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Prostate-specific antigen after neoadjuvant androgen suppression in prostate cancer patients receiving short-term androgen suppression and external beam radiotherapy: pooled analysis of four NRG Oncology RTOG randomized clinical trials

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Abstract

Purpose: To validate if prostate specific antigen (PSA) level after neoadjuvant androgen suppression (neoAS) is associated with long-term outcome after neoAS and external radiation therapy (RT) with concurrent short-term AS in prostate cancer patients.

Methods: 2404 patients treated with neoAS prior to RT and concurrent AS (without post-RT AS) were pooled from trials A, B, C, and D. Multivariable models were used to test associations between the pre-specified dichotomized post-neoAS, pre-RT PSA (≤0.1 vs. >0.1 ng/mL) groupings and clinical outcomes.

Results: Median follow-up for surviving patients was 9.4 years. Median post-neoAS, pre-RT PSA was 0.3 ng/mL, with 32% of patients ≤0.1 ng/mL. Race, Gleason score, T-stage, N-stage, pre-treatment PSA, and duration of neoAS were associated with the groups of patients with PSA ≤0.1 and >0.1 ng/mL. In univariate analyses, post-neoAS, pre-RT PSA >0.1 ng/mL was associated with increased risks of biochemical failure (hazard ratio [HR] 2.04; p<0.0001), local failure (HR 2.51; p<0.0001), distant metastases (HR 1.73; p=0.0006), cause-specific mortality (HR 2.36; p<0.0001), and all-cause mortality (HR 1.24; p=0.005). In multivariable models that also included baseline and treatment variables, post-neoAS, pre-RT PSA >0.1 ng/mL was independently associated with increased risk of biochemical failure (HR 2.00; p<0.0001), local failure (HR 2.33; p<0.0001), and cause-specific mortality (HR 1.75; p=0.03).

Conclusion: Patients with PSA >0.1 ng/mL after neoAS and before RT start had less favorable clinical outcomes than patients with PSA was ≤0.1 ng/mL. The role of post-neoAS, pre-RT PSA presently, relative to PSA obtained along the continuum of medical care, is not presently defined, but could be tested in future clinical trials.

Summary:

We assessed for association between PSA after neoAS and before EBRTand outcomes in prostate cancer patients treated on four NRG Oncology RTOG trials. Patients with PSA >0.1 ng/mL had inferior clinical outcomes compared with patients in whom nPSA was ≤0.1 ng/mL.

Keywords

Prostate cancer; external beam radiotherapy; prostate specific antigen; androgen suppression

Introduction

For men with clinically localized prostate cancer with some unfavorable prognostic features, phase III randomized trials established standard therapy as 2-month duration neoadjuvant androgen suppression (neoAS) followed by radiotherapy (RT) and concurrent AS.[1,2]

For patients treated with neoAS and RT, previous studies examined the prognostic value of prostate-specific antigen (PSA) after neoAS and before initiation of RT. Retrospective studies demonstrated that lower PSA was associated with improved biochemical progression-free survival (bPFS),[3–9] cause-specific survival,[4,5,8] and overall survival (OS) or all-cause mortality (ACM).[3,6] The value of post-neoAS PSA has also been assessed in 2 post hoc analyses of phase III randomized trials.[10,11] In one trial with 378 men assigned either 3 or 8 months of neoAS before RT, PSA >0.1 (vs. ≤0.1) ng/mL was associated with worse bPFS, but not with OS.[10] In another trial with 414 men assigned 2 or 5 months of neoAS, PSA ≥0.4 (vs. <0.4) ng/mL was associated with bPFS in patients assigned 5 months of neoAS but not in those assigned 2 months of neoAS; post-neoAS PSA was not associated with distant metastasis (DM) or with OS in this study.[11]

Based on the variable findings to date, we sought to clarify whether patients with a lower PSA after neoAS and before the start of RT have a more favorable outcome. We conducted a post hoc analysis including patients enrolled on 4 trials involving neoAS and RT with concurrent, short-term AS.[1,2,12,13] On the basis of results from previous observational studies and post hoc analyses of randomized controlled trials, we hypothesized that post-neoAS, pre-RT PSA would be independently associated with biochemical failure (BF), clinical failure, and survival outcomes.

