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Original Article

Early biochemical predictors of survival in intermediate and high-risk prostate cancer treated with radiation and androgen deprivation therapy

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ABSTRACT

Background and purpose: To identify early biochemical predictors of survival in intermediate- and high-risk prostate cancer patients with a pre-treatment PSA <20 ng/mL following definitive radiation therapy (RT) and androgen deprivation therapy (ADT).

Materials and methods: A single-institution review of 2566 intermediate and high-risk prostate cancer patients treated with definitive RT and neoadjuvant and concurrent ADT from 1990 to 2012 was performed. The first prostate-specific antigen (PSA) value within three months of ADT initiation (post-ADT PSA) and the first PSA within three months after RT completion (post-RT PSA) were recorded. 1275 had baseline PSA <20 ng/mL and either post-ADT or post-RT PSA available. Median follow-up was 7.6 years. The relationship between post-treatment PSA kinetics and biochemical relapse (BR), distant metastasis (DM), prostate cancer specific death (PCSD) and overall survival (OS) was modeled using Cox regression univariate and multivariate analysis (MVA).

Results: MVA demonstrated a strong association between a post-RT PSA $\geq$0.09 ng/mL and a significantly higher risk of BR (HR: 1.93; 95% CI: 1.45–2.57; $p < 0.001$), DM (HR: 2.97; 95% CI: 2.01–4.39; $p < 0.001$), PCSD (HR: 2.99; 95% CI: 1.73–5.15; $p < 0.001$) and OS (HR: 1.49; 95% CI: 1.18–1.86; $p < 0.001$). Post-RT PSA reduction of $\geq$95% relative to the baseline PSA was associated with a significantly lower risk of BR (MVA HR: 0.58; 95% CI: 0.41–0.83; $p = 0.003$) and DM (MVA HR: 0.47; 95% CI: 0.30–0.76; $p = 0.002$).

Conclusion: A PSA value $\geq$0.09 ng/mL early after RT completion is associated with significantly worse prognosis across all clinical outcomes, and an early PSA reduction of $\geq$95% is associated with reduced risk of BR and DM. These findings may identify patients who require early aggressive systemic management for high-risk disease.

The National Comprehensive Cancer Network (NCCN) has outlined pre-treatment risk stratification paradigms for localized prostate cancer that broadly predict clinical outcomes and directly inform clinical management, reflected by the low-, intermediate-, and high-risk groupings [1–3]. Long-term, randomized clinical trials have demonstrated that combination androgen deprivation therapy (ADT) and external beam radiation therapy (EBRT) improves progression-free and overall survival outcomes for intermediate- and high-risk prostate cancer patients [4–8]. Due to this evidence, ADT in conjunction with high-dose radiotherapy is recognized as a standard of care treatment for prostate cancer. However, in recent years several groups have sought to further refine risk stratification based on MRI disease characteristics, molecular imaging findings and genomic data to better predict survival outcomes and guide more precise and effective treatment strategies [9–12].

Here, we aimed to identify biochemical predictors of clinical response early following treatment completion in intermediate- and high-risk prostate cancer patients. We show that, in a cohort of over 1000 patients treated with combination ADT and radiation therapy (RT), biochemical responses within three months following ADT initiation and RT completion predict long-term disease-free and overall survival outcomes. Additionally, these data provide guidance about how to identify patients early on during the treatment process who may benefit from more aggressive systemic treatments.

Methods and materials

A retrospective review was conducted in prostate cancer patients who underwent radiotherapy treatment in conjunction with ADT between 1990 and 2012 at our institution. Patients had a histologic diagnosis of prostate adenocarcinoma based on tran-

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srectal ultrasound-guided biopsy specimens, which were reviewed by urologic pathologists at our institution, and were diagnosed and evaluated as described previously [13,14]. Information was collected regarding NCCN risk grouping [9], Gleason score, tumor stage, baseline prostate specific antigen (PSA) pre-treatment, radiation treatment type and dose, duration of ADT treatment, and the first recorded PSA within three months following ADT initiation and within three months following RT completion.

