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How Can Men Destined for Biochemical Failure After Androgen Deprivation and Radiotherapy be Identified Earlier?

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Abstract

Purpose—The significance of prostate-specific antigen (PSA) increases during the recovery of androgen after androgen deprivation therapy (ADT) and radiotherapy for prostate cancer is not well understood. This study sought to determine whether the initial PSA increase from undetectable after completion of all treatment predicts for eventual biochemical failure (BF).

Methods and Materials—Between July 1992 and March 2004, 163 men with a Gleason score of 8–10 or initial PSA level >20 ng/mL, or Stage T3 prostate cancer were treated with radiotherapy (median dose, 76 Gy) and ADT and achieved an undetectable PSA level. The first detectable PSA level after the cessation of ADT was defined as the PSA sentinel rise (SR). A PSA-SR of >0.25, >0.5, >0.75, and >1.0 ng/mL was studied as predictors of BF (nadir plus 2 ng/mL). Cox proportional hazards models were used for univariate and multivariate analyses for BF adjusting for pretreatment differences in Gleason score, stage, PSA level (continuous), dose (continuous), and ADT duration (<12 vs. ≥12 months).

Results—Of the 163 men, 41 had BF after therapy. The median time to BF was 25 months (range, 4–96). The 5-year BF rate stratified by a PSA-SR of ≤0.25 vs. >0.25 ng/mL was 28% vs. 43% ($p = 0.02$), ≤0.5 vs. >0.5 ng/mL was 30% vs. 56% ($p = 0.0003$), ≤0.75 vs. >0.75 ng/mL was 29% vs. 66% ($p < 0.0001$), and ≤1.0 vs. >1.0 ng/mL was 29% vs. 75% ($p < 0.0001$). All four PSA-SRs were independently predictive of BF on multivariate analysis.

Conclusion—The PSA-SR predicts for BF. A PSA-SR of >0.5 ng/mL can be used for early identification of men at greater risk of BF.

Keywords

Prostate cancer; Radiotherapy; Androgen deprivation therapy; Prostate-specific antigen; Biochemical failure

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Introduction

Monitoring the prostate-specific antigen (PSA) level is paramount to the surveillance of men after definitive treatment of prostate cancer. An increasing PSA level is predictive of the development of distant metastasis and death (1,2). The current standard definition of a biochemical failure (BF) after radiotherapy (RT) for prostate cancer is a PSA level >2 ng/mL more than the nadir PSA (nadir plus 2) (3). Although this definition is suitable for all men treated definitively with RT, it has been criticized for delaying the detection of an increasing PSA level after RT and androgen deprivation therapy (ADT).

The combination of RT and ADT is used widely for the treatment of intermediate and high-risk prostate cancer. With the initiation of ADT, the PSA level should become undetectable and remain there for the duration of androgen suppression. After the withdrawal of ADT, the PSA level has an opportunity to increase. Although not all increases in this setting predict for eventual nadir plus 2 BF (4), some sharp increases initially are worrisome. The significance of the early PSA kinetics after RT and ADT is not well understood. Our goal was to identify what initial PSA level after the withdrawal of ADT predicts for BF.

Methods and Materials

Between May 1, 1992 and December 31, 2004, 397 men with Stage T1c-T3 Nx-N0M0 (2002 American Joint Committee on Cancer) adenocarcinoma of the prostate were treated with definitive RT and concurrent ADT in the Department of Radiation Oncology at Fox Chase Cancer Center. All men underwent transrectal ultrasound-guided biopsy of the prostate before treatment. The T stage was determined solely from the palpation findings on digital rectal examination without upstaging from biopsy information or radiographic imaging. All pathology slides for cases diagnosed at referring institutions were reviewed at the Fox Chase Cancer Center. Cases with a discrepancy in diagnosis or grading with the outside institutions' findings were examined by a panel of oncologic pathologists until a consensus diagnosis was reached. All patients had a pretreatment PSA level available before treatment and had serial PSA values available after treatment.

