Virchows Arch [Pathol Anat] (1986) 409:395–405

Virchows Archiv A

Incidental prostatic carcinoma: morphometry correlated with histological grade*

Ryuichi Yatani[1], Taizo Shiraishi[1], Kaneyoshi Akazaki[2], Takuji Hayashi[3], Lance K. Heilbrun[4], and Grant N. Stemmermann[4]

[1] Department of Pathology, Mie University School of Medicine, 2-174 Edobashi, Tsu, Mie-ken 514, Japan;
[2] Aichi Cancer Center Research Institute, 81-1159, Kanokoden, Tashiro-cho, Chigusa, Nagoya, Aichi 464, Japan;
[3] Laboratory Department, Kuakini Medical Center, 347 N. Kuakini Street, Honolulu, HI 96817, USA;
[4] Japan-Hawaii Cancer Study, 347 N. Kuakini Street, Honolulu, HI 96817, USA

Summary. The histological grades of prostatic carcinoma, as defined by Gleason, were correlated with three methods of morphometry in 254 step-sectioned prostates obtained at autopsy. The variables studied were 1) the number of tumours in each prostate; 2) bilaterality and 3) tumour volume. Each characteristic yielded a statistically significant correlation with histological grade. The strongest correlations were obtained using tumour volume. These autopsy studied help to explain the inconsistent results obtained from morphometric analyses of surgical material, and lend support to the Gleason system as a means of predicting tumour behavior.

Key words: Incidental prostatic carcinoma – Morphometry – Histological grading

Introduction

Prostatic carcinomas found incidentally in specimens removed in the treatment of benign hypertrophy are usually at an early stage of development. In 1975, Jewett (1975) subdivided such cancers into two categories: stage A_1 and A_2. He suggested that the former had a low biological activity, while the latter had a tendency to progress. This subclassification of stage A prostatic carcinoma has been used widely, because a patient with stage A_2 tumour is considered to need treatment, whereas the others does not. The criteria used to assign tumours into those subclasses, however, have

* Supported in part by research contracts PH 64-10, NCI-72-3213, N01-CP-53521; Grant R01-CA-33644; and the Grant-in-Aid for Cancer Research (33) from the Ministry of Health and Welfare

Offprint requests to: G.N. Stemmermann at the above address

not been uniform. For instance, stage A_1 prostatic carcinoma was defined as cancer in 3 chips in specimens obtained at transurethral resection (TUR) by Boxer (1977), 5 chips by Golimbu et al. (1978) and Parfitt et al. (1983); less than 50 percent gland involvement by Donohue et al (1977); or one lobe involvement by Catalona and Scott (1978). Some of these criteria have been combined with histological grading.

These methods have generally based their criteria on morphometric factors, such as the number of positive chips, the percent involved areas or the number of involved lobes, and they have compared these factors with patient survival (Sheldon et al. 1970). In studies of this type, the data are not consistent from study to study. A morphometric study can be influenced by the type of surgical procedure used to obtain study material, the amount of tissue excised, the number of chips examined, etc. (Newman et al. 1982). Because it is difficult to collect a large number of cases with uniform morphometric data, statistics based on morphometric analysis of surgical specimens should be read with care.

Although a study using autopsy material cannot give the prognosis of a tumour, it can provide more exact morphometry. Careful step-sectioning of the entire prostate permits the examiner to estimate the volume, location, and multiplicity of cancers within the prostate. Histological grading has been correlated with the biological activity of prostatic carcinoma (Gleason 1966; Murphy and Whitmore 1979). If the histological grade of prostatic cancer truly reflects its biological activity, it would be a more useful means of distinguishing stage A_1 from A_2 tumours than would morphometry of surgical material.

We have examined the latent carcinomas found among 254 Japanese men. The source of these specimens was a collection of 993 prostates obtained from subjects in Hawaii and Japan. We have correlated the morphometry with the histologic grades of 382 cancers found in these specimens.