Materials and methods

Patients and treatment

The study cohort consisted of evaluable patients enrolled on trials A, B, C, and D who were randomized to treatment arms including neoAS followed by RT with concurrent AS, but no adjuvant post-RT AS.[1,2,12,13] Eligibility criteria and treatment details for these trials have been previously reported.[1,2,12,13] Briefly, neoAS and concurrent AS was to consist of both an oral anti-androgen (flutamide or bicalutamide) and a luteinizing hormone-releasing hormone (LHRH) analogue (goserelin or leuprolide) for all patients. NeoAS was initiated 2 months prior to RT for all patients, except for arm 2 of trial D (neoAS initiated 28 weeks before RT).[2] For all 4 studies, pre-RT PSA was recorded if obtained; however, it was protocol-mandated for trials B and D only. If several PSA determinations were obtained between the start of neoAS and RT, only the single PSA value immediately before RT was used.

The protocol-specified total RT dose to the prostate ± seminal vesicles was 65–70 Gy (A), 66.6 Gy (B) and 70.2 Gy (C and D). Patients enrolled in trial A were to receive elective pelvic nodal RT (44–46 Gy), whereas its use (50.4 Gy) was randomly assigned to one-half of trial C participants, and was selectively used in trials B and D based on the estimated risk of nodal involvement (46.8 Gy).

Statistical methods

Post-neoAS, pre-RT PSA was analyzed as a dichotomized variable using a pre-specified cut point of 0.1 ng/mL, based on results from a previous post hoc analysis of a randomized trial.[3] Additional exploratory analyses were performed using cut points of the group median

value (≤0.3 vs. >0.3 ng/mL), a cut point also used by Cury *et al.*,[14] and ≤1 vs. >1 ng/mL as also suggested by Cury et al.[14] Correlations between post-neoAS, pre-RT PSA (≤0.1 vs. >0.1 ng/mL) and baseline patient characteristics and treatment parameters were analyzed using Pearson's Chi-square test for categorical variables.

All outcomes were calculated from the initiation of RT. The cumulative incidence of BF (post-RT nadir PSA + 2 ng/mL),[15] local failure (LF) determined by clinical examination, DM, and cause-specific mortality (CSM) were estimated for patients with post-neoAS, pre-RT PSA level ≤0.1 ng/mL and >0.1 ng/mL, respectively. For univariate analyses, the method of Gray[16] was used to evaluate the effect of post-neoAS, pre-RT PSA level on each endpoint, with death without the event treated as the competing risk. For multivariable analyses, the Fine-Gray method[17] was used to evaluate the adjusted effect of post-neoAS, pre-RT PSA, with baseline characteristics and treatment parameters included as covariates. For OS, the Kaplan-Meier method[18] estimated survival for patients with post-neoAS, pre-RT PSA level ≤0.1 ng/mL and >0.1 ng/mL. Median survival times were estimated with 95% confidence interval (CI). For univariate analyses, the hazard ratio (HR) of the dichotomized post-neoAS, pre-RT PSA level was calculated using Cox proportional hazard[19] and was tested using the log-rank test.[20] For multivariable analysis, baseline characteristics and treatment parameters were included in the Cox model to evaluate the adjusted effect of post-neoAS, pre-RT PSA on OS. A backward variable selection procedure was used with only potentially significant variables ($p<0.10$) retained in the model. All statistical tests were two-sided with p-value <0.05 considered statistically significant. SAS v9.4 (©SAS Institute, Cary, NC) was used for all statistical analyses.

Further analyses were performed in patient subgroups according to National Comprehensive Cancer Network (NCCN) risk-group classification. Low-risk is T1-T2a, Gleason score ≤6, and PSA <10 ng/mL; intermediate-risk is T2b-T2c, Gleason score 7, or PSA 10–20 ng/mL; high risk is T3a, Gleason 8–10, or PSA >20 ng/mL. For this analysis, patients with NCCN "very high-risk" (specifically, T3b-T4) or regional node-positive (N1) were included as high-risk.

Results

A total of 3962 patients were assigned to treatment and potentially eligible for inclusion in the study. A total of 1558 patients (39%) were excluded from the analysis due to no pre-RT PSA recorded (n=1432), no neoAS reporting (n=57), or no RT reporting (n=69). The exclusion rates by study were: A (69%), B (37%), C (63%), and D (17%). A total of 2404 patients were included in the final study cohort. Patient characteristics for the included vs. excluded patients are detailed in supplementary figure 1.