All patients were treated with a five-to-seven-field conformal radiation treatment plan with 15 MV photons and/or interstitial low- or high-dose rate brachytherapy with a palladium, iodine, or iridium radioactive source. Patients received ADT at the discretion of the treating physician. ADT was administered through at least thirty days of bicalutamide (50 mg daily) followed by a one-to-three-month injection of leuprolide or monthly injections of degarelix alone. Patients generally received a six-month total course of neoadjuvant and concurrent ADT followed by adjuvant ADT, with 747 patients receiving a three- to six-month course of neoadjuvant ADT, 289 patients receiving less than three months of neoadjuvant ADT, and 218 patients receiving more than six months of neoadjuvant ADT (Table 1). While it was common practice at our institution during this time period to administer shorter course ADT, today the practice is at least 18–24 months of ADT for high-risk prostate cancer.

Patients with NCCN low-risk disease were excluded and in addition those with baseline PSA ≥20 ng/mL were excluded to limit the potentially confounding variable of patients who present with very high baseline PSA values and possible subclinical metastatic disease, since we focus our analysis on those with localized disease. Patients without a recorded PSA value within seven days to three months following ADT initiation and within three months after completion of RT were excluded.

Biochemical failure was defined per the Phoenix definition of a PSA at least 2 ng/mL above the nadir PSA. Metastasis was diagnosed radiographically and cause of death was recorded. The 30-day linear rate of change between baseline PSA and the first PSA within three months after ADT initiation (post-ADT) PSA was calculated, as well as the 30-day linear rate of change between the baseline PSA and the first PSA after completion of RT (post-RT) PSA.

Time to event was calculated from the end of RT for post-ADT PSA analysis and from post-RT lab date for post-RT PSA analysis in Cox regression models. Five- and 10-year incidence estimates for all-cause mortality, cause-specific mortality, incidence of biochemical recurrence, and incidence of distant metastasis, as well as five- and 10-year overall survival rates were calculated. All-cause mortality was modeled using Cox regression, and the hazard ratio was reported for each covariate of interest in both the univariate and multivariate models. Other outcomes were modeled using Cox regression for competing risks and cause-specific sub-distribution hazard ratios for the event. Post-ADT and post-RT PSA were determined to be significantly associated with the outcomes in univariate Cox models and, subsequently, maximal cut-off values of post-ADT and post-RT PSA were found using the maximal chi-square method in the univariate overall survival model [15,16]. Results of six multivariate models were shown as follows: post-ADT PSA reduction, rate of change, and maximal cut-off and post-RT PSA reduction, rate of change, and maximal cut-off as the predictors of interest and each model with NCCN risk group, Gleason score, T stage, radiation treatment type and duration, ADT treatment, and baseline PSA as covariates.

Results

Baseline characteristics

Two thousand, five hundred sixty-six intermediate- and high-risk prostate cancer patients received RT between 1990 and 2012 at a single institution. Of those patients, 1275 had baseline PSA <20 ng/mL and either post-ADT PSA (n = 1058) or post-RT PSA (n = 931) information available and were included in the analysis. Median follow-up time was 7.6 years (range: 16 days to 25 years).

Over half (n = 707, 55%) of the patients had intermediate-risk disease, with Gleason ≥7 (n = 1073, 84%) and clinical T1-to-T2 disease (n = 1043, 82%; Table 1). The majority received EBRT alone (n = 1067, 84%; median dose: 81 Gy). The median baseline PSA was 8.2 ng/mL and the median post-ADT and post-RT PSA values were 1.7 and 0.1 ng/mL, respectively (Table 1).

Table 1
Baseline characteristics (n = 1275).

