Published in final edited form as:

Eur Urol. 2014 March ; 65(3): 620–627. doi:10.1016/j.eururo.2012.11.052.

Detectable Prostate-Specific Antigen Nadir During Androgen-Deprivation Therapy Predicts Adverse Prostate Cancer Specific Outcomes: Results from the SEARCH Database

Christopher J. Keto^{a,b}, William J. Aronson^{c,d}, Martha K. Terris^{e,f}, Joseph C. Presti^{g,h}, Christopher J. Kaneⁱ, Christopher L. Amling^j, and Stephen J. Freedland^{a,b,*}

^aDuke University School of Medicine, Durham, NC, USA

^bVeterans Affairs Medical Center, Durham, NC, USA

^cUniversity of California at Los Angeles Medical Center, Los Angeles, CA, USA

^dVeterans Affairs Medical Center, Greater Los Angeles, Los Angeles, CA, USA

^eMedical College of Georgia, Augusta, GA, USA

^fVeterans Affairs Medical Center, Augusta, GA, USA

^gStanford University Medical Center, Palo Alto, CA, USA

^hVeterans Affairs Medical Center, Palo Alto, CA, USA

ⁱUniversity of California at San Diego, San Diego, CA, USA

^jOregon Health and Science University, Portland, OR, USA

Abstract

Background—A prostate-specific antigen (PSA) level <0.2 ng/ml on androgen-deprivation therapy (ADT) is correlated with better outcomes. However, not all men reach a nadir PSA level within 8 mo. Whether the lowest PSA on ADT—specifically, <0.2 ng/ml—can be used for risk stratification is untested.

*Corresponding author. Division of Urology, DUMC, Box 2626, Duke University School of Medicine, Durham, NC 27710, USA. Tel. +1 919 668 5946; Fax: +1 919 668 7093. steve.freedland@duke.edu (S.J. Freedland).

Author contributions: Stephen J. Freedland had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Keto, Freedland.

Acquisition of data: Keto, Freedland, Kane, Presti, Terris, Aronson, Amling.

Analysis and interpretation of data: Keto, Freedland.

Drafting of the manuscript: Keto.

Critical revision of the manuscript for important intellectual content: Freedland, Kane, Presti, Terris, Aronson, Amling.

Statistical analysis: Keto.

Obtaining funding: Freedland.

Administrative, technical, or material support: Freedland.

Supervision: Freedland.

Other (specify): None.

Financial disclosures: Stephen J. Freedland certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Objective—We examined the predictive value of small but detectable PSA nadir values on prostate cancer (PCa)-specific outcomes in men treated with early ADT after radical prostatectomy (RP).

Design, setting, and participants—We performed a retrospective review of men treated with ADT after RP before metastases from the SEARCH database. We identified 402 men treated with ADT for elevated PSA following RP, of whom 294 men had complete data. Median follow-up after PSA nadir was 49 mo. All men had a PSA nadir <4 ng/ml; 223 men (76%) had an undetectable nadir.

Intervention—ADT for an elevated PSA following RP with no radiographic evidence of metastatic disease.

Outcome measurements and statistical analysis—*PSA nadir on ADT* was defined as the lowest PSA value during ADT. Proportional hazards models and the C index were used to test the association and predictive accuracy, respectively, between PSA nadir and PCa-specific outcomes.

Results and limitations—Men with a PSA nadir between 0.01 and 0.2 ng/ml had a greater risk of progression to castration-resistant PCa (CRPC) (hazard ratio [HR]: 5.14; $p < 0.001$), metastases (HR: 3.98; $p = 0.006$), and PCa-specific mortality (PCSM) (HR: 5.33; $p = 0.003$) than men with an undetectable nadir. When data were restricted to men followed with ultrasensitive PSA values (sensitivity of 0.01 ng/ml), the C index of PSA nadir alone for predicting CRPC, metastases, and PCSM was 0.88, 0.91, and 0.96, respectively.

Conclusions—A PSA nadir on ADT, even at a very low level, strongly predicts progression to CRPC, metastases, and PCSM. Men with a detectable PSA nadir during ADT should be considered for clinical trials.

Keywords

Prostate cancer; Androgen-deprivation therapy; Prostate-specific antigen

1. Introduction

Prostate cancer (PCa) is a common, costly, and extremely heterogeneous disease [1–3]. Despite primary therapy, many patients will develop a rising prostate-specific antigen (PSA) level [4]. Although optimal timing and duration of secondary treatments such as androgen-deprivation therapy (ADT) are controversial, many men receive ADT before metastases [5] despite known ADT adverse effects [6–8]. As men with nonmetastatic PCa have no clinical response, PSA decline from baseline is used to evaluate ADT response. A previous study showed that men with nonmetastatic PCa whose PSA level after 8 mo of continuous ADT was >0.2 ng/ml were at greater risk of PCa-specific mortality (PCSM) than men with a nadir—the lowest value achieved at any time point during ADT—of <0.2 ng/ml [9]. Other studies investigating the PSA nadir or the value of PSA at a given time point (ie, 7–8 mo) are conducted for men with metastases [10,11] or mixed cohorts [12]. Not all men on ADT reach a PSA nadir within 8 mo.

