The Significance of Erythrocyte Sedimentation Rate as a Prognostic Factor for Patients with Prostate Cancer: Gunma Urological Oncology Study Group Investigation

Kyoichi Imai,[1] Takanori Suzuki,[1] Mikio Kobayashi,[1] Hidetoshi Yamanaka,[1] Yukio Tomaru[2] and Jin Sato[3]

[1]Department of Urology, Gunma University School of Medicine, 3-39 Showa, Maebashi, Gunma 371, [2]Department of Urology, Kiryu Kosei Hospital, 6-3 Orihime, Kiryu, Gunma 376 and [3]Department of Urology, Gunma Cancer Center Hospital, 671-1 Takabayashi, Ota, Gunma 373

The Gunma Urological Oncology Study Group has performed a multivariate statistical analysis of prognostic factors based on 353 patients with prostate cancer diagnosed between 1974 and 1984. This paper discusses the prognostic significance of erythrocyte sedimentation rate (ESR) in these patients with prostate cancer. Based on three ranges (<20, $>20-<50$, >50 mm/h) of ESR, a significant difference of survival rates among the patients was found by means of univariate analysis. ESR apparently includes components which represent anemia or infection. Hemoglobin, frequently used as a prognostic factor, was compared with ESR by means of multivariate analysis, and ESR was found to be a more useful prognostic factor than hemoglobin. Moreover ESR showed the highest partial coefficient value among the items studied (clinical stage, pathological differentiation, age, acid phosphatase, gait disturbance). It seems that ESR includes not only anemia and infection components but also provides a clue to the degree of bone metastasis or the degree of prostate cancer progression.

Key words: Prostate cancer — Erythrocyte sedimentation rate — Prognostic factor

The investigation of prognostic factors in patients with prostate cancer may be of value in understanding the natural history of the disease and may also assist in planning and analyzing the results of clinical trials. Moreover, the information obtained would be beneficial in assessing the prognosis and deciding on better therapy forms for individual patients.

Since prostate cancer occurs mainly in elderly men,[1-5] the survival rate of patients with this disease will be strongly influenced by their general condition and their probable cause of death without prostate cancer. Therefore it is necessary to investigate prognostic factors including those factors which represent the general condition of individual patients. The prognostic factors in reports using multivariate analysis[1-4, 6] and univariate analysis[5-10] have been roughly classified into nine catagories: 1) stage (M0 and M1, ureteral dilation, ABCD classification,[11] anemia, etc.), 2) pathological malignant potential of cancer cells (Gleason score, Gaeta's classification, differentiation, etc.), 3) tumor markers (acid and/or alkaline phosphatase), 4) hormonal environment (testosterone, growth hormone, etc.), 5) therapy or response to treatment, 6) past history and complications (especially those relating to cardiovascular disease), 7) general condition (performance status, weight loss, gait disturbance, anemia, etc.), 8) symptoms (pain, etc.), 9) others (race, etc.). We have been researching appropriate factors which represent the condition of patients with prostate cancer from the viewpoint of general urologists who can use these tests in their clinics.

This paper presents an examination of the characteristics of the erythrocyte sedimentation rate (ESR) by using multivariate analysis. The significance of ESR as a prognostic factor is evaluated along with the degree of pathological differentiation, clinical stage, age, serum acid phosphatase and gait disturbance instead of performance status. The characteristics of ESR are also analyzed in relation to the cause of death.

MATERIALS AND METHODS

Among 1,036 patients with histologically proven and newly diagnosed prostate cancer in 19 hospitals from 1974 to 1987, 353 patients who had information recorded for all six of the significant items (Table I) were used for this study. Patients' ages ranged from 48 to 98 years with a mean age of 73.3 years. As the first-line treatment, 336 of the patients had received endocrine therapy (endocrine therapy alone was 63.4%, in combination with chemotherapy 14.3%, in combination with transurethral resection or subcapsular prostatectomy 7.3%, and with others 10.3%); the majority were given estrogen or LHRH agonist (Leuprolide) and a few were orchiectomized. Radiation therapy was performed in 21 patients with or without other treatment. Radical prostatectomy was performed in 23 patients (stage A, 1; stage B, 14; stage C, 7; stage D, 1).