Exclusion criteria were necessary to ensure that all men had a PSA increase for evaluation on the release of ADT. Men were excluded from the study population if (1) an undetectable PSA level was not achieved during ADT ($n = 66$), (2) the PSA level increased during ADT (*e.g.*, androgen-insensitive disease, $n = 17$), or (3) the PSA level did not increase after the release of ADT ($n = 130$). An additional 23 patients did not have at least one PSA value after the nadir and were excluded from the study. An undetectable PSA level was defined as ≤ 0.2 ng/mL. This was used to eliminate the bias associated with more sensitive PSA assays in the latter part of this study. A total of 163 men remained and were the focus of this study.

Treatment and follow-up

Three-dimensional conformal RT ($n = 118$) and intensity-modulated RT (IMRT) ($n = 45$) techniques were used. Our three-dimensional conformal RT and IMRT techniques have been previously reported (5,6). The patients were treated in the supine position in a custom-made alpha cradle for immobilization. The radiation dose reported here was the International Commission of Radiation Units and Measurements reference dose (7). The dose was prescribed to the 95% isodose of the beam arrangements and normalized so that the planning target volume was included within the 95% isodose line. All patients were treated with 10–18-MV photons. The IMRT patients were treated with 10-MV photons. The median total dose for all patients was 76 Gy (range, 62–83 Gy). ADT was accomplished with a luteinizing hormone-releasing hormone agonist alone. The proportion of men receiving an antiandrogen was 66%. Of the 163 men, 55 (34%) received flutamide, 51 (31%) bicalutamide, and 1 nilandron. The median ADT

duration was 12 months (range, 4–53 months). Of the 163 men, 52% received <12 months of ADT and 71% received <24 months.

Follow-up typically consisted of serum PSA determination 3 months after RT completion, every 6 months for 2 years, and every 6–12 months thereafter. Digital rectal examinations were typically performed at 3 months after RT completion and then at 6–12 months. The median follow-up was 72 months (range, 16–156 months). For the 130 men who did not have a PSA increase after the release of ADT, the median follow-up was 47 months (range, 4–137 months). BF was defined as the nadir (undetectable) PSA level plus 2.0 ng/mL. The interval to BF was measured from ADT completion. Serum testosterone was not routinely measured during the study period; therefore, recovery from androgen suppression could not be formally established. It was assumed that recovery from hormone suppression was evidenced by an increase in the PSA level. Therefore, the first increase in PSA after the release of ADT from the PSA nadir (*i.e.*, undetectable or ≤ 2 ng/mL) was the focus of this study. This initial increase has been referred to as the PSA sentinel rise (SR).

Statistical analysis

We examined the relationship of the PSA-SR and the rate of BF. SRs of >0.25, >0.5, >0.75, and >1.0 ng/mL were analyzed. The distributions of freedom from BF were calculated using the Kaplan-Meier product limit method. The Mantel log-rank test was used to compare the BF rates. Cox proportional hazards regression analysis was used to identify factors associated with BF on univariate analysis (8). Stepwise logistic regression analysis was performed for multivariate analysis, including Gleason score, T stage, initial PSA level, radiation dose, ADT duration, and PSA-SR (*i.e.*, >0.25, >0.50, >0.75, or >1.0 ng/mL). A *p* value ≤ 0.05 was considered statistically significant; all analyses were done using Statistical Analysis Systems statistical software (SAS Institute, Cary, NC). To further understand the relationship between PSA-SR and BF, the PSA-SR was analyzed as a categorical variable with five intervals determined by the cutpoints (*i.e.*, 0.10–0.25, 0.26–0.50, 0.51–0.75, 0.76–1.00, and >1.00 ng/mL). Cox multivariate analysis (adjusting for Gleason score, pretreatment PSA level, and T stage) was performed to assess the risk of BF for each PSA-SR interval compared with the smallest interval (0.10–0.25 ng/mL). The institutional review board approved the data collection and outcome analysis of patients in the institutional database.

Results

Patient and follow-up characteristics

Various clinical, pathologic, and treatment variables for the study population are shown in Table 1. Of the 163 men, 73% were considered to have high-risk prostate cancer defined as Stage T3, Gleason score 8–10, or pretreatment PSA level >20 ng/mL. The median pretreatment PSA level was 17.1 ng/mL (range, 1.8–137 ng/mL). The median interval from ADT completion to the PSA-SR was 6.3 months (range, 1–60 months).

