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ORIGINAL ARTICLE

Preoperative Gleason score, percent of positive prostate biopsies and PSA in predicting biochemical recurrence after radical prostatectomy

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Summary

Purpose: *To determine the factors that can improve the prediction of biochemical recurrence after radical prostatectomy for the patients with prostate adenocarcinoma.*

Methods: *Our study included 182 patients with prostate adenocarcinoma who were biopsied and underwent radical surgical treatment at the Clinic of Urology, Clinical Center of Serbia, Medical Faculty in Belgrade from 1994 to 2004. Patients were prospectively followed-up and monitored for a minimum of 8 years and data were statistically processed by multivariate regression analysis. We arranged the predictors into 3 regressive models. In the first model the predictors were clinical stage of the disease, preoperative Gleason score, F/T PSA ratio and PSA. In the second model these predictors were accompanied with the number of positive biopsies and percent of positive prostate biopsies. In the third model, patient follow-up was added to the predictors. In all 3 models biochemical recurrence was considered as a dependent variable.*

Results: *On multivariate analysis, patient follow-up ($p<0.0001$), percent of positive prostate biopsies ($p<0.0001$), bioptic Gleason score ($p<0.0001$) and preoperative PSA ($p<0.003$) were significant independent predictors of biochemical recurrence. The most successful prediction of recurrence that provided accurate prognosis for 80% of the patients was obtained by the third model using the percent of positive prostate biopsies, PSA and patient follow-up.*

Conclusion: *As stated in multivariate analysis, the independent predictors according to the significance are the follows: patient follow-up, percent of positive prostate biopsies, bioptic Gleason score and preoperative PSA, whereas preoperative F/T PSA ratio is dependent predictor. The number of positive biopsies and clinical stage of the disease are of no significance.*

Key words: *biochemical recurrence, prediction, prostate cancer, PSA, radical prostatectomy*

Introduction

Radical prostatectomy typifies the gold standard in curing localized carcinoma of the prostate for patients with a life expectancy longer than 10 years [1,2]. However, a certain number of patients will experience biochemical recurrence. PSA, bioptic Gleason score and clinical stage of disease are the most frequently used prognostic factors for biochemical recurrence. In our study we tried to determine which factors could improve the prediction of biochemical recurrence.

Methods

Patients with prostate adenocarcinoma who had undergone radical surgical treatment at the Clinic of Urology, Clinical Center of Serbia, from 1994 to 2004 were prospectively investigated. A total of 182 patients with adequate clinical follow-up (8 years minimum) who were also biopsied at our Clinic were included in this study. Clinically determined stage based on digital rectal examination, transrectal ultrasound, PSA and bioptic medical reports were compared to pathological Gleason score and the disease stage. Subsequently, statistical correlation was made between the factors that anticipate clinical and pathological disease stage and

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Table 1. Distribution of patients according to preoperative Gleason score and clinical stage of disease

Preoperative Gleason score	*Without biochemical recurrence*		*With biochemical recurrence*		*Total*	*%*
	Number	*%*	*Number*	*%*		
< 7	127	81.4	29	18.59	156	87.9
7 (3+4)	2	16.67	10	83.33	12	6.0
7(4+3)	0	0.0	6	100	6	2.2
≥8	1	12.5	7	87.50	8	3.8
Total	130	71.43	52	28.57	182	100
Clinical stage	*Without biochemical recurrence*		*With biochemical recurrence*		*Total*	*%*
	Number	*%*	*Number*	*%*		
A	25	89.29	3	10.71	28	15.4
B1	85	86.73	13	13.27	98	53.8
B2	19	40.43	28	59.57	47	25.8
C	1	11.11	8	88.89	9	4.9
Total	130	71.43	52	28.57	182	100

the occurrence of biochemical recurrence, that also represents the level of disease aggressiveness.

Biochemical recurrence was monitored by assessing PSA serum levels following radical prostatectomy every 3 months up to the sixth month, and twice a year thereafter. During monitoring, patiens with PSA increase above 0.2 ng/ml were classified as patients with biochemical recurrence, which also means disease relapse. Only patients in whom the level of PSA two months after radical prostatectomy was under that level were included into this study, since that level is the sign that surgical cancer removal was complete.

Patients were divided into 2 basic groups, with and without biochemical recurrence, and studied in 3 regressive models which included the following preoperative predictors as independent variables: preoperative Gleason score, preoperative PSA serum level, F/T PSA ratio, clinical stage of disease, number of positive prostate biopsies, percent of positive biopsies, and patient follow-up. Biochemical reccurrence was considered as dependent variable.

