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Clinical and Genomic Characterization of Low-Prostate-specific Antigen, High-grade Prostate Cancer

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.Org/10.1016/j.eururo.2018.01.043.

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Abstract

Background: The consequences of low prostate-specific antigen (PSA) in high-grade (Gleason 8–10) prostate cancer are unknown.

Objective: To evaluate the clinical implications and genomic features of low-PSA, high-grade disease.

Design, setting, and participants: This was a retrospective study of clinical data for 494 793 patients from the National Cancer Data Base and 136 113 patients from the Surveillance, Epidemiology, and End Results program with cTl–4N0M0 prostate cancer (median follow-up 48.9 and 25.0 mo, respectively), and genomic data for 4960 patients from the Decipher Genomic Resource Information Database. Data were collected for 2004–2017.

Outcome measurements and statistical analysis: Multivariable Fine-Gray and Cox regressions were used to analyze prostate cancer-specific mortality (PCSM) and allcause mortality, respectively.

Results and limitations: For Gleason 8–10 disease, using PSA 4.1–10.0 ng/ml (n = 38 719) as referent, the distribution of PCSM by PSA was U-shaped, with an adjusted hazard ratio (AHR) of 2.70 for PSA ≤2.5 ng/ml (n = 3862, p < 0.001) versus 1.97,1.36, and 2.56 for PSA of 2.6–4.0 (n = 4199), 10.1–20.0 (n = 17 372), and >20.0 ng/ml (n = 16 114), respectively. By contrast, the distribution of PCSM by PSA was linear for Gleason ≤7 (using PSA 4.1 −10.0 ng/ml as the referent, n = 359 898), with an AHR of 0.41 (p = 0.13) for PSA ≤2.5 ng/ml (n = 37 812) versus 1.38, 2.28, and 4.61 for PSA of 2.6–4.0 (n = 54 152), 10.1–20.0 (n = 63 319), and >20.0 ng/ml (n = 35 459), respectively ($p_{\text{iteraction}}$ < 0.001). Gleason 8–10, PSA ≤2.5 ng/ml disease had a significantly higher PCSM than standard high-risk/very high-risk disease with PSA >2.5 ng/ml (AHR 2.15, p = 0.002; 47-mo PCSM 14% vs 4.9%). Among Gleason 8–10 patients treated with radiotherapy, androgen deprivation therapy was associated with a survival benefit for PSA >2.5 ng/ml (AHR 0.87; p< 0.001) but not ≤2.5 ng/ml (AHR 1.36; p = 0.084; $p_{\text{interaction}}$ = 0.021). For Gleason 8–10 tumors, PSA ≤2.5 ng/ml was associated with higher expression of neuroendocrine/small-cell markers compared to >2.5 ng/ml (p = 0.046), with no such relationship for Gleason ≤7 disease.

Conclusions: Low-PSA, high-grade prostate cancer has very high risk for PCSM, potentially responds poorly to androgen deprivation therapy, and is associated with neuroendocrine genomic features.

Patient summary: In this study, we found that low-prostate-specific antigen, high-grade prostate cancer has a very high risk for prostate cancer death, may not respond well to androgen deprivation therapy, and is associated with neuroendocrine genomic features. These findings suggest that current nomograms and treatment paradigms may need modification.

Keywords

Androgen deprivation therapy; Genomics; Neuroendocrine; Gleason score; Prostate cancer; Prostate-specific antigen; Small-cell cancer

1. Introduction

Most prostate cancers are adenocarcinomas, and a high tumor grade (Gleason 8–10) is an established high-risk feature. Treatment options include radical prostatectomy (RP) or radiotherapy with long-course androgen deprivation therapy (ADT) [1].

Prostate cancer is typically highly androgen-dependent and exquisitely sensitive to ADT [2]. In addition, PSA production is positively regulated by androgens [3]. Although PSA is typically elevated in high-grade disease, some patients present with the discordant scenario of high-grade disease and low PSA. The clinical and biological implications of low PSA in high-grade prostate cancer are unclear [4]. Low-PSA, high-grade disease may represent a unique entity with underlying dedifferentiated biology, and as such may respond poorly to current standard treatments, particularly ADT. However, there are few clinical and biological data to support this hypothesis [5–8].

The canonical low-PSA-producing prostate cancer is neuroendocrine prostate cancer, including the small-cell variant, which represents an aggressive and hormone-resistant entity [9–12]. There is low sensitivity for the detection of neuroendocrine features on biopsy or RP specimens [9]. Emerging genomic characterization of neuroendocrine prostate cancer has identified common mutations that represent a “molecular signature” that may aid in detection and targeted therapy [12–15]. Whether low-PSA, high-grade disease shares genomic features with neuroendocrine prostate cancer has not been explored.

Understanding the biology and behavior of low-PSA, high-grade prostate cancer is highly relevant; there is an active effort to improve the understanding and outcomes of aggressive localized prostate cancers through the utilization of genomics and application of targeted agents [16–19]. Therefore, we characterized the prognostic and predictive values of low PSA in high-grade prostate cancer, as well as the genomic features of this entity among men diagnosed with prostate cancer.

