Biochemical and Clinical Significance of the Posttreatment Prostate-Specific Antigen Bounce for Prostate Cancer Patients Treated With External Beam Radiation Therapy Alone

A Multiinstitutional Pooled Analysis

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BACKGROUND. The posttreatment prostate-specific antigen (PSA) bounce phenomenon has been recognized in at least 20% of all patients treated with radiation. The purpose of the current report was to determine if there was a difference in biochemical and clinical control between the bounce and nonbounce (NB) patients using pooled data on 4839 patients with T1-2 prostate cancer treated with external beam radiation therapy (RT) alone at 9 institutions between 1986 and 1995.

METHODS. The median follow-up was 6.3 years. A posttreatment PSA bounce was defined by a minimal rise of 0.4 ng/mL over a 6-month follow-up period, followed by a drop in PSA level of any magnitude. Endpoints included no biochemical evidence of disease (bNED) failure (BF) (ASTRO definition), distant failure (DF), cause-specific failure (CSF), and overall survival (OS). Patients were stratified by pretreatment PSA, Gleason score, T stage, age, dose, and risk group.

RESULTS. In all, 978 (20%) patients experienced at least 1 posttreatment PSA bounce. Within 3 subgroups (risk group, pretreatment PSA, and age), statistically significant differences of remaining bounce-free were observed on univariate analysis. Patients < 70 years had a 72% chance of remaining bounce-free at 5 years compared with 75% for older patients ($P = .04$). The NB patients had 72% bNED control at 10 years compared with 58% for the bounce patients. The effect of a bounce remained statistically significant on multivariate analysis ($P < .0001$). No statistically significant difference in DF, CSF, or OS was observed.

CONCLUSIONS. Patients treated with external beam radiation therapy alone who experience a posttreatment PSA bounce have increased risk of BF. However, this did not translate into a difference in clinical failure with the available follow-up in the current study. ***Cancer* 2006;107:1496–502.** © *2006 American Cancer Society.*

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The posttreatment prostate-specific antigen (PSA) bounce phenomenon was first recognized in patients treated with combined

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external beam radiation therapy (EBRT) and permanent prostate implants. In a study by Critz et al.[1] in 2000, 30% of patients treated with both an implant and EBRT experienced a bounce. At first, the PSA bounce was thought to be unique to these patients; however, Hanlon et al.[2] reported that 30% of patients treated with 3D conformal EBRT alone also experienced PSA bounces after treatment. Additional data from Cavanagh et al.[3] and Rosser et al.[4] supported the general recognition that the PSA bounce phenomenon is common in patients treated with radiation and is not modality-specific.

Whereas these series described the frequency, timing, and magnitude of the bounce, the available data on its clinical significance is scarce. Were there different biochemical and clinical control rates between patients with a bounce and those without? Can physiological and interassay variations of the PSA test itself be separated from a true bounce? In 2002, 9 institutions combined data on almost 5000 patients treated with EBRT, and we presented our main results in several prior reports.[5–7] The purpose of this analysis is to determine the biochemical and clinical significance of the PSA bounce in patients treated with EBRT alone using the power of large patient numbers and long follow-up of this multiinstitutional pooled dataset.

MATERIALS AND METHODS

Patient Population

Nine participating institutions with long-term patient follow-up collaborated in this study. These institutions included the Cleveland Clinic, Fox Chase Cancer Center, Mallinckrodt Institute of Radiology at Washington University, Massachusetts General Hospital, Mayo Clinic-Rochester, Memorial Sloan-Kettering Cancer Center, University of Michigan, University of Texas M. D. Anderson Cancer Center, and William Beaumont Hospital. Institutional Review Board approval was obtained by each principal investigator at each participating institution before the data were transferred to a single statistical center. Informed consent was obtained from each subject per institutional guidelines. Data on 4839 patients with clinical AJCC staging system (2002) Stage T1b, T1c and T2N0M0 biopsy-proven adenocarcinoma of the prostate were combined into a unified study database. The percentage of patients con-tributed by each institution ranged from 6% to 16% of the total study population.