In this cohort, including only men with a detectable PSA level after ADT withdrawal, 41 BFs occurred after therapy, representing 25% of the population. The median PSA-SR was 0.4 ng/mL (range, 0.2–8.4 ng/mL). The median time to BF after completion of all therapy was 25 months (range, 4–96 months).

Univariate and multivariate analyses

Figures 1–4 show the Kaplan-Meier estimates of freedom from biochemical failure stratified by four PSA-SR values (>0.25, >0.50, >0.75, and >1.0 ng/mL). Each PSA-SR was a statistically significant cutpoint for eventual BF. The multivariate results are shown in Table 2. All SRs tested were independently predictive of BF. The hazard ratio for BF with a PSA-SR of >0.25

ng/mL ($n = 59$), >0.50 ng/mL ($n = 25$), >0.75 ng/mL ($n = 17$), and >1.0 ng/mL ($n = 12$) was 2.0, 3.7, 5.4, and 6.0, respectively. In the same model, a PSA-SR >0.5 ng/mL was predictive of distant metastasis ($n = 5$, $p = 0.03$) but not overall survival ($n = 28$). When all cutpoints were included in the multivariate analysis, only the Gleason score was significant (data not shown). The interval to a PSA-SR >0.5 ng/mL was also studied in a model that included the Gleason score, T stage, pretreatment PSA level, radiation dose, ADT duration, and PSA-SR >0.5 ng/mL; however, it was not predictive of BF and did not significantly alter the results (data not shown).

Figure 5 shows the results of a Cox multivariate analysis with PSA-SR stratified into five intervals and illustrates the increasing risk of BF with increasing PSA-SR. Five intervals were analyzed as a hazard ratio relative to the smallest interval SR. PSA-SR (Wald chi-square = 19.0, $p = 0.0008$) and Gleason score ($p = 0.012$) were significant predictors of BF in a model including T stage and pretreatment PSA level. In this model, the estimated hazard ratio for a PSA change of >1 ng/mL compared with the smallest group was 6.4 ($p < 0.0001$); the hazard ratios for the other PSA change groups were not statistically significant ($p > 0.05$).

Discussion

Routine follow-up after therapy for high-risk prostate cancer includes interval PSA measurements, with PSA usually becoming undetectable during ADT. The withdrawal of ADT typically leads to an increase in the PSA level. This is often a time of great trepidation for the patient and uncertainty for the clinician. It can take months to years before it is truly known whether the PSA is normalizing with the reinstitution of testosterone or the patient is destined for BF. We have identified early characteristics of this initial PSA increase that are predictive of BF.

Men receiving ADT typically have intermediate- to high-risk prostate cancer and therefore are at a greater risk of BF. BF has been shown to precede distant metastasis and death (9,10). Earlier identification of BF is therefore paramount for effective salvage therapy. Many series have studied the predictors of various outcomes after the use of ADT, such as Gleason score and PSA nadir, both of which have been shown to correlate with outcome (11–14). To our knowledge, this is the first report specifically addressing the initial post-ADT PSA level to identify men at increased risk of eventual BF.

We examined the value of the initial absolute increases after withdrawal of ADT on subsequent BF. We have called this the “sentinel rise.” Four discrete SR cutpoints were examined: >0.25 , >0.5 , >0.75 , and >1.0 ng/mL. Each SR we explored was a statistically significant predictor of eventual BF. The Gleason score was the only other predictor for BF in this cohort. Figures 1–4 give the rates of freedom from biochemical failure at 5 years stratified by SR. The implication of the SR is important for both prognostic information and earlier intervention, such as more frequent PSA measurements or the reinstitution of ADT. Although these data suggest that all men should be monitored closely after the release of ADT, a PSA-SR >0.5 ng/mL appears to be the most clinically significant cutpoint for the purpose of recommending more frequent PSA evaluations to detect BF early. Early BF has been shown to predict for an increased risk of distant metastasis and prostate cancer-specific mortality (15). The 5-year freedom from biochemical failure rate for 15% of the population studied ($n = 25$) with a PSA-SR >0.5 ng/mL was 44% compared with 70% when the PSA-SR was ≤ 0.5 ng/mL. The median PSA-SR in this study was 0.4 ng/mL.