Materials and methods

The 993 prostates obtained at autopsy were fixed in formaldehyde and shipped to the Aichi Cancer Center in Nagoya, Japan. Prostates were examined from men over 50 years of age without prior prostatic surgery or diagnosis of prostatic carcinoma. Only intact prostate glands were accepted. The 417 Hawaiian Japanese prostates were collected in Honolulu, Hawaii, and the 576 Japanese prostates were collected from many cities of Japan.

Examination procedures were the same as those reported by Akazaki and Stemmermann (1973) and Guileyardo et al. (1980; 1982). Each prostate was step-sectioned at 3 mm intervals, vertical to the urethra, and each section was numbered. The blocks were embedded in paraffin, and sections were cut at the thickness of 5–7 μm. These sections were stained with haematoxylin and eosin. All slides were prepared by the same technologist.

Initially, the tumours were classified as either infiltrative or noninfiltrative (Akazaki and Stemmermann 1973; Yatani et al. 1982). They were re-evaluated according to the Gleason system in which tumours were classified into five categories (G1, G2, G3, G4 and G5). Guileyardo et al. (1982) established the reproducibility of these grades, and our interpretation of this system is shown in Figs. 1–5. The highest grade encountered in each prostate, regardless of the number of tumours it contained, was the designated grade for each subject.

Each tumour was outlined by pen so as to estimate the volume and the number in each prostate. The slides were then transilluminated, and the tumour outlines traced onto paper.

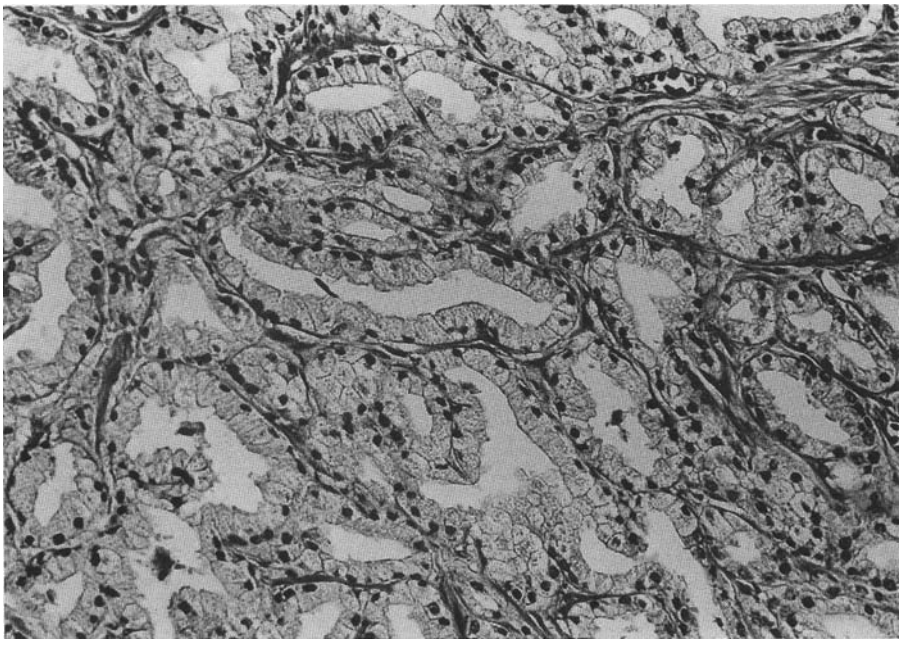

Fig. 1. Gleason Grade 1. A well differentiated tumour with back to back glands, uniform basal nuclei and abundant pale cytoplasm.