To our knowledge, no study had examined whether men with detectable PSA nadir levels (even small amounts <0.2 ng/ml) are at higher PCSM risk compared with men with undetectable PSA nadirs. Additionally, no study had examined whether PSA nadir levels predict metastases in men with nonmetastatic disease treated with ADT for biochemical failure. We hypothesized that men having a detectable PSA nadir of any level during ADT would be at greater risk of castration-resistant PCa (CRPC), metastases, and PCSM than men achieving an undetectable nadir. To test this hypothesis, we investigated whether

having a detectable PSA nadir during ADT predicted PCa-specific outcomes in men treated with ADT for elevated PSA after radical prostatectomy (RP) in a multicenter cohort.

2. Methods

2.1. Study population

After obtaining institutional review board approval from each institution, data from men who received RP without prior ADT or radiotherapy between 1988 and 2009 at five US Department of Veterans Affairs hospitals in the United States (West Los Angeles, CA; Palo Alto, CA; Augusta, GA; Asheville, NC; and Durham, NC) were combined into the SEARCH database [13]. Of 2892 men, we excluded 2451 men (85%) not treated with ADT and 39 men (1%) with a positive bone scan prior to ADT. Of the remaining 402 men, we excluded men with missing data on pre-ADT PSA ($n = 31$), pathologic Gleason score ($n = 7$), margin status ($n = 11$), seminal vesicle invasion ($n = 11$), extracapsular extension ($n = 13$), PSA nadir during ADT ($n = 46$), and follow-up after reaching PSA nadir ($n = 4$), as well as men treated solely with low-dose antiandrogen (ie, 50 mg bicalutamide once daily) ($n = 29$), resulting in a final population of 294 men.

All patients were followed with serial PSA measurements and clinic visits at the discretion of the attending physician. Prior to the early 2000s, the PSA assays had a sensitivity of <0.1 ng/ml; starting around 2001, ultrasensitive PSA tests were used that had a detection threshold of 0.01 ng/ml.

The medical centers used different PSA assays: The West Los Angeles center, before June 2000, used the Hybritech Tandem-E PSA assay (Beckman Coulter, Inc., Fullerton, CA, USA), and since June 2000 that center used the Hybritech PSA Assay (Beckman Coulter, Inc.). The Palo Alto center, before December 2005, used the Bayer Immuno 1 PSA Assay (Bayer Corporation, Tarrytown, NY, USA), and since December 2005 it used the Hybritech PSA Assay. The Augusta center, before June 2003, used the ACS PSA Assay (Chiron Diagnostics, East Walpole, MA, USA), and since June 2003 that center used the Elecsys PSA Assay (Roche-Boehringer Mannheim, Mannheim, Germany). The Durham center used the AxSYM PSA Assay (Abbott Laboratories, Abbott Park, IL, USA) before February 2001, and has used the Hybritech PSA Assay since February 2001 [14].

We defined *PSA nadir* as the lowest PSA level on ADT. The *pre-ADT PSA* was the PSA level closest to, but prior to, ADT (< 1 yr prior to ADT). *CRPC* was defined using the Prostate Cancer Working Group 2 criteria: a 25% PSA increase from the nadir and an increase of ≥ 2 ng/ml [15]. *Distant metastases*, defined as bone or visceral or distant adenopathy (not pelvic adenopathy), were determined by review of radionuclide bone scans, magnetic resonance imaging scans, computed tomography scans, plain radiograph reports, and clinical progress notes. The decision to perform radiographic imaging was at the discretion of the attending physician. *PCSM* was defined as death in any patient with metastases showing PCa progression following ADT.

2.2. Statistical analysis

Baseline characteristics were compared among PSA nadir groups using Kruskal-Wallis and χ^2 tests. We used Cox proportional hazards models to test the predictive value of PSA nadir on progression to CRPC, metastases, and PCSM. The date of PSA nadir during ADT was time zero. We performed a secondary analysis using the ADT start date as time zero and including time to ADT nadir in the model, as well as a model including only men with data on pre-ADT PSA doubling time (PSA DT). Potential predictors, including PSA nadir, pre-ADT PSA, black race, extracapsular extension, seminal vesicle invasion, margin status, pathologic Gleason score (2–6, 7, 8–10), age at ADT, calendar year of RP, lymph node

metastases, time to ADT nadir, salvage external-beam radiation therapy, and PSA persistence following RP, were each tested in univariable models. We combined the statistically significant predictors into a multivariable model for each clinical outcome. PSA nadir was analyzed as a categorical (undetectable, 0.01–0.2 ng/ml, >0.2 ng/ml) and continuous logarithmically transformed variable of PSA +1. Kaplan-Meier plots and the log-rank test were used to analyze differences in PCa-specific outcomes across PSA nadir groups. Harrell's C concordance statistic (C index) was calculated to analyze the predictive accuracy of the models. All statistical analyses were performed using Stata v.11.0 (StataCorp, College Station, TX, USA), and $p < 0.05$ was considered significant.

