

A study of the correlation of prostatic pathology and serum prostate-specific antigen (PSA) levels: a perspective from Papua New Guinea

D.P. MURTHY^{1,2}, U. RAY³, J. MOREWAYA³ AND S.K. SENGUPTA^{1,4}

**Faculty of Medicine, University of Papua New Guinea, Port Moresby and
Department of Pathology, Port Moresby General Hospital, Papua New Guinea**

SUMMARY

A review of serum prostate-specific antigen (PSA) values from January 1994 to May 1997 and their correlation with the histopathology of prostate specimens was carried out in the Department of Pathology, Port Moresby General Hospital. The study has shown that this biochemical investigation has not been properly used for the maximum benefit of the patient population. Remedial measures are suggested to improve the sensitivity and specificity of PSA in a setting with limited resources.

Introduction

Prostate-specific antigen (PSA) is a 33 kDa serine protease from the normal secretory epithelial cells of the prostate which is secreted into the prostatic ductal system. It catalyses the liquefaction of seminal coagulum. Normal levels of PSA are usually less than 4 ng/ml, but they vary according to the age of the patient (1). PSA levels less than 4 ng/ml in men of 60 years or less and levels less than 6.5 ng/ml in men aged 60-80 years are normal. PSA is elevated by any change that disrupts the normal architecture of the prostate which allows diffusion of protease into the microvascular circulation. Raised serum PSA levels are seen in prostatitis, infarcts and benign prostatic hyperplasia, but the most clinically important elevations are seen with prostatic adenocarcinoma. PSA is the most important and clinically useful biochemical marker of the prostate because it is produced by and is specific for prostatic tissue (2). Since its isolation in the 1970s (3,4) PSA has proved an invaluable marker in the early detection of prostatic cancer and its recurrence. Digital

rectal examination (PR) is advised as a means of diagnosing prostatic disease in the clinical setting. There is a considerable debate on whether men over 50 should be screened for prostatic cancer, which is recommended by the American Urological Association and not recommended by the British Association of Urological Surgeons and the Urological Society of Australasia. In all cases PSA estimation should be carried out in conjunction with PR examination.

PSA estimation was introduced as a routine laboratory investigation in the Clinical Biochemistry Laboratory of Port Moresby General Hospital in 1994. Ever since its introduction, there has been a growing demand for this test. This study was carried out with the objectives of (a) the assessment of the utility of PSA as a tumour marker in our laboratory, (b) correlating the PSA levels and the prostatic pathology as observed in the surgical pathology specimens received in the Histopathology Division of Port Moresby General Hospital, and (c) recommending appropriate measures to derive the maximum

¹ Department of Pathology, Faculty of Medicine, University of Papua New Guinea, PO Box 5623, Boroko, NCD 111, Papua New Guinea

² Present address: Griffith Pathology Laboratory, Griffith Base Hospital, PO Box 1013, Griffith, NSW 2680, Australia

³ Department of Pathology, Port Moresby General Hospital, Free Mail Bag, Boroko, NCD 111, Papua New Guinea

⁴ Present address: Gribbles Pathology, Adelaide, South Australia

benefit from this investigation in a setting with limited resources.

Materials and Methods

The records of histopathology reports of the Department of Pathology of Port Moresby General Hospital were reviewed from 1993 to June 1997 and information related to surgical pathology specimens of the prostate received during this period was collected. The slides of the sections stained with haematoxylin and eosin and other appropriate stains were reviewed to record the histopathological diagnosis in each case. Carcinoma of the prostate was graded according to Gleason's scoring system. The files of the reports of prostate-specific antigen in the Division of Clinical Biochemistry were reviewed to collate the information about the patients and the clinical diagnosis. The surgical pathology and the clinical biochemistry reports were reviewed together to correlate the PSA levels and the histopathological diagnosis. The PSA estimations were carried out by the method of immunoassay kits (Abbott's Diagnostics).

