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The Current Role of Prostatic Acid Phosphatase and Prostate-Specific Antigen in the Management of Prostate Cancer

Sugandh D. Shetty, MD,* and Joseph C. Cerny, MD*

Cancer of the prostate (CAP) is the most common cancer in the American male with 132,000 new cases expected to be diagnosed in 1992 (1). It is also the second leading cause of cancer-related deaths with 34,000 men projected to die this year (1). Early diagnosis depends upon the availability of a sensitive and specific tumor marker. Prostatic acid phosphatase (PAP) has been used for staging and monitoring CAP for the last 50 years (2). Recently, with the development of prostate-specific antigen (PSA), interest in PAP has diminished considerably.

Prostatic Acid Phosphatase

PAP is a sialoglycoprotein, molecular weight 100,000 daltons, secreted by the prostatic acinar cells (2). Ultrastructurally it is present in the lysosomes, secretory vacuoles, and golgi bodies (3). PAP is secreted into the acinar and the ductal lumen and is present in high concentration in the ejaculate. Due to the large size of the PAP molecule, serum levels rise only after cancer has penetrated the prostate capsule. Since its isolation in 1938 by Gutman and Gutman (4) and the demonstration of its response to endocrine manipulation of prostate cancer by Huggins and Hodges (5), acid phosphatase has been extensively studied regarding its usefulness for early diagnosis, staging, and monitoring CAP (2,6-12). However, because similar isoenzymes are present in virtually every tissue in the body, the nonspecificity of the PAP test has limited its diagnostic value. Even though radioimmunoassays are more sensitive than the former enzymatic assays, PAP values cannot be used reliably in screening (13). In addition to diurnal and individual variation, PAP levels rise after digital rectal examination (DRE), prostatic massage, cystoscopy, or transurethral resection of the prostate (2,14,15).

Although testing for PAP has declined because of the availability of PSA, such tests were the best available means to monitor patients with CAP for nearly five decades. Several studies have shown that in pathologically confirmed stage A and B disease (Table 1) PAP is in the normal range and patients with localized disease who had elevated PAP levels later developed bony metastasis (6-10). Thus, raised PAP levels can be used to predict extracapsular penetration even though 20% of patients with skeletal metastasis have normal values (2). In assessing whether normal PAP predicts extracapsular extension, Bahnson and Catalona (11) studied 102 patients with surgically staged,

clinically localized CAP and found that 22 (88%) of 25 patients whose PAP (enzymatic assay) was in the upper half of the normal range had stage C or D disease. By comparison, only 53% of 77 patients with lower range of normal PAP had stage C or D disease. Similarly, Oesterling et al (12) reported that the rate of capsular penetration and seminal vesicle involvement was 11% and 0%, respectively, in patients whose PAP level was in the lower range of normal, compared to 50% capsular penetration and seminal vesicle involvement for patients in the upper normal range. In addition, PAP has been used to predict skeletal metastasis in patients being followed after radical prostatectomy, radiotherapy, and hormonal manipulation (2,13).

Currently the role of PAP is limited to initial detection of extraprostatic extension of the adenocarcinoma where imaging studies such as transrectal ultrasonography (TRUS) or computed tomography have been equivocal. PAP can also be used in monitoring patients with stage C and D adenocarcinoma who are on either radiotherapy or hormonal therapy.

Prostate-Specific Antigen

PSA, a glycoprotein of the serine protease group similar to kallikrein, has a molecular weight of 33,000 daltons and is a much smaller molecule than PAP (16). Produced by the prostatic acinar epithelium, PSA has been located ultrastructurally in the rough endoplasmic reticulum and is stored in vesicles and vacuoles (3). PSA production is thought to be androgen-dependent (17-19). Physiologically, PSA liquifies the semen, degrading the seminal vesicular proteins. In 1971 Hara et al (20) first isolated the protein from human semen and called it gamma seminoprotein. Wang and coworkers (16) extracted the protein from human prostate and termed it prostate-specific antigen. In 1980 Papsidero et al (21) isolated the same antigen from the serum of prostate cancer patients. Since then, many studies have shown its assay to be useful in diagnosis, screening, staging, and monitoring of prostate cancer (22-28). Several studies have con-