	N	Frequency (%) or median (range)
NCCN risk group	1275	
Intermediate risk		707 (55%)
High risk		568 (45%)
Gleason score	1274	
≤5		29 (2%)
6		172 (14%)
7		644 (51%)
8		254 (20%)
9		159 (12%)
10		16 (1%)
T stage	1269	
T1c		464 (37%)
T2a		234 (18%)
T2b		200 (16%)
T2c		145 (11%)
T3a		103 (8%)
T3b		74 (6%)
T3c		41 (3%)
T4		2 (<1%)
Treatment category	1275	
EBRT alone		1067 (84%)
Brachytherapy alone		137 (11%)
Combination therapy		71 (5%)
EBRT dose (cGy)	1138	
Median (range)		8100 (3250, 8640)
Brachytherapy dose (cGy)	208	
Median (range)		100 (16.5, 144)
Brachytherapy dose rate	208	
LDR		152 (73%)
HDR		56 (27%)
Neoadjuvant treatment duration	1254	
<3 months		289 (23%)
3–6 months		747 (60%)
>6 months		218 (17%)
Baseline PSA	1275	
Median (range), ng/mL		8.2 (0.2, 20.0)
Post-ADT PSA	1058	
Median (range), ng/mL		1.7 (0.0, 36.5)
Reduction from baseline (%)		
<50%		263 (25%)
50–90%		480 (45%)
>90%		315 (30%)
30-day rate of change from baseline (ng/mL/30 days)		
<3.5 decrease		427 (40%)
3.5–10 decrease		445 (42%)
>10 decrease		186 (18%)
Post-RT PSA (ng/mL)	931	
Median (range)		0.1 (0, 18.8)
% reduction from baseline		
<95%		133 (14%)
≥95%		798 (86%)
30-day rate of change from baseline (ng/mL/30 days)		
<1 decrease		420 (45%)
1–2 decrease		367 (40%)
>2 decrease		144 (15%)

ADT: androgen deprivation therapy; EBRT: external beam radiation therapy; HDR: high dose rate; LDR: low dose rate; NCCN: National Comprehensive Cancer Network; PSA: prostate specific antigen; RT: radiation therapy.

Eighty-two percent of patients had a ≤10 ng/mL 30-day decline in post-ADT PSA relative to baseline PSA and 85% of patients had a ≤2 ng/mL 30-day decline in post-RT PSA relative to baseline PSA (Table 1). Patients whose PSA declined more rapidly following ADT initiation had a higher baseline PSA; however, these patients did not have a significantly different NCCN risk profile or Gleason score distribution compared to patients whose PSA declined more slowly after the start of neoadjuvant ADT (Supplemental Table 1).

In univariate Cox models, post-RT PSA is significantly associated with overall survival ($p = 0.01$), cause-specific mortality, biochemical recurrence and distant metastasis (all $p < 0.001$). From univariate Cox regression using the overall survival outcome, the maximal cut-off value for determining high versus low post-RT PSA values was determined to be 0.09 ng/mL. Post-ADT PSA is not significantly associated with overall survival ($p = 0.37$) or cause-specific mortality ($p = 0.18$) but is significantly associated with biochemical recurrence ($p = 0.04$) and distant metastasis ($p = 0.003$). The maximal cut-off value for determining high versus low post-ADT PSA values was determined to be 4.55 ng/mL.

Biochemical recurrence

The incidence of biochemical recurrence at five and ten years was 16.8 (95% CI 14.7–19.0) and 25.9 (95% CI 23.2–28.6), respectively (Supplemental Table 2). High-risk disease, higher Gleason score, and higher clinical T stage were associated with a significantly greater risk of biochemical recurrence (Table 2).

Based on univariate and multivariate analyses, patients whose PSA fell 3.5–10 ng/mL over 30 days following ADT initiation had a significantly higher risk of biochemical recurrence (multivariate HR: 1.43; 95% CI: 1.02–2.00; $p = 0.04$; Table 2). However, those whose PSA fell >10 ng/mL after ADT initiation did not have statistically significant increased risk of biochemical recurrence in multivariate analysis.

Regarding post-RT PSA, patients whose PSA fell ≥95% following completion of RT relative to baseline PSA had a 42% lower risk of biochemical recurrence based on multivariate analysis (HR: 0.58; 95% CI: 0.41–0.83; $p = 0.003$; Table 2, Fig. 1a). A post-RT PSA value of ≥0.09 ng/mL was associated with a significantly greater risk of biochemical recurrence relative to patients with a post-RT PSA of <0.09 ng/mL (Fig. 1b, HR: 1.93; 95% CI: 1.45–2.57; $p < 0.001$).

Distant metastasis

The five- and ten-year incidence of distant metastasis was 7.7 (95% CI: 6.3–9.3) and 13.7 (95% CI: 11.6–15.9), respectively (Supplemental Table 2). Patients with high-risk disease, higher Gleason

Table 2
Biochemical recurrence.