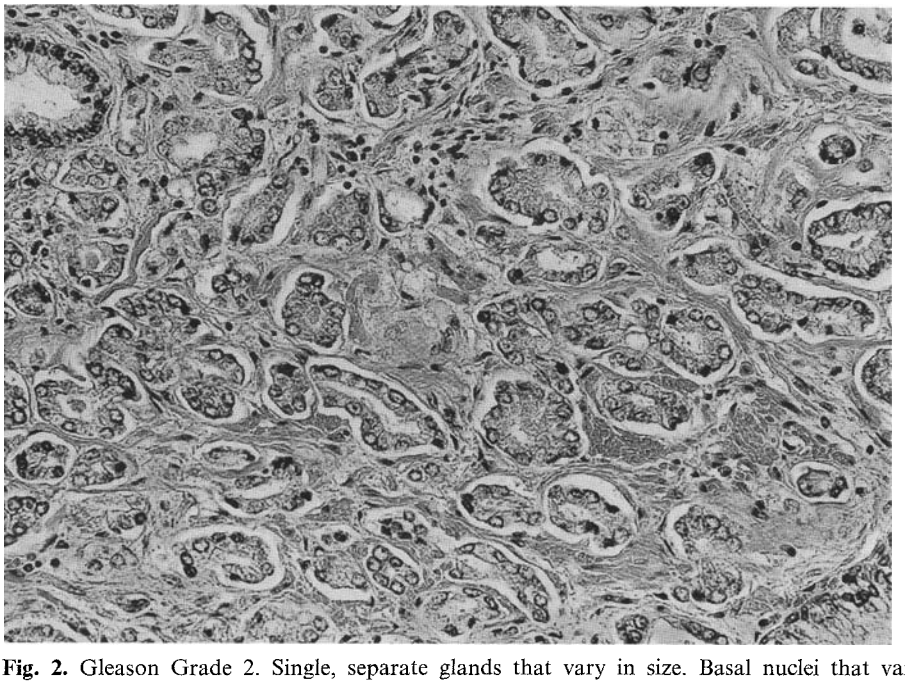

Fig. 2. Gleason Grade 2. Single, separate glands that vary in size. Basal nuclei that vary in size and staining characteristics.

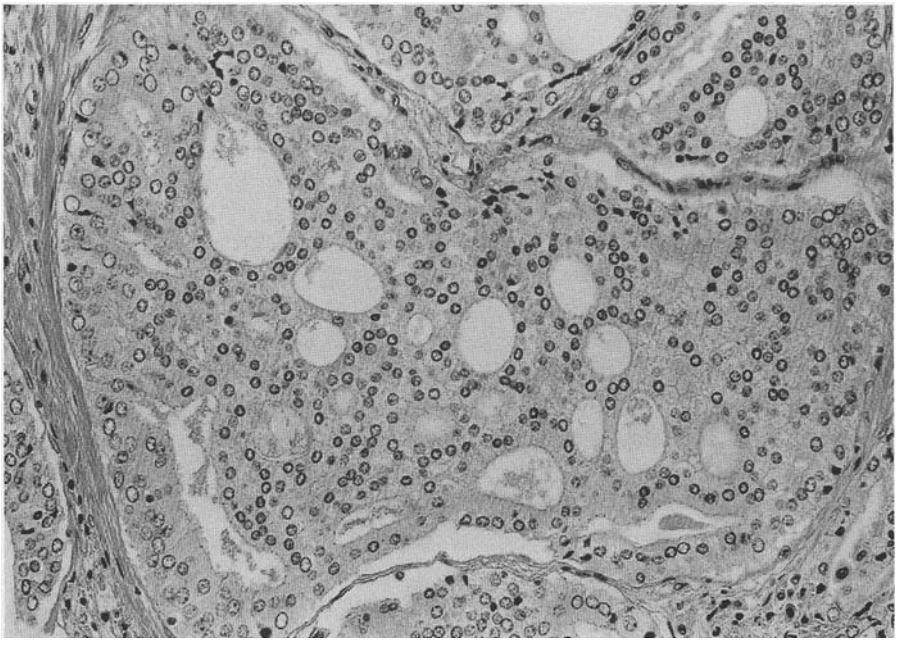

Fig. 3. Gleason Grade 3. Tumour cells from cribriform sheets. Basal polarity of nuclei lost at periphery of sheets.