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Table 1
Clinical Staging of Prostate Cancer

Stage	Definition
A	Incidental cancer
A1	< 5% of tissue (Gleason < 4)
A2	> 5% of tissue (Gleason > 4)
B1	Palpable nodule extending into < 50% of one lobe
B2	Palpable nodule larger than B1, limited to one lobe
B3	Bilateral palpable cancer
C	Palpable cancer extending into one or both seminal vesicles
D1	Positive pelvic lymph nodes
D2	Skeletal or visceral metastasis

firmed the identity of PSA and gamma seminoprotein (17,29). There are two assays currently available for PSA. The radiometric monoclonal antibody assay (Tandem-R, Hybritech) is the most widely used and has a normal range of 0.2 to 4.0 ng/mL (22,23,25-30). The polyclonal assay (Prosccheck) developed by Yang (31) is also used by some investigators (15,24,32-36) and the normal range varies from 0.2 to 2.6 ng/mL.

PSA and Benign Prostatic Hyperplasia

The increase in glandular size characteristic of benign prostatic hyperplasia (BPH) results in increased PSA production by the prostatic epithelium. Armitage et al (22) studied 139 patients with clinical BPH using the Tandem-R assay. Of the 121 patients with histologic diagnosis of BPH, the mean PSA was 5.9 ng/mL, while in the 18 who were found to have latent cancer (stage A) mean PSA was 18.3 ng/mL. PSA levels were higher in men with larger prostate glands and those who presented with acute urinary retention had a mean PSA of 11.5 ng/mL, compared to 3.8 ng/mL in those whose symptoms were only of prostatism, independent of the glandular size. Morote et al (25) reported PSA levels > 10 ng/mL in more than 50% of BPH patients with acute urinary retention and indwelling catheters. Hudson et al (28) reported that only 21% of men with BPH have elevated PSA (> 4 ng/mL) and only 2% have PSA > 10 ng/mL. Table 2 shows the incidence of PSA > 10 ng/mL (Tandem-R) in several studies of BPH (28,37-40). Yang (31), using the Prosccheck assay, found 62% of men with BPH to have PSA > 2.5 ng/mL, and Stamey et al (15), using the same assay, found 86% of 73 BPH patients to have elevated PSA (mean 7.9 ng/mL). Observing the rate of fall of PSA after prostatectomy and relating it to the mass of resected adenomatous tissue, Stamey et al (15) concluded that BPH tissue elevates serum PSA level by 0.3 ng/mL/g. However, Weber et al (18) could not demonstrate such a consistent correlation between serum PSA and the BPH tissue, probably because of the variable epithelial content in the hyperplastic glands. Prostatic intraepithelial neoplasia (PIN) has been shown to be responsible for the raised PSA in some BPH patients (41,42). Utilizing TRUS, Babaian et al (43) estimated prostate gland volume in 408 men and found a statistically significant correlation of PSA with prostate volume and to a lesser degree with patient age. In our study of 124 patients uti-

Table 2
BPH and Incidence of Raised PSA > 10 ng/mL

Reference	Number of Patients with Raised PSA > 10 ng/mL
Hudson et al (28)	3 of 168 (2%)
Myrtle et al (37)	7 of 352 (2%)
Ercole et al (38)	10 of 357 (3%)
Oesterling et al (39)	7 of 72 (10%)
Cooner et al (40)	8 of 197 (4%)
Henry Ford Hospital (unpublished data)	14 of 124 (11%)

lizing TRUS and PSA, we found a linear relationship between gland volume and PSA (unpublished data).

While BPH does clearly elevate serum PSA, clinical application of this correlation must be judiciously employed. While there seems to be a volume-dependent linear correlation between PSA and BPH tissue, levels above 10 ng/mL are infrequent in BPH. Therefore, PIN and occult CAP must also be considered as contributing factors for elevated PSA in patients with presumed BPH.

