Independent predictors of biochemical recurrence after radical prostatectomy: a single center experience

Marius Kinčius[1,2], Aivaras Jonas Matjošaitis[2], Darius Trumbeckas[2], Ramūnas Mickevičius[2], Daimantas Milonas[2], Mindaugas Jievaltas[2]

[1]Institute for Biomedical Research, Lithuanian University of Health Sciences, Kaunas, Lithuania

[2]Clinic of Urology, Lithuanian University of Health Sciences, Kaunas, Lithuania

KEY WORDS

prostate ◗ prostate cancer ◗ radical prostatectomy ◗ biochemical recurrence

ABSTRACT

Introduction. The aim of study was to establish pretreatment and postoperative factors which could predict the early biochemical recurrence after radical prostatectomy.

Materials an method. 754 patients had undergone radical prostatectomy since January 2002 to December 2008 in our department and were included in this prospective study. Exclusion criteria were: neoadjuvant or adjuvant treatment (radiation or hormonal treatment) and N+. Following parameters were evaluated: age, PSA at time of biopsy, time period from biopsy to operation, biopsy and postoperative Gleason score, stage, high grade intraepithelial neoplasias, perineural invasion. Biochemical recurrence was detected if PSA value after radical prostatectomy was ≥0.2 ng/ml. All factors likely to be predictive were evaluated by univariate analysis (Log-rank test). Multivariate analysis using Cox model was completed for all factors with p value <0.1 at univariate analysis.

Results. Final analysis was done using data of 496 patients. We detected 53 (10.7%) biochemical recurrences. Calculated actuarial biochemical recurrence free survival reached 64%. Multivariate analysis highlighted that PSA >10 ng/ml (HR 2.45, p = 0.008), pathological stage ≥pT3 (HR 2.371, p = 0.02), postoperative Gleason score ≥7 (HR 2.149, p = 0.049), positive surgical margins (HR 2.482, p = 0.014) and absence of high grade intraepithelial neoplasia in removed prostate (HR 0.358, p = 0.006) are independent factors influencing biochemical recurrence after radical prostatectomy.

Conclusion. Patients with higher PSA, locally advanced disease, positive surgical margins, and Gleason score ≥7 are at the highest risk for biochemical recurrence.

INTRODUCTION

Routine use of prostate specific antigen (PSA) testing has affected prostate cancer detection rates and contributed to a favorable shift in tumor stage therefore allowing radical treatment in earlier disease stages. Radical prostatectomy is an excellent cancer treatment modality, which provides an outstanding cancer control in most men with localized diseases [1]. However, despite advancements and improvements in surgical technique, approximately 25-35% of patients will experience biochemical recurrence over a 10-year period after radical prostatectomy [2]. Over time, the majority of these men will eventually develop distant metastases and will die of prostate cancer. Due to the exquisite sensitivity of PSA to detect disease recurrence early, many patients have a time period between biochemical recurrence and the development of local recurrence and distant metastases [3]. Therefore, better risk understanding are needed to identify men who are at higher risk for prostate cancer death and who may benefit from aggressive salvage treatment and to identify those who are at low risk for prostate cancer death and can be safely observed.

The goal of the current study was to attempt to establish pretreatment and postoperative clinical and pathological variables in predicting early biochemical recurrence after radical prostatectomy.

MATERIALS AND METHODS

Patients

We identified 623 patients treated with retropubic radical prostatectomy for clinically localized prostate cancer from January 2002 to December 2008 at Kaunas Medicine University Hospital. Of these men, 494 (79.3%) were included in the current study. We excluded 129 men from the analysis due to insufficient follow-up (n = 24), preoperative hormonal therapy (n = 46), positive lymphnodes (n = 16), immediate postoperative adjuvant radiation therapy based on poor pathological features (n = 6), immediate postoperative adjuvant hormonal therapy (n = 34), and immediate postoperative mortality (n = 3). None of patients included into the study received adjuvant radiation or hormonal therapy prior to biochemical progression defined as a two consequent PSA rises above 0.2 ng/ml [4]. Postoperative follow up was obtained through routine serum PSA assays and digital rectal examination performed quarterly for the first year, semiannually for second year, and yearly thereafter. The minimal follow-up was 1 year, and the mean length of follow-up was 18 months (range from 12 to 72 months).