3. Results

Median follow-up after RP was 73 mo, and median follow-up after PSA nadir was 49 mo. Among the 294 men, 55 men developed CRPC, 42 men developed metastases, and 31 men developed PCSM. Most men ($n = 223$; 76%) had an undetectable PSA nadir, with 47 men (16%) having a nadir of 0.01–0.2 ng/ml and 24 men (8%) having a PSA nadir >0.2 ng/ml (Table 1). Among men with a nadir >0.2 ng/ml, the median nadir was 0.5 ng/ml (interquartile range: 0.3–1.5); only eight patients had a nadir >1 ng/ml, and none had a nadir 4.0 ng/ml. Men with higher PSA nadirs had a higher pre-ADT PSA ($p < 0.001$), had a higher PSA at first bone scan on ADT ($p < 0.001$), and were more likely to have undergone combined androgen blockade ($p = 0.001$). Men with a higher PSA nadir (as a continuous variable) were more likely to progress to CRPC (hazard ratio [HR]: 2.32; $p < 0.001$). When PSA nadir was divided into groups, men with a PSA nadir >0.2 ng/ml (HR: 44.42; $p < 0.001$) or 0.01–0.2 ng/ml (HR: 5.14; $p < 0.001$) were significantly more likely to progress to CRPC than men with an undetectable nadir (Table 2). The estimated 4-yr risk of CRPC across PSA nadir groups (undetectable, 0.01–0.2 ng/ml, and >0.2 ng/ml) was 7%, 27%, and 93%, respectively (Fig. 1a). Other independent predictors of CRPC included pre-ADT PSA, seminal vesicle invasion, and Gleason score 8–10. The predictive accuracy (C index) of the multivariable model predicting progression to CRPC without PSA nadir was 0.75, and the C index was 0.86 with PSA nadir in the model (categorical).

Men with a higher PSA nadir (continuous) were also more likely to develop metastases (HR: 1.64; $p = 0.004$). Among PSA nadir groups, men with a PSA nadir >0.2 ng/ml (HR: 12.42; $p < 0.001$) or 0.01–0.2 ng/ml (HR: 3.98; $p = 0.006$) were significantly more likely to develop metastases (Table 3). The 4-yr risk of metastases across PSA nadir groups (undetectable, 0.01–0.2 ng/ml, and >0.2 ng/ml) was 3%, 14%, and 72%, respectively (Fig. 1b). Other independent predictors of metastases included pre-ADT PSA and seminal vesicle invasion. The predictive accuracy (C index) of the multivariable model predicting metastases without PSA nadir was 0.72, and the C index was 0.84 with PSA nadir in the model (categorical).

Finally, men with a higher PSA nadir (continuous) were more likely to die of PCa (HR: 1.51; $p = 0.034$). When categorized, men with a PSA nadir >0.2 ng/ml (HR: 8.27; $p < 0.001$) or a PSA nadir 0.01–0.2 ng/ml (HR: 5.33; $p = 0.003$) were more likely to die of PCa than men with an undetectable nadir (Table 4). Pre-ADT PSA was the only other significant predictor of PCSM. The 4-yr PCSM rates for the undetectable, 0.01–0.2 ng/ml, and >0.2 ng/ml nadir groups were 2%, 3%, and 42%, respectively (Fig. 1c). The predictive accuracy (C index) of the multivariable model predicting PCSM without PSA nadir was 0.75, and the C index was 0.83 with PSA nadir in the model (categorical).

Among the subset of men with pre-ADT PSA DT data, pre-ADT PSA DT was a significant univariable predictor of CRPC, metastases, and PCSM ($p < 0.001$). However, when added into a multivariable model that included PSA nadir, pre-ADT PSA DT was not statistically significant as a predictor of any outcome. Additionally, we tested whether using the ADT

start date as time zero and including the time to PSA nadir as a covariable altered the models; we found that the results were similar, in that higher nadir predicted poorer outcome.

Given that some men were followed with *nonultrasensitive* PSA tests, we performed a subanalysis examining men followed after ADT exclusively with ultrasensitive PSA tests ($n = 149$, 51%) and assessed whether ultrasensitive PSA could be used for risk stratification for development of CRPC ($n = 15$), metastases ($n = 7$), and PCSM ($n = 3$). Among these men with a median follow-up of 35 mo after PSA nadir, the risk of CRPC (Fig. 2a), metastases (Fig. 2b), or PCSM (Fig. 2c) was significantly related to PSA nadir (all log-rank: $p < 0.0001$). Even when analyses were limited to PSA nadir <0.2 , PSA nadir as a continuous variable significantly predicted CRPC ($p = 0.001$), metastases ($p = 0.018$), and PCSM ($p = 0.005$). To test whether this was better than nonultrasensitive PSA tests, PSA nadir values were assigned to what they would have been had a nonultrasensitive assay been used. For example, all men with a PSA of 0.01–0.09 ng/ml (ie, <0.1 ng/ml) were assigned as *undetectable*. Men with a PSA of 0.10–0.19 ng/ml were assigned a PSA of 0.1 ng/ml. After doing so, the predictive accuracy (C index) of ultrasensitive PSA nadir as a single continuous variable was better than the nonultrasensitive assay for predicting CRPC (0.88 compared with 0.77), metastases (0.91 compared with 0.83), and PCSM (0.96 compared with 0.85).