Effect of Prostate Manipulation on PSA

Yuan and Catalona (44) studied the relationship of PSA, DRE, prostatic massage, TRUS, and needle biopsy. DRE had no influence on 5- and 90-minute post-DRE PSA levels. Only 5% of patients had elevated PSA after massage and 8% after TRUS, but PSA was elevated in 89% after needle biopsy (5 minutes) and in a third of those it remained high even after two weeks. The postbiopsy rise in PSA occurred following multiple biopsies (more than four). Prostatic size, baseline PSA, and the presence of prostate cancer had no influence on persistence of raised PSA. However, using the Prosccheck assay, Stamey et al (15) demonstrated a significant rise in PSA and PAP following prostate massage, cystoscopy, and biopsy. Inflammatory conditions of the prostate gland such as acute prostatitis also cause elevated PSA (29).

PSA and Carcinoma of Prostate

Since PAP was the standard tumor marker for CAP before PSA was available, earlier studies compared its efficacy to that of PAP. Stamey et al (15) compared PSA and PAP levels in 127 untreated patients with CAP. PSA was raised above 2.5 ng/mL (Prosccheck) in 122 (96%) patients, including 7 of 12 patients with stage A and all 115 patients with stages B to D. However, PAP was raised in only 57% of the patients: none with stage A, 9% with B1, 39% with B2, 40% with B3, 64% with C, and 96% with D2. Myrtle et al (37), who studied 553 CAP patients using Tandem-R assay, found raised PSA in 81% while only 43% had raised PAP. The increased sensitivity is present in early disease. For all stages of prostate cancer, PSA is elevated more frequently than PAP, probably because its small molecular size readily permits diffusion across the basement membrane into

Table 3
PSA Values for BPH and Organ-Confined CAP*

Reference	Total Patients		Percentage of Patients with PSA in the Range of					
	BPH	CAP	< 4 ng/mL		4-10 ng/mL		> 10 ng/mL	
			BPH	CAP	BPH	CAP	BPH	CAP
Hudson et al (28)	168	103	79	38	19	26	2	36
Lange et al (30)	357	31	79	45	18	32	3	23
Partin et al (45)	72	185	47	45	46	44	7	11
	597	319	75	43	22	37	3	20

*Adapted from Oesterling JE. Prostate specific antigen: A critical assessment of the most useful marker for adenocarcinoma of the prostate. *J Urol* 1991;145:907-23.

the circulation. Stamey et al (24,32) showed a linear relationship of PSA between cancer volume and Gleason score. However, a consistent relationship between the PSA and poorly differentiated tumors could not be confirmed by Partin et al (45). Stamey et al (32) evaluated changes in PSA values after radical prostatectomy. Given PSA half-life (2.5 to 3 days), they concluded that cancerous tissue raises serum PSA by 3 ng/mL/g.

Role of PSA in Screening

Since PSA is an improved marker for CAP, interest in its possible role in screening is considerable. As previously noted, the minimal elevations of PSA which are found in BPH patients cause difficulty. In an exhaustive review, Oesterling (29) compared PSA values of patients with BPH to those of patients with localized (organ-confined) CAP (Table 3). As many as 43% of CAP patients had normal PSA (< 4 ng/mL) while 25% of patients with BPH had PSA > 4 ng/mL. In patients with organ-confined CAP, PSA > 4 ng/mL had a 64% diagnostic accuracy and PSA > 10 ng/mL had a 70% diagnostic accuracy. The positive predictive value (PPV) was 49% and 75% for PSA > 4 ng/mL and > 10 ng/mL, respectively. Thus, due to overlap with both BPH and inflammatory prostatic disease, PSA is not specific enough to be used alone for screening.