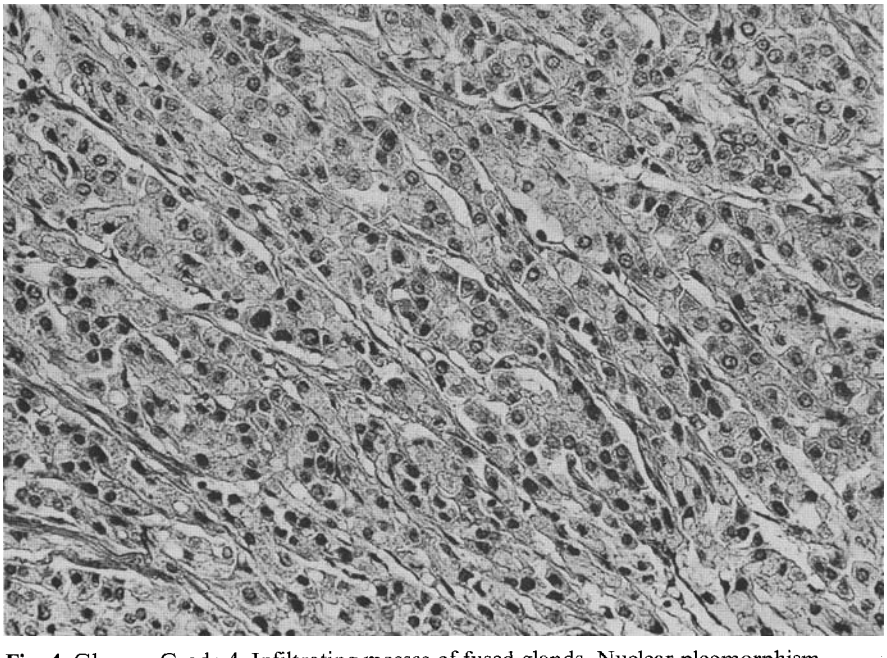

Fig. 4. Gleason Grade 4. Infiltrating masses of fused glands. Nuclear pleomorphism.

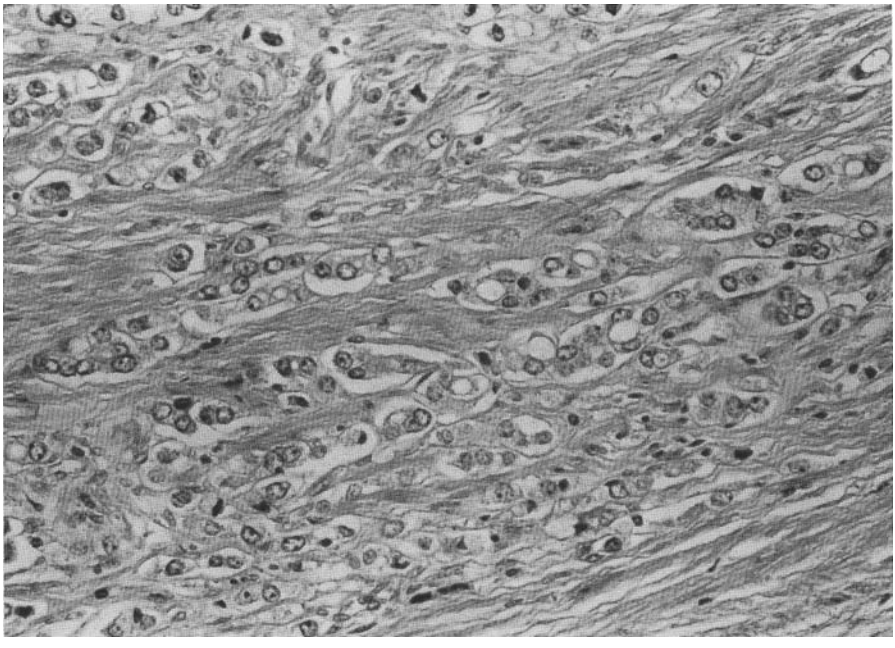

Fig. 5. Gleason Grade 5. Very poorly differentiated. Diffusely infiltrating single cells that vary greatly in size and staining characteristics.