All data were prospectively collected under an institutional review board-approved protocol. We assessed the following perioperative and postoperative clinical and pathological factors: age, PSA time at time of biopsy, time period between biopsy and operation, biopsy Gleason score, Gleason score after operation, stage, positive surgical margin, high grade intraepithelial neoplasias (HPIN), perineural invasion of cancer.

Statistical analysis

Parameters were categorized: age ≤65, >65 years; PSA ≤10, >10 ng/ml; time period between biopsy and operation: ≤60 or >60

Table 1. Clinical and pathological characteristics of the study population

Number of patients		All	BR-	BR+	p value
		494	441	53	
Age (years)					
	Mean (±SD)	64.8 ±6.3	64.7 ±6.3	64.8 ±6.4	p = 0.792
					Mann-Whitney test
Serum PSA (ng/ml)					
	<10	370 (74.9%)	342 (92.4%)	28 (7.6%)	p <0.001
	>10.1	124 (25.1%)	99 (79.8%)	25 (20.2%)	$\chi 2$ test
Biopsy Gleason score					
	4-6	401 (81.1%)	365 (91%)	36 (9%)	p = 0.003
	7-10	93 (18.9%)	76 (81.7%)	17 (18.3%)	$\chi 2$ test
Prostatectomy Gleason score					
	4-6	261 (52.8%)	245 (93.8%)	16 (6.2%)	p <0.001
	7-10	233 (47.2%)	196 (84.1%)	37 (15.9%)	$\chi 2$ test
pT stage					
	T2a/b/c	370 (74.9%)	344 (93%)	26 (7%)	p <0.001
	T3a/b	124 (25.1%)	97 (78.2%)	27 (21.8%)	$\chi 2$ test
Surgical margins					
	Positive	180 (36.4%)	144 (32.7%)	36 (67.9%)	p <0.001
	Negative	314 (63.6%)	297 (67.3%)	17 (32.1%)	$\chi 2$ test
High grade intraepithelial neoplasia					
	Positive	217 (43.9%)	204 (46.3%)	13 (24.6%)	p <0.001
	Negative	277 (56.1%)	237 (53.7%)	40 (75.4%)	$\chi 2$ test
Perineural cancer invasion					
	Positive	225 (45.5%)	189 (42.9%)	36 (67.9%)	p <0.001
	Negative	269 (54.5%)	252 (57.1%)	17 (32.1%)	$\chi 2$ test
Period between prostate biopsy and radical prostatectomy (days)					
	Mean (±SD)	75.3 ±55	73.4 ±56	91.1 ±60	p = 0.053
					Mann-Whitney test

days; Gleason score: ≤6, ≥7; pT stage pT1-2, pT3-4; presence or absence of positive surgical margins, HPIN and perineural invasion in pathological samples. All data were analyzed using SPSS v15 statistical analysis software (Stata Corporation).

We used Chi-square and Mann Whitney rank sum tests for linear trends to compare categorical and nonparametric clinical and pathological characteristics respectively. The biochemical disease-free survival rates with 95% confidence interval were estimated with the Kaplan-Meier product limit method. All factors likely to be predictive for early biochemical recurrence after radical prostatectomy were evaluated by univariate analysis. Multivariate analysis using the Cox proportional hazard model was completed for all factors with p<0.1 at univariate analysis. Statistical significance was set at p<0.05 for all analyses.