4. Discussion

Previous data found that a lower PSA nadir during ADT is associated with better PCa-specific outcomes in men with advanced PCa [9,10,12,16]. However, the definition of *lower* has ranged from <0.2 to <4.0 ng/ml. Whether men with small but detectable PSA nadir levels (<0.2 ng/ml but still detectable) on ADT can be further risk-stratified is untested. Additionally, the relationship between PSA nadir in men with nonmetastatic PCa and development of metastases is likewise untested. We hypothesized that relative to men with an undetectable PSA nadir, men with a detectable PSA nadir, even a very low level, are at increased risk of CRPC, metastases, and PCSM. To test this hypothesis, we analyzed the risk of PCa-specific outcomes after reaching a PSA nadir on ADT in men initiating early ADT after RP. We found that any detectable PSA nadir during ADT was strongly predictive of CRPC, metastases, and PCSM even when the PSA nadir was <0.2 ng/ml.

Traditionally, in men with distant metastases starting ADT, a PSA nadir >4 ng/ml has been correlated with increased PCSM [10,11]. Other cohorts of men with and without distant metastases suggested that a PSA nadir >1 ng/ml was associated with PCSM [12]. One study found that men with nonmetastatic PCa on ADT were at greater risk of PCSM if their PSA was >0.2 ng/ml 8 mo after ADT [9]. Our results were in line with the general findings from previous studies that higher PSA nadir is associated with greater PCa progression risk.

In our cohort, in which all PSA nadirs were <4 ng/ml, there was a remarkable survival difference at 4 yr between the undetectable and the >0.2 ng/ml nadir groups. Among men with PSA nadirs >0.2 ng/ml, we estimated that 34% would die of PCa at 4 yr compared with just 2% of men with an undetectable nadir. Men with nadirs 0.01–0.2 ng/ml also had increased risk of CRPC, metastases, and PCSM compared with men with an undetectable nadir, though the 4-yr estimated risk of PCSM was only 6%. Our results suggest that the goal of early ADT should be to reach an undetectable PSA nadir. Beyond nadir, we found that pre-ADT PSA and Gleason score 8–10 significantly predicted CRPC, metastases, and PCSM. Perhaps these predictors can further stratify men with low but detectable PSA nadirs for counseling regarding entry into clinical trials.

Some PSA values in our cohort were prior to introducing ultrasensitive PSA testing. We speculated that some of the “undetectable” nadirs may have been detectable at very small amounts if an ultrasensitive assay had been used. To explore this idea, we performed a subanalysis among men who were followed after ADT exclusively with ultrasensitive PSAs. In this subset, the risk of adverse outcomes among men with an undetectable ultrasensitive PSA nadir was exceedingly low. Furthermore, the accuracy of ultrasensitive PSA nadir for predicting CRPC, metastases, and PCSM was extremely high (87%). Further study of ultrasensitive PSA in men on ADT with longer follow-up is warranted to confirm the high predictive accuracy. Using the PSA nadir on ADT is limited because it is unknown before starting ADT. Therefore, we examined differences in baseline characteristics across nadir groups. Men with nadirs >0.2 ng/ml had significantly higher pre-ADT PSA levels. A previous study found that men with higher pre-ADT PSA levels were less likely to achieve an undetectable nadir [17]. There were no other significant differences in baseline features across nadir groups. Perhaps higher pre-ADT PSA levels may help identify men unlikely to reach an undetectable PSA nadir on ADT and thus could help risk stratify men before ADT, identifying those patients who should be counseled regarding clinical trials.

One possible reason why a man may not achieve an undetectable nadir on ADT is inadequate androgen deprivation. Perhaps some men in our study had an inadequate dose of ADT, which could result from reduced frequency of administration, patient noncompliance, or other explanations such as obesity wherein the volume of distribution of drug is higher and thus the effective dose is lower [18]. This idea suggests that for these men, assessment of serum testosterone levels may be helpful. For example, men who are not within the castration range may benefit from additional hormone therapy or a change in the primary regimen. Furthermore, previous studies have shown that men with higher testosterone levels, even within the castration range, have worse outcomes [19,20]. Therefore, even men within the higher end of the castration range may benefit from additional hormonal ablation.