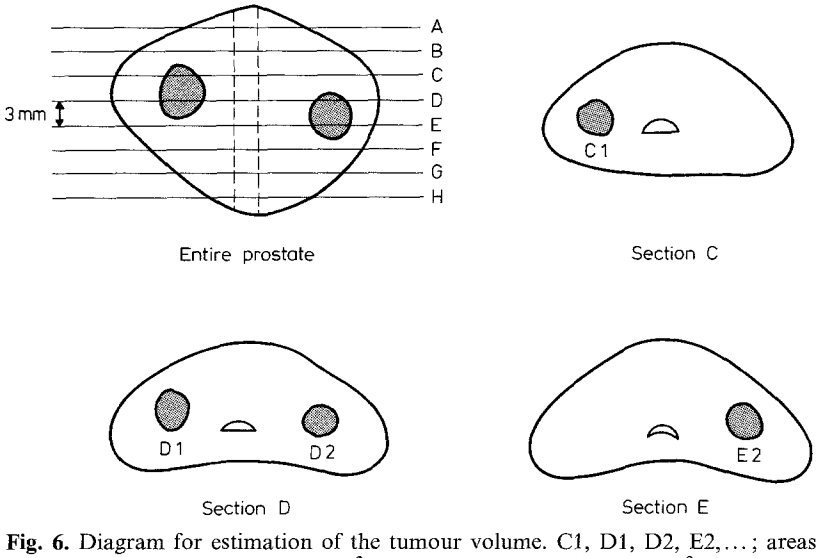

Fig. 6. Diagram for estimation of the tumour volume. C1, D1, D2, E2,...; areas of tumour measured by image analyzer (mm^2). Estimated total volume (mm^3) $=(C1 \times 3)+(D1 \times 3)+(D2 \times 3)+(E2 \times 3)+(\ldots)=(C1+D1+D2+E2+\ldots) \times 3$

These tracings were examined with an image analyzer (KONTRON, West Germany) to provide area measurements of the flat-plane images. The sum yielded an estimate of tumour volume when multiplied by 3 mm, because the prostate was cut and examined at 3 mm intervals. Because tumours may have irregular outlines, we appreciate that this method probably does not yield an exact volume, but comparable inaccuracies can be expected for all tumours. Neoplastic glands located in the same position of successive sections were assumed to be part of the same tumour (Fig. 6).

A circle was drawn with a radius of 1 cm from the center of the urethra in each prostate in order to assess the frequency of tumours in the periphery of the organ (i.e., tumours most likely to be missed in transurethral resections).

Preliminary comparisons of Hawaiian and Japanese subjects utilized two-sample *t*-test or continuity-corrected chisquare tests. Univariate analyses of histological grade involved simple zero-order Pearson correlations. Multivariate analyses included partial correlation and multiple linear regression (Snedecor and Cochran 1967). Standardized regression coefficients were computed by multiplying the unstandardized coefficient by the ratio of standard deviations of the dependent variable (Gleason grade) and the independent variable (SAS Institute 1982).

Results

The Hawaiian and Japanese subjects are compared according to age and pathological variables in Table 1. The Hawaii subjects were older, a difference that was statistically significant ($p=0.025$). The Japanese had heavier prostates ($p=0.054$). Because the other variables did not show any significant differences, the Hawaiian and Japanese subjects were combined in subsequent analyses.

There were 382 cancers among the 254 subjects with prostate cancer. Among these, 183 (47.9%) involved tissues that were less than 1 cm from the center of the urethra, 124 (32.5%) were located more than 1 cm from the urethra, and the inner margins of 75 cancers (19.6%) were at 1 cm from the urethra.

The number of cases in each Gleason grade were: G1-70; G2-121; G3-53; G4-9; G5-1. Because there were only 10 cases that fell into grades 4 and 5, these grades were combined. The distribution of different Gleason grades among tumours of the Hawaii men were 25, 72, 27 and 4; and among the Japanese were 45, 49, 26 and 6, respectively.