RESULTS

The average age of the 494 men at the time of surgery was 64.8 ±6.3 years (range 47 to 78). Preoperative PSA level in 370 (74.9%) patients was less than 10 ng/ml. The remaining 25.1% of men had PSA greater than 10 ng/ml. Extraprostatic cancer invasion was diagnosed in 124 (25.1%) cases postoperatively. There was evident Gleason score migration from 4-6 to 7-10 comparing biopsy and postoperative Gleason scores. Gleason score upgrading from 4-6 to 7-10 and was observed in 154 cases. However downstaging from Gleason score 7-10 to 4-6 was found only in 14 patients. Positive surgical margins were found in 180 out of 494 cases. Almost half of patients had perineural invasion and high grade intraepithelial neoplasia in postoperatively examined prostates (Table 1)

We have estimated 53 (10.7%) patients with biochemical diseases recurrence during the follow-up period. Biochemical recurrence was noticed in 49 (92.5%) patients throughout the first year and only four were detected later during the follow-up. Even 47.2% of all biochemical recurrences were identified during three months after radical prostatectomy (Table 2). Actuarial biochemical recurrence free survival was plotted in Kaplan-Meier curve. Overall five-year biochemical free survival was 64% (Fig. 1).

Univariate analysis showed that age, perineural cancer invasion, biopsy Gleason score and time period from cancer positive biopsy to radical prostatectomy do not influence biochemical recurrence. Our study revealed that main factors potentially influencing early biochemical recurrence were preoperative PSA, absence of HGPIN, prostatectomy Gleason score, pT stage and status of surgical margins (Table 3).

Multivariate analysis highlighted that preoperative PSA more than 10ng/ml (HR 2.45, 95% CI 1.267-4.736, p = 0.008), postoperative pathological stage pT3a/b (HR 2.371, 95% CI 1.147-4.903, p = 0.02), postoperative Gleason score ≥7 (HR 2.149, 95% CI

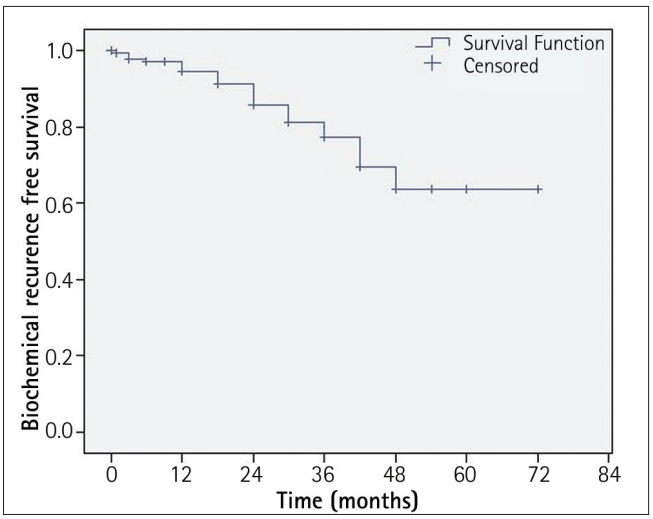

Fig. 1. ***Biochemical recurrence free survival.*** *Actuarial biochemical recurrence free survival was plotted in Kaplan-Meier curve. Overall five years biochemical free survival in our cohort reaches 64%.*

1.005-4.595, p = 0.049) and positive surgical margins (HR 2.482, 95% CI 1.203-5.119, p = 0.014) are independent factors influencing early biochemical recurrence after radical prostatectomy (Table 4). Interestingly we found that presence of HGPIN in removed prostate statistically significant reduce chances of biochemical recurrence (HR 0.358, 95% CI 0.172-0.747, p = 0.006) (Table 4).

DISCUSSION

The finding of increased serum PSA concentrations after radical treatment of local prostate cancer is considered evidence of disease recurrence. Therefore the prospect of biochemical disease recurrence determined by PSA monitoring produces a constant fear in patients and decreases their quality of live as much as postoperative erectile dysfunction or urinary incontinence [5-7]. Consequently it is very important to predict possibility of disease early recurrence after primary radical treatment due to localized prostate cancer.