All patients had a pretreatment PSA level. No patient received planned androgen suppression therapy before, during, or after radiation therapy (RT). Only patients treated at least 5 years before the date of data submission were included to ensure relatively long-term follow-up, such that the study period was predefined as extending from January 1986 through December 1995. The clinical characteristics of the patients and tumors are described in Table 1.

TABLE 1
Pretreatment Patient and Tumor Characteristics for the Patients in This Analysis

Pretreatment PSA level (ng/mL)	No. of patients (%)
0–3.9	631 (13.0)
4.0–9.9	2000 (41.3)
10–19.9	1313 (27.1)
20.0–29.9	427 (8.8)
30+	468 (9.7)
Gleason score	
2–4	781 (16.1)
5–6	2335 (48.3)
7	1034 (21.4)
8–0	418 (8.6)
Unknown	271 (5.6)
T classification*	
T1b	305 (6.3)
T1c	1048 (21.7)
T2a	1412 (29.2)
T2b	1257 (26.0)
T2c	778 (16.1)
T1-T2	39 (0.8)
Age (y)	
40–64	883 (18.2)
65–69	1072 (22.2)
70+	2719 (56.2)
Unknown	165 (3.4)
Nadir PSA level (ng/mL)	
0–0.49	1654 (34.2)
0.50–0.99	1498 (31.0)
1.00–1.99	1025 (21.2)
2+	661 (13.7)
Unknown	1 (—)

PSA indicates prostate-specific antigen.
* T classification according to the 2002 AJCC staging system.

Treatment

Details concerning treatment technique and biochemical and clinical outcome have been reported elsewhere.[5,7] In brief, the technique and dose varied by treatment year and institution, with a trend toward higher doses and more conformal techniques in later years. All patients received at least 60 Gy to the prostate. For the group treated to < 70 Gy, the median dose was 67 Gy, and for the group treated to ≥ 70 Gy, the median was 72 Gy. These were also the median doses for all 3 risk groups[6] for the 70 Gy cutpoint. Median doses for patients treated to < 72 Gy versus ≥ 72 Gy were 67 Gy and 76 Gy, respectively.

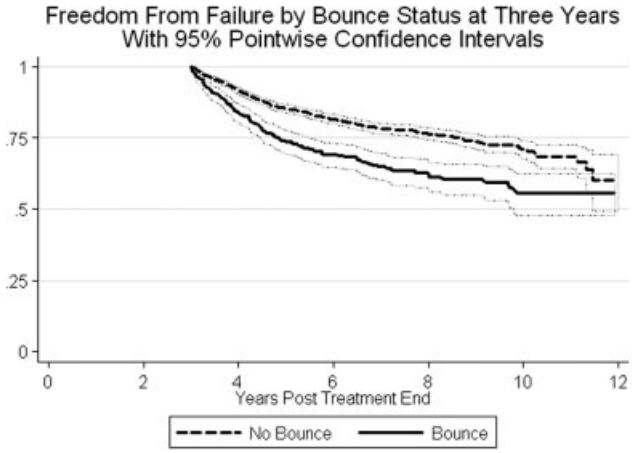

FIGURE 1. Freedom from biochemical failure (FBF) for the entire dataset for the bounce and nonbounce patients.

These were the median doses for the low and intermediate risk groups based on the 72 Gy cutpoint, whereas the high-risk patients treated to < 72 Gy received a median dose of 68 Gy versus a median of 76 Gy for those treated to ≥ 72 Gy. Seventy percent of patients were treated with conventional and 30% with 3D conformal techniques.

Biochemical and Clinical Endpoints

Treatment outcome was measured in terms of biochemical (PSA) and clinical disease-free survival. Biochemical failure was defined according to the ASTRO definition, which is the only current consensus definition,[8] and patients without biochemical failure were considered to have no biochemical evidence of disease (bNED). Clinical failure (CF) was defined as documentation of local, regional, or distant disease recurrence (using imaging or biopsy evidence). A distant failure (DF) was considered to have occurred only if the patient had clinical or radiographic signs of distant metastatic disease. Patients who died of causes other than prostate cancer were censored at the time of death. Follow-up frequency with PSA levels between participating institutions varied, although most patients had 2 to 4 PSA levels per year for the first 5 years and 1 to 2 PSA levels each year thereafter. Median follow-up was 6.8 years (range, 0.56–15.4 years). Two thousand and forty-nine patients were still available for analysis at 5 years, 616 at 8 years, and 179 at 10 years after RT.

