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DNA IN RADICAL PROSTATECTOMY SPECIMENS

Prognostic value of tumor ploidy

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Abstract

In a series of 94 patients with prostatic adenocarcinoma the prognostic significance of some factors was studied after radical prostatectomy. DNA ploidy was assessed by flow cytometry of cells from deparaffinized specimens. Gleason sum, seminal vesicle status and ploidy turned all out to be important predictors of disease progression. The ploidy status significantly enhanced the ability to prognostically evaluate patients with intermediate grade carcinoma compared to tumor grade alone. Patients with seminal vesicle invasion and aneuploidy had a very poor prognosis which prompts trials with alternatives of adjuvant therapy in this patient population.

Key words: Prostatic cancer, prognostic factors, DNA ploidy, tumor grade, seminal vesicle invasion.

Previous studies have demonstrated that the Gleason histopathologic grading provided a reasonable prediction of outcome after radical prostatectomy. Patients with Gleason sums of 7 or less fared better than patients with a Gleason sum of 8, 9 or 10. However, people have criticized the Gleason sum as it is necessarily subjective and may be difficult to reproduce (1–4). Even more importantly, the predictive value of the Gleason score among patients with intermediate grade tumors is less good. Lee et al. (5), in an attempt to determine a more accurate method for predicting the biologic risk of prostatic carcinoma, undertook analysis of 88 deparaffinized radical prostatectomy specimens in order to determine the relative predictive values for disease recurrence on the basis of tumor ploidy, Gleason sum and seminal vesicle involvement (stage).

For the purpose of this study, the population of 94 patients who underwent radical prostatectomy as primary treatment for prostatic adenocarcinoma were identified. Sixty-five of these patients demonstrated seminal vesicle invasion by light microscopy. An additional 29 patients without seminal vesicle involvement were selected on the basis of Gleason sum cluster alone in order to adequately represent the diverse spectrum of histopathologic grade in prostatic adenocarcinoma. Nine tumors were of gleason sum 2 to 4, 14 tumors were of 5 to 7, and 6 were of Gleason sum 8, 9 or 10. All patients prior to prostatectomy had normal serum acid phosphatase levels, normal bone scan, and no evidence of nodal metastases on the basis of pelvic lymphadenectomy. The first evidence of failure was determined by the appearance of biopsy proved local recurrence, a positive bond scan or the appearance of a persistent elevation of serum prostatic acid phosphatase. No patient received subsequent therapy (chemotherapy, radiation therapy, hormonal therapy, or steroids) until distant disease was identified. Methodology for ploidy analysis has been previously described (5–8). Flow cytometry was performed successfully on 88 specimens.

The clinical recurrence of disease was examined by ploidy, stage, and Gleason sum. An examination of the occurrence of treatment failure when stratified by Gleason sum and ploidy demonstrated that the predominance of aneuploidy occurred in the recurrent group (Fig. 1). Recurrent disease was noted with a marked increase in frequency among patients with seminal vesicle involvement and in patients with aneuploidy (Table 1). While the incidence of recurrence in the total population as a function of Gleason sum was also statistically significant, this significance occurred at a lower confidence level. Interestingly, when the entire population was stratified into posi-

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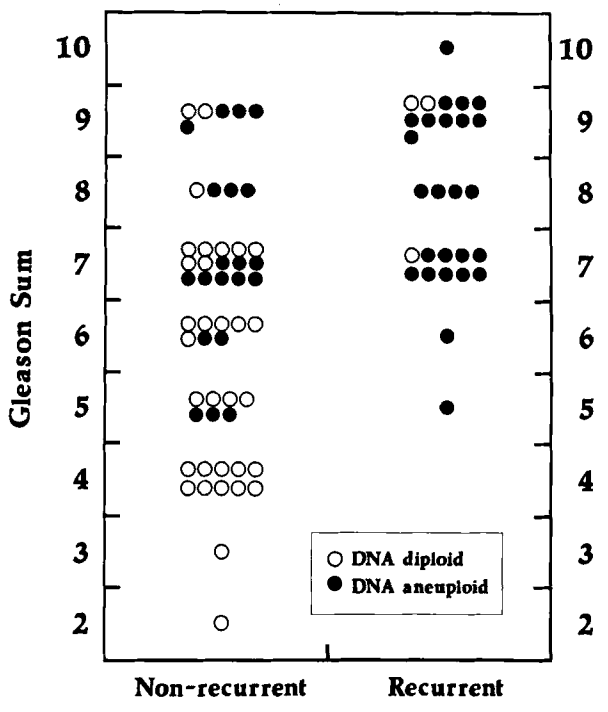