There are several widely adopted predictive nomograms that calculate the final pathological stage. However, in the long-term, after treatment they lack predictive value for biochemical disease recurrence. This is an important issue because biochemical recurrence shows a local or systemic prostate cancer pattern that could advocate the start of adjuvant treatment and consistently delay development of metastases and prolong disease specific survival. Distant metastasis develops in around 34% of patients with biochemical recurrence and is the main cause for therapeutic intervention within 10-years after primary treatment [3].

Biochemical recurrence with median follow-up of 18 months in our study reaches 11%, mainly due to a short follow-up period. Calculated actuarial five-year biochemical recurrence increases up to 36%. Such high 5-year biochemical recurrence rates leave us to expect better results in the future knowing that actuarial 10-years biochemical recurrence in a series published from John Hopkins varies by only 26% to 32% [8, 9].

There is no clear evidence how often patients should be followed up after radical prostatectomy up to date. European urology guidelines suggest that patients, during the first postoperative year, should be tested for PSA once in a quarter, during the second and third year – semiannually and afterwards – once in a year. Our results confirm that this follow-up schedule is proper because even 92% of all biochemical recurrences (Table 2) were detected during the first year after radical prostatectomy, therefore it is very important to follow up patients quarterly during the first year. Such

Table 2. Time of biochemical recurrence after radical prostatectomy

Time	Patients (n)
3 months	25
6 months	6
9 months	7
12 months	5
>18 months	4

Biochemical recurrence was noticed in 49 (92.5%) patients throughout the first year and only four were detected later during the follow-up. Even 47.2% of all biochemical recurrences were identified during three months after radical prostatectomy.

Table 3. Potential risk factors affecting early biochemical recurrence for patients with prostate carcinoma treated after radical prostatectomy (univariate analysis)

Variables	Subcategories	p value (Long rank)
Age	≤65, >65	0.505
High grade intraepithelial neoplasia	Yes, no	0.009
Perineural cancer invasion	Yes, no	0.727
PSA	≤10, >10	0.01
Biopsy Gleason score	≤6, ≥7	0.501
Prostatectomy Gleason score	≤6, ≥7	0.049
pT Stage	T1-2, T3a/b	0.05
Surgical margins	R0, R1	0.021
Period between prostate biopsy and radical prostatectomy	≤60 days, >60 days	0.405

dramatic percentage of biochemical recurrence detected during the first postoperative year could be explained with late PSA era arrival to Lithuania and high numbers of patients with pT3 stage have been operated and high percentage of positive surgical margins were detected in our patients cohort (Table 1). As reported by Roehl et al. the main parameters that could specifically and sensitively predict early disease biochemical recurrence are prostatectomy Gleason score, preoperative PSA, clinical tumor, and pathological stage [2]. Our data confirm that pathological stage, preoperative PSA, prostatectomy Gleason score and surgical margin status are the best independent prognostic factors (Table 4). However, additionally, we found that presence of HGPIN in pathological specimen slightly reduce the risk of biochemical recurrence.

It is clearly shown that men who had low PSA levels preoperatively had significantly fewer high-grade tumors and significantly better biochemical outcomes after undergoing RP compared with men who had elevated PSA levels [10]. Our study data confirms these findings and shows that men with lower PSA levels represent a favorable risk group (Table 4).

Pathological stage pT3 and higher similarly enhance likelihood of biochemical recurrence. This is largely related to neoplastic extra-capsular invasion [11, 12].

