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Correlation between Serum PSA and Cancer Volume in Prostate Glands of Different Sizes

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Abstract

OBJECTIVES—Although early studies showed a strong correlation between PSA and tumor volume, it has been suggested that PSA is no longer a valid marker for PCa and only correlates with prostate size. The objective of this study was to further evaluate the relationship of PSA with prostate size and tumor volume in a contemporary surgical series.

METHODS—From 2003 to 2009, 1234 men with data on prostate weight and total tumor volume underwent radical prostatectomy by a single surgeon. Prostate size was classified into tertiles: small (≤41.2 grams), medium (41.3–54.5 grams) and large (≥54.6 grams). Pearson correlation coefficients were used to examine the relationship of PSA with prostate size and tumor volume across different prostate sizes.

RESULTS—Median preoperative PSA was 4.9 ng/ml (SD ± 4.6), mean prostate size was 51.7 grams, and mean tumor volume was 5.6 cc. PSA had a significant correlation with prostate size only at a prostate weight ≥54.6 gm (p=0.01). Regardless of prostate size, PSA had a more robust significant correlation with tumor volume than with prostate size (all p<0.0001).

CONCLUSIONS—PSA was significantly correlated with prostate size only in the largest prostate glands, but was significantly associated with tumor volume in small, medium, or large prostates. Thus, PSA continues to be a better marker for tumor volume than for prostate size.

Keywords

prostate cancer; prostate-specific antigen; PSA; tumor volume; pathology

INTRODUCTION

Prostate-specific antigen (PSA) has been widely used as a screening tool since it was approved by the U.S. Food and Drug Administration as an aid to the early detection of prostate cancer in 1994. The PSA-driven stage migration of prostate cancer, in conjunction with improvements

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in treatment, are primarily responsible for the 40% reduction in prostate cancer specific mortality rates observed between 1993 and 2006 in the U.S. [1, 2]

The malignant potential of prostate cancer is associated with tumor volume at diagnosis, and studies early in the PSA era showed a robust correlation between serum PSA levels and tumor volume.[3, 4] In a landmark study involving 379 men who underwent radical prostatectomy, Stamey and colleagues reported a strong correlation between preoperative PSA with the volume of the largest tumor focus using a computerized planimetric method.[5] In the multivariable model, both tumor volume and percentage of Gleason 4/5 in tumors were independent predictors of biochemical recurrence after treatment.[5] Moreover, 86% of men with a tumor volume of 0.5 to 2 cc were free of tumor recurrence compared with 61% of those with a tumor volume of 2 to 6 cc, 33% with a tumor volume of 6 to 12 cc, and 3% with a tumor volume >12 cc.[5]

Our research group has previously shown that both serum PSA levels and tumor volume determined by visual estimation were associated with biochemical recurrence. Specifically, for every 5% increase in tumor volume, we found an 11% increase in the biochemical recurrence rate.[6] In a different patient population treated from 1999 to 2003, the maximum tumor diameter correlated with actual tumor volume and preoperative PSA, and was also associated with biochemical recurrence.[7]

Nevertheless, the correlation between preoperative PSA and tumor volume later in the PSA era has been questioned. In contrast to their original observations, Stamey and colleagues reported an erosion in the association of serum PSA with tumor volume.[8, 9] In a series of 1300 radical prostatectomies performed from 1993 to 2003, Stamey et al divided the cases into four 5-year time intervals.[10] The correlation between PSA and tumor volume decreased over time, and a regression analysis comparing the first and last periods showed that preoperative PSA ultimately correlated with prostate size but no longer correlated with tumor volume.[10] The authors suggested that the loss of correlation with tumor volume may compromise the current usefulness of PSA for early prostate cancer detection.[10]

In the present study, we sought to further evaluate the relationship of serum PSA with prostate size and tumor volume in a contemporary radical prostatectomy series. Specifically, we tested whether PSA had a stronger correlation with prostate size or tumor volume in contemporary prostate cancer patients.

MATERIAL AND METHODS

From March 2003 to March 2009, 1234 consecutive men underwent radical prostatectomy by a single surgeon (W.J.C.).[11] Clinical and pathologic features were prospectively recorded in a database. This protocol received institutional board approval and all included patients provided written informed consent.

Prostate size was determined by weighing the surgical specimen. The histologic examination then included the following: after inking the whole specimen, 2 mm tissue slices of the distal prostatic urethra and bladder neck were removed to determine the presence of positive surgical margins at these sites. The prostate was then fixed in 10% formalin. Subsequently, the prostate was bisected vertically, and horizontal cuts were made at approximately 4 mm intervals from the apex to the base, which usually resulted in an average of 8 to 10 blocks for histologic examination per patient. Tumor foci were identified, and the percentage of cancer was visually estimated.[6] Tumor volume was then calculated by multiplying the estimated percentage of cancer and prostate volume.