	Univariate		Multivariate	
	SDHR (95% CI)	*P*	SDHR (95% CI)	*P*
NCCN High risk	1.86 (1.48, 2.34)	<0.001		
Reference: Intermediate risk				
Gleason score	1.24 (1.10, 1.40)	<0.001		
Per 1-point increase				
T stage	1.22 (1.15, 1.30)	<0.001		
Per 1-stage increase				
Treatment				
Reference: EBRT alone				
Brachytherapy alone	1.19 (0.72, 1.97)	0.50		
Combination therapy	0.78 (0.52, 1.19)	0.25		
Neoadjuvant treatment duration				
Reference: <3 months				
3–6 months	1.32 (0.98, 1.77)	0.07		
>6 months	1.22 (0.83, 1.77)	0.31		
Post-ADT PSA reduction*				
Reference: <50%				
50–90%	1.02 (0.74, 1.40)	0.90	0.99 (0.72, 1.38)	0.97
>90%	0.91 (0.63, 1.31)	0.61	0.87 (0.60, 1.26)	0.46
Post-ADT PSA 30-day rate of change*				
Reference: <3.5 decrease				
3.5–10 decrease	1.61 (1.20, 2.15)	0.001	1.43 (1.02, 2.00)	0.04
>10 decrease	1.84 (1.29, 2.62)	<0.001	1.34 (0.81, 2.22)	0.26
Post-ADT maximal cutoff*				
Reference: <4.55 ng/mL				
≥4.55 ng/mL	1.35 (1.01, 1.80)	0.05	1.27 (0.93, 1.73)	0.13
Post-RT PSA reduction†				
Reference: <95%				
≥95%	0.67 (0.48, 0.93)	0.02	0.58 (0.41, 0.83)	0.003
Post-RT PSA 30-day rate of change†				
Reference: <1 decrease				
1–2 decrease	1.39 (1.04, 1.85)	0.03	1.03 (0.66, 1.62)	0.88
>2 decrease	1.16 (0.77, 1.75)	0.46	0.51 (0.23, 1.14)	0.10
Post-RT maximal cutoff†				
Reference: <0.09 ng/mL				
≥0.09 ng/mL	1.77 (1.35, 2.31)	<0.001	1.93 (1.45, 2.57)	<0.001

End of radiotherapy is used as baseline date for all time-to-event models except those including post-RT PSA values where the post-RT PSA lab date is used.
Post-ADT and post-RT maximal cutoff values were determined using the maximal Chi-square method in the univariate overall survival model.
Except where noted, the sample size is 1275, with 295 recurrences and 255 competing death events.
ADT: androgen deprivation therapy; CI: confidence interval; EBRT: external beam radiation therapy.
NCCN: National Comprehensive Cancer Network; PSA: prostate specific antigen; RT: radiation therapy.
SDHR: subdistribution hazard ratio.
* Sample size: 1058; number of events: 245 recurrences and 207 competing death events.
† Sample size: 931; number of events: 217 recurrences and 210 competing death events.