The distribution of histological grade by multiplicity of tumours in each prostate is shown in Table 2. About half of the cancers were multifocal

Table 1. Comparison of Hawaii and Japan subjects by age and pathological variables*

Variable	Hawaii ($n=128$)	Japan ($n=126$)	p-value[a]
Age at death (years)	74.1 ± 9.64	71.4 ± 9.85	0.025
Weight of prostate (g)	30.2 ±12.4	33.1 ±11.9	0.054
Gleason grade	2.10± 0.80	1.94± 0.87	0.136
No. of cancer foci	1.98± 1.27	1.90± 1.18	0.606
% of bilateral tumour	43.8%	38.9%	0.510
Tumour volume (mm^3)	257 ±548	248 ±441	0.892

[a] From *t*-test, except for % of bilateral tumour, for which chi-square was used

* Values shown are mean ± standard deviation

Table 2. Distribution of cases by histological grade and multiplicity

Gleason grade	No. of cancer foci				Total
	1	2	3	4–	
1	39	17	9	5	70
2	67	28	12	14	121
3	19	8	14	12	53
4,5	4	3	0	3	10
Total	129	56	35	34	254

Table 3. Distribution of cases by histological grade and location

Gleason grade	Unilateral (%)	Bilateral (%)	Total
1	50 (34)	20 (19)	70
2	74 (50)	47 (45)	121
3	20 (13)	33 (31)	53
4,5	5 (3)	5 (5)	10
Total	149 (100)	105 (100)	254

Table 4. Distribution of cases by histological grade and tumour volume

Gleason grade	Tumour volume (mm^3)				Total
	<9	10–39	40–129	>130–	
1	6	30	27	7	70
2	2	39	42	38	121
3	1	2	11	39	53
4,5	0	0	0	10	10
Total	9	71	80	94	254

(125/254=49.2%). Multiple tumours were least frequent with low grade cancers and most frequent with high grade cancers.

Table 3 shows the distribution of the histological grades of prostate cancer by laterality. Among 149 unilateral tumours, 124 (83.2%) were at Gleason grades 1 or 2. Among 105 bilateral tumours, 67 (63.8%) were at Gleason grades 1 or 2. Table 4 compares the histological grade with the volume of prostate cancer. Only 7 of 70 G1 tumours (10%) exceeded 130 mm^3. There was a regular increase in the frequency of tumours exceeding 130 mm^3 with each Gleason grade: G2 – 31.4%, G3 – 73.6%, and G4, G5 – 100%.

Table 5. Correlation analysis of variables potentially related to histological grade

Variable	Pearson correlation	Partial correlation[a]
Age at death (years)	0.209*	N/A
Weight of prostate (g)	0.016	N/A
No. of cancer foci	0.232**	0.213*
Bilaterality (0 = no, 1 = yes)	0.215*	0.188***
Tumour volume	0.470**	0.457**

** $p < 0.0001$; * $p < 0.001$; *** $p < 0.01$
N/A = Not applicable

[a] Controlling for age at death and weight of prostate

Table 6. Multiple regression model of gleason grade and pathology variables

Variable	b[a]	S.E. (b)[b]	p-value[c]	B[d]
No. of cancer foci	0.098	0.052	0.063	0.143
Bilateral tumour (0 = no, 1 = yes)	−0.126	0.134	0.349	−0.074
Tumour volume (mm^3)	0.0007	0.0001	0.0001	0.441
Age at death (years)	0.013	0.005	0.009	0.147
Weight of prostate (g)	−0.002	0.004	0.533	−0.035
Intercept	0.860	0.369	0.021	N/A

N/A = Not applicable

[a] b = Unstandardized regression coefficient
[b] S.E. (b) = Standard error of b
[c] For testing whether b is significantly different from zero
[d] B = Standardized (unit-free) b

There was a statistically significant positive correlation between tumour volume and histological grade (Table 5). The degree of correlation was still substantial ($r = 0.457$) after adjustment for age and prostate weight. The positive relationship between histological grade and tumour multiplicity was confirmed by Pearson correlation analysis (Table 5). Since age at death and prostate weight differed significantly between the two sources of our study material (Table 1), and age was correlated with histological grade, we reanalyzed the data, taking these factors into account (Table 5). There was still a significant partial correlation ($r = 0.213$) between the number of cancer foci and the histological grade. There was a weaker, but still significant, correlation ($r = 0.188$) between bilaterality and histological grade (Table 5), after controlling for age at death and weight of the prostate.

