0022-5347/05/1731-0079/0
THE JOURNAL OF UROLOGY®

Vol. 173, 79–81, January 2005
Printed in U.S.A.
DOI: 10.1097/01.ju.0000145827.20277.e9

PROSTATE CANCER IN A LARGE PROSTATE IS ASSOCIATED WITH A DECREASED PROSTATE SPECIFIC ANTIGEN FAILURE RATE AFTER BRACHYTHERAPY

STEVEN LEHRER,* NELSON N. STONE AND RICHARD G. STOCK

From the Departments of Radiation Oncology and Urology (NNS), Mount Sinai Medical Center, New York and Veterans Affairs Medical Center, Bronx, New York

ABSTRACT

Purpose: A large prostate has been found to correlate with improved prostate cancer survival in men undergoing radical prostatectomy. In the current study we analyzed the relationship of prostate size and prostate specific antigen (PSA) failure in men undergoing brachytherapy for localized prostate cancer.

Materials and Methods: We studied data on 613 men who had undergone ^{125}I radioactive seed implantation. Average patient age ± SD was 65 ± 7.2 years. Average prostate volume ultrasonically measured at seed insertion was 40 ± 15 ml. All patients had a minimum of 2 years of followup.

Results: Men with a large prostate had increased freedom from failure compared to men with a small prostate. Failure time in men with an intermediate size prostate was between that for large and small prostates. This difference in failure rates was significant (log rank test $p = 0.0002$). We further analyzed our data with Cox regression. Large prostate size significantly correlated with increased time to PSA failure ($p = 0.013$) and it was independent of the significant effects of Gleason score, PSA, disease stage ($p < 0.001$), minimal radiation dose covering 90% of prostate volume ($p = 0.008$) and hormone treatment, including androgen ablation ($p = 0.001$).

Conclusions: Some investigators have postulated that paracrine signals acting to regulate epithelial proliferation in benign prostatic hypertrophy have beneficial influences on coexistent prostate cancer. Our finding that the effect of prostate size is independent of Gleason score, PSA and disease stage supports the paracrine signal mechanism. If a circulating substance, such as a cytokine, might be responsible for improved survival, this substance might be useful for treating prostate cancer. Moreover, since we found that prostate size is independent of PSA, Gleason score and tumor stage for predicting outcome, we hypothesize that patients with a small prostate treated with brachytherapy might benefit from hormone treatment and larger radiation doses. These measures are now generally reserved for men with more advanced tumors, higher PSA and increased Gleason scores.

KEY WORDS: prostate, survival, prostatic neoplasms, prostatectomy, brachytherapy

Disease related factors, including initial prostate specific antigen (PSA), Gleason score and stage, are significant predictors of biochemical failure in men with prostate cancer treated with brachytherapy.[1] PSA density (PSA/prostate volume) has been advocated as a predictor of biochemical failure because it corrects for the increased PSA associated with a large prostate,[2] although the use of PSA density is controversial.[3] However, a large prostate does not adversely affect cancer control in men undergoing radical retropubic prostatectomy. In 1 study tumors within larger prostates were of lower stage, lower Gleason grade, smaller volume, more often clinically insignificant and not different in the number or distribution of positive surgical margins. During a limited median followup of 20 to 25 months patients with a prostate of 75 gm and more were less likely to have biochemical recurrence.[4]

The lower likelihood of biochemical recurrence might be the result of early diagnosis.[4,5] However, early diagnosis might not account for the increased survival of all patients with cancer who have a large prostate. Indeed, some investigators have postulated that paracrine signals acting to regulate epithelial proliferation in benign prostatic hypertrophy (BPH) have beneficial influences on coexistent cancer.[6] In the current study we analyzed the relationship of prostate size and PSA failure in men undergoing brachytherapy for localized prostate cancer.

Submitted for publication May 11, 2004.
* Correspondence: Radiation Oncology, Box 1236, Mount Sinai Medical Center, 1 Gustave L. Levy Pl., New York, New York 10029 (e-mail: stevenlehrer@hotmail.com).

METHODS

We studied data on 613 men who underwent ^{125}I radioactive seed implantation from November 1990 to April 2002. Average patient age ± SD was 65 ± 7.2 years. Average prostate volume ultrasonically measured at seed insertion was 40 ± 15 ml (median 38.6). The smallest prostate was 11.5 ml and the largest one was 125 ml.