Several investigators (26,27,33,46) have studied the use of PSA in conjunction with DRE and TRUS in early detection of CAP. Cooner et al (27) reported on 1,807 symptomatic patients seen in a urologic clinic. All were evaluated using PSA, DRE, and TRUS. Patients with hypoechoic lesions shown by TRUS had biopsies. When both DRE and TRUS were negative, biopsies were not performed regardless of the PSA level. When PSA was > 10 ng/mL in the presence of abnormal DRE, PPV approached 80%. For PSA level of 4 ng/mL with abnormal DRE, PPV fell to 45%. For PSA > 10 ng/mL with negative DRE, the PPV fell to 31% (Table 4). Catalona et al (26) measured PSA in 1,653 healthy men over 50 years of age, a true screening study. Those who had PSA > 4 ng/mL had DRE and TRUS. Biopsies were performed for abnormal DRE and/or TRUS. Only 107 (6%) had PSA of 4.0 to 9.9 ng/mL and 30 (2%) had PSA > 10 ng/mL. Only 22% of those with PSA < 10 ng/mL who had biopsy were shown to have CAP whereas 67% of those with PSA > 10 ng/mL had CAP. Twelve (32%) and 16 (43%) of these pa-

tients with CAP had normal DRE and TRUS, respectively, and would have been missed if these modalities were utilized alone. Multivariate analysis of PSA as the predictor of cancer (compared to that of age, DRE, and TRUS) disclosed that PSA had significant predictive ability. Lee et al (46) examined 256 men who had hypoechoic lesions demonstrated by TRUS, 106 (41%) of whom had CAP. Positive DRE and raised PSA (> 2.6 ng/mL, Prosccheck) in these patients had a PPV of 71% for CAP (Table 5) (33). Raised PSA had greater diagnostic significance than positive DRE. However, Brawer and Lang (47) noted a 32% false-negative rate (PSA < 4 ng/mL) and 58% of the cancers would have been missed if 10 ng/mL had been chosen as the cutoff level. In 54 unselected CAP patients studied at Henry Ford Hospital, 22% had PSA < 4 ng/mL and would therefore have been misdiagnosed by the test. Due to the poor specificity of PSA, several other parameters have been suggested to aid early detection of CAP. Prostate-specific antigen density (PSAD), defined as the ratio of PSA over prostate volume, has been suggested (48,49). We analyzed 335 patients who underwent TRUS for suspicious DRE or an elevated PSA (> 4 ng/mL) and found that a PSAD of 0.12 had the best efficacy values (sensitivity, specificity, positive and negative predictive value) for the PSA range of 4 to 10 ng/mL (unpublished data, Table 6). PSAD > 0.15 has been suggested by other investigators (50). Another suggested parameter for early detection of CAP is rising PSA level. Stamey (34) recommends annual PSA testing in those with borderline levels, for rising PSA titers should alert the physician to a malignant process in the prostate.

Although PSA is raised in many patients with localized CAP, its use in screening cannot be justified because of its high false-negative rate, as well as the poor PPV for patients with lower range elevations. However, a combination of PSA and DRE with or without TRUS improves the detection rate of CAP.

PSA in Staging

Despite a linear correlation between PSA and pathological stage, the use of PSA for preoperative staging is limited by the overlap of levels between stages. PSA levels of > 10 ng/mL were found in 11% to 23% of patients with organ-confined CAP (29,45). However, using the Prosccheck assay, Stamey et al (32) reported that patients with PSA < 10 ng/mL have little chance

Table 4
Positive Predictive Value of DRE and PSA*

PSA	Digital Rectal Examination	
	+	-
< 4 ng/mL	16.9%	9.3%
4 to 10 ng/mL	45%	20%
> 10 ng/mL	76.7%	30.9%

*Adapted from Cooner WH, Mosely BR, Rutherford CL Jr, et al. Clinical application of transrectal ultrasonography and prostate specific antigen in the search for prostate cancer. *J Urol* 1988;139:758-61.

+ = Abnormal on DRE (nodule, induration, asymmetry).
- = Prostate with normal consistency.

for seminal vesicle and lymph node involvement. On the other hand, patients with PSA > 50 ng/mL carried a 90% chance of lymph node involvement. Oesterling et al (39) found that the false-positive rate of PSA as predictor of extracapsular penetration was 74% and 65% for a cutoff level of 4 and 10 ng/mL, respectively. The ratio of polyclonal to monoclonal assay values in the same patient has been reported to predict lymph node involvement (51). The ability of PSA to predict skeletal metastasis has been studied by Chybowski et al (52) who found that PSA < 20 ng/mL had a negative predictive value of 99.7%. Similarly, the negative accuracy of PSA < 20 ng/mL was 92%. These results suggest that the expensive isotope bone scan may be unnecessary in CAP patients with PSA < 20 ng/mL.