In the first model the predictors were: clinical stage of disease, preoperative Gleason score, F/T PSA ratio and total PSA. In the second model these predictors were accompanied with the number of positive biopsies and the percent of positive prostate biopsies. In the third model, patient follow-up was added to the predictors. In all 3 models biochemical recurrence was considered as depended variable.

Statistics

Simple descriptive statistics, such as mean ± standard deviation, were used for continuous variables, such as PSA, F/T PSA, number and percent of positive biopsies and follow-up, while numbers (percents) were used for categorical variables. The Kolmogorov-Smirnov test was used to check if PSA, F/T PSA, number and percent of positive biopsies and follow-up had normal distribution. Quantitative variables were compared using ANOVA F test, and categorical variables were compared using contingency tables and chi-square or Kruskal-Wallis test. Chi-square test was used to compare clinical stage and Gleason score between two groups of patients (one group without relapse and the other with relapse). A p value less than 0.05 was considered statistically significant.

For correlations between variables we used Pearson correlation for the linear relationship between two variables.

Results

Demographic, clinical and developmental hisDistribution of patients according to preoperative Gleason score and clinical stage of disease is shown in Table 1. In patients with Gleason score < 7 127 cases (81.4%) did not relapse and 29 cases (18.59%) had biochemical relapse. In patients with Gleason score ≥ 7 3 patients (11.54%) did not relapse while 23 (88.46%) patients developed biochemical relapse (Gleason score ≥ 7 vs 7, x^2 p<0.0001).

Twenty-five (89.29%) stage A patients did not relapse. Relapse occurred in 41 (28.28%) patients in stage B (B1 and B2), and in 8 (88.89%) stage C patients.

There were significantly more patients with relapse in the group with clinical stage C (x^2, p<0.0001). Patients with clinical stage A had about 3.8 times (OR=3.88, 95% CI 1.12 – 13.51) less probability for relapse, whereas this probability increased with higher clinical stage, so it was 12-fold times higher in clinical stages B2 and C (OR=12.38, 95% CI 5.80-26.39).

Univariate analysis for PSA, F/T PSA, number

Table 2. Univariate analysis - ANOVA F test (for parameters with ordinary distribution); Z test (for parameters with non-ordinary distribution)

		Mean	*SD*	*95% confidence interval for the mean*		*Min*	*Max*	*ANOVA*	*Median*	*Kruskal Wallis, p*
				Lower	*Upper*					
Preoperative PSA	Without relapse	9.75	5.02	8.92	10.58	2.6	24.2	0.0001	8.95	0.0001
	With relapse	13.23	6.18	11.26	15.21	3.8	24		16.70	
	Total	10.51	5.33	9.78	11.24	2.39	24.2		10.00	
Preoperative F/T PSA	Without relapse	0.13	0.05	0.11	0.14	0.03	0.33	0.191	0.12	0.040
	With relapse	0.10	0.05	0.08	0.13	0.05	0.22		0.08	
	Total	0.12	0.05	0.11	0.13	0.03	0.33		0.11	
Number of positive biopsies	Without relapse	3.07	1.79	2.77	3.37	1	6	0.001	3.00	0.001
	With relapse	4.18	1.86	3.65	4.72	0	6		5.00	
	Total	3.36	1.87	3.09	3.63	0	6		3.00	
Percent of positive biopsies	Without relapse	19.800	15.2981	17.092	22.508	5.0	80.0	0.0001	15.00	0.0001
	With relapse	44.438	22.0862	36.475	52.400	10.0	80.0		40.50	
	Total	23.774	18.8425	21.048	26.500	5.0	80.0		15.00	
Patient follow-up	Without relapse	80.75	36.92	76.65	85.85	12	131.00	0.0001	88.00	0.0001
	With relapse	23.78	12.46	20.76	26.79	6	82.00		24.00	
	Total	66.92	41.00	62.04	71.79	6	131.00		61.00	

SD: standard deviation

and percent of positive biopsies and patient follow-up is shown in Table 2.

The mean preoperative PSA value of all of the patients was 10.51 ±5.3 (median 10, 95% CI 9.78 – 11.24). The preoperative PSA in the group without relapse was 9.75 ± 5.02 (median 8.95), while in the group with relapse it was significantly higher (mean 13.23 ± 6.18, median=16.70; Kruskal-Wallis test p<0.0001).

The mean preoperative F/T PSA value of all of the patients was 0.12 ±0.05 (median 0.11, 95% CI 0.11 – 0.13). The mean preoperative F/T PSA in the group without relapse was 0.13 ± 0.05 (median=0.12), and in the group with relapse it was lower (0.10 ± 0.05; median=0.08; Kruskal-Wallis test p<0.04).