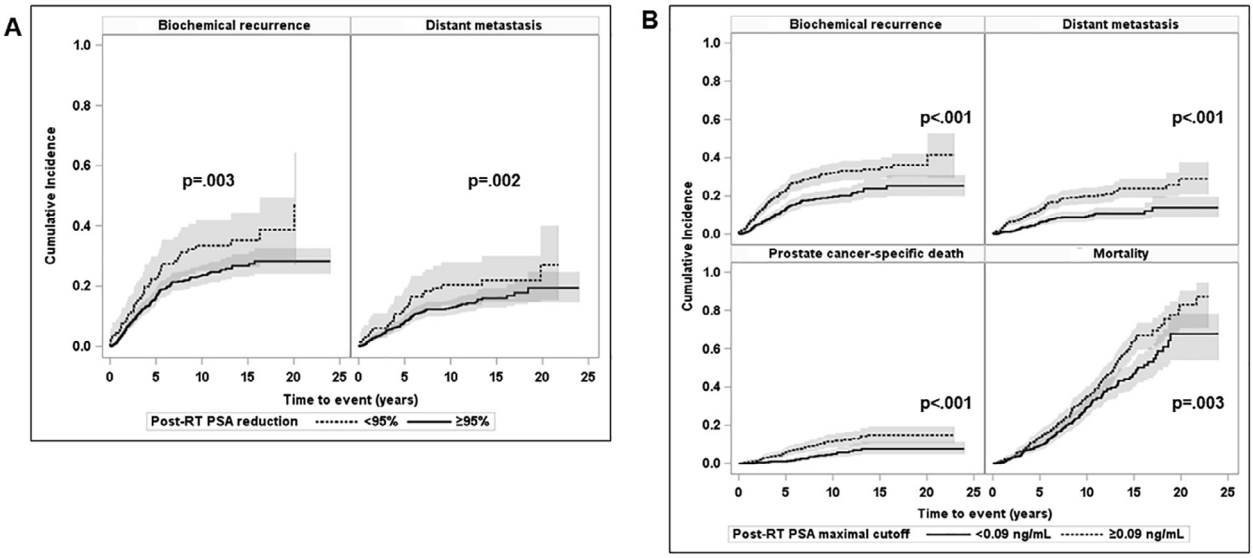

Fig. 1. Cumulative incidence of biochemical recurrence and distant metastasis in patients with a post-radiation therapy (RT) prostate specific antigen (PSA) reduction of ≥95% and <95% within three months after completing RT (A) and of biochemical recurrence, distant metastasis, prostate cancer specific death, and overall mortality in patients with a first post-radiation therapy (RT) prostate specific antigen (PSA) ≥0.09 ng/mL or <0.09 ng/mL within three months after completing RT (B).

Table 3
Distant metastasis.

	Univariate		Multivariate	
	SDHR (95% CI)	*P*	SDHR (95% CI)	*P*
NCCN High risk	3.18 (2.30, 4.39)	<0.001		
Reference: Intermediate risk				
Gleason score	1.65 (1.43, 1.92)	<0.001		
Per 1-point increase				
T stage	1.33 (1.22, 1.44)	<0.001		
Per 1-stage increase				
Treatment				
Reference: EBRT alone				
Brachytherapy alone	1.54 (0.80, 2.97)	0.19		
Combination therapy	1.10 (0.67, 1.81)	0.70		
Neoadjuvant treatment duration				
Reference: <3 months				
3–6 months	1.55 (1.00, 2.38)	0.05		
>6 months	1.86 (1.12, 3.08)	0.02		
Post-ADT PSA reduction*				
Reference: <50%				
50–90%	1.05 (0.70, 1.60)	0.80	1.02 (0.66, 1.56)	0.94
>90%	0.94 (0.59, 1.51)	0.80	0.91 (0.56, 1.48)	0.71
Post-ADT PSA 30-day rate of change*				
Reference: <3.5 decrease				
3.5–10 decrease	1.68 (1.15, 2.46)	0.007	1.35 (0.86, 2.14)	0.20
>10 decrease	1.94 (1.22, 3.07)	0.005	1.34 (0.68, 2.61)	0.40
Post-ADT maximal cutoff*				
Reference: <4.55 ng/mL				
≥4.55 ng/mL	1.41 (0.99, 2.02)	0.06	1.36 (0.93, 1.98)	0.11
Post-RT PSA reduction†				
Reference: <95%				
≥95%	0.66 (0.43, 1.01)	0.06	0.47 (0.30, 0.76)	0.002
Post-RT PSA 30-day rate of change†				
Reference: <1 decrease				
1–2 decrease	1.23 (0.84, 1.80)	0.28	0.84 (0.47, 1.51)	0.56
>2 decrease	1.06 (0.63, 1.79)	0.83	0.41 (0.15, 1.15)	0.09
Post-RT maximal cutoff†				
Reference: <0.09 ng/mL				
≥0.09 ng/mL	2.28 (1.59, 3.28)	<0.001	2.97 (2.01, 4.39)	<0.001

End of radiotherapy is used as baseline date for all time-to-event models except those including post-RT PSA value where the post-RT PSA lab date is used.
Post-ADT and post-RT maximal cutoff values were determined using the maximal Chi-square method in the univariate overall survival model.
Except where noted, the sample size is 1275, with 169 metastases and 296 competing death events.
ADT: androgen deprivation therapy; CI: confidence interval; EBRT: external beam radiation therapy.
NCCN: National Comprehensive Cancer Network; PSA: prostate specific antigen; RT: radiation therapy.
SDHR: subdistribution hazard ratio.
* Sample size: 1058; number of events: 147 metastases and 238 competing death events.
† Sample size: 931; number of events: 126 metastases and 238 competing death events.

score, and higher clinical T stage were significantly more likely to have distant metastasis ($p < 0.001$; Table 3).