A posttreatment PSA bounce was defined by a minimal rise of 0.4 ng/mL over a 6-month follow-up period, followed by a drop in PSA level of any magnitude. Overall biochemical and clinical control was determined for the group and univariate (UVA) and multivariate (MVA) analyses were performed. Patients were also stratified into 3 risk groups based on prognosis to determine if this was associated with a PSA bounce. The 3 groups included low risk (Group 1), T1/2a, Gleason score (GS) ≤ 6 and PSA ≤ 10 ng/mL; intermediate risk (Group 2), T1/2a, GS ≤ 7 and PSA 10–20 ng/mL or T2b/c,GS ≤ 7 and PSA ≤ 20 ng/mL; high risk (Group 3), GS 8–10 or PSA > 20 ng/mL. An additional analysis was also performed to determine if the PSA bounce could be a function of laboratory error or act as a surrogate for a high nadir PSA. Data management and statistical calculations were done using Stata 7.0[9] and SAS 8.2[10] software.

RESULTS

A posttreatment PSA bounce was observed in 978 (20%) patients. Seven hundred twenty-one patients experienced 1 bounce, whereas 257 patients had multiple bounces. bNED control for the patients with bounce (B) was 58% versus 72% for nonbounce (NB) at 10 years. This difference was statistically significant ($P < .0001$) (Fig. 1). A significant difference in the clinical endpoints of distant failure (DF), cause-specific survival (CSS), and overall survival (OS) between the B and NB patients was not observed (Table 2). However, it should be noted that there was much attrition in this series, as expected. Of the 3796 patients at risk at 3 years, 342 were still at risk and under observation at 10 years. With the attrition observed in this series, there was 80% power to detect a hazard ratio (HR) of at least 1.97 for distant failure. With no loss to attrition, there would have been 80% power to detect an HR of at least 1.73. The observed HR for distant failure was 1.17 ($P = .49$) with a 95% confidence interval of (0.76,1.79). The median height of the bounce was greater for patients receiving < 70 Gy compared with ≥ 70 Gy (0.8 vs. 0.7) but this did not translate into statistically significant differences in bNED status (26.4% vs. 26.1%, $P = .87$). Radiation dose did not affect the frequency or number of bounces.

Univariate Analysis

Within 3 subgroups (risk group, pretreatment PSA, and age), statistically significant differences of remaining bounce-free were observed on UVA analysis using the log-rank test. Patients < 70 years had a 72% chance of remaining bounce-free at 5 years compared with 75% for older patients ($P = .04$) (Table 3). Using the Wald chi-square test, UVA of the subsets (risk group, PSA, GS, T stage, age, and dose) demonstrated that the effect of bounce on subse-

TABLE 2
10-Year Freedom from Biochemical and Clinical Failure Based on Bounce Status at 3 Years

	No bounce by 3 years, %			Bounce by 3 years, %			
Event	Estimate	Lower	Upper	Estimate	Lower	Upper	*P*
Biochemical control	71.9	68.8	74.8	57.9	51.0	64.1	<.0001
Distant metastases-free survival	94.7	93.3	95.8	92.9	89.3	95.3	.485
Cause-specific survival	92.3	90.0	94.0	92.7	87.6	95.8	.720
Overall survival	65.3	62.4	68.0	68.0	62.1	73.1	.312

TABLE 3
Univariate Predictors of PSA Bounce at 5 Years

Factor	Level	5-year bounce-free, %	Log-rank *P*
Risk group*	1	75.9	
	2	73.9	.0008
	3	66.5	
Pretreatment PSA	0–9.9	77.5	
	10–19.9	68.9	<.0001
	20.0+	62.8	
Gleason score	2–6	73.7	
	7	72.0	.485
	8–10	74.8	
T classification†	T1b,T1c,T2a	73.7	.895
	T2b,T2c	73.3	
Age	≤70 y	71.7	.043
	>70 y	75.1	
Radiation dose	≤7000 cGy	73.6	.872
	>7000 cGy	73.9	

PSA indicates prostate-specific antigen; GS, Gleason score.
* Risk group 1 (low risk): T1/2a, GS ≤ 6 and PSA ≤ 10 ng/mL (low risk); Risk group 2 (intermediate risk): T1/2a, GS ≤ 7 and PSA 10–20 ng/mL or T2b/c, GS ≤ 7 and PSA ≤ 20 ng/mL; Risk group 3 (high risk): GS 8–10 or PSA > 20 ng/mL.
† T classification according to the 2002 AJCC staging system.