PSA in Monitoring CAP

Considering the half-life of PSA (2.5 to 3 days), serum levels should be undetectable three weeks after radical prostatectomy (29,30). Persistently raised PSA after this period suggests residual benign or malignant prostatic tissue. Stamey et al (32) showed that 95% of patients with elevated PSA three to six months after radical prostatectomy had positive margins, seminal vesicle involvement, or lymph node disease. Lange et al (30) performed anastomotic biopsy on patients with raised PSA three to six months after surgery. Although none had detectable residual or recurrent disease, 39% were shown to have biopsy-posi-

Table 5
Positive Predictive Value for a Hypochoic Lesion on TRUS*

PSA (Prosccheck)	Digital Rectal Examination	
	+	-
> 2.6 ng/mL	71%	34%
0.2 to 2.6 ng/mL	26%	5%

*Adapted from Lee F, Torp-Pedersen ST, Littrup PJ, et al. Hypochoic lesions of the prostate: Clinical relevance of tumor size, digital rectal examination, and prostate-specific antigen. *Radiology* 1989;170:29-32.

tive local disease. Local adjuvant radiotherapy has been advocated for those with raised PSA after radical prostatectomy.

Stamey et al (35), studying 183 patients who received radiotherapy for localized disease, observed that only 11% had undetectable PSA at a mean of 5 years posttreatment. Most of the patients (82%) showed a rapid fall of PSA during the first year, but in only 8% did the fall continue beyond one year. Rising PSA levels, seen in 51% of the 80 patients followed for more than one year, correlated with the development of skeletal metastasis and positive prostate biopsy. However, patients who develop D2 disease following radiotherapy for local disease have much lower PSA levels than do those with untreated D2 disease (35).

The response of PSA to antiandrogen therapy is more dramatic than that to radiotherapy. Stamey et al (36) suggest that the PSA level six months after beginning hormonal therapy is prognostic of whether the patient would respond favorably to the treatment. In addition to the antitumor effect of hormonal therapy, androgen-dependent PSA deregulation may be responsible for the rapid fall. Rising PSA in patients with CAP suggests progression and the need for further therapy.

Summary

Although PSA is considered to be the true serum marker of prostatic tissue and a valuable indicator for cancer in the gland, knowledge of its significance and limitations is essential to its use for screening, staging, and monitoring CAP. PSA may be

Table 6
Efficacy of Various PSAD Values in Differentiating BPH and CAP in PSA Range of 4 to 9.9 ng/mL

	PSAD Values				
	0.08	0.10	0.12	0.15	0.2
Sensitivity	97%	90%	87%	70%	53%
Specificity	28%	48%	60%	71%	86%
Positive predictive value	27%	32%	37%	40%	50%
Negative predictive value	97%	95%	94%	90%	87%

Sensitivity: True positive (TP)/TP + false-negative (FN).
Specificity: True negative (TN)/TN + false-positive (FP).
Positive predictive value: TP/TP + FP.
Negative predictive value: TN/TN + FN.
Diagnostic accuracy: TP + TN/TP + TN + FP + FN.

used in conjunction with DRE for early detection of CAP. Men with abnormal DRE should have a TRUS with or without biopsy. In men older than 50 years and with negative DRE and PSA < 4 ng/mL, annual evaluations are prudent. In patients with a PSA range of 4.0 to 9.9 ng/mL, high-risk groups such as black males and those with a positive family history should have TRUS. Males with negative DRE in the PSA range of 4.0 to 9.9 ng/mL should have TRUS to evaluate prostate volume and PSAD. Biopsy should be considered in those with PSAD > 0.15. Men with PSA > 10 ng/mL, even in the presence of an enlarged benign prostate, should have multiple directed biopsies under TRUS guidance.

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