Table I. Items Studied for Multivariate Analysis

Item	Category			
	1	2	3	4
Age	≤ 59 (19)	60–69 (85)	70–79 (180)	≥ 80 (69)
Gait disturbance	can walk (282)	on chair (51)	in bed (20)	
ESR	≤ 20 (172)	21–50 (120)	>50 (61)	
Acid phosphatase	normal (151)	abnormal (202)		
Stage	A (27)	B (61)	C (73)	D (192)
Tumor differentiation	well (56)	moderately (153)	poorly (144)	

( ): number of patients

To find out what ESR represents, the relationships with not only the five items used in the multivariate analysis (Table I), but also the red and white blood cell count, hemoglobin, GOT, GPT serum protein concentration, platelets and fever (which may affect the ESR value[12]) were investigated. We used the ESR value which was measured immediately at admission, expressed as "mm per hour," because the ESR value is easily influenced by medical care, for example prostate biopsy or other examinations.

The stage in this study was decided on the basis of the reports from each clinician who had made the diagnosis after clinical examination. The examination rate was as follows; cystoscopy 50.1%, urethrography 89.2%, intravenous pyelography 84.1%, vesiculography 8.8%, lymphangiography 46.2%, CT scanning including the prostate 57.8%, sonography 32.3%, rectal digital examination 99.7%, skeletal scintigraphy 90.1% and skeletal X-ray survey 43.4%. To decide the grade of bone metastasis according to Soloway category,[13] skeletal scintigraphs of 117 patients were reevaluated.

The cause of death was decided from the records, obtained by telephone or letter. The range of observation time was from 1 to 181 months and the average was 51 months. The independency between items studied was evaluated in terms of the coefficient of correlation and by the chi-square test. The significance of ESR as a prognostic factor was evaluated by the quantification method 1 multivariate analysis.[14]

RESULTS

We found a significant difference of survival rates ($P<0.01$) between each ESR category by univariate analysis.[4] The interrelationships between ESR and other items mentioned in "Materials and Methods" were analyzed (Table II). A very high correlation between ESR and the anemia factor, namely the hemoglobin and red blood cell count, was observed. A relatively high

Table II. Interrelationships between ESR and Other Factors

Factor	Number of patients	Coefficient of correlation
Hemoglobin	340	0.6165
Red blood cells	339	0.4084
Body temperature	348	0.3631
White blood cells	329	0.3238
Platelets	329	0.1874
GPT	326	0.0694
Serum protein	308	0.0565
GOT	325	0.0509

Table III. ESR and Fever

Fever (°C)	ESR (%)			
	≤ 20	21–49	≥ 50	Total
<37	141 (47.3)	102 (34.2)	55 (18.5)	298 (100)
≥ 37–<38	2 (6.7)	3 (10.0)	25 (83.3)	30 (100)
≤ 38	2 (10.0)	1 (5.0)	17 (85)	20 (100)

correlation was observed with the white blood cell count, which may represent anemia or infection. A relatively high correlation ($r=0.36361$) between body temperature and ESR was also found. When the body temperature was stratified into three categories, a significant relationship ($P<0.01$) between body temperature and ESR was found as well (Table III).

As it is well known that anemia is caused by bone metastasis,[3, 6] the relationship between ESR and the stage or degree of bone metastasis was investigated. A significant relationship between ESR and stage ($P<0.05$ in A:B:C:D, $P<0.01$ in A+B+C:D) can be observed (Table IV). Among 192 patients with stage D, the skeletal scintigraphs of 117 patients, for whom records were complete, were reevaluated, and they were stratified into

Table IV. ESR and Stage

Stage	ESR (%)			
	≤20	21–49	≥50	Total
A	12 (44.4)	10 (37.0)	5 (18.5)	27 (100)
B	35 (57.4)	21 (34.4)	5 (8.2)	61 (100)
C	43 (58.9)	23 (31.5)	7 (9.6)	73 (100)
D	82 (42.7)	66 (34.4)	44 (22.9)	192 (100)

Table V. ESR and Degree of Bone Metastasis

Bone metastasis grade	ESR (%)			
	≤20	21–49	≥50	Total
1	34 (49.3)	19 (27.5)	16 (23.2)	69 (100)
2–3	7 (19.4)	11 (30.6)	18 (50.0)	36 (100)
4	2 (16.7)	3 (25.0)	7 (58.3)	12 (100)

Table VI. ESR and Cause of Death

Cause of death	ESR (%)			
	≤20	21–49	≥50	Total
Prostate cancer	37 (44.6)	27 (32.5)	19 (22.9)	83 (100)
Others	35 (43.8)	36 (45.0)	9 (11.3)	80 (100)
Unknown	9	5	6	20

three categories, grade 1, grades 2–3 and grade 4 according to Soloway category. There was a significant relationship between ESR and the grade of bone metastasis ($P<0.01$) when the later was stratified into grade 1 and grades 2–4 (Table V).