Table 6 gives the results of multiple linear regression analysis of Gleason grade as a function of the three pathology variables, and two covariates (age at death and prostate weight). Tumour volume is the factor most strongly associated with Gleason grade. Next in importance is the number of cancer foci; and last, bilaterality. Age at death is still an important covariate, but prostate weight is not.

Discussion

We have examined 254 Japanese cases of prostatic carcinoma obtained at autopsy in Hawaii and Japan, using step-serial sections and standardized procedure and diagnostic criteria (Akazaki and Stemmermann 1973; Guileyardo et al. 1980; Yatani et al. 1982). We found 382 tumours among the 254 prostates showing areas of malignant change. A third of these tumours may have been missed had the diagnosis depended upon curettings derived from a transurethral resection (i.e., they were located more than 1 cm from the urethra).

We obtained a significant partial correlation between the histological grade and the multiplicity of prostatic carcinomas ($p < 0.001$). Kastendieck et al. (1976) analyzed 50 total prostatectomies by step-section, and showed that 30 percent of cancers were unifocal. Byar and Mostofi (1972) examined step-serial sections of 208 clinically diagnosed prostatic cancers and established correlations between the prognosis of the patient and some pathological features of prostatic carcinoma. In their report, the majority of tumours were multiple, and there were fewer 7-year survivors among men with multiple tumours than among those with a single tumour. Because of the small number of cases of a single tumour, the survival difference between men with single and multiple tumours was not statistically significant. In contrast will these reports, half of our subjects had a single tumour, and we obtained a statistically significant correlation between the histological grade and the number of cancer foci. These differences may be explained by differences in clinical and autopsy material. It is reasonable to expect that prostate carcinomas encountered as incidental findings at autopsy will be at an earlier stage than those producing symptoms. Although we show a statistically significant correlation between tumour multiplicity and the histological grade, the level of significance was not quite as strong as that between tumour grade and tumour volume (Table 5). These differences are more substantial when assessed on the basis of multiple regression of the Gleason grade (Table 6).

Catalona and Scott (1978) defined stage A_1 prostatic carcinoma as one involving a single lobe. Since the lobes of the prostate cannot be distinguished histologically in the adult, we classified tumours as unilateral and bilateral. This standard has been adopted by the Japanese Uro-Pathologic Committee (1984). Byar and Mostofi (1972) also examined the relationship between the location of prostatic carcinoma and the prognosis of patients. They reported that about 80% of tumours were bilateral, and there was no statistical difference in survival of patients with unilateral and bilateral tumours. Kastendieck et al. (1976) reported that 76% of their tumours were bilateral. In this report, 41% were bilateral, with a tendency to show higher histological grades in bilateral cases.

The size of prostatic carcinoma has been found to correlate with biological activity in most studies. Cantrell et al. (1981) estimated the histological differentiation and volumes of 117 prostatic carcinomas diagnosed either by transurethral resection or enucleation, among which 14 cancers showed

progression in a 4-year follow-up. Both volume and histological differentiation could be correlated with progression. Surgical material, if limited to that obtained by transurethral resection, does not permit identification of multicentric tumours, and, as noted above, may fail to sample one-third of the latent tumours within the organ. If the paraurethral portions of the prostate do yield a large volume of tumour, it seems reasonable to assume that local progression has already begun, and in such cases, the appearance of clinical progression in the next four years is not unexpected.

Guileyardo et al. (1982), studying autopsy material from black and white autopsy subjects, were able to provide a more accurate appraisal of the relationship of tumours volume to tumour histology. They associated small tumours with lower Gleason grades. Our study confirms and extends their findings; and indicates that the relation between tumour volume and histology also holds true for the Japanese, a population that is at much lower risk of clinical progression than were Guileyardo's subjects (1980).

