SERUM γ-SEMINOPROTEIN DETERMINATION IN PROSTATIC CANCER

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Serum γ-seminoprotein (γ-Sm) was evaluated as a new marker for prostatic cancer in comparison with prostatic acid phosphatase (PAP). The sensitivity of γ-Sm and PAP for untreated prostatic cancer was 81% and 67%, respectively. γ-Sm showed a higher positive rate over all stages than in benign prostatic hypertrophy (BPH). There was no correlation between γ-Sm and PAP in prostatic cancer. Improved sensitivity was obtained by simultaneous measurement of γ-Sm and PAP. Specificity of γ-Sm and PAP for BPH was 87% and 90%, respectively. γ-Sm normalized after endocrine therapy for stage D2 more often than did PAP. These results indicate that γ-Sm is another useful marker to evaluate prostatic cancer.

Key words: γ-seminoprotein, Prostatic acid phosphatase, Prostatic cancer, Benign prostatic hypertrophy

INTRODUCTION

Prostatic acid phosphatase (PAP) is the most widely used standard serum marker for prostatic cancer. However, the problem of low sensitivity in the early stages and a 15~20% false negative rate, even in stage D2, has been noted[1]. Prostate specific antigen (PA), a relatively new marker for prostatic cancer, has been clinically evaluated[2-4]. PA was found to be more sensitive in the earlier stages than PAP and less specific for benign prostatic hypertrophy (BPH)[3-5].

Recently, γ-seminoprotein (γ-Sm), another new marker for prostatic cancer, has appeared[6]. Clinical application of γ-Sm has been reported thereafter[7-10]. This study was undertaken to explore the usefulness of serum γ-Sm as a diagnostic tool to detect prostatic cancer and to evaluate its usefulness as a parameter for monitoring the therapeutic response to treatment in prostatic cancer.

MATERIALS AND METHODS

Specimens

Sera from 141 patients with histologically confirmed prostatic cancer between 1985 and 1987 were used in this study. The numbers of patients used were 10, 7, 11, 29, 20 and 64 in stages A1, A2, B, C, D1 and D2, respectively. Stages were classified according to the Whitmore-Jewett Staging System[11]. Sera from 404 patients with BPH were assayed for comparison.

Assay of γ-Sm and PAP

Serum γ-Sm was measured with an enzyme immunoassay (EIA) system containing a monoclonal antibody against γ-Sm (Chugai Pharmaceutical Co., Ltd., Tokyo, Japan). Quantitation of serum PAP was obtained using a radiommunoassay kit (PAP-RIA EIKEN; EIKEN Chemical Co., Ltd, Tokyo, Japan). Cut-off values for γ-Sm and PAP were 4 ng/ml and 3 ng/ml, respectively.

Sensitivity, Specificity and Efficiency

The sensitivity was calculated as the ratio of the number with elevated levels compared to untreated prostatic cancer. Specificity was defined as the proportion of patients exhibiting normal values among patients with BPH. Efficiency was calculated using the formula: (sensitivity (%) × specificity (%))/100.

Changes in γ-Sm and PAP During the Course of Endocrine Therapy in Prostatic Cancer

Serum γ-Sm and PAP was measured 2, 4, 8 and 12 weeks after the start of treatment in 28 patients with stage D2 prostatic cancer receiving endocrine therapy in combination with or without chemotherapy and radiotherapy. Clinical response to treatment was evaluated at 3 months according to the National Prostatic Cancer Project Criteria[12].

Statistical analysis was calculated using the Student's t test.

RESULTS

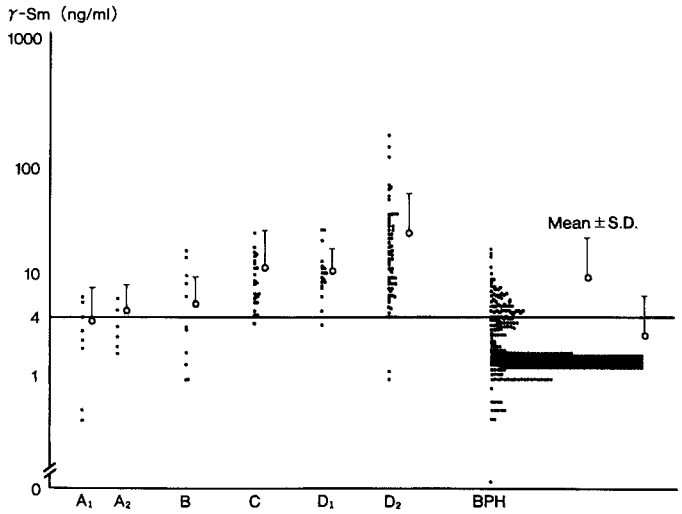
γ-Sm and PAP in Prostatic Cancer and BPH