Mean followup was 53 ± 24 months. Patient followup included digital rectal examinations and serial PSA measurements, usually every 6 months. In some cases followup data were obtained by review of the medical records or telephone interview with the patient and/or primary physician. Table 1 shows disease stages, initial PSA, Gleason scores and minimal radiation dose covering 90% of prostate volume (D90).

All patients underwent radioactive seed implantation as primary definitive therapy. The initial selection criterion for

TABLE 1. *Tumor characteristics and radiation doses*

	No. Pts
Stage:	
T1a	1
T1b	4
T1c	326
T2a	168
T2b	96
T2c	17
T3a	1
PSA (ng/ml):	
4 or Less	67
Greater than 4–10 or less	457
Greater than 10–20 or less	77
Greater than 20	12
Gleason score:	
6 or Less	605
7	7
8–10	1
D90 (rads):	
Less than 16,000	151
16,000–18,000	327
Greater than 18,000	135

hormonal therapy was prostate gland size. All patients with prostate gland volume 50 cm^3 or greater on transrectal ultrasonography received hormonal ablation with the intent of gland size reduction. After 1995 adverse features, including PSA 10 ng/ml or greater, Gleason score 7 or greater, or stage T2b or greater were added to the selection criteria. A total of 180 patients (29%) received peri-implantation hormonal ablative therapy in addition to brachytherapy, most often consisting of luteinizing hormone releasing hormone agonist and antiandrogen for 3 months before and 2 to 3 months after the implantation procedure. No patient received external beam radiation therapy as part of initial therapy.

A real-time ultrasound guided technique was used for all implants. Prostate volumetric studies were performed intraoperatively by planimetry with transrectal ultrasound imaging using an ultrasound unit (Bruel and Kjaer, Decatur, Georgia) before seed placement. A modified nomogram was used to provide activities for given volumes to deliver a prescription dose of 160 Gy. One month after implantation patients underwent computerized tomography based dosimetry. Dosimetry was performed using a previously described in-house designed system and/or Pinnacle Systems (ADAC Laboratories, Milpitas, California). The implant dose was defined as the dose delivered to 90% of the prostate volume on dosimetry after implantation.[1]

Prostate volume is a risk factor for severity of symptoms and urinary retention. After adjusting for age men with prostate volume greater than 50 ml are 3.5 times more likely to have moderate or severe symptoms and 2.4 times more likely to have a maximum flow rate of less than 10 ml per second than are men with a smaller gland. In addition, men with a prostate of greater than 30 ml have 3 times the incidence of acute urinary retention.[7,8]

We used this information to divide the men in our study into 3 prostate volume groups, namely 1—161 with a small (less than 30 ml), 2—323 with an intermediate (30 to 50 ml) and 3—129 with a large (greater than 50 ml) prostate. We used previously established criteria to estimate the risk of PSA failure by dividing the men into 3 risk groups, namely 1—440 at low risk with PSA 10 ng/ml or less, stage T2a or less, or Gleason 6 or less, 2—133 at medium risk with PSA greater than to 15 ng/ml or less, Gleason 7 or stage T2b and 3—40 at high risk with PSA greater than 15 ng/ml, stage greater than T2b, or Gleason 8 or greater.

In a recent study the 8-year freedom from biochemical failure rate after treatment was 88% in low, 81% in moderate and 65% in high risk cases.[1] Biochemical failure was defined using the American Society for Therapeutic Radiology and Oncology definition, that is 3 consecutive PSA increases.[9]

RESULTS

Figure 1 shows cumulative PSA failure vs time in months as a function of prostate size. Men with a large prostate had increased freedom from failure compared to men with a small prostate. Failure time in men with an intermediate size prostate was between that for large and small prostates. The difference in failure rates in the 3 groups was significant (log rank test $p = 0.0002$). At 10 years 84% of men with a small, 94% with a medium and 98% with a large prostate had not experienced PSA failure. Table 2 lists mean failure-free survival times in the 3 size groups.

PSA failure was associated with the standard risk groups defined based on PSA, Gleason score and disease stage. Men in the low risk group had increased freedom from failure compared to men in the high risk group. Failure time in men in the medium risk group was between that for low and high risk (fig. 2). The difference in failure rates in the 3 risk groups was significant (log rank test $p < 0.0001$). Table 3 shows PSA failure in the risk groups. Table 4 shows cumulative PSA failure-free survival by initial PSA and tumor stage.

We further analyzed our data with Cox regression. Large prostate size significantly correlated with increased time to PSA failure ($p = 0.013$) and it was independent of the significant effects of Gleason score, PSA, disease stage (ie risk group $p < 0.001$), D90 ($p = 0.008$) and hormone treatment, including androgen ablation ($p = 0.001$). Table 5 lists Cox regression details.