In summary, this study shows that the most substantial predictor of the histological grade in this Japanese population is prostate tumour volume, followed by age at death, and the number of neoplastic foci. These findings support the concept that the Gleason grade of prostate cancer will predict the biological behavior of this tumour.

References

Akazaki K, Stemmermann GN (1973) Comparative study of latent carcinoma among Japanese in Japan and Hawaii. J Natl Cancer Inst 50:1137–1144

Boxer RJ, Kaufman JJ, Goodwin WE (1977) Radical prostatectomy for carcinoma of the prostate. J Urol 117:208–213

Byar DP, Mostofi FK (1972) Carcinoma of the prostate. Prognostic evaluation of certain pathologic features in 208 radical prostatectomies. Cancer 30:5–13

Cantrell BB, DeKlerk DP, Eggleston JC, Boitnott JK, Walsh PC (1981) Pathological factors that influence prognosis in stage *A* prostatic cancer. The influence of extent versus grade. J Urol 125:516–520

Catalona WJ, Scott WW (1978) Carcinoma of the prostate. A review. J Urol 119:1–8

Donohue RE, Pfister RR, Weigel JW, Stonington OG (1977) Pelvic lymphadenectomy in stage *A* prostatic cancer. Urol 9:273–275

Gleason DF (1966) Classification of prostatic carcinoma. Cancer Chemother Rep 50:125–128

Golimbu M, Schinella R, Moraler P, Kurusu S (1978) Differences in pathological characteristics and prognosis of clinical A_2 prostatic cancer from A_1 and *B* disease. J Urol 119:618–622

Guileyardo JM, Johanson WD, Welsh RA, Akazaki K, Correa P (1980) Prevalence of latent prostate carcinoma in two US populations. J Natl Cancer Inst 65:311–316

Guileyardo JM, Sama DP, Johnson WD, Akazaki K, Correa P (1982) Incidental prostatic carcinoma. Tumour extent versus histologic grade. Urol 20:40–42

Japanese Urological Association and the Japanese Pathological Society (1984) General rule for clinical and pathological studies on prostate cancer. Kanehara, Tokyo

Jewett HJ (1975) The present status of radical prostatectomy for stages *A* and *B* prostatic cancer. Urol Clin North Am 2:105–124

Kastendieck H, Altenahr E, Hüsselmann H, Bressel M (1976) Carcinoma and dysplastic lesions of the prostate. A histo-morphological analysis of 50 total prostatectomies by step-section technique. Z Krebsforsch 88:33–54

Murphy GP, Whitmore WF Jr (1979) A report of the workshop on the current status of the histologic grading of prostatic cancer. Cancer 44:1490–1494

Newman AJ Jr, Graham MA, Carlton CE Jr, Lieman S (1982) Incidental carcinoma of the prostate at the time of transurethral resection. Importance of evaluating every chip. J Urol 128:948–950

Parfitt HE Jr, Smith JA Jr, Seaman JP, Middleton RG (1983) Surgical treatment of stage A_2 prostatic carcinoma. Significance of tumour grade and extent. J Urol 129:763–765

SAS Institute, Inc. (1982) SAS User's Guide: Statistics, 1982 Edition. SAS Intitute, Cary, NC

Sheldon CA, Williams RD, Fraley EE (1980) Incidental carcinoma of the prostate. A review of the literature and critical reappraisal of classification. J Urol 124:626–631

Snedecor GW, Cochran WG (1967) Statistical methods, Ed. 6. Iowa State University Press, Ames, Iowa

Waterhouse J, Miura C, Shanmugaratnam K, Powell J (1982) Cancer in Five Continents, Vol. IV. International Agency for Research on Cancer, Lyon, France

Yatani R, Chigusa I, Akazaki K, Stemmermann GN, Welsh RA, Correa P (1982) Geographic pathology of latent prostatic carcinoma. Int J Cancer 29:611–616

Accepted February 10, 1986