For the purposes of analysis, prostate size was categorized into tertiles based upon the weight distribution in our sample: small (≤41.2 grams), medium (41.3–54.5 grams), and large (≥54.6 grams). We then used Pearson correlation coefficients to determine the relationship between the PSA level at the time of prostate cancer diagnosis with prostate size and tumor volume, stratified by prostate size. Subset analysis was performed after excluding 67 men who received neoadjuvant hormonal therapy. All statistical analyses were performed with SAS® software (SAS Institute, Cary, NC).

RESULTS

Clinical and pathologic characteristics of our patients are shown in Table 1. Most men were younger than 60 years at the time of surgery, and 95% were Caucasian. The median preoperative PSA was 4.9 ng/ml (SD ± 4.6; range 0.2 to 63.3 ng/ml), and 530 men (43%) had a PSA between 4.1 and 6.0 ng/ml. Seventy-five percent of the cancers were clinical stage T1c. Most patients had an enlarged prostate, with 95% of the glands being >30 cc. The mean prostate size was 51.7 grams (SD ± 19.7; median 47.3 cc; range 16.0 to 254.7 grams), and most tumors were well-differentiated based upon the biopsy Gleason score.

Postoperative pathologic examination revealed that 82% of the tumors were organ-confined; however, 18% had extra-capsular tumor extension, and 17% had positive surgical margins. The proportion of men with seminal vesicle invasion (4%) or pelvic lymph node metastases (0.6%) was small. The majority of tumors (85%) measured less than 10 cc by visual estimation. Overall, the mean tumor volume was 5.6 cc (SD ± 6.2 cc; median 3.7 cc; range <0.1 to 71.2 cc). Figure 1 shows the frequency distribution of preoperative PSA, prostate size, and tumor volume in our patient population.

The correlation of preoperative PSA with tumor volume (R^2 =0.13) was more robust than with prostate size (R^2 =0.01), as shown in Figure 2. Table 2 shows the correlation between PSA with prostate size and tumor volume according to prostate size tertile. Preoperative PSA was significantly associated with prostate size only in men with the largest glands; whereas, it was significantly correlated with tumor volume irrespective of prostate size. In the subset of 1167 men without neoadjuvant therapy, preoperative PSA had a modest, statistically significant association with prostate size in the second (Pearson 0.10, p=0.04) and third tertiles (Pearson 0.12, p=0.02). However, the correlation of PSA to prostate size was not significant among men with prostate size in the first tertile (Pearson 0.0, p=0.88). By contrast, PSA had a stronger, statistically significant correlation with tumor volume in all three tertiles (Pearson 0.35, 0.27 and 0.42, respectively, all p<0.0001).

COMMENTS

The widespread acceptance of PSA as an important screening tool has resulted in a significant stage migration of prostate cancer, with most tumors being detected at an earlier stage and smaller volume.12 Additionally, the introduction of lower PSA cutoffs has further contributed to the increasing proportion of smaller, organ-confined cancers.[11, 13] It is not surprising, therefore, that the striking correlations between PSA and cancer volume observed in the past are less robust. Nevertheless, this led some investigators to conclude that in the modern PSA era, PSA might be a better marker for benign prostatic hyperplasia (BPH) than prostate cancer.[10]

The clinical characteristics of our patients were similar to those of other contemporary series. Most were diagnosed through an elevation in PSA with a normal digital rectal examination (DRE). The fact that almost all of our patients had a prostate size >30 grams is not surprising, considering the prevalence of BPH at this age range; similar findings were reported in other radical prostatectomy series.[14]

There was a relatively weak correlation between preoperative PSA and prostate size in our cohort. Indeed, PSA was associated with prostate size only in larger glands (>54.5 grams). However, the correlation of PSA with tumor volume remained significant across all prostate sizes. Other investigators have confirmed our findings in patients treated during the PSA era, using diverse methodologies to determine tumor size - maximal tumor diameter,[7] maximum tumor volume,5 visual estimate of the percentage of cancer,15 and morphometric analyses in completed embedded specimens.16 All of these methodologies have technical limitations[17] that may be responsible for the conflicting findings on the relationship between PSA and tumor volume. On one hand, standard pathologic processing of prostatectomy specimens may not adequately sample tumor areas with very small lesions, and the multifocality of prostate cancer may lead to a suboptimal evaluation of total tumor volume.[17] On the other hand, complete embedding and evaluation of the whole prostate is technically demanding, costly, and rarely performed outside of research protocols. [17, 18]

As mentioned above, to some extent PSA has become a victim of its own success as a tumor marker.[19] With the widespread screening and the finding of smaller tumors, the “noise” of BPH and prostatitis may interfere with the “signal” of serum PSA levels, making PSA less specific as a marker for cancer, especially in older men. This is likely the main reason for the decreasing correlation reported between PSA levels and the size of the largest, so-called “index” tumor in other series.[19] Further, because prostate cancer is often a multifocal disease, the correlation between PSA and tumor volume might be obscured if only the largest “index” tumor is measured.[19]