TABLE 4
Effect of PSA Bounce on Subsequent Biochemical Failure

	Subset	Hazard ratio	*P*
	Overall	1.73	<.0001
Risk group*	1	1.48	.048
	2	1.72	<.0001
	3	1.89	.0007
Pretreatment PSA	0–9.9	1.65	.0002
	10–19.9	1.53	.009
	20.0+	1.93	.0012
Gleason score	2–6	1.68	<.0001
	7	1.97	.0005
	8–10	1.67	.150
T classification†	T1b,T1c,T2a	1.70	<.0001
	T2b,T2c	1.78	<.0001
Age	≤70 y	1.80	<.0001
	>70 y	1.66	<.0001
Radiation dose	≤7000 cGy	1.69	<.0001
	>7000 cGy	1.81	.0002

PSA indicates prostate-specific antigen; GS, Gleason score.
* Risk group 1 (low risk): T1/2a, GS ≤ 6 and PSA ≤ 10 ng/mL (low risk); Risk group 2 (intermediate risk): T1/2a, GS ≤ 7 and PSA 10–20 ng/mL or T2b/c, GS ≤ 7 and PSA ≤ 20 ng/mL; Risk group 3 (high risk): GS 8–10 or PSA > 20 ng/mL.
† T classification according to the 2002 AJCC staging system.

quent bNED was statistically significant across all the groups except GS 8–10 (Table 4).

Multivariate Analysis

When controlling for the effect of pretreatment PSA, GS, and EBRT dose, the effect of a bounce remained statistically significant on MVA (HR 1.67, $P < .0001$). Pretreatment PSA, GS, and dose were independent predictors of bounce magnitude. The predicted median bounce for patients with PSA < 10, Gleason 2–6, and dose < 7000 cGy is 0.65 ng/mL based a multivariate median regression. The effect on bounce for each pretreatment or treatment variable is shown in Table 5. This information can be used to calculate the predicted median bounce for patients in different prognostic groups. The predicted median bounce for patients with a pretreatment PSA > 20, Gleason 2–6, and dose > 7000 cGy would be 0.90 ng/mL (0.65 ng/mL + 0.40 ng/mL +0.00 ng/mL − 0.15 ng/mL = 0.90 ng/mL) (Table 5).

PSA Nadir and Bounce

To determine the relation between nadir, bounce, and bNED, the data were divided into 4 approximately equal size groups based on 3-year nadir (0.0–0.30, 0.31–0.57, 0.60–1.00, and > 1.00 ng/mL). The freedom from failure was compared between those that experienced a bounce by 3 years and those that did not experience a bounce by 3 years within each of the four nadir groups. In 3 of the 4 nadir groups, the B patients did worse than the NB patients. In 1 of the groups (0.31–0.57 ng/mL), there was no statistically significant difference between the B and NB patients (Fig. 2).

TABLE 5
Multivariate Analysis on PSA Bounce Height

Base group*	Strata	0.65
Pretreatment PSA	<10	0.00
	10–19.9	0.15
	20.0+	0.40
Gleason score	2–6	0.00
	7	0.15
	8–10	0.20
Radiation dose	≤7000 cGy	0.00
	>7000 cGy	−0.15

PSA inidicates prostate-specific antigen.
* Base group is PSA < 10 ng/mL and Gleason score 2–6 and radiation dose < 7000 cGy. The predicted median bounce is 0.65 for this group.