A PSA reduction of ≥95% relative to baseline PSA following RT was associated with a significantly lower likelihood of distant metastasis based on multivariate analysis (HR: 0.47; 95% CI: 0.30–0.76; $p = 0.002$; Table 3, Fig. 1a); a post-RT PSA value ≥0.09 ng/mL was associated with a nearly three-fold greater risk of distant metastasis relative to a PSA <0.09 ng/mL (HR: 2.97; 95% CI: 2.01–4.39; $p < 0.001$; Fig. 1b).

Prostate cancer-specific death

The five- and 10-year incidence of prostate cancer-specific death (PCSD) was 2.6 (95% CI: 1.8–3.6) and 7.3 (95% CI: 5.7–9.1), respectively (Supplemental Table 2). High-risk disease, higher Gleason score, and higher clinical T stage were associated with a greater risk of PCSD (Table 4).

The degree of post-RT reduction in PSA value relative to baseline was not significantly associated with PCSD; however, those who had a post-RT PSA value ≥0.09 ng/mL had a nearly three-fold greater risk of PCSD relative to those with a post-RT PSA value <0.09 ng/mL based on multivariate analysis (HR: 2.99; 95% CI: 1.73–5.15; $p < 0.001$; Table 4, Fig. 1b).

Overall survival

The five- and 10-year overall survival rates were 90% (95% CI: 88.2–91.7) and 70.3% (95% CI: 67.1–73.3), respectively. Patients with high-risk disease, higher Gleason score, and higher T stage were more likely to have reduced overall survival (OS) relative to those with more favorable clinical and pathologic characteristics (Table 5).

Patients with a post-RT PSA ≥0.09 ng/mL had a 49% greater risk of all-cause mortality relative to those with a post-RT PSA <0.09 ng/mL based on multivariate analysis (HR: 1.49; 95% CI: 1.18–1.86; $p < 0.001$; Table 5, Fig. 1b).

Discussion

To our knowledge, this is the largest retrospective study of PSA kinetics immediately prior to and following RT in patients with intermediate- and high-risk prostate cancer receiving ADT. This study provides evidence for the prognostic value of PSA measurements as early as three months following RT completion. These findings also indicate a strong association between early post-RT PSA levels ≥0.09 ng/mL and a significantly higher risk of biochemical failure, distant metastasis, PCSD, and death from all causes. Moreover, we found that patients who experienced a ≥95% reduc-

Table 4
Prostate cancer-specific death.

	Univariate		Multivariate	
	SDHR (95% CI)	*P*	SDHR (95% CI)	*P*
NCCN High risk	3.43 (2.13, 5.52)	<0.001		
Reference: Intermediate risk				
Gleason score	1.48 (1.18, 1.85)	<0.001		
Per 1-point increase				
T stage	1.34 (1.19, 1.50)	<0.001		
Per 1-stage increase				
Treatment				
Reference: EBRT alone				
Brachytherapy alone	0.33 (0.05, 2.35)	0.27		
Combination therapy	0.61 (0.25, 1.51)	0.29		
Neoadjuvant treatment duration				
Reference: <3 months				
3–6 months	1.15 (0.67, 2.00)	0.61		
>6 months	1.05 (0.52, 2.14)	0.88		
Post-ADT PSA reduction*				
Reference: <50%				
50–90%	1.02 (0.59, 1.77)	0.94	0.96 (0.55, 1.70)	0.90
>90%	0.70 (0.36, 1.36)	0.29	0.66 (0.34, 1.28)	0.22
Post-ADT PSA 30-day rate of change*				
Reference: <3.5 decrease				
3.5–10 decrease	0.90 (0.52, 1.56)	0.71	0.86 (0.46, 1.59)	0.62
>10 decrease	1.74 (0.97, 3.13)	0.06	1.41 (0.60, 3.29)	0.43
Post-ADT maximal cutoff*				
Reference: <4.55 ng/mL				
≥4.55 ng/mL	1.42 (0.85, 2.35)	0.18	1.42 (0.83, 2.42)	0.21
Post-RT PSA reduction†				
Reference: <95%				
≥95%	0.66 (0.37, 1.19)	0.17	0.58 (0.31, 1.09)	0.09
Post-RT PSA 30-day rate of change†				
Reference: <1 decrease				
1–2 decrease	1.09 (0.65, 1.83)	0.75	1.32 (0.61, 2.84)	0.48
>2 decrease	1.10 (0.55, 2.21)	0.79	1.35 (0.38, 4.76)	0.64
Post-RT maximal cutoff†				
Reference: <0.09 ng/mL				
≥0.09 ng/mL	2.40 (1.45, 3.99)	<0.001	2.99 (1.73, 5.15)	<0.001