Additionally, one study suggests that gonadotrophin-releasing hormone (GnRH) antagonists may provide superior outcomes compared with GnRH agonists [21]. Perhaps men who achieve a low but detectable PSA nadir on GnRH agonist monotherapy with insufficient androgen deprivation should receive secondary hormonal manipulation (ie, antiandrogen therapy or an androgen biosynthesis inhibitor) or a change in the primary regimen (ie, a switch to a GnRH antagonist) in an attempt to achieve better hormonal blockade leading to an undetectable PSA nadir. Caution should be used in relying on these data to determine the optimal starting time for ADT because of the lack of comparison with a comparable group of men who did not undergo ADT. Thus, though outcomes for men with an undetectable PSA nadir were quite favorable, it is possible that long-term outcomes in the absence of ADT would also have been favorable. The favorable outcomes with ADT could be viewed alternatively as overtreatment, which remains a major issue for the contemporary management of PCa—even for men with recurrent disease. Our study had the inherent limitations of all retrospective analyses. All men received RP as primary treatment, and whether these results apply to men with a prostate in place is unclear. We did not have data to confirm castration testosterone levels at the onset of ADT failure. Our study was relatively small, with a limited number of PCa-specific events. This limitation was even greater when examining the men followed with only ultrasensitive PSAs, so larger studies with longer follow-up are required to validate these findings. Additionally, there were only a small number of men in the PSA nadir >0.2 ng/ml group. Finally, we did not have information regarding the coefficient of variation for the various PSA assays. However, inaccuracies in measuring PSA would likely lead to lower accuracy in assigning a man to an appropriate PSA nadir category, thus making the PSA nadir value less accurate. However, despite this limitation, PSA nadir was a very strong predictor of clinical outcome. In the

future, more accurate measures of PSA nadir may yield even stronger prognostic information.

5. Conclusions

We found that a detectable PSA nadir (> 0.01 ng/ml) is strongly predictive of progression to CRPC, metastases, and PCSM. Our results also suggest that ultrasensitive PSA testing may be more useful for assessing PSA levels in this group of men. Men who undergo early ADT after RP and do not achieve an undetectable PSA nadir should be considered for secondary hormonal manipulation, change in primary regimen, or entry into clinical trials.

Acknowledgments

Funding/Support and role of the sponsor: Department of Veterans Affairs, the Department of Defense, Prostate Cancer Research Program (CJK, SJF), NIH R01CA100938 (WJA), NIH Specialized Programs of Research Excellence Grant P50 CA92131-01A1 (WJA), Georgia Cancer Coalition (MKT), and the American Urological Association Foundation/Astellas Rising Star in Urology Award (SJF). Views and opinions of and endorsements by the authors do not reflect those of the US Army or the Department of Defense.

References

1. Stokes ME, Black L, Benedict A, Roehrborn CG, Albertsen P. Long-term medical-care costs related to prostate cancer: estimates from linked SEER-Medicare data. *Prostate Cancer Prostatic Dis.* 2010; 13:278–84. [PubMed: 20212521]
2. Center MM, Jemal A, Lortet-Tieulent J, et al. International variation in prostate cancer incidence and mortality rates. *Eur Urol.* 2012; 61:1079–92. [PubMed: 22424666]
3. Heidenreich A, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer, I: screening, diagnosis, and treatment of clinically localised disease. *Eur Urol.* 2011; 59:61–71. [PubMed: 21056534]
4. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA.* 1999; 281:1591–7. [PubMed: 10235151]
5. Sharifi N, Gulley JL, Dahut WL. Androgen deprivation therapy for prostate cancer. *JAMA.* 2005; 294:238–44. [PubMed: 16014598]
6. Freedland SJ, Eastham J, Shore N. Androgen deprivation therapy and estrogen deficiency induced adverse effects in the treatment of prostate cancer. *Prostate Cancer Prostatic Dis.* 2009; 12:333–8. [PubMed: 19901933]
7. Pagliarulo V, Bracarda S, Eisenberger MA, et al. Contemporary role of androgen deprivation therapy for prostate cancer. *Eur Urol.* 2012; 61:11–25. [PubMed: 21871711]
8. Mottet N, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer, II: treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol.* 2011; 59:572–83. [PubMed: 21315502]
9. Stewart AJ, Scher HI, Chen MH, et al. Prostate-specific antigen nadir and cancer-specific mortality following hormonal therapy for prostate-specific antigen failure. *J Clin Oncol.* 2005; 23:6556–60. [PubMed: 16170163]
10. Hussain M, Tangen CM, Higano C, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). *J Clin Oncol.* 2006; 24:3984–90. [PubMed: 16921051]
11. Miller JJ, Ahmann FR, Drach GW, Emerson SS, Bottaccini MR. The clinical usefulness of serum prostate specific antigen after hormonal therapy of metastatic prostate cancer. *J Urol.* 1992; 147:956–61. [PubMed: 1371568]
12. Kwak C, Jeong SJ, Park MS, Lee E, Lee SE. Prognostic significance of the nadir prostate specific antigen level after hormone therapy for prostate cancer. *J Urol.* 2002; 168:995–1000. [PubMed: 12187207]