2. Patients and methods

2.1. Study cohorts

2.1.1. NCDB and SEER—The National Cancer Data Base (NCDB) captures 70% of incident cancers in the USA [20] and identified 494 793 patients diagnosed with cT1–4N0M0 prostate cancer from 2004 to 2011. The Surveillance, Epidemiology and End Results (SEER) program encompasses 28% of the US population [21] and identified 136 113 men diagnosed with cT1–4N0M0 prostate cancer from 2010 to 2013. Patients with neuroendocrine or small-cell histology were excluded. PSA values in SEER from 2010 onwards have been audited for accuracy [22].

Therapy received included RP, radiotherapy (external beam radiotherapy [EBRT] or brachytherapy), and ADT (only available in the NCDB). Gleason scores reflect pathologic grade when available or biopsy otherwise. Race was classified as Black or non-Black. The CharlsonDeyo comorbidity score was reported by the NCDB and was also used.

2.1.2. GRID—The Decipher Genomic Resource Information Database (GRID), a global expression database for urologic oncology (NCT02609269) that includes basic demographic and baseline clinical information, was queried for patients with available grade group and PSA. This cohort comprises of anonymized data from clinical use of the Decipher test between February 2014 and February 2017. Genome-wide expression profiles of formalin-fixed, paraffin-embedded RP samples for 4960 patients from the Decipher GRID with histologically confirmed prostate adenocarcinoma (by central pathology) were analyzed.

2.2. Statistical analysis

2.2.1. Baseline characteristics—The Wilcoxon rank-sum and Mantel-Haenszel $\chi 2$ tests were used to compare distributions of continuous and categorical covariates, respectively, stratified by predetermined PSA levels [8].

2.2.2. Prognostic analysis: estimates of PCSM and ACM by PSA level, stratified by Gleason score—The primary independent variable of interest was PSA level at diagnosis (stratified by Gleason ≤7 vs 8–10), and endpoints were prostate cancer-specific mortality (PCSM for SEER, which provides cause of death) and all-cause mortality (ACM for NCDB, which only provides vital status).

We used multivariable Fine-Gray competing-risks and Cox regressions to define hazard ratios by PSA level stratified by Gleason score for PCSM (SEER) and ACM (NCDB), respectively. Variables included in the models were PSA level (≤2.5, 2.6–4.0,4.1–10.0 [referent], 10.1–20.0, >20.0 ng/ml), clinical tumor stage (T1 [referent], T2, T3, T4), age (continuous), race (nonBlack [referent], Black), initial treatment (none [referent], RP, radiotherapy; adjusted for ADT in the NCDB), and Charlson-Deyo comorbidity score in the NCDB (0 [referent], 1, ≥2). To ascertain the risk of PCSM and ACM in low-PSA, high-grade disease, our models included PSA level (≤2.5 vs >2.5 ng/ml) × Gleason (≤7 vs 8–10) as an interaction term.

A second set of Fine-Gray competing-risks and Cox regressions were used to define hazard ratios for PCSM and ACM by National Comprehensive Cancer Network (NCCN) risk groups [1] compared to Gleason 8–10 disease with PSA ≤2.5 ng/ml. The risk group (high/very high risk [Gleason 8–10, cT3–4, or PSA >20 ng/ml] with PSA >2.5 ng/ml [referent], Gleason 8–10 with PSA ≤2.5 ng/ml, intermediate risk [Gleason 7, cT2b-c, or PSA 10–20 ng/ml], and low/very low risk [Gleason ≤6, cTl–2a, and PSA <10 ng/ml]) was included in the models, in addition to the clinical and demographic factors listed above. Using these models, adjusted cumulative incidence plots for PCSM and Kaplan-Meier curves for ACM were generated.

2.2.3. Predictive analysis: estimates of ACM by receipt of ADT for Gleason 8–10 disease treated with EBRT, stratified by PSA level—There were 24 605 patients

with Gleason 8–10 disease who received EBRT as initial therapy (Supplementary material). Multivariable Cox regression was used to define hazard ratios for ACM by receipt of ADT, stratified by PSA level (≤2.5 vs >2.5 ng/ml). Parameters included in the model were receipt of ADT (no [referent] vs yes), clinical tumor stage, age, race, and Charlson-Deyo score (referents listed above). To ascertain the response to ADT in low-PSA, high-grade disease, our model included PSA (≤2.5 vs >2.5 ng/ml) × ADT (yes vs no) as an interaction term.

We used the adjusted Kaplan-Meier method to generate ACM curves stratified by PSA level and receipt of ADT. Furthermore, we applied multivariable Cox regression to analyze ACM as a function of Gleason score and PSA level in a cohort of 5326 patients who received salvage ADT after RP to ascertain the risk of ACM in low-PSA, high-grade disease with pathologically confirmed Gleason score (Supplementary material).

2.2.4. Decipher GRID genomic analyses—We characterized the transcriptomic differences between tumors with PSA ≤2.5 and >2.5 ng/ml using 62 trained and validated prostate cancer expression signatures from GRID including signatures related to prognosis [23], androgen receptor signaling [24], and neuroendocrine/small-cell disease (Supplementary material) [19]. The Wilcoxon test was used to assess significant differences, and the Benjamini-Hochberg method was used for multiple testing adjustment.