Patient and treatment characteristics are provided in Table 1. The median follow-up duration for surviving patients was 9.4 years (interquartile range [IQR] 8.5–10.7). The median interval from initiation of neoAS to PSA measurement was 56 days (IQR 53–154). The median interval from PSA measurement to initiation of RT was 6 days (IQR 1–13). The median post-neoAS, pre-RT PSA value was 0.3 ng/mL (IQR 0.1–0.7; range 0–413), and the mean was 1.15 ng/mL (standard deviation 9.62, skewness 35.17). Seven hundred and sixty-

five patients (32%) had post-neoAS, pre-RT PSA ≤0.1 ng/mL and 1639 patients (68%) had PSA >0.1 ng/mL.

Several patient and treatment characteristics were significantly associated with dichotomized post-neoAS, pre-RT PSA (Table 1), including race, T stage, N stage, Gleason score, pre-neoAS baseline PSA, NCCN risk group, neoAS duration, and study. Variables associated with greater likelihood of post-neoAS, pre-RT PSA >0.1 ng/mL were non-white race, higher T and N stages, higher Gleason score, higher pre-neoAS baseline PSA, NCCN high risk group, shorter neoAS duration, and treatment on studies A, B, or C.

At five years follow-up, the cumulative incidence (95% CI) of BF for the group with post-neoAS, pre-RT PSA ≤0.1 ng/mL was 12 (10–14)%, and it was 27 (25–29)% for the group with PSA >0.1 ng/mL; the cumulative incidence of LF was 2 (1.3–3.3)% vs. 7 (5.9–8.4)%, DM 4 (2.4–5.1)% vs. 6 (4.6–6.8)%, CSM 1 (0.5–2.0)% vs. 2 (1.8–3.3)%, and OS 88 (85–90)% vs. 85 (83–86)%, respectively. At ten years, the cumulative incidence of BF was 21 (18–24)% vs. 37 (34–39)%, LF 4 (2.9–6.1)% vs. 11 (9–12)%, DM 6 (4.1–8.1)% vs. 10 (8.2–11.2)%, CSM 4 (2.6–6.1)% vs. 8 (6.7–9.8)%, and OS 66 (62–70)% vs. 59 (57–62)%, respectively.

On univariate analyses, post-neoAS, pre-RT PSA >0.1 ng/mL (vs. ≤0.1) was associated with an increased incidence of BF, LF, DM, CSM, and ACM (Table 2 and Figure 1). Similar results were found when PSA was analyzed as a dichotomized variable using a cut point of 0.3 ng/mL or of 1 ng/mL, although associations between PSA and endpoints were strongest using a cut point of 0.1 ng/mL (Table 2).

On multivariable analyses, PSA >0.1 ng/mL was associated with BF, LF, and CSM, but not DM or ACM (Tables 2 and 3). Covariates significantly associated with DM were younger age, T3/T4, pre-neoAS PSA, Gleason 7 and 8–10, and treatment on study D. Covariates significantly associated with OS were older age, T¾, and Gleason 8–10. Similar results were found when using a cut point of 0.3 ng/mL or 1 ng/mL.

Subset analyses according to NCCN risk groupings were performed also, focusing on intermediate- (Supplemental Table 1) and high- (Supplemental Table 2) risk groups, because neoAS is a component of standard treatment. In the intermediate risk group, a post-neoAS, pre-RT PSA >0.1 ng/mL was associated with a higher incidence of BF and LF, but not DM, CSM, or ACM. In the high risk group, a post-neoAS, pre-RT PSA >0.1 ng/mL was associated with a higher incidence of BF, LF, and DM, but not CSM or ACM.

Discussion

In this large and diverse cohort of patients treated with neoAS followed by definitive external beam RT with concurrent, short-term AS for localized prostate cancer, we sought to determine whether the PSA level after neoAS, and immediately before the start of RT, is a prognostic biomarker. That is, does an unfavorable PSA response to neoAS portend worse long-term disease outcome? We found that several different PSA cutoff values were prognostically associated with BF, LF, and CSM. Although the risk of DM and of ACM was higher (HR 1.24 and 1.15, respectively) with higher post-neoAS, pre-RT PSA levels, we did

not observe a statistically significant association with these clinical endpoints. The seeming discrepancy between CSM and ACM associations may be due to the effect of a proportionally high death rate from non-prostate cancer attribution (82% of all deaths) in our study population. We can only speculate about the lack of statistical association between post-neoAS, pre-RT PSA and DM, but suspect that the relatively small number of such events coupled with variable and discretionary use of (relatively insensitive) diagnostic imaging (mainly bone scan “as indicated” to pursue patient symptoms) contribute to this observation. Additionally, use of AS at the time of BF and before onset of DM may decrease or delay DM in a way that might impact the relationship between post-neoAS, pre-RT PSA and DM.

