Large Scale Genomic Instability as an **Additive Prognostic Marker** in Early Prostate Cancer

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Introduction

Prostate cancer is the most frequent type of cancer among Norwegian men[1]. The individual prognosis for the prostate cancer patient is hard to predict, despite well established prognostic factors like Gleason score and preoperative serum prostate specific antigen (PSA). We tested DNA ploidy as a prognostic factor for clinical outcome in 186 patients treated with radical prostatectomy.

Methods

DNA ploidy was measured using an automatic image cytometry system. The results were correlated with Gleason score, preoperative PSA, age at surgery and Mostofi grade. Disease-free survival (time to relapse) was estimated by the Kaplan Meier method and the log-rank test was used to assess the prognostic value of the different variables. Independent correlations were examined by a Cox proportional hazard regression model.

Results

The mean follow up time after surgery was 91. 8 months. Of the 186 cases, 52% were identified as diploid, 33% as tetraploid and 16% as aneuploid. During the observation time, 23% of the diploid, 36% of the tetraploid and 62% of the aneuploid cases suffered from relapse. DNA ploidy (Fig.1a), Gleason score (Fig. 1b), Mostofi grading and preoperative PSA were all significant predictors of relapse in a univariate analysis (Table 1). In a multivariate analysis, only DNA ploidy and Gleason score were independent predictors of recurrence of disease (Table 2).

Of the 186 cases, 68 were identified with Gleason score 7. In this group, DNA ploidy (Fig. 2a) was the only significant predictor of recurrence of disease, compared to Gleason 3+4 versus 4+3 (Fig. 2b), preoperative PSA, age at surgery and Mostofi grade (Table 3). In a categorical multivariate analysis, aneuploid cases had a 11.6 higher chance of getting recurrence of disease than cases with a diploid tumour.

Table 1 Disease free survival related to prognostic factors for all 186 patients

Variables	Total patients	5 year DFS*	10 year DFS*	P-value (log-rank test)
Age at surgery				
<60	42	65.4%	53.3%	
60-69	116	70.0%	62.3%	
≥70	28	88.4%	77.8%	
Preoperative PSA (ng/ml)				
0-4	30	81.8%	70.3%	
5-10	30	86.4%	77.5%	
11-20	65	75.5%	64.9%	0.013
>20	60	54.5%	48.5%	
Gleason score				
2-6	37	97.3%	90.1%	
7	69	78.6%	70.1%	<0.001
8-10	79	53.4%	43.1%	
Mostofi grade				
1	51	86.2%	81.2%	
2	130	65.4%	55.0%	0.011
3	4	75.0%	75.0%	
DNA Ploidy				
Diploid	96	80.5%	72.9%	
Tetraploid	61	67.8%	61.6%	<0.001
Aneuploid	29	49.5%	31.8%	

*DFS Disease Free Survival

Table 2 Cox regression multivariate analysis for all 186 patients

Variables	P	Hazard ratio	(95 % CI)
Preoperative PSA (ng/ml)	0.113		
0-4		1.00	
5-10	0.129	0.40	(0.12-1.30)
11-20	0.837	1.10	(0.45-2.65)
>20	0.504	1.34	(0.57-3.17)
Gleason score			
2-6		1.00	
7	0.059	3.58	(0.95-13.47)
8-10	0.005	7.51	(1.84-30.61)
Mostofi grade	0.548		
1		1.00	
2	0.575	0.77	(0.32-1.90)
3	0.508	0.48	(0.06-4.19)
DNA ploidy	0.014		
Diploid		1.00	(0.80-2.67)
Tetraploid	0.214	1.46	
Aneuploid	0.003	2.80	(1.41-5.56)

Table 3 Disease free survival related to prognostic factors for Gleason 7 patients

Variables	Total patients	5 year DFS	10 year DFS	P-value (log-rank test)
Age at surgery				
<60	18	77.0%	68.5%	
60-69	39	72.1%	64.2%	0.294
≥70	11	90.0%	90.0%	
Preoperative PSA (ng/ml)				
0-4	9	100.0%	100.0%	
5-10	10	80.0%	68.6%	
11-20	28	85.2%	72.3%	0.013
>20	21	56.2%	56.2%	
Mostofi grade				
1	20	74.7%	67.9%	
2	47	79.5%	70.0%	0.858
3	1	100.0%	100.0%	
DNA Ploidy				
Diploid	36	88.7%	84.8%	
Tetraploid	26	74.3%	64.7%	<0.001
Aneuploid	6	25.0%	0.0%	
Gleason score				
3+4	37	77.1%	69.0%	
4+3	31	70.9%	70.9%	0.778

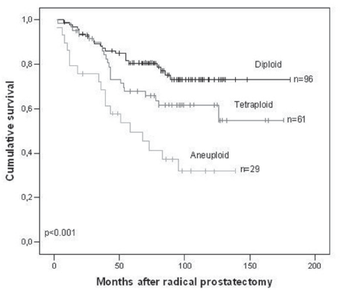

Figure 1a Disease free survival according to DNA Ploidy

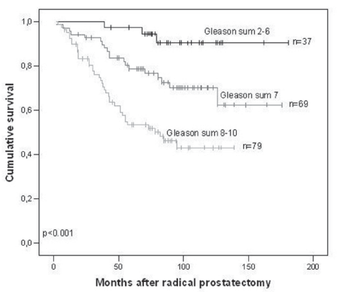

Figure 1b Disease free survival according to Gleason score

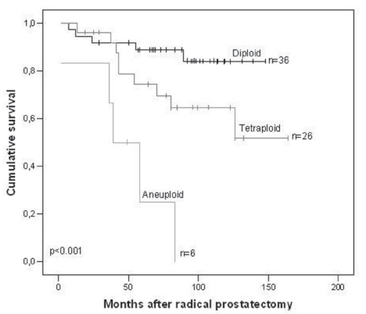

Figure 2b Disease free survival according to Gleason score for Gleason 7 patients

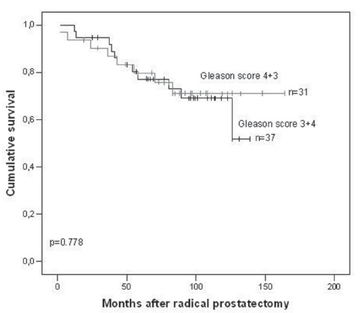

Figure 2a Disease free survival according to DNA Ploidy for Gleason 7 patients

Conclusion

DNA Ploidy may give important information in predicting recurrence of prostate cancer and could be implemented as an additive marker to Gleason score

1 Cancer Registry of Norway IoPcR. Cancer in Norway 2005. 2006.