Figure 1 shows the γ-Sm levels determined in various stages of untreated prostatic cancer and BPH. The γ-Sm values increased with advancing stage of cancer, being significantly higher than in BPH in stage C, D1 and D2. The PAP levels were also elevated with progressing stage, with significant differences from BPH in stage C and D1 (Fig. 2). In sensitivity, γ-Sm was superior to PAP for each respective stage as well as in overall stage. Although the false positive rate was higher for γ-Sm than PAP, efficiency was better with γ-Sm; γ-Sm and PAP values were 35 and 27% in stage A1, 37 and 13% in stage A2, 40 and 25% in stage B, 72 and 65% in stage C, 74 and 67% in stage D1, 83 and 73% in stage D2 and 70 and 61% in overall stage, respectively.

Simultaneous Determination of γ-Sm and PAP

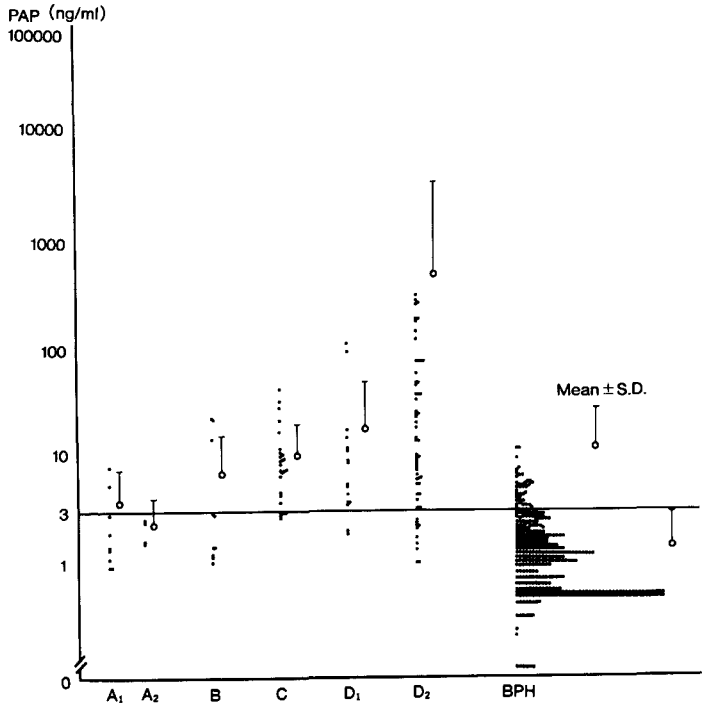
The use of two markers to diagnose prostatic cancer, increased the sensitivity in overall stage, as well as for each respective stage (Table 1). However, the false positive rate also increased to 20% in sera from patients with BPH.

Correlation Between Serum γ-Sm and PAP in



	A1	A2	B	C	D1	D2	BPH
No. of patients	10	7	11	29	20	64	404
Sensitivity or false positive rate	40%	43%	46%	83%	85%	95%	13%
Mean ± S.D.	3.8±3.9	4.7±3.6	5.4±4.5	12.5±16.0	11.2±7.3	25.2±36.8	2.5±4.1
Versus BPH	N.S.	N.S.	N.S.	p<0.01	p<0.01	p<0.01	

Fig. 1. Relation of the concentration of γ-Sm to the clinical stage of 141 patients with prostatic cancer and 404 patients with BPH.



No. of patients	10	7	11	29	26	64	404
Sensitivity or false positive rate	30%	14%	27%	72%	75%	81%	10%
Mean ± S.D.	3.6±3.8	2.3±1.7	6.9±9.1	10.1±10.3	18.6±33.1	543.3±3166.7	1.4±1.5
Versus BPH	N.S.	N.S.	N.S.	p<0.01	p<0.05	N.S.	

