available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Prostate Cancer

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. Kane*[i], *Christopher L. Amling*[j], *Stephen J. Freedland*[a,b,*]

[a] *Duke University School of Medicine, Durham, NC, USA;* [b] *Veterans Affairs Medical Center, Durham, NC, USA;* [c] *University of California at Los Angeles Medical Center, Los Angeles, CA, USA;* [d] *Veterans Affairs Medical Center, Greater Los Angeles, Los Angeles, CA, USA;* [e] *Medical College of Georgia, Augusta, GA, USA;* [f] *Veterans Affairs Medical Center, Augusta, GA, USA;* [g] *Stanford University Medical Center, Palo Alto, CA, USA;* [h] *Veterans Affairs Medical Center, Palo Alto, CA, USA;* [i] *University of California at San Diego, San Diego, CA, USA;* [j] *Oregon Health and Science University, Portland, OR, USA*

Article info

Article history:
Accepted November 27, 2012
Published online ahead of print on December 6, 2012

Keywords:
Prostate cancer
Androgen-deprivation therapy
Prostate-specific antigen

Abstract

Background: A prostate-specific antigen (PSA) level <0.2 ng/ml 8 mo after starting 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.
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.

* 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.
E-mail addresses: steve.freedland@duke.edu, christopherjketo@yahoo.com (S.J. Freedland).

0302-2838/$ – see back matter Published by Elsevier B.V. on behalf of European Association of Urology.
http://dx.doi.org/10.1016/j.eururo.2012.11.052

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) have been 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

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.