The range of positive surgical margins after radical prostatectomy for prostate cancer has been cited by previous single-institution retrospective series as 10-48% [13]. In a multi-institutional assessment of 5,831 patients, Karakiewiz et al. found that patients with positive surgical margins had a 3.7 fold increase of biochemical recurrence [14]. However the importance of positive surgical margins is diminishing due to the ongoing downstaging of prostate cancer

Table 4. Significant factors affecting early biochemical recurrence after radical prostatectomy for patients with prostate carcinoma by multivariate analysis using Cox's proportional hazard model

	β-coefficient	Standard error	Hazard ratio	CI (95%)	p value
HPIN	-1.027	0.375	0.358	0.172-0.747	0.006
PSA	0.896	0.336	2.45	1.267-4.736	0.008
Prostatectomy Gleason score	0.765	0.388	2.149	1.005-4.595	0.049
pT Stage	0.863	0.371	2.371	1.147-4.903	0.02
Surgical margins	0.909	0.369	2.482	1.203-5.119	0.014

in the era of PSA [15]. This is confirmed in our study: only 2.48 fold increase in biochemical recurrence in patients with positive surgical margins (Table 4). Our study results are comparable with those published by Simon et al. Only 20% of patients with positive surgical margins develop biochemical recurrence compared to 5.5% of those with negative margins [16].

Prostatectomy Gleason score showed to be an independent predictor for early biochemical recurrence [17]. It is logic that this grade more accurately reflects the underlying biology of the disease than biopsy Gleason score. However new histological parameters such as tertiary Gleason pattern are evaluated. Hattab et al. revealed that a tertiary Gleason pattern in pathological specimens, especially 5, is the strongest predictor of a worse outcome in patients with Gleason grade 7 prostatic adenocarcinoma [18].

Another frequently investigated pathological parameter is HGPIN. HGPIN are detected in around 86-88.4% of cases after radical prostatectomy [19]. However, in our study we found only 43.9% of patients with HGPIN operated due to prostate cancer. Such low number of HGPIN in our cohort of patient with prostate cancer could be due to quite new diagnosis and different interpretation between pathologists. Interestingly our operated patients with HGPIN showed to have better biochemical recurrence free survival (Table 4).

How HGPIN is associated with biochemical recurrence is not known and controversial. Qian et al. found direct correlation between HGPIN volume and prostate cancer volume after radical prostatectomy, and it was associated with higher pathological stage and poorer tumor differentiation [20]. Pierozario et al. in their study revealed that patients with HGPIN in the prostate specimens after radical prostatectomy had a higher prevalence of biochemical recurrence. Biochemical recurrence-free survival with median follow-up of 50-months was 81% in HGPIN group vs. 87.3% in patients without HGPIN. Patients with HGPIN had almost 2-fold higher chances of developing biochemical recurrence after radical prostatectomy [21]. However there are studies that oppose previously mentioned studies and support our results. Lopez showed that patients with prostate cancer and HGPIN were associated with higher age, better tumor differentiation, lower tumor volume [22]. High volume multicenter studies are needed to clarify this question in more detail.

CONCLUSION

Preoperative PSA, postoperative Gleason score, pathological stage, positive surgical margins are the most important predictors for early biochemical recurrence. Highest biochemical recurrence rates are detected during the first postoperative year therefore PSA testing for these patients are highly recommended quarterly.