13. Banez LL, Loftis RM, Freedland SJ, et al. The influence of hepatic function on prostate cancer outcomes after radical prostatectomy. *Prostate Cancer Prostatic Dis.* 2010; 13:173–7. [PubMed: 20195294]
14. Chang SL, Freedland SJ, Terris MK, et al. Freedom from a detectable ultrasensitive prostate-specific antigen at two years after radical prostatectomy predicts a favorable clinical outcome: analysis of the SEARCH database. *Urology.* 2010; 75:439–44. [PubMed: 19819536]
15. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol.* 2008; 26:1148–59. [PubMed: 18309951]
16. Benaim EA, Pace CM, Lam PM, Roehrborn CG. Nadir prostate-specific antigen as a predictor of progression to androgen-independent prostate cancer. *Urology.* 2002; 59:73–8. [PubMed: 11796285]
17. Alexander BM, Chen MH, Carroll P, D’Amico AV. Prostate-specific antigen level at initiation of hormonal therapy after prostate-specific antigen failure following prostatectomy or radiotherapy and therapeutic response. *Urology.* 2007; 70:320–3. [PubMed: 17826497]
18. Smith MR. Obesity and sex steroids during gonadotropin-releasing hormone agonist treatment for prostate cancer. *Clin Cancer Res.* 2007; 13:241–5. [PubMed: 17200361]
19. Morote J, Orsola A, Planas J, et al. Redefining clinically significant castration levels in patients with prostate cancer receiving continuous androgen deprivation therapy. *J Urol.* 2007; 178:1290–5. [PubMed: 17698136]
20. Perachino M, Cavalli V, Bravi F. Testosterone levels in patients with metastatic prostate cancer treated with luteinizing hormone-releasing hormone therapy: prognostic significance? *BJU Int.* 2010; 105:648–51. [PubMed: 19747358]
21. Tombal B, Miller K, Boccon-Gibod L, et al. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. *Eur Urol.* 2010; 57:836–42. [PubMed: 19962227]

Take-home message

The prostate-specific antigen (PSA) nadir on androgen-deprivation therapy (ADT), even at very low levels, strongly predicts progression to castration-resistant prostate cancer, metastases, and prostate cancer specific mortality. Men with a detectable PSA nadir during ADT should be considered for clinical trials.

a No. at risk

Undetectable ADT nadir	200	179	146	123	105	78	65	49
ADT nadir 0.01–0.2 ng/ml	36	29	23	13	5	3	1	1
ADT nadir >0.2 ng/ml	12	4	2	0	0	0	0	0
Events, cumulative no.	13	27	33	39	45	50	52	54

b No. at risk

Undetectable ADT nadir	200	182	149	129	110	83	68	54
ADT nadir 0.01–0.2 ng/ml	38	31	23	14	6	3	1	1
ADT nadir >0.2 ng/ml	17	12	7	4	3	2	1	1
Events, cumulative no.	5	13	21	23	29	35	38	38

c No. at risk

Undetectable ADT nadir	202	183	152	131	115	89	73	56
ADT nadir 0.01–0.2 ng/ml	38	34	27	18	6	3	1	1
ADT nadir >0.2 ng/ml	19	14	10	6	5	3	2	1
Events, cumulative no.	1	5	8	11	16	21	23	27

Fig. 1.

(a) Cumulative incidence of castration-resistant prostate cancer by prostate-specific antigen (PSA) nadir on androgen-deprivation therapy (ADT) groups; (b) cumulative incidence of metastases by PSA nadir on ADT groups; (c) cumulative incidence of prostate cancer specific mortality by PSA nadir on ADT groups; all $n = 294$.

a No. at risk

	0	12	24	36	48	60	72	84	96
Undetectable ADT nadir	82	72	51	40	30	18	14	4	
ADT nadir 0.01–0.2 ng/ml	29	24	18	10	2	2	1	1	
ADT nadir >0.2 ng/ml	4	2	1	0	0	0	0	0	
Events, cumulative no.	4	7	9	12	14	14	14	14	15

b No. at risk

	0	12	24	36	48	60	72	84	96
Undetectable ADT nadir	82	72	51	41	31	18	14	5	
ADT nadir 0.01–0.2 ng/ml	30	26	18	11	3	2	1	1	
ADT nadir >0.2 ng/ml	5	3	2	1	1	1	0	0	
Events, cumulative no.	1	3	5	5	6	7	7	7	7

Fig. 2.

(a) Cumulative incidence of castration-resistant prostate cancer by prostate-specific antigen (PSA) nadir on androgen-deprivation therapy (ADT) groups in men with ultrasensitive PSA nadirs; (b) cumulative incidence of metastases by PSA nadir on ADT groups in men with ultrasensitive PSA nadirs; (c) cumulative incidence of prostate cancer-specific mortality by PSA nadir on ADT groups in men with ultrasensitive PSA nadirs; all $n = 149$.