The prognostic association of post-neoAS, pre-RT PSA with disease-specific outcomes was previously studied in different settings – after neoAS,[3–6,8–11] near the end of RT,[11,14,21] or during post-RT event monitoring.[4,14,21–24] The prognostic value of PSA after neoAS and before RT has now been evaluated in 2 previous post hoc analyses of phase III randomized trials,[10,11] and in this pooled analysis of 2404 participants in 4 phase III randomized trials. In those prior 2 analyses,[10,11] post-neoAS, pre-RT PSA was associated with BF but not with LF, DM, CSM, or OS. Our research thus presents new findings using data derived from the prospective clinical trial setting, rather than retrospective observational series.[5,6,8,9]

Alexander *et al.*[10] used a post-neoAS, pre-RT PSA complete response cut point (0.1 ng/mL) as in our study, but their sample size (353 patients) was modest in comparison; this and the shorter follow-up duration of their patients may have limited the opportunity to identify an association between PSA and other clinical outcomes. Lamb *et al.*[11] may have encountered similar limitations (414 patients), but their analysis also included post-RT nadir PSA in the multivariate regression, and ours did not. Our study was not affected by these potential limitations, as it included a large sample size (2404 patients) with a prolonged follow-up duration (median, 9.4 years). In our view, these features along with the protocol-specified treatment parameters and rigorous data quality control measures used in randomized controlled trials provides sound and conclusive evidence regarding the prognostic value of post-neoAS, pre-RT PSA.

Our findings closely resemble those of Foo *et al.*[4] and of Zelefsky *et al.*[8] who also observed an association of post-neoAS, pre-RT PSA with BF and CSM (and DM also in the study of Zelefsky *et al.*). Although the duration of neoAS was associated with BF in our study, we found no such association with other endpoints. In a similar vein, Alexander *et al.*[10] and Foo *et al.*[4] did not identify an association of neoAS duration with any clinical endpoint. Nonetheless, there may be a temptation to extend the duration of neoAS in some patients based on a potential reduction in BF. However, such a consideration is not relevant for low-risk disease, because neoAS is not generally warranted for these patients.[1] It also has limited relevance for the patient with high-risk or locally-advanced (T3/T4 and/or N1/N2) disease, because long-term AS is standard of care in this setting[12,25,26] and patients so treated were not included in our study. The main focus would thus be on patients with intermediate-risk disease, where short-term AS improves outcomes compared with RT alone.[1,27,28] However, prior randomized controlled trials showed no benefit to extended (7–8 months) vs. standard

(2–4 months) duration neoAS.[2,29,30] Extending the duration of neoAS based on PSA monitoring does not therefore appear warranted at present.

If PSA after neoAS should not presently inform decision-making about the duration of AS, then what purpose might its measurement serve? Although our research cannot address underlying mechanisms, PSA response to neoAS may be an early signal of its effect on androgen receptor-regulated gene expression that drives cell proliferation, serving to identify patients in whom its effects may be greatest. Studies of primary AS in the context of localized[31] and metastatic disease[31,32] support this view. Kitagawa *et al.*[31] reported that nadir PSA <0.2 ng/mL and time from AS start to nadir PSA ≥9 months were associated with improved progression-free and overall survival, when adjusted for age, Gleason score, baseline PSA level, and T, N and M Stages. Hussain *et al.*[32] noted also that the risk of death was less with lower nadir PSA values after induction AS in Intergroup randomized clinical trial INT-0162.

Other studies investigated the prognostic value of PSA level at the end of short-term AS and RT,[4,11,14,21] which was at (or close to) the end of RT or at the end of AS if it was given briefly thereafter. The pooled secondary analysis of the Dana Farber Cancer Institute trial 95096 and the Trans-Tasman Radiation Oncology Group trial 96.01 by D'Amico *et al.*[21] is particularly noteworthy in this regard. D'Amico *et al.* selected a PSA cut point of 0.5 ng/mL from the antecedent literature, and noted that PSA >0.5 (vs. ≤0.5) ng/mL taken at the completion of 6-month-duration AS (which was about 2 months after RT in the Trans-Tasman trial and about 4 months after RT in the Dana Farber trial) was associated with, and a surrogate for, an increased risk of CSM.[21] Lamb *et al.*[11] and Cury *et al.*[14] reached a similar conclusion using slightly different PSA cut points (≤0.4 ng/mL and ≤0.3 ng/mL. respectively). Their studies also found an association between PSA at this time point and BF, LF, and DM.