Results

A total number of 320 prostatic biopsies were available for review during the study period of 4.5 years. These included prostatectomy specimens, transurethral resection specimens (TURP) and 'tru cut' biopsies (Table 1). Nodular hyperplasia of the prostate (benign prostatic hyperplasia) was the most frequent lesion. It was observed in the age range of 40 to 82 years and was associated with prostatitis in 25% of the cases. Carcinoma was identified as a coexistent pathology in 2 cases. The details are included in Table 2. A total number of 26 cases of adenocarcinoma of the prostate were identified in the study material. The mean age of these patients was 61 years. The tumour was graded as well differentiated (Gleason score ≤ 4) in 46% of cases, moderately differentiated (Gleason score 5-7) in 27% of cases and poorly differentiated (Gleason score ≥ 8) in 12% of cases. An accurate grading on the basis of Gleason score was not possible in 4 cases, as the biopsy material was inadequate for grading (Table 3).

TABLE 1

NUMBER OF PROSTATIC PATHOLOGY SPECIMENS EXAMINED DURING THE STUDY PERIOD

Year	Prostatectomy	TURP	Biopsy	Total
1997 (to May 1997)	11	15	0	26
1996	39	47	7	93
1995	70	0	4	74
1994	56	8	10	74
1993	50	3	0	53
Total	226	73	21	320

TURP = transurethral resection of the prostate

TABLE 2

BENIGN PROSTATIC HYPERPLASIA (NODULAR HYPERPLASIA OF THE PROSTATE)

Total number	282
	Excision 209
	TURP 66
	Biopsy 7
Age range	40-82 years
Associated pathology	Prostatitis 71
	Carcinoma 2
	Granulomatous prostatitis 3
	Tuberculosis 1
	Carcinoma of the bladder 1

TURP = transurethral resection of the prostate

TABLE 3

CARCINOMA OF THE PROSTATE

Total number	26	
Age range	50-70 years	
Mean	61.4 years	
Histological grading	Well differentiated	12
	Moderately differentiated	7
	Poorly differentiated	3
	Not graded	4

PSA was estimated in 261 cases from January 1994 to May 1997. A steady increase in demand for estimation of serum PSA levels was noted during the study period, with 77 requests for a 5-month period in 1997. The PSA levels varied from 0.03 ng/ml to 744 ng/ml. These were reviewed in relation to carcinoma and benign prostatic hyperplasia (the two major clinical settings).

The PSA values were divided into 5 groups - ≤ 4 ng/ml, 4.1-10 ng/ml, 10.1-20 ng/ml, 20.1-100 ng/ml and > 100 ng/ml - and analyzed according to age and clinical diagnosis. The details are displayed in Tables 4 to 9. Of the 45 cases of carcinoma, the PSA was > 100 ng/ml in 20% and in the range of 20-100 ng/ml in 22%.

TABLE 4

TOTAL NUMBER OF CASES OF PSA ESTIMATION ACCORDING TO AGE AND PSA RANGE

Age in years	PSA level					Total
	≤ 4.0 ng/ml	4.1-10 ng/ml	10.1-20 ng/ml	20.1-100 ng/ml	> 100 ng/ml	
< 40	6	2	3	1	0	12
41-50	9	5	4	2	4	24
51-60	26	11	9	9	7	62
61-70	8	6	5	7	3	29
> 70	3	3	4	2	2	14
Age not recorded	59	11	15	22	13	120
Total	111	38	40	43	29	261

TABLE 5

CASES WITH PSA VALUES OF 0-4 NG/ML

Clinical diagnosis	Age in years	Age in years	Age in years	Age in years	Age in years	Total
	< 40	41-50	51-60	61-70	> 70	
Carcinoma	0	3	6	3	1	13
Benign prostatic hyperplasia	6	6	20	5	2	39
Total	6	9	26	8	3	52

TABLE 6

CASES WITH PSA VALUES OF 4.1-10 NG/ML

Clinical diagnosis	Age in years < 40	Age in years 41-50	Age in years 51-60	Age in years 61-70	Age in years > 70	Total
Carcinoma	0	2	3	1	0	6
Benign prostatic hyperplasia	2	3	8	6	3	22
Total	2	5	11	7	3	28

TABLE 7

CASES WITH PSA VALUES OF 10.1-20 NG/ML

Clinical diagnosis	Age in years < 40	Age in years 41-50	Age in years 51-60	Age in years 61-70	Age in years > 70	Total
Carcinoma	0	1	3	3	0	7
Benign prostatic hyperplasia	3	3	6	2	4	18
Total	3	4	9	5	4	25