REFERENCES

1. Chun FK, Graefen M, Zacharias M et al: *Anatomic radical retropubic prostatectomy long term recurrence free survival rates for localized prostate cancer.* World J Urol 2006; 24: 273-280.
2. Roehl KA, Han M, Ramos CG: *Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results.* J Urol 2004; 172 (3): 910-914.
3. Pound CR, Partin AW, Eisenberger MA et al: *Natural history of progression after PSA elevation following radical prostatectomy.* JAMA 1999; 281: 1591-1597.
4. Cookson MS, Aus G, Burnett AL et al: *Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes.* J Urol 2007; 177 (2): 540-545.
5. Weber BA, Roberts BL, Mills TL et al: *Physical and emotional predictors of depression after radical prostatectomy.* Am J Mens Health 2008; 2 (2): 165-171.
6. Hashine K, Kusuhara Y, Miura N et al: *A prospective longitudinal study comparing a radical retropubic prostatectomy and permanent prostate brachytherapy regarding the health-related quality of life for localized prostate cancer.* Jpn J Clin Oncol 2008; 38 (7): 480-485.
7. Catalona WJ, Carvalhal GF, Mager DE, Smith DS: *Potency, continence and complication rates in 1,870 consecutive radical retropubic prostatectomies.* J Urol 1999; 162 (2): 433-438.
8. Han M, Partin AW, Zahurak M et al: *Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer.* J Urol 2003; 169 (2): 517-523.
9. Nielsen ME, Makarov DV, Humphreys E et al: *Is it possible to compare PSA recurrence-free survival after surgery and radiotherapy using revised ASTRO criterion--"nadir + 2"?* Urology 2008; 72 (2): 389-395.
10. Freedland SJ, Aronson WJ, Kane CJ et al: *Biochemical outcome after radical prostatectomy among men with normal preoperative serum prostate-specific antigen levels.* Cancer 2004; 101 (4): 748-753.
11. Xylinas E, Drouin SJ, Comperat E et al: *Oncological control after radical prostatectomy in men with clinical T3 prostate cancer: a single-centre experience.* BJU Int 2009; 103 (9): 1173-1178.
12. Roche JB, Malavaud B, Soulié M et al: *Pathological stage T3 prostate cancer after radical prostatectomy: a retrospective study of 246 cases.* Prog Urol 2008; 18 (9): 586-594.
13. Blute ML, Bostwick DG, Bergstralh EJ et al: *Anatomic site-specific positive margins in organ confined prostate cancer and its impact on outcome after radical prostatectomy.* Urology 1997; 50 (5): 733-739.
14. Karakiewicz PI, Eastham JA, Graefen M et al: *Prognostic impact of positive surgical margins in surgically treated prostate cancer: multi-institutional assessment of 5831 patients.* Urology 2005; 66 (6): 1245-1250.
15. Swindle P, Eastham JA, Ohori M et al: *Do margins matter? The prognostic significance of positive surgical margins in radical prostatectomy specimens.* J Urol 2008; 179 (5): S47-S51.
16. Simon MA, Kim S, Soloway MS: *Prostate specific antigen recurrence rates are low after radical retropubic prostatectomy and positive margins.* J Urol 2006; 175 (1): 140-145.
17. Freedland SJ, Partin AW, Epstein JI, Walsh PC: *Biochemical failure after radical prostatectomy in men with pathologic organ-confined disease: pT2a versus pT2b.* Cancer 2004; 100 (8): 1646-1649.
18. Hattab EM, Koch MO, Eble JN et al: *Tertiary Gleason pattern 5 is a powerful predictor of biochemical relapse in patients with Gleason score 7 prostatic adenocarcinoma.* J Urol 2006; 175 (5): 1695-1699.

19. Kovi J, Mostofi FK, Heshmat MY, Enterline JP: *Large acinar atypical hyperplasia and carcinoma of the prostate*. Cancer 1988; 61: 555-561.
20. Qian J, Wollan P, Bostwick DG: *The extent and multicentricity of high-grade prostatic intraepithelial neoplasia in clinically localized prostatic adenocarcinoma*. Hum Pathol 1997; 28: 143-148.
21. Pierorazio PM, Lambert SM, Matsukhani M et al: *High-grade prostatic intraepithelial neoplasia is an independent predictor of outcome after radical prostatectomy*. BJU Int 2007; 100: 1066-1070.
22. Lopez JI: *Prostate adenocarcinoma detected after high-grade prostatic intraepithelial neoplasia or atypical small acinar proliferation*. BJU Int 2007; 100: 1272-1276.

Correspondence
Marius Kinčius
2, Eivenių Street
50009 Kaunas
phone: +370 698 041 57
marius_kincius@yahoo.com