Table 1
Baseline characteristics of men receiving early androgen-deprivation therapy by prostate-specific antigen nadir groups

Variable	All men	Undetectable	0.01–0.2 ng/ml	>0.2 ng/ml	p
Men, no. (%)	294 (100)	223 (76)	47 (16)	24 (8)	–
Pre-ADT PSA, ng/ml, median (IQR)	2.1 (0.5–6.3)	1.7 (0.4–4.8)	1.6 (0.53–7.3)	10.5 (6.1–16.4)	<0.001
Race, no. (%)					0.868
Black	109 (37)	81 (36)	19 (40)	9 (38)	
White	185 (63)	142 (64)	28 (60)	15 (62)	
Pathologic Gleason score, no. (%)					0.104
2–6	45 (15)	31 (14)	7 (15)	7 (29)	
7	161 (55)	128 (57)	26 (55)	7 (29)	
8–10	88 (30)	64 (29)	14 (30)	10 (42)	
Age at start of ADT, yr (IQR)	67 (60–72)	66 (60–72)	67 (59–74)	67 (61–72)	0.680
Lymph node metastasis, no. (%)	22 (7)	19 (9)	1 (2)	2 (8)	0.189
Extracapsular extension, no. (%)	137 (47)	110 (49)	17 (36)	10 (42)	0.228
Seminal vesicle invasion, no. (%)	98 (33)	79 (35)	10 (21)	9 (38)	0.157
Surgical margin status, no. (%)	190 (65)	146 (65)	32 (68)	12 (50)	0.278
Time to nadir, mo, median (IQR)	5.9 (3.2–10.1)	5.9 (3.2–9.4)	6.2 (3.2–13.5)	638 (3.3–10.6)	0.479
Intermittent ADT, no. (%)	29 (10)	20 (9)	9 (19)	0 (0)	0.025
ADT modality, no. (%)					0.001
LHRH agonist	184 (63)	152 (68)	23 (49)	9 (38)	
Bilateral orchiectomy	21 (7)	16 (7)	1 (2)	4 (17)	
CAB	89 (30)	55 (25)	23 (49)	11 (46)	
PSA test frequency during the first year of ADT, median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	0.730
PSA persistence after RP, no. (%)	198 (67)	148 (66)	30 (64)	20 (83)	0.207
PSA at first bone scan on ADT, ng/ml, median (IQR)*	0.4 (0–3.9)	0.1 (0–2)	0.5 (0.1–2.2)	9.5 (2.8–20.3)	<0.001
Secondary EBRT, no. (%)	153 (52)	116 (52)	26 (55)	11 (46)	0.751

ADT = androgen-deprivation therapy; PSA = prostate-specific antigen; IQR = interquartile range; LHRH = luteinizing hormone-releasing hormone; CAB = combined androgen blockade; RP = radical prostatectomy; EBRT = external-beam radiation therapy.

* n = 113 observations.

Table 2

Predictors of progression to castration-resistant prostate cancer*

Variable	HR	95% CI	p
<i>Univariable analysis</i>			
ADT PSA nadir relative to undetectable			
0.01–0.2 ng/ml	3.54	1.67–7.52	0.001
>0.2 ng/ml	36.17	17.47–74.89	<0.001
ADT PSA nadir, continuous	2.89	2.18–3.84	<0.001
Pre-ADT PSA, log-transformed	1.78	1.47–2.17	<0.001
Black race	0.86	0.49–1.52	0.606
Extracapsular extension	1.15	0.68–1.97	0.597
Seminal vesicle invasion	2.19	1.29–3.72	0.004
Surgical margin status	0.75	0.43–1.29	0.299
Pathologic Gleason sum relative to 2–6			
7	0.83	0.33–2.09	0.694
8–10	2.78	1.16–6.67	0.022
Age at the start of ADT	0.98	0.95–1.02	0.271
Calendar year of RP	0.99	0.93–1.04	0.635
Lymph node metastases	1.92	0.86–4.28	0.113
Time to ADT nadir	1.01	0.97–1.05	0.601
Salvage external-beam radiation therapy	1.03	0.61–1.76	0.903
PSA persistence after RP	1.73	0.91–3.29	0.093
<i>Multivariable analysis using PSA nadir ADT as a continuous variable</i>			
PSA nadir ADT	2.32	1.71–3.14	<0.001
Pre-ADT PSA, log-transformed	1.80	1.42–2.28	<0.001
Seminal vesicle invasion	2.12	1.22–3.67	0.007
Gleason sum 8–10 relative to 2–6	2.18	0.87–5.42	0.095
<i>Multivariable analysis using PSA nadir ADT as a categorical variable</i>			
PSA nadir ADT relative to undetectable			
0.01–0.2 ng/ml	5.14	2.33–11.32	<0.001
>0.2 ng/ml	44.42	18.84–104.75	<0.001
Pre-ADT PSA, log-transformed	1.81	1.37–2.37	<0.001
Seminal vesicle invasion	2.45	1.38–4.36	0.002
Gleason sum 8–10 relative to 2–6	3.96	1.54–10.20	0.004

HR = hazard ratio; CI = confidence interval; ADT = androgen-deprivation therapy; PSA = prostate-specific antigen; RP = radical prostatectomy.