The mean number of positive biopsies for all of the patients was 3.36 ±1.87 (median 3.00, 95% CI 3.09 – 3.63). The average number of positive biopsies in the group without relapse was 3.07 ± 1.79 (median 3.00), and in the group with relapse it was significantly higher (mean 4.18 ± 1.86, median 5.00) (ANOVA F test p<0.001).

The mean percent of positive biopsies for the total number of patients was 23.77% (median 15.00, 95% CI 21.05 – 26.50). The mean percent of positive biopsies in the group without relapse was 19.80 ± 15.29 (median=15.00), and in the group with relapse it was significantly higher (44.44 ± 22.08, median 0.50; Kruskal-Wallis test p<0.0001).

The mean patient follow-up for the total number of patients was 66.92 months (95% CI 62.04 – 71.79), minimum follow up was 6 months and maximum 131 months. In the group without relapse the mean follow-up was 80.75 ± 36.92 months (median 88), and in the group with relapse it was significantly lower (23.78 ± 12.46 months, median 24; Kruskal-Wallis test p<0.0001).

In our series patients with relapse had significantly higher preoperative PSA, higher mean number of positive biopsies and higher percents of positive biopsies, and significantly shorter follow-up time.

Table 3. Correlation between independent predictors compared to occurrence of biochemical recurrence

Pearson's coefficient of correlation	*Preoperative Gleason score*	*Preoperative PSA interval*	*Preoperative F/T PSA interval*	*Clinical stage*	*Percent of positive biopsies*	*Number of positive biopsies*	*Patient follow-up*
Biochemical recurrence R coefficient	0.482	0.359	-0.206	0.028	0.538	0.061	-0.715
p-value	0.0001	0.003	0.094	NS	0.0001	NS	0.0001

NS: not significant

Table 4. Value of R coefficient of dependent variables – 3 regression models

Model	*R*	*R^2*	*Adjusted R^2 (additional variability)*	*R^2 Change*	*F Change*	*df1*	*df2*	*Significance F Change*
1	0.518 (a)	0.258	0.203	0.258	4.694	4	54	0.003
2	0.618 (b)	0.381	0.310	0.123	5.182	2	52	0.009
3	0.797 (c)	0.635	0.584	0.253	35.335	1	51	0.0001

1: Predictors: clinical stage of disease, preoperative Gleason score, F/T PSA ratio and preoperative PSA; 2: Predictors: clinical stage of disease, preoperative Gleason score, F/T PSA ratio, preoperative PSA, number of positive biopsies and percent of positive prostate biopsies; 3: Predictors: clinical stage of disease, preoperative Gleason score, F/T PSA ratio, preoperative PSA, number of positive biopsies, percent of positive prostate biopsies and patient follow-up. Dependent variable in all 3 models was biochemical recurrence

Using regression analysis, the correlation between the predictors as independent variables according to the occurrence of biochemical recurrence is shown in Table 3.

In particular, statistically significant correlations between the occurrence of biochemical recurrence and the independent variables were as follows:

a) Increasing level of preoperative Gleason score ($p<0.0001$), higher level of preoperative PSA ($p<0.003$), and higher percent of positive biopsies ($p<0.0001$) were independently by associated with occurrence of relapse.
b) Clinical stage of disease, number of biopsies and F/T PSA ratio did not affect the occurrence of relapse. Lower F/T PSA ratio correlated with frequent occurrence of biochemical recurrence, but without statistical significance ($p=0.094$).
c) The occurrence of biochemical recurrence was significantly associated with shorter patient follow-up ($p<0.0001$).

The results of each of the 3 regressive models are presented in Table 4.

In the multivariate regression analysis of the first model, coefficients $R=0.518$ and $R^2=0.258$ showed statistical significance of joint influence of the following predictors: preoperative Gleason score, PSA, F/T PSA ratio and clinical disease stage.

In the second model, with the inclusion of the number of positive biopsies and the percent of positive biopsies, the R coefficient which for this model was $R=0.618$, $R^2=0.381$ and changed $R^2=0.123$ increased and in multivariate regression analysis indicated the higher level of statistical significance of the joint action of selected predictors.

In the third model, with the inclusion of patient follow-up, the R coefficient increased again, which for this model was $R=0.797$, $R^2=0.635$ and adjusted $R^2=0.548$, and in the multivariate regression analysis indicated the highest level of statistical significance of the joint action of selected predictors (preoperative Gleason score, PSA, F/T PSA ratio, clinical disease stage, number of positive biopsies, percent of positive biopsies and patient follow-up), which with their joint action influenced the occurrence of biochemical recurrence, i.e. the possibility of prediction in 80% of the cases, certain occurrence of biochemical recurrence in nearly 64% of the patients and with additional variability in 58.4% of the cases.