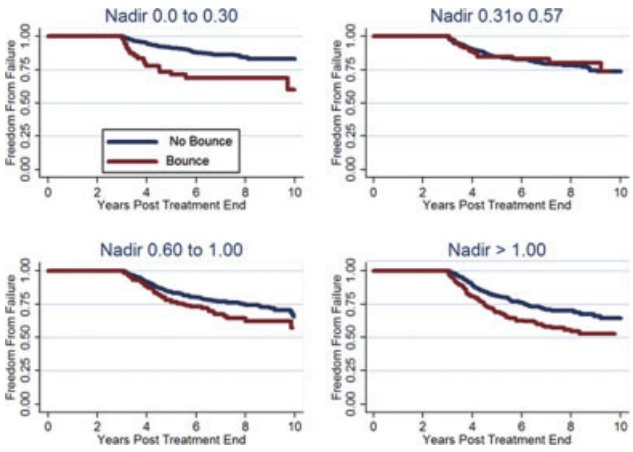

FIGURE 2. Relation between posttreatment prostate-specific antigen (PSA) nadir, bounce, and freedom from biochemical failure.

DISCUSSION

In this study we examined and report the clinical significance of the post-EBRT PSA bounce and found that patients who experience a posttreatment PSA bounce have an increased risk of biochemical failure. However, this did not translate into a difference in clinical failure during the available duration of follow-up. The PSA bounce was first reported in 1997 by Wallner et al.[11] and in 2000 by Critz et al.[1] In that report, the PSA bounce phenomenon was described in a series of 779 early-stage patients treated with permanent prostate implants and EBRT. In this group, a transient rise in PSA was found in 35% of the patients. The bounce was defined as an increase of 0.1 ng/mL or greater above the preceding level followed by a subsequent decrease below that level. The median time to the bounce was 18 months and more than 90% occurred within 3 years. The median bounce height was 0.4 ng/mL (0.1–15.8 ng/mL). No independent predictors of bounce were identified and no clinical or biochemical correlation was made with the bounce.[1] Cavanaugh et al.[3] made similar observations in 591 patients treated with implants with or without EBRT at the Seattle Prostate Institute. Fifty percent of these patients received an I-125 prostate implant alone, 20% were treated with Pd-103, and about one-quarter were treated with combination EBRT and an implant. As with the Critz et al.[1] report, one-third of patients had a PSA bounce within 3 years. This group defined a bounce as a temporary increase ≥ 0.2 ng/mL. The median time to the bounce was 20.4 months and there was no correlation between PSA bounce and clinical or biochemical failure.[3]

Although the PSA bounce was first identified in implant patients, this phenomena is not unique to this treatment modality and instead appears related to radiation treatment in general. These first 2 reports focused on patients that had at least part of their treatment with an implant. Hanlon et al.[2] reported the Fox Chase Cancer Center experience with patients treated with 3D conformal EBRT alone. In this series, 306 patients received a median radiation dose of 74 Gy. The PSA bounce was defined as a minimum rise of 0.4 ng/mL over 6 months, followed by a drop of any magnitude. As with the implant series, one-third of patients bounced. Lower radiation doses (73 Gy vs. 75 Gy) and higher pretreatment PSA levels were independent predictors of bounce. This was the first series to suggest that patients who bounced had lower rates of bNED control, 69% versus 52% at 5 years ($P = .0024$). No clinical correlation was observed with a median follow-up of 79 months.[2] The findings in the present study mirror those seen in the Fox Chase series where decreased bNED control rates did not translate into inferior clinical control, which may be a function of the ASTRO definition requirement of several consecutive rises. Both studies had long follow-up, although the present study had significantly larger patient numbers with a greater range of doses. One study that reported contrary results was that by Rosser et al.[4] In that study, 964 patients were also treated with EBRT alone. A lower percentage of patients experienced a bounce (12%) and those who bounced had improved bNED control at 5 years (82.1% vs. 57.7%). The dose range was more constrained in that study and the bounce was unrelated to age, race, PSA, Gleason score, T stage, and dose.[4] No large series have directly compared EBRT alone to treatment with an implant alone, so no specific conclusion can be made about how different the bounce is between modalities, but possible explanations for these differences could be related to the dose intensification effect of brachytherapy and the different patient populations between the 2 radiation techniques.