The value of ESR as an indicator of prostate cancer death was evaluated. No significant relationship between ESR and the cause of death was found (Table VI), even if this relationship was analyzed only in patients with stage D (data not shown). When ESR was stratified into two categories (<50 and >50 mm/h), a significant relationship between the two was found ($P<0.05$). Early in our studies it appeared that age, pathological differentiation, stage and acid phosphatase were all associated with prostate cancer death.[4]

As the interrelationship between ESR and hemoglobin among the blood examination data was the strongest, and as hemoglobin has been frequently used in multivariate analysis studies of prostate cancer, the value of these two items as prognostic factors was compared by multivariate analysis quantification method 1 (Table VII). The partial coefficient value of ESR (0.2392) obtained in the analysis

Table VII. Comparison of Hemoglobin or ESR Effect on Multivariate Analysis (Quantification Method I)

Factor	Including ESR	Including hemoglobin
Age	0.1978	0.1565
Stage	0.1596	0.1842
Differentiation	0.1870	0.1888
Gait disturbance	0.1829	0.1863
Acid phosphatase	0.0345	0.0393
ESR	0.2392	—
Hemoglobin	—	0.0667
Multiple correlation ratio	0.4241	0.3713

including ESR was the highest among the items studied and it was higher than that including hemoglobin instead of ESR (0.0667). As a result, the multiple correlation ratio including ESR (0.4241) was higher than that including hemoglobin (0.3713). The independence of the six items studied in this multivariate study was analyzed (data not shown). ESR was significantly related with gait disturbance. However, ESR behavior as a prognostic factor was different from the gait disturbance factor (see the "Discussion" section).

DISCUSSION

Stage, pathological classification of cancer cells, age, sex and tumor markers are frequently used as prognostic factors for cancer. However, a prognostic factor study for prostate cancer should be done not only with these items but also with others expressing general condition, since this disease is frequently detected in old people. Since ESR examinations is easy and cheap, and is not harmful to patients, it would be clinically valuable if it were a good prognostic factor.

ESR is a classical non-specific examination and the details of its mechanism are not clear.[12] It is well known that ESR is influenced by red blood cell count, serum protein concentration or albumin, α_2 globulin, fibrinogen, infection, etc. The relationship between ESR and other clinical data which might influence it was investigated in patients with prostate cancer. Among them, factors concerning infection and anemia were postulated as items which might influence ESR. However, the proportion of patients with more than 37.0°C fever was only 14.4%. The number of patients with fever was so small that it was not an adequate sample to investigate the role of fever as a prognostic factor. The value of ESR was related to hemoglobin and hemoglobin was related to bone metastasis (data not shown). The multivariate analysis showed that hemoglobin was less significant as a

prognostic factor than ESR. This might mean that ESR included not only anemia as a component but also others. This view is supported by the significant relation to infection and performance status (treated as gait disturbance here). Moreover, the result of the multivariate study showing the significance of ESR was based on data from the third observation year after the initial diagnosis.[4] If ESR is a factor which represents general condition, the significance should be shown from the beginning, as is the case with gait disturbance.[4] When the patients with prostate cancer were stratified into stage A + B + C and stage D, the significance of ESR in stage D was highest among the items studied and not so high in stage A + B + C (data not shown). This result suggests that ESR may reflect the degree of stage D prostate cancer, and it was coincident with the results obtained by the analysis of bone metastasis and ESR. This can be interpreted as showing that ESR includes not only infection, anemia and the degree of bone metastasis factor but also other unknown, factor(s), and ESR works well as a "summary"

parameter. The items which evaluate the same component as the prognostic factor have to be excluded from the multivariate analysis study.