*
n = 294; events = 55.

Table 3

Predictors of metastases*

Variable	HR	95% CI	p
<i>Univariable analysis</i>			
ADT PSA nadir relative to undetectable			
0.01–0.2 ng/ml	3.04	1.19–7.76	0.020
>0.2 ng/ml	16.50	8.33–32.70	<0.001
ADT PSA nadir, continuous	2.29	1.68–3.13	<0.001
Pre-ADT PSA, log-transformed	1.72	1.38–2.14	<0.001
Black race	0.78	0.40–1.53	0.471
Extracapsular extension	1.07	0.58–1.98	0.823
Seminal vesicle invasion	2.14	1.16–3.93	0.014
Surgical margin status	0.94	0.49–1.79	0.852
Pathologic Gleason sum relative to 2–6			
7	0.59	0.20–1.73	0.335
8–10	2.88	1.11–7.49	0.030
Age at the start of ADT	0.98	0.94–1.02	0.382
Calendar year of RP	0.98	0.92–1.05	0.626
Lymph node metastases	2.08	0.80–5.40	0.131
Time to ADT nadir	1.01	0.96–1.05	0.757
Salvage external-beam radiation therapy	1.31	0.71–2.42	0.393
PSA persistence after RP	1.25	0.63–2.49	0.520
<i>Multivariable analysis using PSA nadir ADT as a continuous variable</i>			
PSA nadir ADT	1.64	1.17–2.29	0.004
Pre-ADT PSA, log-transformed	1.73	1.33–2.25	<0.001
Seminal vesicle invasion	1.92	1.02–3.64	0.045
Gleason sum 8–10 relative to 2–6	1.56	0.58–4.18	0.374
<i>Multivariable analysis using PSA nadir ADT as a categorical variable</i>			
PSA nadir ADT relative to undetectable			
0.01–0.2 ng/ml	3.98	1.50–10.55	0.006
>0.2 ng/ml	12.42	5.85–26.37	<0.001
Pre-ADT PSA, log-transformed	1.61	1.20–3.84	0.002
Seminal vesicle invasion	2.00	1.04–3.84	0.038
Gleason sum 8–10 relative to 2–6	2.02	0.75–5.39	0.163

HR = hazard ratio; CI = confidence interval; ADT = androgen-deprivation therapy; PSA = prostate-specific antigen; RP = radical prostatectomy.

*
n = 294; events = 42.

Table 4

Predictors of prostate cancer specific mortality*

Variable	HR	95% CI	p
<i>Univariable analysis</i>			
ADT PSA nadir relative to undetectable			
0.01–0.2 ng/ml	4.01	1.40–11.50	0.010
>0.2 ng/ml	13.12	5.70–30.19	<0.001
ADT PSA nadir, continuous	2.21	1.55–3.14	<0.001
Pre-ADT PSA, log-transformed	1.73	1.34–2.24	<0.001
Black race	0.96	0.45–2.05	0.925
Extracapsular extension	0.98	0.48–2.00	0.957
Seminal vesicle invasion	2.36	1.16–4.82	0.018
Surgical margin status	0.67	0.33–1.37	0.273
Pathologic Gleason sum relative to 2–6			
7	0.997	0.27–3.71	0.997
8–10	3.42	1.01–11.62	0.048
Age at the start of ADT	0.99	0.94–1.04	0.582
Calendar year of RP	0.95	0.87–1.03	0.212
Lymph node metastases	1.61	0.48–5.41	0.439
Time to ADT nadir	1.02	0.98–1.07	0.316
Salvage external-beam radiation therapy	1.26	0.62–2.57	0.528
PSA persistence after RP	0.91	0.43–1.94	0.805
<i>Multivariable analysis using PSA nadir ADT as a continuous variable</i>			
PSA nadir ADT	1.51	1.03–2.22	0.034
Pre-ADT PSA, log-transformed	1.77	1.29–2.43	<0.001
Seminal vesicle invasion	1.99	0.93–4.24	0.075
Gleason sum 8–10 relative to 2–6	1.96	0.56–6.87	0.293
<i>Multivariable analysis using PSA nadir ADT as a categorical variable</i>			
PSA nadir ADT relative to undetectable			
0.01–0.2 ng/ml	5.33	1.78–15.97	0.003
>0.2 ng/ml	8.27	3.35–20.43	<0.001
Pre-ADT PSA, log-transformed	1.70	1.20–2.41	0.003
Seminal vesicle invasion	2.07	0.96–4.48	0.065
Gleason sum 8–10 relative to 2–6	2.31	0.67–7.98	0.187

HR = hazards ratio; CI = confidence interval; ADT = androgen-deprivation therapy; PSA = prostate-specific antigen; RP = radical prostatectomy.

*
n = 294; events = 31.