Recent series have focused on both identifying independent predictors of the PSA bounce and determining its effect on outcome. Merrick et al.[12] identified younger age, T stage, first implant PSA, and V150 (the volume of prostate receiving 150% of the prescribed dose) as predictors of PSA bounce, although there was no significant difference in bNED control. Fewer patients were in that series (218) and all received either I-125 or Pd-103 implants (120 patients also received supplemental EBRT). One-quarter of these patients experienced a bounce, defined as a transient increase $\geq$ 0.2 ng/mL.

Stock et al.[13] summarized the risk of experiencing a PSA bounce in their dataset using 3 different definitions of bounce in 373 patients who received I-125 or Pd-103 implants (337 I-125 and 36 Pd-103 implants) alone. Those authors defined bounce as a PSA rise $\geq$ 0.1 ng/mL, a PSA rise $\geq$ 0.4 ng/mL, and finally $>$ 35% over the previous value. The likelihood of developing a bounce at 5 years was 31%, 17%, and 20% for the 3 definitions, respectively. The median time to developing a bounce was 19.5 months for the first 2 definitions and 20.5 months for the third definition. Pretreatment PSA, GS, and T stage were not predictive of a bounce for any of the definitions. The first definition was predictive of bounce for those patients whose D90 was $>$ 160 Gy (38% vs. 24%).[13] Ciezki et al.[14] reported similar results in their Cleveland Clinic experience of 162 patients treated with an implant. Biochemical failure was also defined using 2 definitions: ASTRO and nadir + 2. At 5 years, bNED control was 87% using the ASTRO definition and 96% for the nadir + 2 definition. Seventy-five (46%) patients experienced a bounce and patients who bounced were less likely to have a BF. Young age was the only independent predictor of bounce on MVA. PSA doubling time did not differentiate a PSA bounce from BF. The median time to the first rise in PSA after the posttreatment nadir for those with a bounce was 15 months versus 30 months (ASTRO, $P = .001$) or 22 months (nadir + 2, $P = .013$). That series included some patients treated with hormones, which may have impacted some of the results.[14]

What is significant in these studies is that multiple definitions were evaluated using the same dataset. The difference between the first 2 definitions is one of sensitivity. The first definition ($\geq$ 0.1 ng/mL) will capture not only the true bounces but also simple variations in the PSA test itself. Younger patients ($\leq$ 65 years) bounced more often using the first definition compared with older patients at 5 years (38% vs. 24%, $P = .009$). Prostate volume ($>$ 35 cm^3 vs. $<$ 35 cm^3) predicted bounce with the second definition (23% vs. 11% at 5 years, $P = .01$). On UVA, only the first definition predicted for PSA control (85% vs. 76% at 5 years, $P = .02$); whereas on MVA, PSA bounce did not predict for PSA failure or control for any definition.[13]

As the current study and the others have shown, the way a bounce is defined can determine the frequency of the event. How does one separate the laboratory error of the PSA test itself from a true PSA bounce? Some have suggested that the bounce may just be laboratory error and that if laboratory error was assumed in a certain percentage of the overall PSA, then patients with higher PSA levels would have a higher chance of bouncing. Taking this assumption to the next stage, one could ask if a PSA bounce is merely a surrogate for a higher nadir PSA. A logical conclusion would then be that patients with higher posttreatment PSA nadirs would have higher bounce and failure rates. However, in our analysis across 4 posttreatment PSA nadir groups (0.0–0.30, 0.31–0.57, 0.60–1.00, and $>$ 1.00 ng/mL), even in patients with the low nadir levels, patients who bounced had lower freedom from biochemical failure rates. Some have hypothesized that bounce could possibly cause false-positive PSA failures. This could be the explanation for the higher PSA failure rate (defined according to the ASTRO definition), but not higher clinical failure rate, in bounce patients seen in this study.

Conclusion

In this analysis, patients treated with external beam RT alone who experience a posttreatment PSA bounce have increased risk of BF. Across almost all strata examined, patients with a posttreatment bounce faced this increased risk. However, with long follow-up this did not translate into a difference in CF. The clinical significance of the PSA bounce is unclear and immediate treatment based on it, especially salvage hormone administration, may not be necessary.

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