2.2.5. Statistical tests—Statistical testing was two-sided with significance set at p = 0.025 after Bonferroni correction (n = 2 Gleason groups in prognostic analyses, ***n*** = 2 PSA groups in predictive analyses) and p = 0.050 for transcriptomic analysis after multiple testing correction. Analyses were performed with Stata/SE 14.2 (StataCorp, College Station, TX, USA) or R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria). The Dana-Farber/Harvard Cancer Center institutional review board granted permission to perform this study.

3. Results

3.1. Baseline characteristics

Baseline characteristics for the NCDB, SEER, and Decipher GRID cohorts are shown in Table 1, Supplementary Table 1, and Supplementary Table 2, respectively. Of the men with Gleason 8–10 tumors in the NCDB cohort, 5.6% presented with PSA ≤2.5 ng/ml. The median follow-up was 25.0 mo for the SEER cohort and 48.9 mo for the NCDB cohort.

3.2. Prognostic outcomes: estimates of PCSM and ACM by PSA level, stratified by Gleason score

Among men with Gleason 8–10 disease and using PSA 4.1–10.0 ng/ml as the referent, the distribution of PCSM in the SEER cohort was U-shaped with respect to PSA, with an adjusted hazard ratio (AHR) of 2.70 (95% confidence interval [Cl] 1.58–4.60; $p < 0.001$) for PSA ≤2.5 ng/ml versus 1.97, 1.36, and 2.56 for PSA 2.6–4.0, 10.1–20.0, and >20.0 ng/ml, respectively (Fig. 1A, Table 2). Similarly, the distribution of ACM in the NCDB cohort was U-shaped with respect to PSA, with an AHR of 1.23 (95% Cl 1.13–1.33; $p < 0.001$) for PSA

≤2.5 ng/ml versus 1.07, 1.30, and 1.50 for PSA 2.6–4.0, 10.1–20.0, and >20.0 ng/ml, respectively (Supplementary Fig. 1A, Table 2).

By contrast, the PCSM distribution was linear for Gleason ≤7 disease, with an AHR of 0.41 (95% Cl 0.13–1.29; $p = 0.13$) for PSA ≤2.5 ng/ml, versus 1.38, 2.28, and 4.61 for PSA 2.6–4.0, 10.1–20.0, and >20.0 ng/ml, respectively (Fig. 1B, Table 2). Similarly, the AHR for ACM was 1.03 (95% Cl 0.99–1.08; $p = 0.14$) for PSA ≤2.5 ng/ml versus 0.83,1.33, and 1.40 for PSA 2.6–4.0, 10.1–20.0, and >20.0 ng/ml, respectively (Supplementary Fig. 1B, Table 2).

Significant interactions between PSA level and Gleason score were noted for both PCSM and ACM (both $_{\text{pinteraction}} \leq 0.001$), indicating that the association between PSA level and survival was different for Gleason 8–10 versus ≤7 tumors.

Gleason 8–10 disease with PSA ≤2.5 ng/ml had a higher risk of PCSM compared to NCCN high-risk/very high-risk disease with PSA >2.5 ng/ml (AHR 2.15, 95% Cl 1.31–3.52; $p = 0.002$; 47-mo adjusted PCSM 14.0% vs 4.9%; Supplementary Table 3, Fig. 1C). Furthermore, Gleason 8–10 disease with PSA ≤2.5 ng/ml was associated with a higher risk of ACM compared to NCCN high-risk/very high-risk disease with PSA >2.5 ng/ml (AHR 1.15, 95% Cl 1.07–1.25; $p < 0.001$; Supplementary Table 3, Supplementary Fig. 1C).

3.3. Predictive outcomes: estimates of ACM by receipt ofADT among patients with Gleason 8–10 disease treated with radiotherapy, stratified by PSA level

Among Gleason 8–10 patients treated with radiotherapy in the NCDB cohort, there was a significant interaction between PSA and ADT ($p_{\text{interaction}} = 0.021$; Supplementary Table 4), such that ADT was associated with an overall survival benefit for PSA >2.5 ng/ml (AHR 0.87, 95% Cl 0.81–0.94; $p < 0.001$; Fig. 2A) but not PSA ≤2.5 ng/ml (AHR 1.36, 95% Cl 0.96–1.94; $p = 0.084$; Fig. 2B).

Furthermore, in patients treated with salvage ADT after RP, PSA ≤2.5 ng/ml was associated with the highest ACM for Gleason 8–10 tumors and the lowest ACM for Gleason ≤7 tumors ($p_{\text{interaction}} = 0.022$; Supplementary Table 5; Supplementary Fig. 2A,B).

3.4. Genomic characteήstics of low-PSA, high-grade tumors

We assessed differences in values for 62 prostate cancer transcriptomic signatures in the Decipher GRID, including signatures related to prognosis [23], androgen receptor (AR) signaling [24], and neuroendocrine/small-cell prostate cancer [19]. After multiple testing adjustment, Gleason 8–10 tumors with PSA ≤2.5 ng/ml were more likely to be associated with neuroendocrine/small-cell genomic signatures and less likely to be associated with an AR signaling signature compared to Gleason 8–10 tumors with PSA >2.5 ng/ml (bothp = 0.046; Fig. 3A,B). No such relationship was seen for Gleason ≤7 tumors (Fig. 3C,D).