Research to date suggests that PSA measurement at or shortly after RT completion may be a more appropriate early assessment of treatment response to neoAS and RT with concurrent AS.[11,14] However, further research is needed to determine the ideal PSA cut point in this setting, and whether the cut point should be adaptable in the presence of other variables (such as baseline PSA and Gleason grading) that also contribute prognostic information. It is also important to recognize that some patients have a delayed PSA response that occurs after completing AS, and this may yet be associated with more favorable outcomes.[14] Some investigators suggested that the duration of AS might be tailored to early PSA response,[21] but we presently urge caution as advocated by others.[4,8,11,14] Rather, the primary analytical results of practice-defining randomized controlled trials[2,12,25,28–30] provide prudent guidance for the time being. A research strategy with random allocation to short-term vs. longer-term AS (or an alternate approach using androgen biosynthesis inhibitors or cytotoxic chemotherapy) based on PSA response may be considered to define personalized medical care more precisely.

There are limitations to the present study, as it is an unplanned secondary analysis of randomized trials conducted for other purposes. Although the prolonged follow-up duration allowed us to assess for possible association between post-neoAS, pre-RT PSA and clinical

endpoints that occur in the long term (specifically DM, CSM, and ACM), the overall medical landscape has changed greatly since our study patients received their care. The International Society of Urological Pathology grading and grouping system is the current standard for the Gleason grade framework,[33] but our database did not allow use of such. Radiological imaging has changed greatly both for diagnostic staging and RT image-guidance, and higher RT dose than prescribed in our study population is presently endorsed as standard of care. We cannot know what significance these practices would have on the outcomes presented herein. However, external beam RT dose escalation has not influenced metastasis-free or cause-specific survival when used with short-term androgen suppression, [34] as in our study cohort.

Conclusion

PSA after neoAS is an early-response biomarker associated with biochemical and clinical endpoints, notably CSM. Although it does not seem prudent to extend the duration of neoAS as a present standard of care based on prior randomized controlled trials.[2,29,30] However, integrating PSA as an early-response biomarker into trials testing adaptive AS strategies may complement use of tissue-based genomic classifiers or molecular subtyping in furthering personalized medical care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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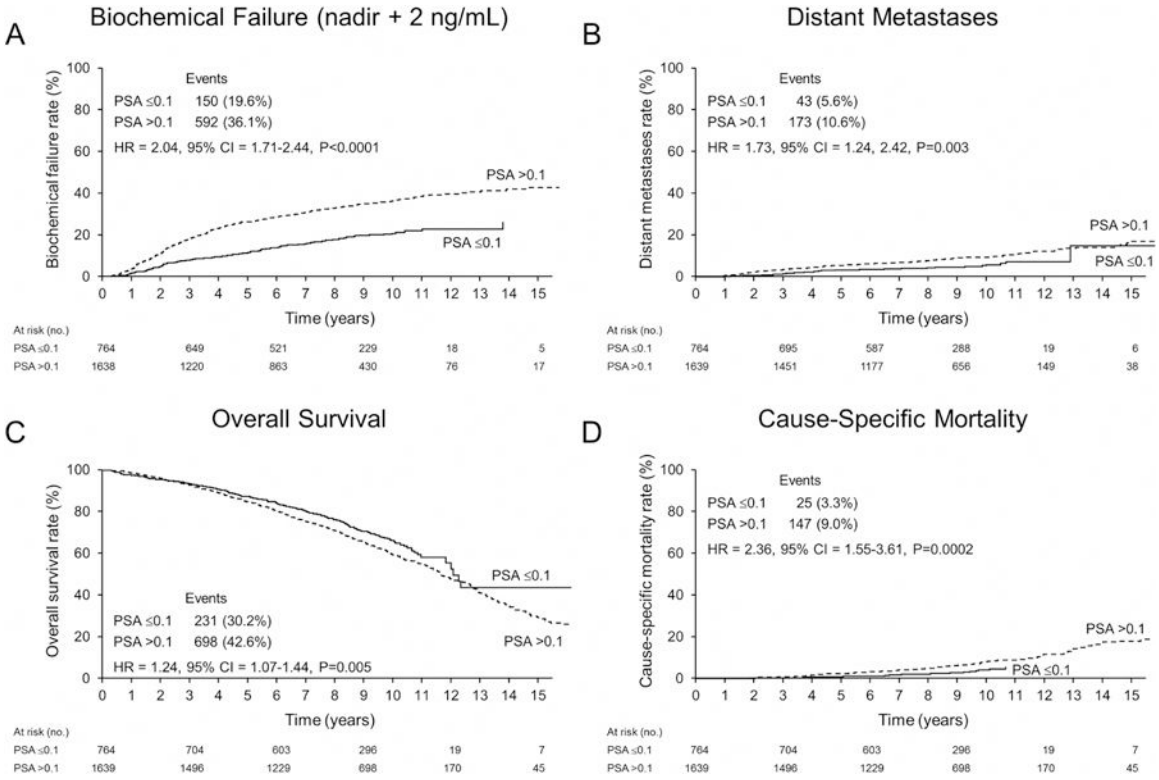

Figure 1.