Fig. 1. Graphic representation of Gleason sum in patient population as function of disease recurrence. Note association of aneuploidy and higher Gleason sums with recurrence. (Reprinted with permission from Lee et al: J Urol 1988; 140: 769–74.)

Table 1

Recurrence as function of ploidy, Gleason sum and seminal vesicle status

	Recurrence (No.)		p-value
	Yes	No	
Seminal vesicle positive			
DNA diploid	3	14	
DNA aneuploid	22	13	<0.005
Gleason ≤7	11	20	
Gleason >7	14	7	<0.05
Seminal vesicle negative			
DNA diploid	0	18	
DNA aneuploid	3	7	0.025
Gleason ≤7	1	22	
Gleason >7	3		<0.025
Total population			
DNA diploid	3	32	
DNA aneuploid	25	20	<0.001
Gleason ≤7	12	42	
Gleason >7	16	10	<0.05
Seminal vesicle negative	3	25	
Seminal vesicle positive	25	27	<0.005

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tive and negative seminal vesicle cohorts, ploidy appeared as the significant predictor of recurrence in patients with seminal vesicle involvement.

Kaplan-Meier analysis assessed the probability of remaining disease-free as a function of seminal vesicle status and ploidy. The probability or remaining free of disease at 60 months when seminal vesicle invasion occurred was only 28% as opposed to 87% in the absence of seminal vesicle involvement (Fig. 2). When ploidy alone was examined, only 9% of aneuploid patients remained disease-free at 60 months as opposed to 85% of those patients with diploid tumors (Fig. 3).

Lastly, it is of interest to examine the relative impact of distribution and disease and ploidy status. Fig. 4 represents the data after patients have been separated into four groups based on ploidy and seminal vesicle status. No failures were seen in the best prognostic group, 18 diploid patients with negative seminal vesicles. When one examines the prognostic parameters analyzed within this study summarizing sensitivity, specificity and predictive value, it is seen that ploidy and seminal vesicle status have similar prognostic significance with very high negative predictive values (91% and 89% respectively) ((9) Table 2). Gleason score prevails as specificity, indicating the marked prevalence of low Gleason sums in those patients who did not have recurrence whereas ploidy and seminal vesicle status are extremely sensitive (89%). There is a high negative predictive value of ploidy in those patients who have seminal vesicle involvement, demonstrating an 82% chance of patients with diploid tumors remaining free of disease even in the presence of clinical extension. In the absence of seminal vesicle involvement, the negative predictive value of ploidy is 100% as compared to 96% for Gleason score.

In summary, ploidy as assessed by flow cytometric analysis of deparaffinized prostatic carcinoma, Gleason sum and seminal vesicle status are important predictors of disease progression. However, ploidy as the objective mesurement of malignant potential and seminal vesicle status as the objective measurement of pathologic stage

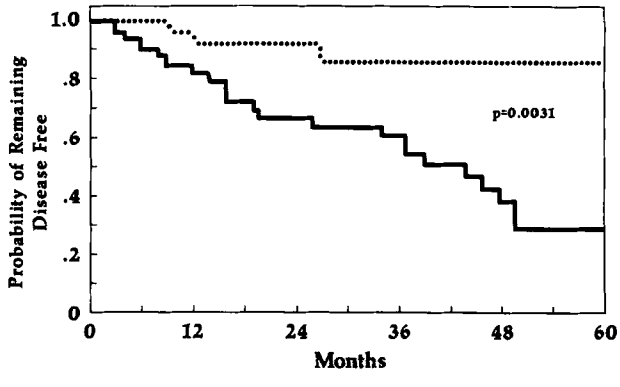

Fig. 2. Kaplan-Meier plot demonstrates significant difference in probability of remaining free of disease between seminal vesicle positive (SV(+) · · · ·) and seminal vesicle negative (SV(−)—) disease. (Reprinted with permission from Lee et al.: J Urol 1988; 140: 769–74.)