The weaknesses of this study were its retrospective nature and the lack of testosterone measurement for the establishment of the release of androgen suppression. Patient selection bias, patient preference, and limited statistical power might explain why the ADT duration was

not a significant predictor of outcome in this series. Serum testosterone levels are now routinely measured, along with PSA. In the present study, men who did not have any increase in PSA level greater than their nadir were presumed to have permanent androgen suppression. It is possible that some patients have a return of testosterone but continue to have a nadir PSA level that does not increase. In contrast, some men might have an increase in their PSA level but still have suppressed testosterone levels; these latter men probably represent a population of patients with a worse prognosis. A prospective evaluation of the PSA-SR after ADT, along with testosterone data, will be necessary to support these data.

Conclusion

After RT and ADT for prostate cancer, the PSA-SR predicts for BF. On the basis of our findings, a PSA-SR >0.5 ng/mL appears to be the most clinically useful. These data can be used on an individual patient basis to address the risk of BF with closer follow-up, including more frequent PSA measurements. Through closer and more careful monitoring, early salvage therapy or participation in a clinical trial could be recommended. Additional studies are needed to confirm these observations and establish an ideal PSA-SR cutpoint.

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References

1. Lee WR, Hanks GE, Hanlon A. Increasing prostate-specific antigen profile following definitive radiation therapy for localized prostate cancer: Clinical observations. *J Clin Oncol* 1997;15:230–238. [PubMed: 8996147]
2. Ritter MA, Messing EM, Shanahan TG. Prostate-specific antigen as a predictor of radiotherapy response and patterns of failure in localized prostate cancer. *J Clin Oncol* 1992;10:1208–1217. [PubMed: 1378886]
3. Roach M III, Hanks G, Thames H Jr, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006;65:965–974. [PubMed: 16798415]
4. Buyyounouski MK, Hanlon AL, Pollack A. The temporal kinetics of PSA after 3D-conformal radiotherapy with androgen deprivation. *Int J Radiat Oncol Biol Phys* 2005;61:1291–1298. [PubMed: 15817330]
5. Horwitz EM, Hanlon AL, Pinover WH, et al. Defining the optimal radiation dose with three-dimensional conformal radiation therapy for patients with nonmetastatic prostate carcinoma by using recursive partitioning techniques. *Cancer* 2001;92:1281–1287. [PubMed: 11571744]
6. Price RA, Murphy S, McNeeley SW, et al. A method for increased dose conformity and segment reduction for SMLC delivered IMRT treatment of the prostate. *Int J Radiat Oncol Biol Phys* 2003;57:843–852. [PubMed: 14529792]
7. Monti AF, Ostinelli A, Frigerio M, et al. An ICRU 50 radiotherapy treatment chart. *Radiother Oncol* 1995;35:145–150. [PubMed: 7569023]
8. Cox R. Regression models and life tables. *J Royal Stat Soc* 1972;34:187–220.
9. Pollack A, Hanlon AL, Movsas B, et al. Biochemical failure as a determinant of distant metastasis and death in prostate cancer treated with radiotherapy. *Int J Radiat Oncol Biol Phys* 2003;57:19–23. [PubMed: 12909210]

10. Horwitz E, Vicini F, Ziaja E, et al. The correlation between the ASTRO consensus panel definition of biochemical failure and clinical outcome for patients with prostate cancer treated with external beam irradiation. *Int J Radiat Oncol Biol Phys* 1988;41:267–272. [PubMed: 9607340]
11. 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;23:6556–6560. [PubMed: 16170163]
12. Neesha A, Rodrigues NA, Chen MH, et al. Predictors of mortality after androgen-deprivation therapy in patients with rapidly rising prostate-specific antigen levels after local therapy for prostate cancer. *Cancer* 2006;107:514–520. [PubMed: 16795068]
13. Buyyounouski MK, Hanlon AL, Eisenberg DF, et al. Defining biochemical failure after radiotherapy with and without androgen deprivation for prostate cancer. *Int J Radiat Oncol Biol Phys* 2005;63:1455–1462. [PubMed: 16169682]
14. Hanlon AL, Diratzouian H, Hanks GE. Posttreatment prostate-specific antigen nadir highly predictive of distant failure and death from prostate cancer. *Int J Radiat Oncol Biol Phys* 2002;53:297–303. [PubMed: 12023133]
15. Buyyounouski MK, Horwitz EM, Pollack A. Interval to biochemical failure is highly prognostic for distant metastasis and prostate cancer-specific mortality following radiotherapy. *Int J Radiat Oncol Biol Phys*. 2007in press