Estimates of (a) biochemical failure (nadir + 2 ng/mL), (b) distant metastases, (c) overall survival, (d) and cause-specific mortality for patients with pre-radiotherapy prostate-specific antigen >0.1 vs. ≤0.1 ng/mL.

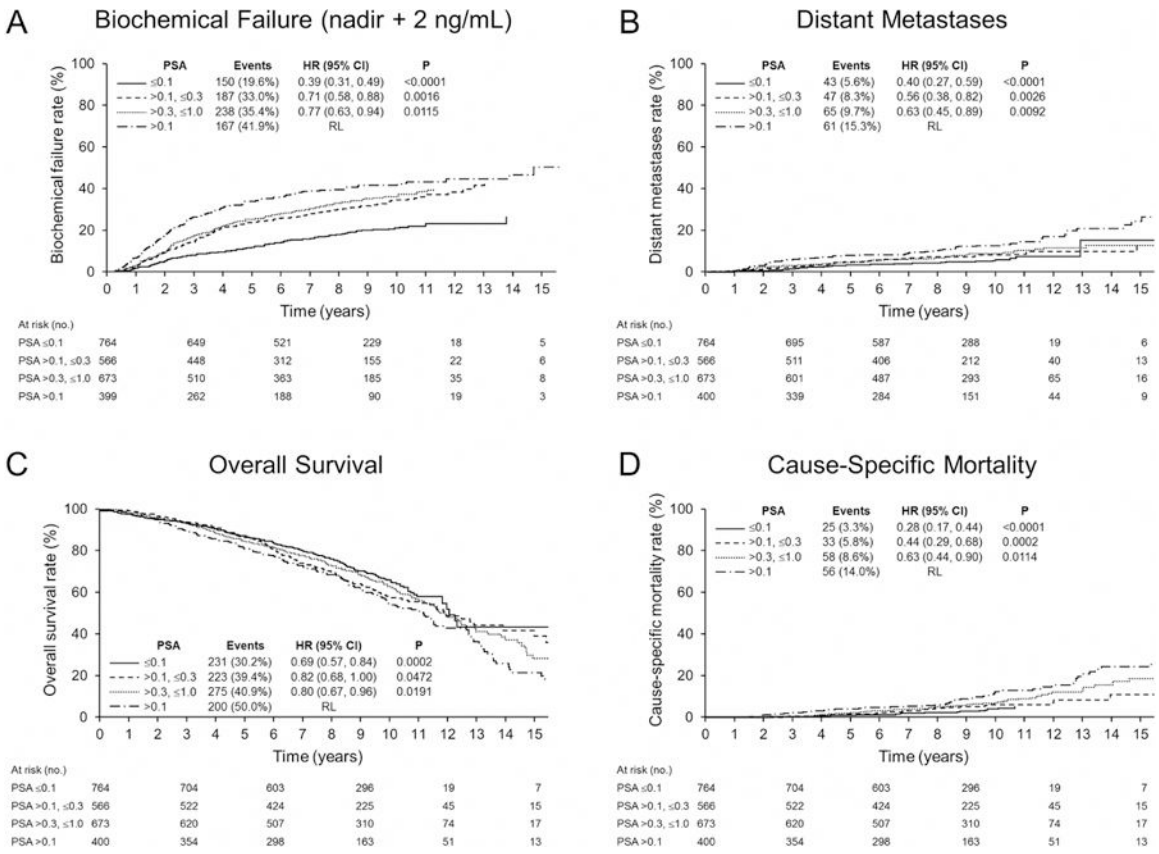

Figure 2.

Estimates of (a) biochemical failure (nadir + 2 ng/mL), (b) distant metastases, (c) overall survival, (d) and cause-specific mortality for patients with pre-radiotherapy prostate-specific antigen ≤0.1 vs. >0.1 and ≤0.3 vs. >0.3 and ≤1 vs. >1 ng/mL.

Table 1.