Table 2

Sensitivity, specificity and predictive value of prognostic parameters for recurrence

	Seminal vesicle positive		Seminal vesicle negative		Total population		
	Ploidy	Gleason	Ploidy	Gleason	Ploidy	Gleason	Seminal vesicle status
Sensitivity (%)	88	56	100	67	89	57	89
Specificity (%)	52	74	72	88	62	81	48
Pos. predictive value (%)	63	67	30	40	56	62	48
Neg. predictive value (%)	82	65	100	96	91	78	89

Ploidy (diploid versus aneuploid), Gleason sum ($\leqslant 7$ versus >7) and seminal vesicle status (negative versus positive). Reprinted with permission from J Urol 1988; 140: 769.

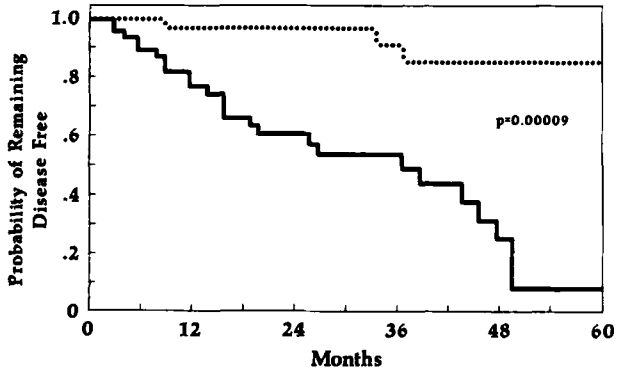

Fig. 3. Kaplan-Meier plot demonstrates marked difference in probability of remaining free of disease between patients with diploid (· · · ·) versus aneuploid (—) tumors. (Reprinted with permission from: Lee et al.: J Urol 1988; 140: 769–74.)

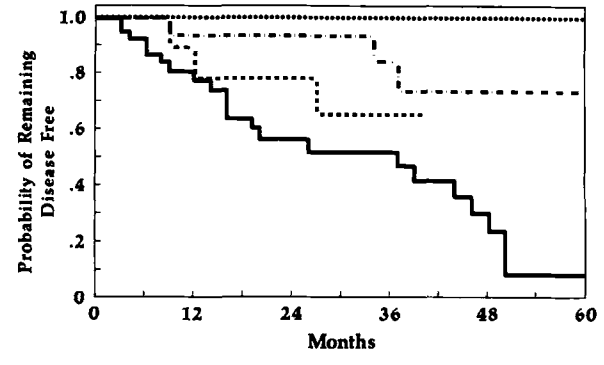

Fig. 4. Kaplan-Meier plot demonstrates probability or remaining free of disease as function of seminal vesicle status and tumor ploidy. Note no disease recurrence in most favorable prognostic group (seminal vesical negative, SV(−), diploid), and poor prognosis associated with presence of concurrent seminal vesicle involvement and aneuploidy (SV(+), seminal vesicle positive). · · · · (SV(−) diploid; · — · — · SV(+) diploid; - - - - SV(−) aneuploid; —SV(+) aneuploid. (Reprinted with permission from: Lee et al.: J Urol 1988; 140: 769–74.)

seem equivalently important when one examines the negative predictive value. Using ploidy status to evaluate patients with intermediate grade prostatic tumors significantly enhances prognostic ability over that of tumor grade alone. The ominous prognosis which is seen with seminal vesicle invasion and aneuploidy prompts one to examine alternatives of adjuvant therapy in this patient population in hopes of providing additional benefit to these high-risk individuals.

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