In this study, gait disturbance was used instead of performance status. These were well correlated with each other (data not shown). The category of gait disturbance is decided at the time of adminission and it is categorized into three degrees. On the other hand, a longer observation time is necessary to decide performance status accurately after admission and this item is categorized into five degrees. This means that gait disturbance is easier and simpler to determine than performance status. However, gait disturbance is influenced by the service system of individual hospitals. As it was difficult to standardize performance status in some records of our group, we used gait disturbance instead of performance status. Depending on the service system, this item is probably more useful as a prognostic factor than performance status.

REFERENCES

1) Adami, H., Norlen, B. J., Malker, B. and Merik, O. Long-term survival in prostate carcinoma, with special reference to age as a prognostic factor. *Scand. J. Urol. Nephrol.*, **20**, 107–112 (1986).

2) Byar, D. P., Huse, R., Bailar, J. C., III and the Veterans Administration Cooperative Urological Research Group. An exponential model relating censored survival data and concomitant information for prostatic cancer patients. *J. Natl. Cancer Inst.*, **52**, 321–327 (1974).

3) Emrich, L. J., Priore, R. L., Murphy, J. P., Brady, M. F. and the investigation of the National Prostatic Cancer Project. Prognostic factors in patients with advanced stage prostate cancer. *Cancer Res.*, **45**, 5173–5179 (1985).

4) Tomaru, T., Koya, K., Kumasaka, H., Satoh, J., Imai, K. and Yamanaka, H. Multivariate analysis study of prognostic factor for prostate cancer. *J. Jpn. Soc. Cancer Ther.*, **22**, 1970 (1987) (in Japanese).

5) Catalona, W. J. and Scott, W. S. Carcinoma of the prostate. *In* "Campbell's Urology, 4th Edition," ed. J. H. Harrison, R. F. Gittes, A. D. Perlmutter, T. A. Stamey and P. C. Walsh, p. 1092 (1979). W. B. Saunders Co., Philadelphia.

6) Pilepich, M. V., Krall, J. M., Sause, W. T., Johnson, R. J., Russ, H. H., Hanks, G. E., Perez, C. A., Zinninger, M. Z. and Martz, K. L. Prognostic factors in carcinoma of prostate. Analysis of RTOG study 75-06. *Int. J. Radiat. Oncol. Biol. Phys.*, **13**, 339–349 (1987).

7) Byar, D. P. and Corle, D. K. Analysis of prognostic factors for prostate cancer in the VACURG studies. *In* "Controlled Clinical Trials in Urological Oncology," ed. L. Denis, G. P. Murphy, G. R. Prout and F. Schreder, pp. 147–186 (1984). Raven Press, New York.

8) Sylvester, R. J., Suciu, S. and Yamanaka, H. Prognostic factors for randomization and stratification and endpoints for the evaluation trials. *In* "EORTCG Genitourinary Group Monograph 5: Progress and Controversies in Oncological Urology II," pp. 257–287 (1988). Alan R. Liss, Inc., New York.

9) Wilson, D. W., Hraper, M. E., Jensen, H. M., Ikeda, R. M., Richards, G., Peeling, W. B., Pierrepoint, C. G. and Griffiths, K. A prognostic index for clinical management of patients with advanced prostate cancer, A British Prostate Study Group Investigation. *Prostate*, **7**, 131–141 (1985).

10) Dayal, H. H., Polissar, L. and Dahlberg, S. Race, socioeconomic status and other prognostic factors for survival from prostate cancer. *J. Natl. Cancer Inst.*, **74**, 1001–1006 (1985).

11) Catalona, W. J. and Scott, W. W. Carcinoma of the prostate. *In* "Campbell's Urology, 5th Edition," ed. P. C. Walsh, R. F. Gittes, A. D. Perlmutter and T. A. Stamey, pp. 1463–1534 (1986). W. B. Saunders Co., Philadelphia.

12) Mutoh, Y. Erythrocyte sedimentation rate. *Medicina*, **26**, 1742–1743 (1989) (in Japanese).

13) Soloway, M. S., Hardeman, S. W., Hickey, D., Raymond, J., Todd, B., Soloway, S. and Moinuddin, M. Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. *Cancer*, **61**, 195–202 (1988).

14) Hurukawa, T. and Tanaka, H. "Multiple Regression Analysis. Quantification I∼II. Program Package for Multivariate Analysis," 1st Ed., pp. 17–39; pp. 128–150 (1983). Igakushoin, Tokyo (in Japanese).