If the individual influence of the predictors on the occurrence of biochemical relapse in each regressive model was analyzed, the results were as follows:

1. In the first model, statistically significant correlation between the predictors -preoperative Gleason score and preoperative PSA - on the occurrence of biochemical recurrence was demonstrated with the following values:

Gleason score with statistically significant influence for T test = 2.895, p<0.005, and preoperative PSA with statistically significant influence for T test = 1.981, p<0.05. The results are presented in Figure 1.

2. In the second model, statistically significant correlation between the predictors - PSA and percent of positive biopsies - on the occurrence of biochemical recurrence was demonstrated with the following values: percentage of biopsies with statistically significant influence for T test = 3.194, p<0.002 and PSA with statistically significant influence for T test = 1.967, p<0.05. The results are shown in Figure 2.
3. In the third model, statistically significant connection between the predictors PSA and percent of positive biopsies was demonstrated. Percent of positive biopsies was strong predictor with statistically significant influence for T test = 3.112, p<0.003, and PSA with statistically significant influence for T test =1.987, p<0.05. Patient follow-up as predictor with statistically significant influence for T test = -5.914, (p<0.001) indicated that relapse occurred more frequently in those with shorter follow-up. The results are presented in Figure 3.

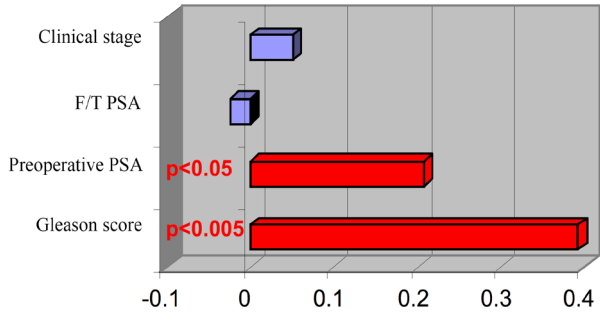

Figure 1. The influence of predictors on the occurrence of biochemical recurrence in Model 1.

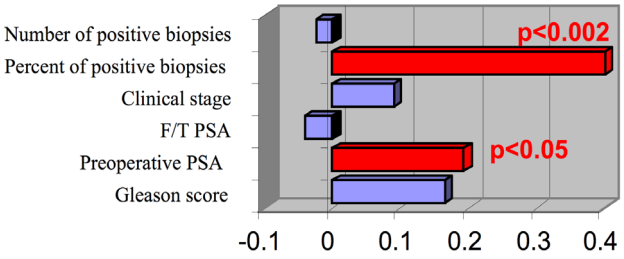

Figure 2. The influence of predictors on the occurrence of biochemical recurrence in Model 2.

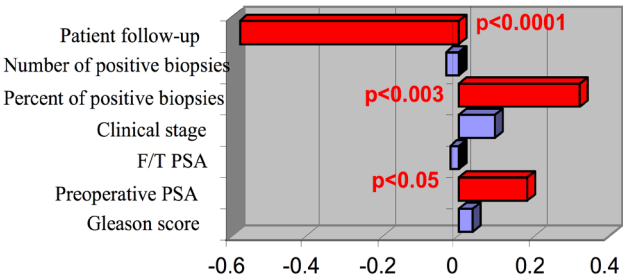

Figure 3. The influence of predictors on the occurrence of biochemical recurrence in Model 3.

Discussion

It is known that patients with Gleason score < 7 have a favorable prognosis.

Univariate and multivariate analysis in this study demonstrated that the bioptic Gleason score is independent predictor of relapse. Roehl et al. [3] reported in their study with 3478 patients that PSA, clinical stage, Gleason score and pathological stage were significantly correlated with relapse. Freedland et al. [4] in their study with 459 patients showed that bioptic Gleason score, the percent of bioptic tissue with cancer and serum PSA were the only significant independent predictors of relapse. In their study, Pierorazio et al. [5] with 9381 patients proved that 80% of the patients with Gleason score 8-10 and who had undergone radical prostatectomy will experience biochemical recurrence within the next 15 years.