End of radiotherapy is used as baseline date for all time-to-event models except those including post-RT PSA value where the post-RT PSA lab date is used.
Post-ADT and post-RT maximal cutoff values were determined using the maximal Chi-square method in the univariate overall survival model.
Except where noted, the sample size is 1275, with 84 dead of disease (DOD) and 320 competing dead of other causes (DOC)/dead of unknown causes (DUC) events.
ADT: androgen deprivation therapy; CI: confidence interval; EBRT: external beam radiation therapy.
NCCN: National Comprehensive Cancer Network; PSA: prostate specific antigen; RT: radiation therapy.
SDHR: subdistribution hazard ratio.
* Sample size: 1058; number of events: 71 DOD and 261 competing DOC/DUC events.
† Sample size: 931; number of events: 67 DOD and 259 competing DOC/DUC events.

Table 5
Overall survival.

	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
NCCN High risk	1.34 (1.10, 1.63)	0.003		
Reference: Intermediate risk				
Gleason score	1.14 (1.04, 1.25)	0.004		
Per 1-point increase				
T stage	1.09 (1.03, 1.15)	0.003		
Per 1-stage increase				
Treatment				
Reference: EBRT alone				
Brachytherapy alone	0.39 (0.16, 0.95)	0.04		
Combination therapy	0.76 (0.52, 1.13)	0.18		
Neoadjuvant treatment duration				
Reference: <3 months				
3–6 months	0.95 (0.74, 1.21)	0.67		
>6 months	0.98 (0.71, 1.34)	0.88		
Post-ADT PSA reduction*				
Reference: <50%				
50–90%	0.84 (0.65, 1.10)	0.21	0.84 (0.65, 1.10)	0.21
>90%	1.00 (0.75, 1.33)	0.99	1.03 (0.77, 1.37)	0.86
Post-ADT PSA 30-day rate of change*				
Reference: <3.5 decrease				
3.5–10 decrease	0.98 (0.76, 1.24)	0.84	0.92 (0.70, 1.22)	0.58
>10 decrease	1.30 (0.97, 1.74)	0.07	1.12 (0.76, 1.67)	0.57
Post-ADT maximal cutoff*				
Reference: <4.55 ng/mL				
≥4.55 ng/mL	1.26 (0.99, 1.61)	0.06	1.22 (0.95, 1.58)	0.12
Post-RT PSA reduction†				
Reference: <95%				
≥95%	0.96 (0.72, 1.27)	0.76	0.87 (0.65, 1.16)	0.34
Post-RT PSA 30-day rate of change†				
Reference: <1 decrease				
1–2 decrease	1.21 (0.95, 1.54)	0.12	1.13 (0.80, 1.59)	0.49
>2 decrease	1.31 (0.97, 1.78)	0.08	1.00 (0.56, 1.78)	0.99
Post-RT maximal cutoff†				
Reference: <0.09 ng/mL				
≥0.09 ng/mL	1.39 (1.11, 1.72)	0.003	1.49 (1.18, 1.86)	<0.001

