)	95% CI for HR	p-value
Doubling Time (mo)	< 6 months vs > 6 months	5.31	3.27, 8.63	<.0001
Salvage Hormone Use	ADT vs Observed	0.43	0.28, 0.69	0.0003
iPSA (ng/ml)	Log transformed, continuous	0.91	0.69, 1.20	0.51
Age at SOT (yrs)	continuous	0.98	0.95, 1.01	0.20
Dose (Gy)	continuous	0.95	0.90, 1.02	0.14
Gleason Score	7–10 vs 2–6	1.85	1.16, 2.97	0.0105
T-stage	T2b–T3 vs T1c–T2a	1.40	0.88, 2.22	0.15
Initial ADT	Yes vs No	0.44	0.25, 0.78	0.005
Technique	IMRT vs Conformal	1.12	0.44, 2.87	0.81

b: Multivariable Analysis for Freedom From Distant Metastases, using Risk Groups instead of Gleason, PSA, and T-stage separately				
Variable	Coding	Hazard Ratio (HR)	95% CI for HR	p-value
Doubling Time (mo)	< 6 months vs > 6 months	5.89	3.64, 9.52	<.0001
Salvage Hormone Use	ADT vs Observed	0.42	0.27, 0.66	0.0002
Risk Group	Intermediate vs Low	1.47	0.70, 3.07	0.30
	High vs Low	1.60	0.75, 3.42	0.22
Age at SOT (yrs)	continuous	0.98	0.96, 1.01	0.23
Dose (Gy)	continuous	0.98	0.92, 1.04	0.43
Initial ADT	Yes vs No	0.49	0.28, 0.87	0.014
Technique	IMRT vs Conformal	1.12	0.44, 2.81	0.81

Abbreviations: HR = Hazard Ratio; ADT = androgen deprivation therapy; iPSA = initial PSA; SOT = start of treatment

Abbreviations: HR = Hazard Ratio; ADT = androgen deprivation therapy; SOT = start of treatment