4. Discussion

In this large, contemporary study of patients from three national cohorts, we found that low-PSA, high-grade prostate cancer appears to be a unique and aggressive entity among men

with prostate cancer, with poor clinical outcomes and genomic features of neuroendocrine dedifferentiation. Characterization of this disease as a unique entity distinguishable by expression profiling from other high-grade prostate adenocarcinomas has not been reported in the literature, and the implications of these findings are highly clinically significant.

We demonstrated that low-PSA, high-grade disease is associated with a more than twofold higher risk of prostate cancer death relative to NCCN high-risk/very high-risk disease, with a large number of deaths occurring within a short interval after diagnosis. Whereas a low PSA is typically seen as portending a favorable prognosis in prostate cancer, our findings suggest that it actually portends a higher risk of PCSM in high-grade disease. In addition, ADT when combined with radiotherapy is known to improve survival in high-grade disease, but our findings suggest that this is actually not true when PSA is ≤2.5 ng/ml. Lastly, low-PSA, high-grade disease is associated with higher expression of markers for neuroendocrine/small-cell disease and lower AR signaling compared to other patients with high-grade disease, while no such difference was detected by PSA for low-grade disease. Lower expression of AR signaling and higher expression of neuroendocrine markers are associated with a neuroendocrine phenotype, which has a poorer response to hormonal therapy and poorer cancer outcome [19,23,24]. Thus, our clinical and genomic data strongly suggest that low-PSA, high-grade prostate cancer is a clinically and biologically unique entity that is associated with poor prognosis and that may not respond well to ADT.

This study has two major clinical implications. First, our results suggest that modification may be needed for existing clinical prognostic tools for prostate cancer, which predict a linear relationship between PSA and prognosis [25–27]. We found that although there is a positive linear relationship between outcomes and PSA for Gleason ≤7 tumors as predicted by prognostic nomograms, these clinical nomograms are inaccurate for high-grade disease, for which the prognosis for low PSA appears to be as equally poor as for elevated PSA. Second, our findings suggest that the current paradigm for treating all high-risk localized disease using radiation and long-term ADT alone may need modification, as our study suggests that low-PSA, high-grade tumors may respond poorly to ADT. The poor prognosis and potentially lower ADT response of low-PSA, high-grade cancer distinguish it from conventional prostate adenocarcinoma, and our expression data provide biological evidence of these clinical observations.

It has been hypothesized that low-PSA, high-grade prostate cancer reflects dedifferentiated, clinically aggressive, and hormone-resistant tumors, but until now the evidence has been limited [5–8]. By demonstrating that low-PSA, high-grade tumors may be potentially resistant to ADT and possess neuroendocrine genomic features, our results provide the first clinical and biological validation of this longstanding hypothesis. Furthermore, these findings also highlight the potential difficulties with detecting this unique aggressive entity, which would not necessarily be diagnosed through PSA screening as the PSA levels would typically be below the threshold to biopsy. Thus, it is likely that such patients with aggressive cancers could be diagnosed based on some combination of digital rectal examination, clinical symptom presentation, and PSA kinetics. Whether there are low-PSA, high-grade tumors that remain latent is unknown, since patients who are discovered to have high-grade disease would be treated as high risk.

Given the poor prognosis and unique characteristics of this disease, there is an urgent need for further molecular, genomic, and clinical characterization as well as clinical trials involving chemotherapy and/or novel targeted agents. We propose movement towards the utilization of new prognostic tools and treatment paradigms in this setting. Genomic signature testing may aid in both identifying neuroendocrine biology that is difficult to capture morphologically and in predicting the prognosis of low PSA in high-grade disease, which current nomograms and clinical testing cannot do accurately. Since low-PSA, high-grade disease tends to be late-presenting given that low PSA does not typically prompt a biopsy, the development of additional biomarkers to aid in early detection of aggressive and poorly differentiated disease is necessary. Furthermore, whether low-PSA, high-grade tumors are a heterogeneous entity with a mixture of tumor types such as aggressive neuroendocrine and more standard-risk prostate adenocarcinoma would need to be determined in developing new approaches to this disease.