Patient and Treatment Characteristics

	All Patients (n=2404)	Post-neo AS PSA ≤0.1 (n=765)		Post-neo AS PSA >0.1 (n=1639)		
Characteristic	**Number**	**Number**	**%**	**Number**	**%**	**P-value**
Age, years	-	-	-	-	-	0.5
Median	70	71		70		
IQR	65–74	65–74		65–74		
Race	-	-	-	-	-	0.01
White	1903	624	33	1279	67	
Black	404	106	26	298	74	
Hispanic or Latino	56	16	29	40	71	
Other	41	19	46	22	54	
T-stage	-	-	-	-	-	<0.0001
T1	996	360	36	636	64	
T2	1130	356	32	774	68	
T3/T4	278	49	18	229	82	
N-stage	-	-	-	-	-	<0.0001
N0	1344	612	45	732	54	
N1/N2	22	1	5	21	95	
NX	1035	152	15	883	85	
Gleason score	-	-	-	-	-	<0.0001
2–6	866	219	25	647	75	
7	1173	451	38	722	62	
8–10	330	94	28	236	72	
Baseline PSA, ng/mL	-	-	-	-	-	0.005
Median	10.7	9.2		11.3		
IQR	6.8–16.3	5.9–13.8		7.3–17.5		
NCCN risk group	-	-	-	-	-	<0.0001
Low	226	47	21	179	79	
Intermediate	1385	528	38	857	62	
High	785	184	23	601	77	
Duration neoAS, days	-	-	-	-	-	<0.0001
≤100	1669	206	12	1463	88	
>100	735	559	76	176	24	
Study	-	-	-	-	-	<0.0001
A	234	20	9	214	91	
B	621	102	16	519	84	
C	232	20	9	212	91	

	All Patients (n=2404)	Post-neo AS PSA ≤0.1 (n=765)		Post-neo AS PSA >0.1 (n=1639)		
Characteristic	**Number**	**Number**	**%**	**Number**	**%**	**P-value**
D	1317	623	47	694	53	

IQR: interquartile range; NCCN: National Comprehensive Cancer Network; neoAS: neoadjuvant androgen suppression.

Table 2.

Associations Between PSA After Neoadjuvant Androgen Suppression and Clinical Endpoints

	Post-neoAS PSA (ng/mL)		Reference		Univariable analysis		Multivariable analysis†	
Endpoint	**Value**	**Events/Pts**	**Value**	**Events/Pts**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Biochemica l failure*	>0.1	592/1638	≤0.1	150/764	2.04 (1.71–2.44)	<0.0001	2.00 (1.61–2.48)	<0.0001
	>0.3	405/1072	≤0.3	337/1330	1.63 (1.41–1.88)	<0.0001	1.29 (1.10–1.51)	0.002
	>1.0	167/399	≤1.0	575/2003	1.66 (1.39–1.98)	<0.0001	1.25 (1.03–1.52)	0.03
Local failure**	>0.1	165/1612	≤0.1	31/762	2.51 (1.71–3.69)	<0.0001	2.33 (1.59–3.43)	<0.0001
	>0.3	112/1051	≤0.3	84/1323	1.66 (1.25–2.21)	0.0002	1.32 (0.98–1.78)	0.07
	>1.0	43/390	≤1.0	153/1984	1.41 (1.01–1.98)	0.02	1.09 (0.77–1.54)	0.63
Distant metastasis	>0.1	173/1639	≤0.1	43/764	1.73 (1.24–2.42)	0.0006	1.24 (0.85–1.79)	0.3
	>0.3	126/1073	≤0.3	90/1330	1.63 (1.24–2.13)	0.0002	1.09 (0.80–1.49)	0.6
	>1.0	6¼00	≤1.0	155/2003	1.89 (1.41–2.54)	<0.0001	1.26 (0.89–1.78)	0.2
Cause-specific mortality	>0.1	147/1639	≤0.1	25/764	2.36 (1.55–3.61)	<0.0001	1.75 (1.06–2.89)	0.03
	>0.3	114/1073	≤0.3	58/1330	2.18(1.59–2.98)	<0.0001	1.51 (1.03–2.22)	0.03
	>1.0	56/400	≤1.0	116/2003	2.21 (1.62–3.03)	<0.0001	1.53 (1.08–2.17)	0.02
All-cause mortality	>0.1	698/1639	≤0.1	231/764	1.24 (1.07–1.44)	0.005	1.15 (0.98–1.35)	0.1
	>0.3	475/1073	≤0.3	454/1330	1.16 (1.02–1.33)	0.02	1.00 (0.87–1.15)	0.9
	>1.0	200/400	≤1.0	729/2003	1.30 (1.11–1.52)	0.001	1.18 (0.99–1.39)	0.06

† Variables included: Age, race, T-stage, N-stage, baseline PSA, Gleason score, duration neoAS, RT dose, RT target, study. A backward selection method was utilized with only significant variables (p<0.10) included in the final model.