Fig. 2. Relation of the concentration of PAP to the clinical stage of 141 patients with prostatic cancer and 404 patients with BPH.

Untreated Prostatic Cancer

The relationship between γ-Sm and PAP values were examined, and there was found to be no correlation between these two markers (Fig. 3).

Changes in γ-Sm and PAP After Initiation of Treatment and Clinical Response

Fig. 4 shows the individual changes in γ-Sm and PAP in 23 patients with elevation in both markers before treatment. In all patients with a partial response (PR), γ-Sm levels returned to the normal range by 12 weeks, as did the PAP levels. In patients remaining objectively stable (OS) 64% continued to have abnormal levels of PAP, whereas most cases showed normalization of γ-Sm. As the OS patients had a well controlled course, normalization of γ-Sm is suggested to be a good indicator of post therapeutic course.

DISCUSSION

The application of RIA and EIA systems using purified PAP from prostatic tissue or seminal plasma has resulted in a noticeable improvement in specificity. However, the advantage for RIA and EIA over conventional enzymatic methods in terms of sensitivity has been controversial. A high percentage of the patients with clinically localized cancer had elevated PAP when measured with RIA and EIA[13,14], which suggested that PAP was valuable for early detection. However, others have claimed low sensitivity for PAP in detecting early stage prostatic cancer[15,16]. We confirmed a low sensitivity for PAP with RIA in the early stages of prostatic cancer.

A specific protein designated γ-Sm is found exclusively in seminal plasma as one of the secretory products of the prostate

Table 1. Comparison of elevated markers (γ-Sm and PAP) in prostatic cancer and BPH

Stage	No. Case	γ-Sm	PAP +	PAP −	elevated γ-Sm and/or PAP
A1	10	+	2(20)	2(20)	5(50)
		−	1(10)	5(50)	
A2	7	+	0(0)	3(43)	4(57)
		−	1(14)	3(43)	
B	11	+	3(27)	2(18)	5(45)
		−	0(0)	6(55)	
C	29	+	18(62)	6(21)	27(93)
		−	3(10)	2(7)	
D1	20	+	14(70)	3(15)	18(90)
		−	1(5)	2(10)	
D2	64	+	50(78)	11(17)	63(98)
		−	2(3)	1(2)	
total	141	+	87(62)	27(19)	122(87)
		−	8(6)	19(13)	
BPH	404	+	14(4)	39(10)	81(20)
		−	28(7)	323(80)	

Data are shown as numbers of cases.
( ) : % of respective stages or group.

gland. An assay kit for the measurement of γ-Sm was developed using antibody directed to this heterogeneous glycoprotein. γ-Sm has been reported to show a tendency to increase with progressive stage of prostatic cancer[7,9,10]. In this study, γ-Sm was abnormal more frequently than PAP at all stages, and abnormal γ-Sm values were obtained in half of the patients in the earliest stage. These results are in agreement with the other Japanese reports[7,17]. Previous reports have shown various rates of specificity of γ-Sm in the patients with BPH[7,9,10,17,18]. Especially high values of γ-Sm in patients with prostatic cancer and BPH were noticed in UK[10]. It is not clear whether these differences are due to race. This study showed a low specificity for γ-Sm when compared with PAP As a correlation between γ-Sm and the weight of BPH has been recently reported[17], the wide range in specificity may be attributable to variation in samples assayed as BPH. Correlation between PAP and weight of BPH has also been reported[5,19]. The higher efficiency of γ-Sm than PAP in all stages of prostatic cancer indicates that γ-Sm is a useful marker for the detection of carcinoma of the prostate. Sensitivity was also increased when the measurement of γ-Sm was combined with that of PAP, whereas minimal increases have been reported with the combination of PA and PAP assays[20–22]. Thus, the combination assay of γ-Sm and PAP is advantageous in the diagnosis of