In moving towards a new treatment paradigm, one hypothesis is that patients with low-PSA, high-grade disease may be the group that would benefit the most from addition of chemotherapy to standard hormonal therapy for high-risk localized disease, on the basis of new randomized evidence showing the benefit of chemo–therapy in localized high-risk disease [16,28]. Furthermore, this group may benefit from early addition of chemotherapy should further studies confirm ADT resistance in these patients. While docetaxel has been favored as the chemotherapy of choice for high-risk localized disease, a platinum-based agent could also be considered in the setting of a clinical trial given the neuroendocrine expression features oflow-PSA, high-grade tumors [1], Ithas been demonstrated that neuroendocrine prostate cancer has significant overexpression and amplification of specific markers, and there are ongoing phase 2 studies evaluating the efficacy of targeted inhibition in the metastatic setting (NCT01799278). Depending on the results of this study, the expansion of targeted inhibition for patients with low-PSA, high-grade disease in an investigative setting may be appropriate. Furthermore, there is a rationale to hypothesize that surgery, either upfront or in combination with radiation and/or systemic therapy, may be a more appropriate initial strategy for this group, given that the disease may be less responsive to ADT. Ultimately, our findings will need to be prospectively validated before we would recommend changes to initial management approaches, although clinicians should proceed with caution and consider aggressive management as clinically indicated. Lastly, it should be noted that an alternative surveillance strategy to PSA monitoring that involves imaging may be needed given that these tumors produce little PSA.

Our findings must be viewed within the inherent limitations of a database analysis. First, SEER does not contain information on ADT or comorbidity status. To account for this limitation, we used the NCDB, which has robust information on these data. Second, the NCDB does not contain information on cause of death. To address this limitation, we used SEER, which contains information on cause of death. Third, it is unknown how many patients were potentially captured by both SEER and NCDB, as such information is unavailable, although we would consider this to be a minor inherent limitation of using both databases balanced against the significant benefit of addressing the limitations of each database by using both. Fourth, the number of patients included in the genomic analyses was smaller than the number for clinical analyses. Nevertheless, there was enough power to

detect a significant difference in genomic expression based on PSA among high-Gleason tumors. Fifth, given that chemotherapy was not considered the standard of care during the study period, only 1393 patients in our cohort received chemotherapy (including only 60 patients with low-PSA, high-grade disease), making our study underpowered to assess response to chemotherapy. Lastly, the follow-up periods for our clinical cohorts were relatively short, but the aggressive nature of low-PSA, high-grade disease allowed us to detect a difference in survival within these short follow-up periods.

5. Conclusions

In summary, low-PSA, high-grade prostate cancer appears to be a unique entity among men with prostate cancer that has very high risk for prostate cancer death, potentially responds poorly to ADT, and is more likely to be associated with neuroendocrine genomic features. Clinicians, researchers, and patients need to be aware of the potentially worse oncologic outcomes associated with this newly characterized disease. We recommend a concerted effort from the prostate cancer research community to guide the development of prognostic tools, novel therapeutics, and clinical management for low-PSA, high-grade prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

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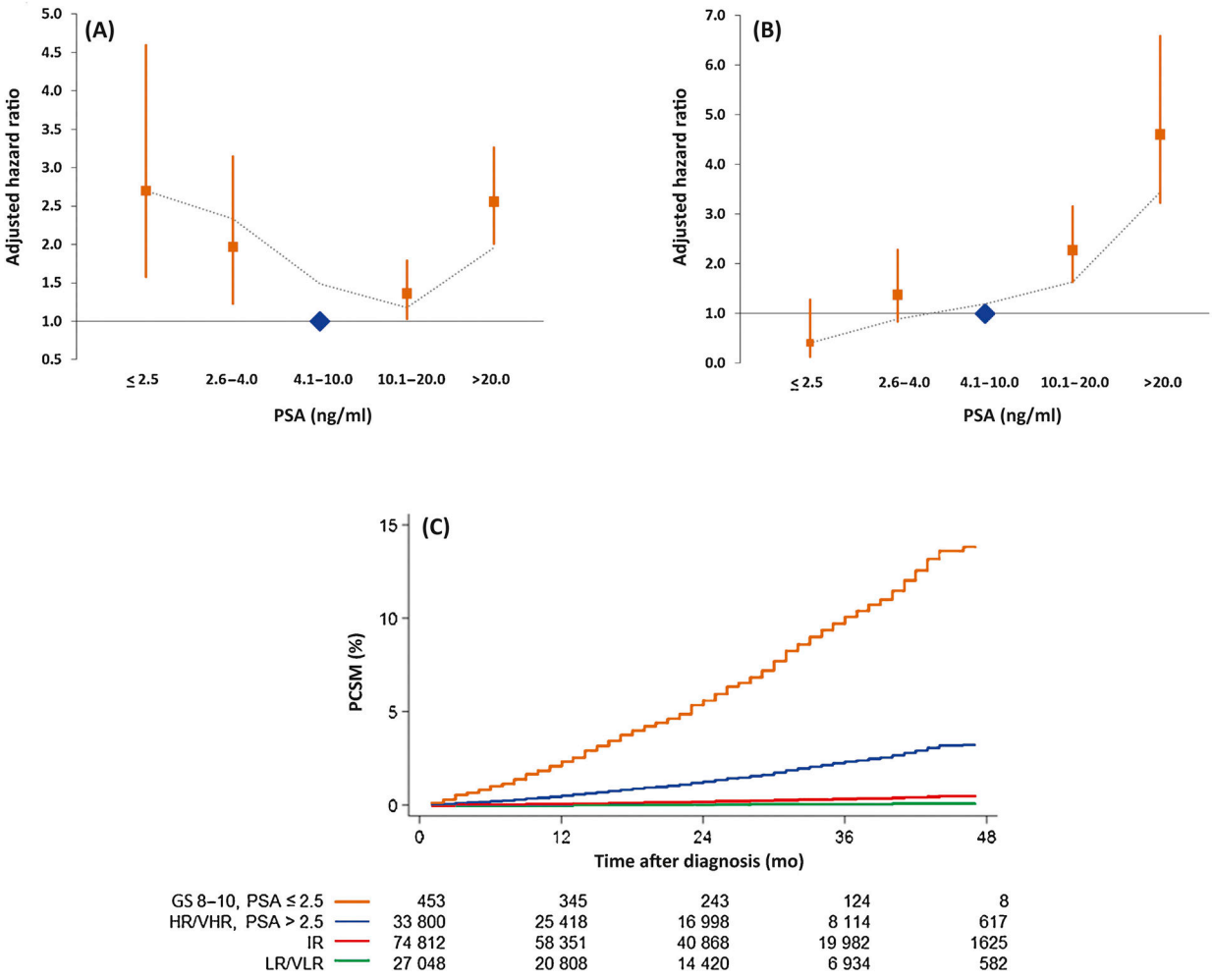