End of radiotherapy is used as baseline date for all time-to-event models except those including post-RT PSA value where the post-RT PSA lab date is used.
Post-ADT and post-RT maximal cutoff values were determined using the maximal Chi-square method in the univariate overall survival model.
Except where noted, the sample size is 1275 patients, with 404 deaths.
ADT: androgen deprivation therapy; CI: confidence interval; EBRT: external beam radiation therapy; HR: hazard ratio; NCCN: National Comprehensive Cancer Network; PSA: prostate specific antigen; RT: radiation therapy.
* Sample size: 1058; number of events: 332 deaths.
† Sample size: 931; number of events: 326 deaths.

tion in post-RT PSA relative to baseline PSA within the first three months following RT had a significantly lower risk of biochemical failure as well as distant metastasis. This study demonstrates that the first PSA level after neoadjuvant ADT and RT is an important indicator of the success of definitive treatment, and that the first post-RT PSA value is not purely a marker of RT alone, but a very early biomarker for the subsequent clinical outcome after combined ADT and RT. Overall, this study identified very early predictors of potentially more aggressive disease subtypes, and, therefore, may help patients who would benefit from earlier intervention with more potent androgen deprivation agents.

Several studies have demonstrated that, in the setting of definitive RT for intermediate- and high-risk disease, a low PSA nadir below a particular threshold during neoadjuvant ADT or a low PSA value just prior to RT initiation is strongly predictive of improved clinical outcomes [3,17–21]. However, there is little insight into early predictors of clinical outcomes after definitive RT. Studies have indicated that a short PSA doubling-time (PSADT) following RT may represent a surrogate for PCSD [22], and a PSA nadir greater than 0.5 ng/mL following RT and ADT has a higher likelihood of biochemical failure [23], particularly in high-risk populations. We found that, if patients do not respond significantly within three months after radiation treatment (as demonstrated by a decline in PSA below a particular threshold), they might be at significant risk of local and distant recurrence as well as death.

The current standard definition for biochemical recurrence after EBRT with or without ADT is a 2-ng/mL rise in PSA above nadir [24,25]. Our data demonstrate that a PSA value as low as or greater than 0.09 ng/mL early after RT completion may be an early sign of greater likelihood of local and distant relapse, and it could be an indication for use of more aggressive treatment approaches. Managing a patient until their PSA has increased 2 ng/mL above the nadir point may markedly delay intervention that could otherwise reduce their risk of death. With the approval of more aggressive androgen blockade agents for very high-risk disease, such as CYP17A1 inhibitor abiraterone acetate [26], early identification of patients who may fail therapy provides an opportunity for proactive management of high-risk phenotypes.

Unexpectedly, in the subgroup of patients whose PSA fell 3.5–10 ng/mL per 30-day period, there was an increased risk of biochemical recurrence in multivariate analysis relative to those whose PSA fell <3.5 ng/mL per 30 days (Table 2). However, these findings are not significant in multivariate analysis for any other clinical outcome or for those whose PSA fell >10 ng/mL per 30-day period. While other groups have observed poor clinical outcomes in patients whose PSA fell more rapidly after ADT initiation,

these studies either involved patients with metastatic disease [27], or involved more dated forms of external beam radiation [28]. These findings should be interpreted with caution, and further study must be performed to determine the relationship between the pace of the PSA decline following treatment and clinical outcome. One limitation of our analysis is that post-ADT and post-RT PSA cut-off values were determined a posteriori and their performance will need to be assessed in another dataset for validation and to determine the generalizability of the results.

A limitation of this study is its retrospective design. It is also possible that treatment paradigms have evolved over the course of 20 years at our institution; however, the majority of patients in this study received EBRT alone with a median dose of 81 Gy. While treatment type was included in multivariate models, the heterogeneity of radiation treatment modality may be a potential confounding variable. We also recognize that ADT administration was at the discretion of the prescribing physician; however, the majority of intermediate- and high-risk patients were treated within three to six months of neoadjuvant ADT. While the practice at the time these patients were treated was a six-month course of ADT for high-risk disease, we recognize that it is our current practice to utilize ADT for 18–24 months for such patients.

Early biochemical response to RT as a surrogate for survival outcomes should be validated prospectively, and, if corroborated, can provide a facile and effective biomarker to guide personalized treatment of high-risk prostate cancer.

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Conflicts of interest notification

There are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.04.003.

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