DISCUSSION

BPH is not a risk factor for prostate cancer.[10] However, BPH and prostate cancer are associated with increased serum PSA. As a result, men with a large prostate are likely to undergo biopsies, after which many asymptomatic prostate cancers are diagnosed.[4] Indeed, PSA testing selects men with a larger prostate for biopsy and there has been a significant increase in the size of prostates removed at radical prostatectomy for early stage cancer since the introduction of PSA testing.[11]

As mentioned, paracrine signals acting to regulate epithelial proliferation in BPH might have beneficial influences on coexistent cancer.[6] Our finding that the effect of prostate size

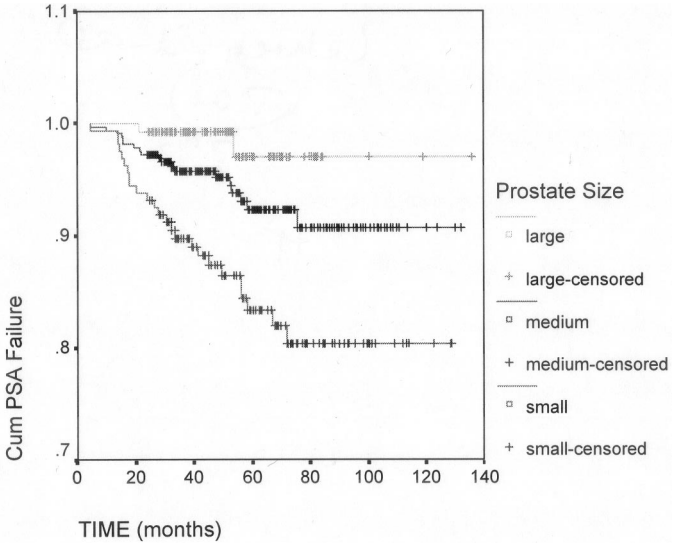

FIG. 1. Cumulative (*Cum*) PSA failure vs time in months as function of prostate size. Men with small prostate (lower curve) were most likely to have early PSA failure, while men with large prostate (upper curve) tended to have late PSA failure. Failure time in men with intermediate size prostates was between that of small and large prostates. This difference in failure rates was significant (log rank test $p = 0.0002$). Cumulative 10-year PSA failure-free survival rate was 97% for large, 91% for medium and 81% for small prostates.

TABLE 2. *Mean time to PSA failure in 613 patients*

Prostate Size	Mos to PSA Failure	SE	95% CI
Small	111	3.27	104–117
Medium	124	1.93	120–128
Large	133	1.99	129–137

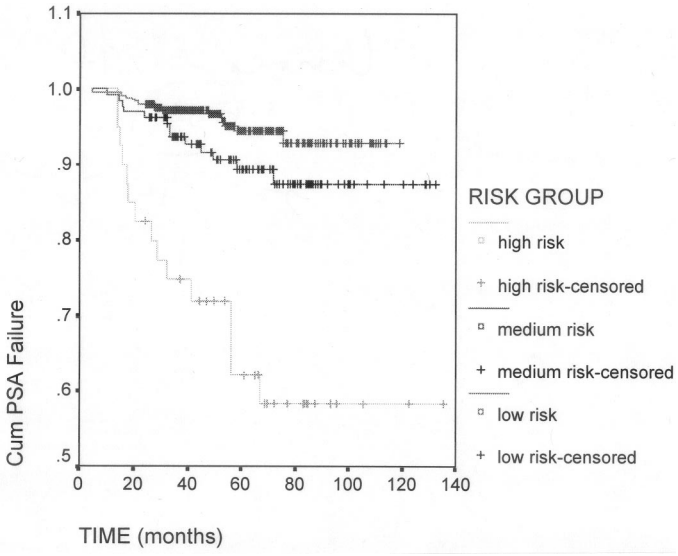

FIG. 2. Cumulative (*Cum*) PSA failure vs risk group, as determined by Gleason score, PSA and tumor stage. Men in low risk group (upper curve) had latest failures, while men in high risk group (lower curve) had earliest failures with men in medium risk group between latest and earliest failures. Difference in failure rates was significant (log rank test $p < 0.0001$). Cumulative 10-year PSA failure-free survival rate was 93% for low, 88% for medium and 59% for high risk.