Fig. 1.

PCSM in the SEER cohort. Adjusted hazard ratios with 95% confidence intervals and moving-average trend lines for the association between PSA and PCSM for (A) Gleason 8–10 and (B) Gleason ≤7 disease. Adjusted cumulative incidence of PCSM by National Comprehensive Cancer Network risk group compared to PSA ≤2.5 ng/ml, Gleason 8–10 disease (C). GS = Gleason score; HR/VHR = high risk/very high risk; IR, intermediate risk; LR/VLR = low risk/very low risk; PCSM = prostate cancer-specific mortality; PSA = prostate-specific antigen; SEER = Surveillance, Epidemiology and End Results.

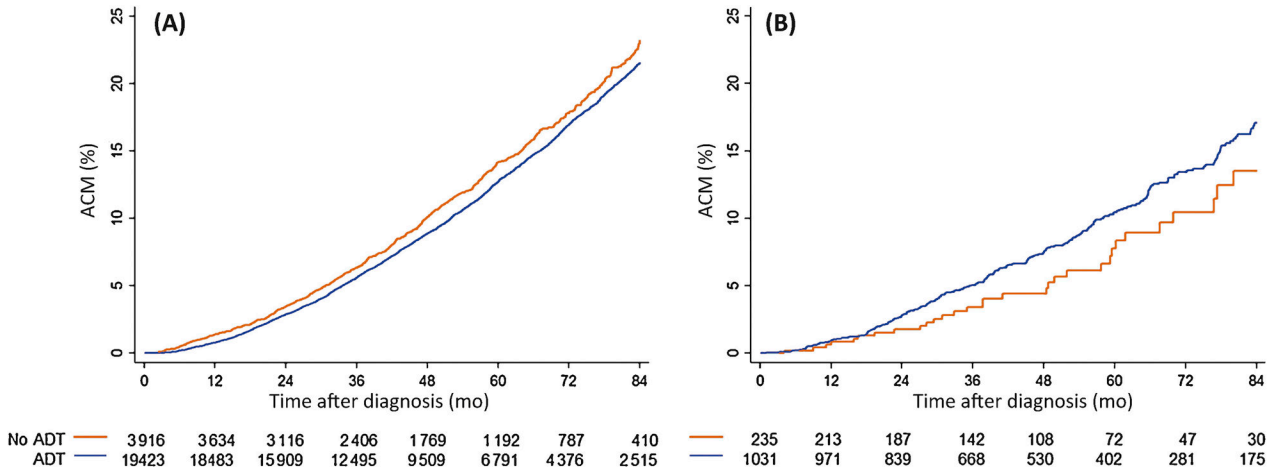

Fig. 2.

Adjusted Kaplan Meier curves of ACM for patients with Gleason 8–10 disease treated with definitive radiotherapy. (A) PSA >2.5 ng/ml and (B) PSA ≤2.5 ng/ml. Patients were identified from the National Cancer Data Base cohort. ACM = all-cause mortality; ADT = androgen deprivation therapy; PSA = prostate-specific antigen.