Our results indicate that the average percent of positive biopsies in univariate analysis was an independent predictor of relapse (p<0.0001). If the percent of positive biopsies was up to 20%, the probability for relapse was 4.12%, and if it was up to 40% the probability for relapse was 56.25%. In this study, the percent of positive biopsies in multivariate analysis (p<0.0001) was one of the most important independent predictor of relapse. These results correlate with the latest Pierorazio et al. work [6]. They added to the usual predictors such as PSA, Gleason score and clinical stage, biopsy parameters (number of high grade cores and > 50% involvement of any core). According to them, high Gleason score (9 or 10), PSA > 10 ng/ml, clinical stage ≥ T2b, increasing number of cores with high-grade cancer and >50% core involvement were predictive of unfavorable pathology, worse 10-year biochemical free survival, metastasis free survival and prostate cancer specific survival. Freedland et al. [7] reported in their retrospective study with 1094 patients that

the percent of prostate needle core biopsy is an important predictor of biochemical relapse. Also, Ramos et al. [8] reported in their study with 1850 patients that the percent carcinoma in prostatectomy specimens in multivariate analysis is an independent predictor of relapse (p<0.0001). Ravery et al. [9] in their univariate analysis showed that the percentage of cancer on biopsy cores is a predictor of positive margins and also an important predictor of relapse. Igdem et al. [10] concluded that high percent of positive prostate core biopsies could be a predictor of biochemical relapse.

The mean PSA value in our study was 10.51 ng/ml and the mean PSA value in patients without relapse was 9.75 ng/ml compared with 13.23 ng/ml of patients with relapse . Also, in our study PSA was independent predictor of biochemical recurrence in both univariate (p<0.0001) and multivariate regression analysis (p<0.003) with high statistical significance. Grossfeld et al. [11] concluded that PSA, Gleason score and the percent of positive biopsies are the most important preoperative predictors of relapse, while D'Amico et al. showed that with the inclusion of PSA, Gleason score, clinical stage and the percent of positive biopsies in multivariate analysis, 90% of the patients with localized disease can be classified into low or high risk groups for biochemical recurrence after radical prostatectomy or radiotherapy [12]. The authors classified the patients with PSA < 10.6 ng/ml, clinical stage < T2 and with bioptic Gleason score < 7, into a group with a low risk for biochemical recurrence. In our study patients with PSA < 9.8 ng/ml carried low risk of relapse.

In univariate analysis, F/T PSA ratio of patients included in this research related to biochemical recurrence did not display a possibility of predicting relapse. The mean value of F/T PSA of patients who experienced relapse was 0.10, and for patients without relapse it was 0.13. Our results are in concordance with the results that Tombal et al. presented in their study [13].

In our study 28.57% of the patients experienced biochemical recurrence and 71.43% did not. The average time to relapse differs for patients with local relapse and for those with metastatic disease. In the present study local relapse appeared after 23.78 months on average and metastatic stage of disease was manifested after 14 months. Patient follow-up was an independent predictor of relapse in both univariate and multivariate analyses (p<0.0001).

As stated previously, in multivariate analysis the independent predictors according to their significance were as follows: patient follow-up, percent of positive prostate biopsies, bioptic Gleason score and preoperative PSA, whereas preoperative F/T PSA ratio was dependent predictor. The number of positive biopsies and clinical disease stage were of no significance. Chun et al. reported in their study that in univariate and multivariate analyses the independent predictors were PSA, Gleason score and clinical stage of disease [14]. Ravery et al. stated that with log rank analysis the independent predictors were the percent of cancer-affected biopsies and the density of PSA [9]. Freedland et al. reporting on 459 patients stated that in multivariate analysis Gleason score (p<0.001), percent of biopsy tissue with cancer (p<0.001) and serum PSA (p=0.001) were the only significant independent predictors of relapse [4], which correlate with our results.

Winkler et al. showed in their study with 375 patients that PSA and percent of positive biopsies are better predictors than those used in a model with conventional variables (PSA, Gleason score and clinical stage of disease). They also reported that the combination of percent of positive biopsies and the 3 conventional variables is not better for prediction than the combination of PSA and the percent of positive biopsies [15]. In our study we also had similar results. In the second and third regressive models where we applied PSA and the percent of positive biopsies, these two variables were independent predictors that can become more important only by adding patient follow-up. In that case Gleason score and other parameters had no influence on prediction. In the first model which is the weakest one with the percent of positive biopsies excluded, Gleason score combined with PSA were independent predictors of biochemical relapse. The best result, that is the prediction for 80% of the patients, was achieved by using the percent of positive prostate biopsies, PSA and patient follow-up. The worst result (prediction for 52% of the patients), was obtained in the analysis where Gleason score and PSA were considered as independent predictors. The addition of Gleason score into a model in which the percent of positive biopsies is included is useless, since in such a model we gain less possibility of predicting biochemical recurrence (62%) in comparison to a model without Gleason score (80%).

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