TABLE 8

CASES WITH PSA VALUES OF 20.1-100 NG/ML

Clinical diagnosis	Age in years < 40	Age in years 41-50	Age in years 51-60	Age in years 61-70	Age in years > 70	Total
Carcinoma	1	0	6	3	0	10
Benign prostatic hyperplasia	0	2	3	4	2	11
Total	1	2	9	7	2	21

TABLE 9

CASES WITH PSA VALUES OF >100 NG/ML

Clinical diagnosis	Age in years < 40	Age in years 41-50	Age in years 51-60	Age in years 61-70	Age in years > 70	Total
Carcinoma	0	2	6	0	1	9
Benign prostatic hyperplasia	0	2	1	3	1	7
Total	0	4	7	3	2	16

PSA values were studied in only 9 histologically proven cases of carcinoma and the values ranged from 3.9 ng/ml to > 100 ng/ml. In one case, it was > 500 ng/ml. Of the 7 histologically suspicious cases of carcinoma of the prostate, PSA values were available in 4 cases, with a range of 21.4 to 624.5 ng/ml, confirming the diagnosis. The group of 120 cases with no recorded age were not analyzed in relation to the different types of clinical diagnosis.

Discussion

In our study, it is observed that not all the cases of surgical pathology specimens of the prostate have been the subject of serum PSA estimations. This is because the specimens are received from all the hospitals in the country since the Histopathology Division of the Department of Pathology, Port Moresby General Hospital is the only histopathology laboratory servicing the whole country. It is also observed that in not all the cases of surgical resection of the prostate in Port Moresby General Hospital is the serum PSA estimation requested. A good clinico-pathological correlation can be achieved only if serum PSA estimations are carried out in all cases of surgical resection of the prostate.

Elevations of serum PSA values were observed in our study both in carcinoma of the prostate and benign prostatic hyperplasia. This is consistent with the observations made by others (1). The PSA values of serum will be raised by any process that disrupts the normal architecture of the prostate allowing the diffusion of PSA into the stroma leading to its entry into the blood through the microvasculature. Thus elevated serum PSA levels are observed in conditions such as prostatitis, prostatic infarcts and benign prostatic hyperplasia though the most clinically important elevations are seen in adenocarcinoma of the prostate (1). Carcinoma produces less PSA per cell than the benign epithelium, but the greater number of malignant cells and the stromal disruption in the malignancy are associated with significant elevations of serum PSA levels (2). The clinical utility of PSA lies in the staging of the prostatic cancer and monitoring the response to therapy (5). Prostate-specific antigen is an important marker in the detection and

management of prostatic carcinoma. Elevations of serum PSA levels correlate well with the recurrence of the tumour and progression after surgery, radiation therapy and androgen ablation therapy (4,6-8). Since it is a sensitive marker for tumour recurrence after treatment, it is useful for early detection of metastases (9).

In our study PSA was useful in advising clinicians to follow up those histologically doubtful cases with elevated serum PSA levels. In our study it was observed that the clinicians were using this marker as a tool to detect prostatic cancer, but in a majority of the cases of cancer the investigation was not repeated as a follow-up. This was possibly due to generally poor follow-up of cases in our setting, since the majority of the patients do not comply with the advice for follow-up due to a lack of understanding of its importance and difficulties with transportation. Treated patients turn up at the hospital only when there is a problem.

Recently 5 new PSA parameters have been described to control for the confounding effects of benign prostatic hyperplasia and prostate volume. These may improve the sensitivity, specificity and clinical utility of PSA (1). It is observed that age-specific ranges of PSA values have not been established in our laboratory setting. It is important that clinicians make an effort to estimate the age of each patient and include it in the laboratory request forms. Age-specific ranges for PSA are important. They increase with advancing age. A single reference range of 0-4 ng/ml is not appropriate for men of all ages (10,11). In our study a similar trend of elevation of serum PSA values with increasing age was observed.

The other parameters of PSA are PSA density (PSA index) (quotient of serum PSA level divided by the ultrasound-calculated prostate volume) (12,13), PSA velocity (rate of change of PSA serum levels with time) (14-16), PSA cancer density (serum PSA times cancer volume divided by prostate volume) (17) and PSA doubling time (17-19). Of these parameters, the PSA doubling time and the PSA velocity can be adopted in our setting of limited resources to improve the sensitivity, specificity and utility of PSA estimations.