* 1 patient excluded from biochemical failure analysis due to failure before post-neoAS PSA

** 29 patients excluded from local failure analysis due to failure before post-neoAS PSA

Table 3.

Multivariable Associations With Clinical Endpoints

		Local failure		Biochemical failure		Distant metastasis		Cause-specific mortality		All-cause mortality	
Covariate[†]	**Comparison**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Post-neoAS PSA, ng/mL	≤0.1 (RL)	-	-	-	-	-	-	-	-	-	-
	>0.1	2.33 (1.59–3.42)	<0.001	2.08 (1.65–2.62)	<0.0001	1.24 (0.85–1.79)	0.3	1.73 (1.08–2.75)	0.02	1.15 (0.98–1.35)	0.1
Age	Continuous	0.96 (0.94–0.98)	0.0002	0.98 (0.97–0.99)	0.0001	0.97 (0.95–0.99)	0.003	0.98 (0.95–1.00)	0.04	1.06 (1.05–1.07)	<0.0001
Race	White (RL)	-	-	-	-	-	-	NS	NS	NS	NS
	Black	0.65 (0.42–1.01)	0.06	0.76 (0.61–0.94)	0.01	0.68 (0.46–1.0.)	0.05	NS	NS	NS	NS
	Other	1.66 (0.94–2.91)	0.08	0.73 (0.49–1.11)	0.14	0.43 (0.15–1.17)	0.1	NS	NS	NS	NS
T-stage	T1 (RL)	-	-	-	-	-	-	-	-	-	-
	T2	3.64 (2.43–5.45)	<0.0001	1.29 (1.08–1.54)	0.006	1.32 (0.90–1.94)	0.16	1.38 (0.89–2.12)	0.15	1.04 (0.89–1.22)	0.6
	T3/T4	4.83 (3.03–7.71)	<0.0001	1.33 (1.01–1.75)	0.04	1.80 (1.11–2.91)	0.02	1.82 (1.05–3.14)	0.03	1.38(1.09–1.74)	0.008
Baseline PSA	Continuous	NS	NS	1.01 (1.01–1.02)	<0.0001	1.01 (1.01–1.02)	<0.0001	1.01 (1.00–1.01)	0.09	NS	NS
Gleason score	2–6 (RL)	NS	NS	-	-	-	-	-	-	-	-
	7	NS	NS	0.97 (0.81–1.16)	0.8	1.63 (1.14–2.34)	0.007	1.51 (1.01–2.24)	0.04	1.08 (0.93–1.26)	0.3
	8–10	NS	NS	1.27 (1.01–1.59)	0.04	2.58 (1.73–3.85)	<0.0001	2.68 (1.74–4.11)	<0.0001	1.33 (1.09–1.62)	0.005
Duration neoAS	≤100 days (RL)	NS	NS	-	-	NS	NS	NS	NS	NS	NS
	>100 days	NS	NS	1.60 (1.25–2.04)	0.0002	NS	NS	NS	NS	NS	NS
Study	A (RL)	NS	NS	-	-	-	-	-	-	-	-
	B	NS	NS	0.53 (0.39–0.72)	<0.0001	0.60 (0.35–1.02)	0.06	0.58 (0.32–1.05)	0.07	0.96 (0.74–1.24)	0.7
	C	NS	NS	0.88 (0.67–1.15)	0.3	0.97 (0.64–1.47)	0.9	1.00 (0.64–1.56)	1.0	0.93 (0.72–1.19)	0.6
	D	NS	NS	0.47 (0.35–0.64)	<0.0001	0.53 (0.32–0.86)	0.01	0.46 (0.27–0.79)	0.005	0.82 (0.64–1.05)	0.1

[†]Variables included: Age, race, T-stage, N-stage, baseline PSA, Gleason score, duration neoAS, RT dose, RT target, study. A backward selection method was utilized with only significant variables (p<0.10) included in the final model.

Patients with missing Gleason score were excluded.

HR: hazard ratio; CI: confidence interval; nPSA: nadir PSA; RL: reference level; neoAS: neoadjuvant androgen suppression; RT: radiotherapy; NS: not significant