TABLE 3. *PSA failure in risk groups*

	No. PSA Failure		% Failure-Free
	No	Yes	
Prostate size:			
Small	136	25	84
Medium	304	19	94
Large	127	2	98
Risk group:			
Low	422	18	96
Medium	120	13	90
High	25	15	62.5
Hormones:			
No	391	42	90
Yes	176	4	98

is independent of risk group (determined by Gleason score, PSA and disease stage) supports the paracrine signal mechanism.

The relationship of large prostate size to improved survival in prostate cancer has 2 important implications. 1) If a circulating substance, such as a cytokine, might be responsible for improved survival, this substance might be useful for treating prostate cancer. 2) Since we found that prostate size is independent of the standard risk factors (PSA, Gleason score and stage) for predicting outcome, we hypothesize that patients at low risk with a small prostate who are treated with brachytherapy might benefit from hormone treatment and larger radiation doses. These measures are now generally reserved for men in the medium or high risk groups, as defined.

TABLE 4. *Cumulative PSA failure-free survival by initial PSA and tumor stage*

	% Survival
PSA (ng/ml):	
4 or Less	95
Greater than 4–10 or less	90
Greater than 10–20 or less	88
Greater than 20	32
Stage:	
T2a or less	92
Greater than T2a	77

TABLE 5. *Prostate size correlations*

	Relative Risk	95% CI	p Value
Vol group	0.517	0.308–0.869	0.013
Risk group	2.72	1.88–3.95	<0.001
D90 group	0.496	0.295–0.834	0.008
Hormones	0.179	0.063–0.505	0.001

Large prostate size significantly correlated with increased time to PSA failure and it was independent of significant effects of Gleason score, PSA, disease stage (ie risk group), D90 and hormone treatment, including androgen ablation.

REFERENCES

1. Kollmeier, M. A., Stock, R. G. and Stone, N.: Biochemical outcomes after prostate brachytherapy with 5-year minimal follow-up: importance of patient selection and implant quality. Int J Radiat Oncol Biol Phys, **57:** 645, 2003
2. Ohi, M., Ito, K., Suzuki, K., Yamamoto, T. and Yamanaka, H.: Diagnostic significance of PSA density adjusted by transition zone volume in males with PSA levels between 2 and 4 ng/ml. Eur Urol, **45:** 92, 2004
3. Lujan, M., Paez, A., Llanes, L., Miravalles, E. and Berenguer, A.: Prostate specific antigen density. Is there a role for this parameter when screening for prostate cancer? Prostate Cancer Prostatic Dis, **4:** 146, 2001
4. Foley, C. L., Bott, S. R., Thomas, K., Parkinson, M. C. and Kirby, R. S.: A large prostate at radical retropubic prostatectomy does not adversely affect cancer control, continence or potency rates. BJU Int, **92:** 370, 2003
5. Stamey, T. A., Yemoto, C. M., McNeal, J. E., Sigal, B. M. and Johnstone, I. M.: Prostate cancer is highly predictable: a prognostic equation based on all morphological variables in radical prostatectomy specimens. J Urol, **163:** 1155, 2000
6. D'Amico, A. V., Whittington, R., Malkowicz, S. B., Schultz, D., Tomaszewski, J. E. and Wein, A.: A prostate gland volume of more than 75 cm3 predicts for a favorable outcome after radical prostatectomy for localized prostate cancer. Urology, **52:** 631, 1998
7. Williams, G.: Other assessments: prostate size and prostate specific antigen. BJU Int, suppl., **85:** 31, 2000
8. Jacobsen, S. J., Girman, C. J., Guess, H. A., Rhodes, T., Oesterling, J. E. and Lieber, M. M.: Natural history of prostatism: longitudinal changes in voiding symptoms in community dwelling men. J Urol, **155:** 595, 1996
9. Taylor, J. M., Griffith, K. A. and Sandler, H. M.: Definitions of biochemical failure in prostate cancer following radiation therapy. Int J Radiat Oncol Biol Phys, **50:** 1212, 2001
10. Chokkalingam, A. P., Nyren, O., Johansson, J. E., Gridley, G., McLaughlin, J. K., Adami, H. O. et al: Prostate carcinoma risk subsequent to diagnosis of benign prostatic hyperplasia: a population-based cohort study in Sweden. Cancer, **98:** 1727, 2003
11. Feneley, M. R., Landis, P., Simon, I., Metter, E. J., Morrell, C. H., Carter, H. B. et al: Today men with prostate cancer have larger prostates. Urology, **56:** 839, 2000