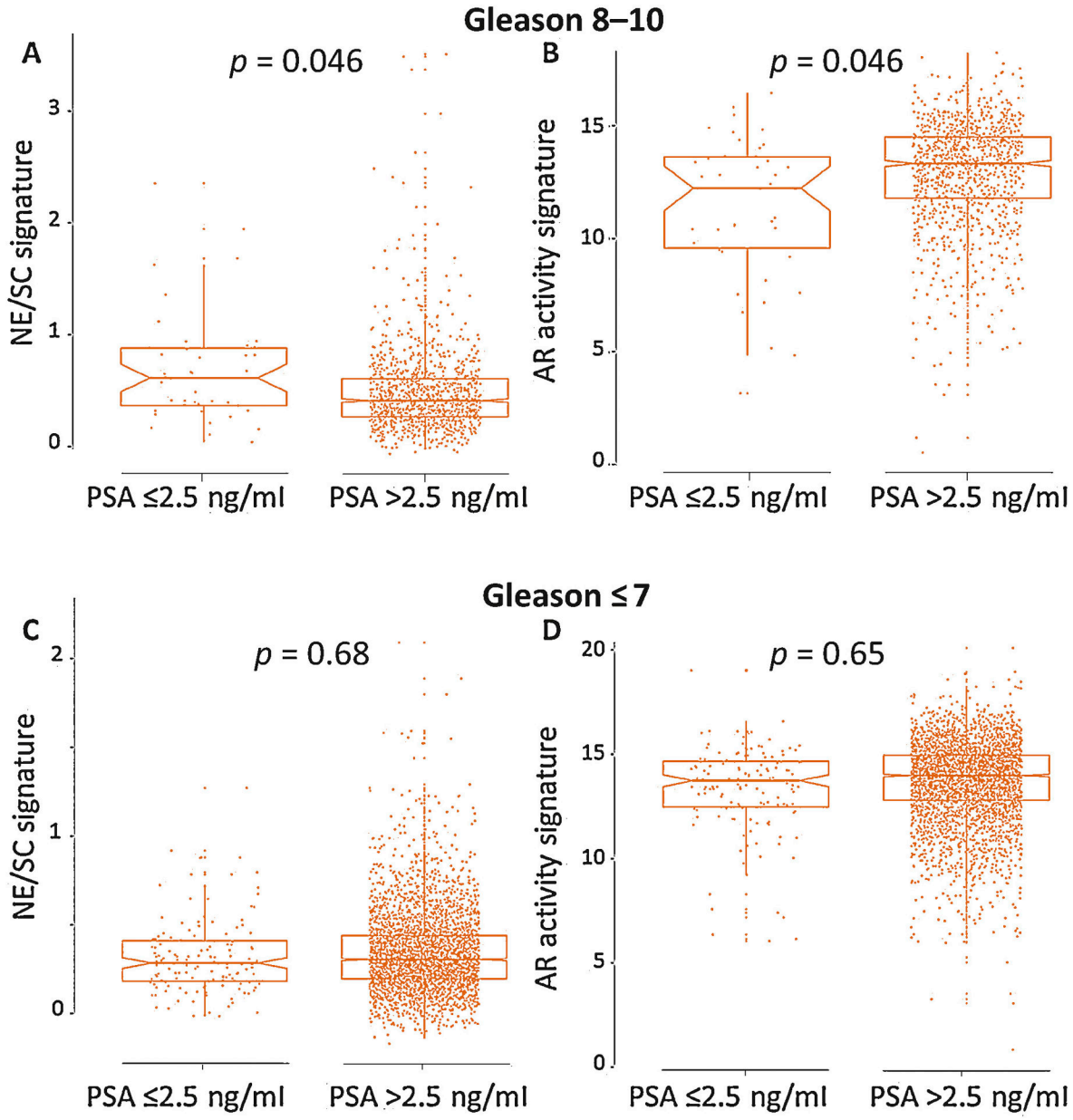

Fig. 3.

Genomic characterization of patients from the Decipher GRID cohort. (A) Neuroendocrine/small-cell signature and (B) AR activity scores were the only prostate cancer signatures (among 62 signatures) that remained significantly associated with prostate-specific antigen groups after adjustment for multiple testing for Gleason 8–10 tumors, but did not remain significant for (C,D) Gleason ≤7 tumors. AR = androgen receptor; NE/SC = neuroendocrine/small-cell; PSA = prostate-specific antigen.

Table 1.

Baseline characteristics by PSA groups among patients in the National Cancer Data Base cohort (N = 494 793)

Characteristic	PSA group				
	≤2.5 ng/ml	**2.6–4.0 ng/ml**	**4.1–10.0 ng/ml**	**10.1–20.0 ng/ml**	**>20.0 ng/ml**
Patients (*n*)	35 654	44 939	311 175	61 288	41 737
Median age, yr (IQR)	63 (57–70)	61 (56–67)	65 (59–70)	67 (61–74)	67 (60–73)
Race, *n* (%)					
Non-Black	31 724 (89)	40 312 (90)	272 397 (88)	50 751 (83)	32 967 (79)
Black	3930 (11)	4627 (10)	38 778 (12)	10 537 (17)	8770 (21)
CDC score, *n* (%)					
0	30 683 (86)	39 222 (87)	267 010 (86)	52 119 (85)	35 631 (85)
1	4365 (12)	5084 (11)	38 474 (12)	7723 (13)	5032 (12)
≥2	606 (2)	633 (1)	5691 (2)	1446 (2)	1074 (3)
Initial definitive therapy, *n* (%)					
None	3447 (10)	3185 (7)	25 206 (8)	7370 (12)	7226 (17)
Radiation therapy	13 065 (37)	13 412 (30)	128 039 (41)	30 654 (50)	21 194 (51)
Radical prostatectomy	18 526 (52)	27 693 (62)	152 282 (49)	21 332 (35)	11 953 (29)
Receipt of ADT, *n* (%)					
Yes	5723 (16)	4753 (11)	52 232 (17)	22 180 (36)	19 252 (46)
No	29 931 (84)	40 186 (89)	258 943 (83)	39 108 (64)	22 485 (54)
Gleason score, *n* (%)					
7 or Less	32 245 (90)	41 769 (93)	281 981 (91)	48 263 (79)	29 853 (72)
8–10	3409 (10)	3170 (7)	29 194 (9)	13 025 (21)	11 884 (29)
Clinical tumor category, *n* (%)					
T1	18 745 (53)	30 573 (68)	232 665 (75)	39 726 (65)	23 921 (57)
T2	15 985 (45)	13 525 (30)	72 554 (23)	18 634 (30)	14 018 (34)
T3	863 (2)	801 (2)	5736 (2)	2757 (4)	3382 (8)
T4	61 (0)	40 (0)	220 (0)	171 (0)	416 (1)