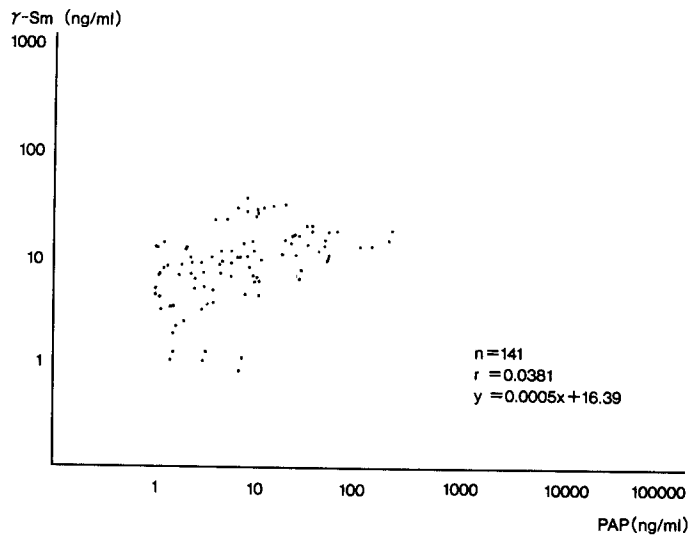


Fig. 3. Correlation between γ-Sm and PAP in untreated prostatic cancer.

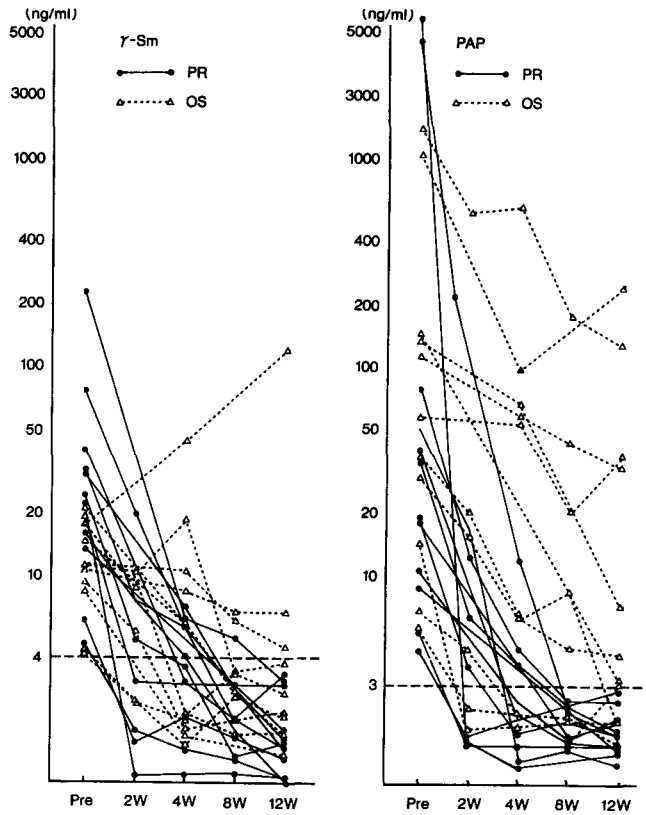


Fig. 4. Changes in γ-Sm and PAP during the course of endocrine therapy in prostatic cancer.

prostatic cancer.

A greater rate of normalization of γ-Sm was observed following treatment in the PR group than in the OS group, as was the case with PAP. Both of these markers therefore reflect the clinical response to treatment. Moreover, the γ-Sm level was normalized more frequently in the OS group than PAP Although PA has also been reported to be useful to monitor therapy[21,23], the measurement of γ-Sm may be an additional indicator.

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和文抄録

前立腺癌における血清γ-セミノプロティンの測定

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前立腺癌の新しいマーカーとして，γ-セミノプロテイン（γ-Sm）と前立腺性酸性ホスファターゼ（PAP）とを比較評価した．未治療前立腺癌における，γ-SMおよびPAPの感度（sensitivity）は，それぞれ81%，67%であった．γ-Smにおいては，すべての病期において前立腺肥大症と比較して陽性率が高かった．前立腺癌において，γ-SmとPAPは相関を示さなかった．γ-SmとPAPを同時に測定することにより，感度が上昇した．γ-SmおよびPAPの特異性（specificity）は，それぞれ87%と90%であった．内分泌療法を施行した病期D2において，γ-SmはPAPよりも，より多く正常化した．

これらの結果より，γ-Smは前立腺癌のもう1つの有用なマーカーであるといえる．

（泌尿紀要 37：341-347，1991）