In conclusion, our study has demonstrated that (a) the age-specific ranges of PSA values should be established in our laboratory, (b) a good clinicopathological correlation can be achieved by assessing PSA values in all cases of prostatic disease and surgical resections, and (c) PSA doubling time and PSA velocity should be determined in our setting with its limited resources, in order to improve the sensitivity, specificity and utility of PSA estimations. To achieve this, the patient population should be adequately educated about the importance of compliance with follow-up instructions.

REFERENCES

- 1 **Bostwick DG.** Prostate-specific antigen: current role in diagnostic pathology of prostate cancer. *Am J Clin Pathol* 1994;102:S31-S37.
- 2 **Oesterling JE.** Prostate specific antigen: a critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. *J Urol* 1991;145:907-923.
- 3 **Hudson MA, Bahnson RR, Catalona WJ.** Clinical use of prostate specific antigen in patients with prostate cancer. *J Urol* 1989;142:1011-1017.
- 4 **Lange PH, Ercole CJ, Lightner DJ, Fraley EE, Vessella R.** The value of serum prostate specific antigen determinations before and after radical prostatectomy. *J Urol* 1989;141:873-879.
- 5 **Ruckle HC, Klee GG, Oesterling JE.** Prostate-specific antigen: concepts for staging prostate cancer and monitoring response to therapy. *Mayo Clin Proc* 1994;69:69-79.
- 6 **Stamey TA, Kabalin JNK, McNeal JE, Johnstone IM, Freiha F, Redwine EA, Yang N.** Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. II. Radical prostatectomy treated patients. *J Urol* 1989;141:1076-1083.
- 7 **Ercole CJ, Lange PH, Mathisen M, Chiou RK, Reddy PK, Vessella RL.** Prostatic specific antigen and prostatic acid phosphatase in the monitoring and staging of patients with prostatic cancer. *J Urol* 1987;138:1181-1184.
- 8 **Brawer MK, Aramburu EAG, Chen GL, Preston SD, Ellis WJ.** The inability of prostate specific antigen index to enhance the predictive value of prostate specific antigen in the diagnosis of prostatic carcinoma. *J Urol* 1993;150:369-373.
- 9 **Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E.** Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med* 1987;317:909-916.
- 10 **Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, Lieber MM.** Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific ranges. *JAMA* 1993;270:860-864.
- 11 **Oesterling JE, Cooner WH, Jacobsen SJ, Guess HA, Lieber MM.** Influence of patient age on serum PSA concentration. An important clinical observation. *Urol Clin North Am* 1993;20:671-680.
- 12 **Benson MC, Whang IS, Pantuck A, Ring K, Kaplan SA, Olsson CA, Cooner WH.** Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. *J Urol* 1992;147:815-816.
- 13 **Seaman EK, Whang IS, Cooner W, Olsson CA, Benson MC.** Predictive value of prostate-specific antigen density for the presence of micrometastatic carcinoma of the prostate. *Urology* 1994;43:645-648.
- 14 **Carter HB, Pearson JD, Metter EJ, Brant LJ, Chan DW, Andres R, Fozard JL, Walsh PC.** Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. *JAMA* 1992;267:2215-2220.
- 15 **Carter HB, Pearson JD.** PSA velocity for the diagnosis of early prostate cancer. A new concept. *Urol Clin North Am* 1993;20:665-670.
- 16 **Partin AW, Pearson JD, Landis PK, Carter HB, Pound CR, Clemens JQ, Epstein JI, Walsh PC.** Evaluation of serum prostate-specific antigen velocity after radical prostatectomy to distinguish local recurrence from distant metastases. *Urology* 1994;43:649-659.
- 17 **Schmid HP, McNeal JE, Stamey TA.** Clinical observations on the doubling time of prostate cancer. *Eur Urol* 1993;23:60-63.
- 18 **Hanks GE, D'Amico A, Epstein BE, Schultheiss TE.** Prostatic-specific antigen doubling times in patients with prostate cancer: a potentially useful reflection of tumor doubling time. *Int J Radiat Oncol Biol Phys* 1993;27:125-127.
- 19 **Schmid HP, McNeal JE, Stamey TA.** Observations on the doubling time of prostate cancer. The use of serial prostate-specific antigen in patients with untreated disease as a measure of increasing cancer volume. *Cancer* 1993;71:2031-2040.