Fig. 1. Freedom from biochemical failure (BF) using prostate-specific antigen (PSA) sentinel rise of 0.25 ng/mL. RT = radiotherapy; AD = androgen deprivation.

Fig. 2. Freedom from biochemical failure (BF) using prostate-specific antigen (PSA) sentinel rise of 0.5 ng/mL. RT = radiotherapy; AD = androgen deprivation.

Fig. 3. Freedom from biochemical failure (BF) using prostate-specific antigen (PSA) sentinel rise of 0.75 ng/mL. RT = radiotherapy; AD = androgen deprivation.

Fig. 4.

Freedom from biochemical failure (BF) using prostate-specific antigen (PSA) sentinel rise of 1.0 ng/mL. RT = radiotherapy; AD = androgen deprivation.

Fig. 5.
Hazard ratios for biochemical failure (BF) stratified by prostate-specific antigen (PSA) sentinel rise.

Table 1

Various patient- and treatment-related characteristics

Variable	Median (range)	n (%)
Age (y)	68 (45–83)	163 (100)
T1-T2		117 (72)
T3		46 (28)
Gleason score	7 (3–10)	
3–6		54 (33)
7		60 (37)
8–10		49 (30)
Pretreatment PSA (ng/mL)	17.1 (1.8–137)	
<10		53 (33)
10–20		47 (28)
>20		63 (39)
Radiation dose (Gy)	76 (62–83)	
ADT duration (mo)		
<12	3.8 (0.9–11.8)	85 (52)
≥12	25.7 (12.0–53.0)	78 (48)
Follow up (mo)	65 (10–167)	

Abbreviations: PSA = prostate-specific antigen; ADT = androgen deprivation therapy.

Table 2

Various multivariate analysis results for biochemical failure

Variable	Baseline	Hazard ratio	95% CI	p
PSA-SR	>0.25 ng/mL	2.0	1.1–3.8	0.03
Gleason score	≥7	2.5	1.1–5.5	0.02
T stage	T3	1.3	0.7–2.5	NS
Pretreatment PSA	Higher *	1.0	1.0–1.0	NS
Radiation dose (Gy)	Higher *	1.0	0.9–1.1	NS
ADT duration	≥12 mo	0.9	0.5–1.8	NS
PSA-SR	>0.5 ng/mL	3.7	1.8–7.8	0.0004
Gleason score	≥7	2.9	1.3–6.7	0.01
T stage	T3	1.5	0.8–3.0	NS
Pretreatment PSA	Higher *	1.0	1.0–1.0	NS
Radiation dose (Gy)	Higher *	1.0	0.9–1.1	NS
ADT duration	≥12 mo	0.7	0.3–1.4	NS
PSA-SR	>0.75 ng/mL	5.4	2.5–12	<0.0001
Gleason score	≥7	2.8	1.3–6.4	0.01
T stage	T3	1.4	0.7–2.6	NS
Pretreatment PSA	Higher *	1.0	1.0–1.0	NS
Radiation dose (Gy)	Higher *	1.0	0.9–1.1	NS
ADT duration	≥12 mo	0.9	0.5–1.9	NS
PSA-SR	>1.0 ng/mL	6.0	2.7–13.6	<0.0001
Gleason score	≥7	2.4	1.1–5.4	0.03
T stage	T3	1.3	0.7–2.4	NS
Pretreatment PSA	Higher *	1.0	1.0–1.0	NS
Radiation dose (Gy)	Higher *	1.0	0.9–1.1	NS
ADT duration	≥12 mo	0.9	0.5–1.9	NS

Abbreviations: SR = sentinel rise; CI = confidence interval; NS = not significant; other abbreviations as in Table 1.

* Continuous variable.