ADT = androgen deprivation therapy; CDC = Charlson-Deyo comorbidity; IQR = interquartile range; PSA = prostate-specific antigen.

[a] $p < 0.001$ for all characteristics comparing across all PSA groups. Percentages may not add to 100 due to rounding.

Table 2.

Adjusted hazard ratios for prostate cancer-specific mortality (SEER cohort) and all-cause mortality (NCDB cohort)

Characteristic	SEER cohort				NCDB cohort			
	Men (*n*)	PCD (*n*)	PCSM AHR (95% CI)	*p* value	Men (*n*)	ACD (*n*)	ACM AHR (95% CI)	*p* value
Gleason score × PSA level	136 113	653	9.39 (2.69–32.80)	<0.001	494 793	45 583	1.17 (1.07–1.28)	0.001
PSA level with Gleason 8–10								
≤2.5 ng/ml	453	17	2.70 (1.58–4.60)	<0.001	3409	655	1.23 (1.13–1.33)	<0.001
2.6–4.0 ng/ml	1029	22	1.97 (1.24–3.15)	0.004	3170	437	1.07 (0.98–1.18)	0.14
4.1–10.0 ng/ml	9525	96	1.0 (referent)		29 194	3947	1.0 (referent)	
10.1–20.0 ng/ml	4347	85	1.36 (1.03–1.79)	0.030	13 025	2753	1.30 (1.24–1.37)	<0.001
>20.0 ng/ml	4230	217	2.56 (2.01–3.26)	<0.001	11 884	3175	1.50 (1.43–1.58)	<0.001
PSA level with Gleason ≤7								
≤2.5 ng/ml	5567	3	0.41 (0.13–1.29)	0.13	32 245	2444	1.03 (0.99–1.08)	0.14
2.6–4.0 ng/ml	12 383	18	1.38 (0.84–2.29)	0.21	41 769	1811	0.83 (0.79–0.87)	<0.001
4.1–10.0 ng/ml	77 917	90	1.0 (referent)		281 981	20 041	1.0 (referent)	
10.1–20.0 ng/ml	15 056	52	2.28 (1.64–3.16)	<0.001	48 263	6206	1.33 (1.29–1.37)	<0.001
>20.0 ng/ml	5606	53	4.61 (3.23–6.59)	<0.001	29 853	4114	1.40 (1.36–1.45)	<0.001
Clinical tumor category								
T1	58 415	279	1.0 (referent)		345 630	27 523	1.0 (referent)	
T2	63 233	251	1.18 (0.98–1.41)	0.073	134 716	15 335	1.13 (1.11–1.16)	<0.001
T3	12 754	77	1.93 (1.45–2.56)	<0.001	13 539	2338	1.38 (1.32–1.44)	<0.001
T4	1447	42	4.37 (3.05–6.28)	<0.001	908	387	2.84 (2.56–3.14)	<0.001
Age (per year increase)	136 113	653	1.04 (1.03–1.06)	<0.001	494 793	45 583	1.06 (1.06–1.06)	<0.001
Race								
Non-Black	114 200	518	1.0 (referent)		428 151	38 401	1.0 (referent)	
Black	21 913	135	1.44 (1.19–1.75)	<0.001	66 642	7182	1.31 (1.28–1.35)	<0.001
Initial definitive treatment[a]								
None	35 645	393	1.0 (referent)		46 577	9548	1.0 (referent)	
Radical prostatectomy	53 440	79	0.22 (0.16–0.29)	<0.001	233 333	8519	0.30 (0.29–0.31)	<0.001
Radiation therapy	47 028	181	0.34 (0.28–0.40)	<0.001	206 364	27 516	0.56 (0.54–0.57)	<0.001
CDC score								
0	N/A	N/A			424 665	36 757	1.0 (referent)	
1	N/A	N/A			60 678	6815	1.55 (1.51–1.59)	<0.001
≥2	N/A	N/A			9450	2011	2.67 (2.55–2.79)	<0.001

ACD = all-cause deaths; ACM = all-cause mortality; AHR = adjusted hazard ratio; CDC = Charlson-Deyo comorbidity; Cl = confidence interval; N/A = not applicable; NCDB = National Cancer Data Base; PCD = prostate cancer deaths; PCSM = prostate cancer-specific mortality; PSA = prostate-specific antigen; SEER = Surveillance, Epidemiology and End Results.

[a]Adjusted for receipt of androgen deprivation therapy for the NCDB cohort.