Although some studies do not identify tumor volume as an independent predictor of prognosis in prostate cancer,[20, 21] it is nevertheless considered so important that all pathologic definitions of clinically significant *versus* potentially harmless prostate cancers incorporate tumor size, [22, 23] and current guidelines on pathologic reporting of prostate cancer recommend an assessment of tumor volume.[24, 25]

Finally, some poorly differentiated prostate cancers are so aggressive that they produce less PSA and may progress even at low PSA levels. Particularly with these tumors, PSA trends may be more important than the absolute PSA levels.19 Our research group and others have reported that accelerated increases in PSA levels in the year before diagnosis are powerful predictors of prostate cancer-specific mortality.26, 27 Accordingly, the new American Urological Association (AUA) PSA guidelines [28] and the updated National Comprehensive Cancer Network (NCCN) recommendations 29 suggest that men undergo an initial evaluation at 40 years of age and, depending on these results in relation to the age-specific PSA reference range, should be screened regularly in order to identify those with increased PSA velocity who are at a greater risk for prostate cancer-specific mortality.27

A limitation of our study is the method of determining tumor volume by visual estimation. Nevertheless, this has been shown to correlate well with the grid morphometric method.[30] Another limitation of our study is that prostate weight was measured from the surgical specimen, which included the seminal vesicles. However, we repeated the analysis after subtracting 7 grams from the prostate weight (approximate average weight of the seminal vesicles), and the correlation coefficients did not change. An alternate approach would be to examine prostate volume using estimations from preoperative imaging studies. Nevertheless, these data were not available for all participants. Moreover, our group has previously shown only a moderate correlation (0.64) between TRUS volume estimates and prostatectomy specimen weight,[31] suggesting that the use of specimen weight in the analysis may provide a more accurate assessment of the correlation of PSA to prostate size.

Despite these limitations, our results demonstrate that PSA continues to correlate better with tumor volume than with prostate size. Thus, we believe that PSA is still a clinically useful tumor marker for the early detection of prostate cancer that, if used intelligently, will sustain the reduction in prostate cancer mortality observed in the U.S. and other countries where screening is practiced. [1, 32]

CONCLUSIONS

In a contemporary radical prostatectomy series, we observed a significant correlation between PSA and prostate size only in the largest prostate glands, while PSA was associated with tumor volume in men with a small, medium or large prostate. PSA continues to be a better marker of tumor volume than for prostate size.

Acknowledgments

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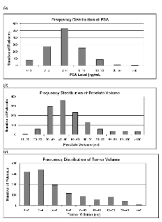

Figure 1.
Frequency distribution of (a) preoperative PSA, (b) prostate volume, and (c) tumor volume.

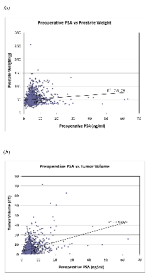

Figure 2.
Pearson's correlation coefficients between PSA with (a) prostate size and (b) tumor volume.

Table 1

Clinical and pathologic characteristics of the study population.

Median age (range; years)	59 (37–76)
Median preoperative PSA (range; ng/ml)	4.9 (0.2–63.3)
Race (% white)	95%
Clinical stage (%)	
T1	75%
≥T2	25%
Biopsy Gleason score (%)	
≤6	69%
≥7	31%
Pathologic Features	
Organ-confined (%)	82%
Prostatectomy Gleason ≥7 (%)	47%
Extra-capsular extension (%)	18%
Positive surgical margins (%)	17%
Seminal vesicle invasion (%)	4%
Pelvic lymph node metastases (%)	0.6%

Table 2

Correlation between preoperative PSA levels with (a) prostate volume, and (b) tumor volume, stratified by prostate size tertile.

(a)					
Prostate weight (tertiles)	**Number of patients**	**Mean Preoperative PSA (ng/ml)**	**Mean prostate weight (gm)**	**Pearson**	***P***
1st (16.0 – 41.2 gm)	411	5.6 (0.2–47.9)	35.1 (16.0–41.2)	0.0	0.83
2nd (41.3 – 54.5 gm)	411	5.7 (0.3–63.3)	47.5 (41.3–54.5)	0.09	0.07
3rd (54.6–254.7 gm)	412	6.4 (0.6–42.3)	72.5 (54.6–254.7)	0.11	0.02

(b)					
Prostate weight (tertiles)	**Number of patients**	**Mean Preoperative PSA (ng/ml)**	**Mean tumor volume (cc)**	**Pearson**	***P***
1st (16.0 – 41.2 gm)	411	5.6 (0.2–47.9)	4.7 (<0.1–31.2)	0.34	<0.0001
2nd (41.3 – 54.5 gm)	411	5.7 (0.2–63.3)	5.7 (0.05–32.5)	0.34	<0.0001
3rd (54.6–254.7 gm)	412	6.4 (0.6–42.3)	6.2(<0.1–71.2)	0.41	<0.0001