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# High-risk prostate cancer: factors predicting biochemical recurrence after radical prostatectomy

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**Background/objective.** Predictive criteria are needed to evaluate the risk of disease progression after radical prostatectomy. Such criteria would help to select patients most likely to benefit from adjuvant or multimodality treatment. Our aim was to identify predictive factors for biochemical recurrence among the pre- and post-operative parameters in high-risk prostate cancer patients after radical prostatectomy.

**Methods.** Data on high-risk prostate cancer patients between 2005 and 2009 were retrospectively reviewed in two cancer centers: National Cancer Institute, Vilnius, Lithuania, and N. N. Alexandrov National Cancer Centre of Belarus, Minsk, Belarus. 199 patients were selected for the study. The pre-operative independent variables were T stage, pretreatment PSA level and Gleason score. Surgical margins and perineural invasion were additionally known for 122 patients. The outcomes measured were biochemical recurrence free and overall survival. The mean follow-up time was 5.8 years.

**Results.** Lower T stage ($p = 0.001$) and pretreatment PSA ($p = 0.0001$) were associated with better survival. In the multivariate analysis of pre-operative factors, high T stage ($p = 0.008$) and pretreatment PSA ($p = 0.009$) were predictive of biochemical recurrence. When postoperative parameters were included in the multivariate analysis, only pretreatment PSA ($p = 0.01$), positive surgical margins ($p = 0.003$) and perineural invasion ($p = 0.03$) remained relevant independent predictors of biochemical recurrence.

**Conclusions.** Pretreatment PSA, positive surgical margins and perineural invasion were independent predictors of biochemical recurrence after radical prostatectomy in high-risk prostate cancer patients, while the T stage became insignificant after adjusting for postoperative parameters.

**Key words:** high-risk prostate cancer, radical prostatectomy, biochemical recurrence

## INTRODUCTION

Prostate cancer is the most common male cancer and the third cause of cancer related death in men in developed countries (1, 2). Two main strategies for treating high-risk prostate cancer are radical prostatectomy (RP) and radiation therapy (3). No consensus exists on which is superior, but published data slightly favour RP (4). This will have to be confirmed in randomized prospective trials, but RP is already widely established as one of the main treatment modalities.

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For a lot of high-risk prostate cancer patients RP is not the definite treatment: disease progression is frequent and 56–78% of patients eventually receive adjuvant radiotherapy or hormonal treatment (5, 6). The earliest manifestation of disease recurrence is biochemical: post-operative PSA rises to ≥0.2 ng/mL, signaling a need for adjuvant treatment.

There is a need for effective predictive criteria to evaluate the risk of disease progression after RP even before biochemical recurrence happens. Such criteria would help to select patients most likely to benefit from adjuvant or multimodality treatment, plan their treatment ahead of recurrence and protect other patients from unnecessary adverse effects of the treatment.

The aim of this study was to identify predictive factors for biochemical recurrence among pre- and post-operative parameters in high-risk prostate cancer patients after radical prostatectomy in two national cancer centers.

## MATERIALS AND METHODS

### Study population

Data on high-risk prostate cancer patients treated with RP only were collected retrospectively in two oncology centers in Vilnius and Minsk. National Cancer Institute, Vilnius, Lithuania (NCI), is one of the biggest prostate cancer treating tertiary health care centers in Lithuania. N. N. Alexandrov National Cancer Center of Belarus, Minsk, Belarus (NCC), is the biggest cancer centre in Belarus, where prostate cancer patients are concentrated.

Medical records of patients who presented to urology departments at NCI and NCC between 2005 and 2009 were reviewed. High-risk patients were defined as T3 or Gleason 8–10 or PSA > 20 ng/mL (one criteria) or those who met two of the following criteria: T2b or greater; Gleason score 7; PSA 10–20 ng/ml.

199 high-risk prostate cancer patients were selected for the study: 77 patients in NCC and 122 in NCI. Post-operative parameters (surgical margins and perineural invasion) were available for NCI patients only.

All the selected patients were treated with RP only. During the standard RP procedure, prostate, seminal vesicles and regional lymph nodes are removed. Bladder and urethra are then reconnected. In the study, RP was either open retropubic or laporoscopic. After the procedure, resected prostate specimens were examined histopathologically for positive surgical margins and perineural invasion.

### Follow-up

The study population includes only patients with adequate follow-up data (the last standard medical examination not less than 3 years after treatment). In both centers after RP, the PSA level is tested at least every 3 months for 1 year, every 6 months for the next 3 years and once a year afterwards.

The outcomes measured were biochemical recurrence free survival (bRFS) during the follow-up. bRFS was defined as the time from surgery to PSA level rise to ≥0.2 ng/mL.

### Statistical analysis

Categorical data were compared by the Chi-square test. Logistic regression models were used to determine, in univariate and multivariate analyses, whether preoperative factors such as age, serum PSA level, pathological stage, biopsy Gleason score and the presence of perineural invasion on biopsy were predictors of bRFS.

Multivariate analyses based on Cox's proportional hazards models were used to ascertain pathological variables that were independent predictors of bRFS. The estimated 5-year risks were determined using the Kaplan–Meier method and compared by log-rank tests. All statistical tests were performed as two-sided with $P < 0.05$ considered to indicate statistical significance.

All statistical analyses were performed using Stata Statistical Software version 11.0 (StataCorp. 2009. Stata Statistical Software: Release 11.0. College Station, TX, USA).

## RESULTS

The characteristics of the patients by a treatment centre are shown in Table 1. There were no significant differences between two treatment centers by the Gleason score and tumor stage distribution. Patients treated in NCI were younger ($p = 0.001$) and fewer had PSA ≥ 10 ($p < 0.0001$). The mean follow-up time was 5.2 years for patients treated in NCC and 6.1 years in NCI (mean overall follow-up time 5.8 years).

The results of the Kaplan–Meier survival analysis are presented in the Figure. The patients treated

**Table 1.** Baseline characteristics of the study group by treatment centre

| Parameter | NCC (N = 77) | | NCI (N = 122) | | |
|---|---|---|---|---|---|
| **Total** | **N** | **%** | **N** | **%** | **p value** |
| Mean age | 64.3 (38–77) | | 61.1 (44–78) | | |
| <65 | 34 | 44.2 | 82 | 67.2 | 0.001 |
| >=65 | 43 | 55.8 | 40 | 32.8 | |
| T stage | | | | | |
| T2b-T2c | 46 | 59.7 | 89 | 73.0 | 0.05 |
| T3 | 31 | 40.3 | 33 | 27.0 | |
| Gleason score | | | | | |
| <7 | 58 | 75.3 | 88 | 72.1 | 0.62 |
| ≥7 | 19 | 24.7 | 34 | 27.9 | |
| Mean PSA level (ng/mL) | 30.2 (6.5–214.6) | | 6.4 (2.0–24.3) | | |
| <10 | 8 | 10.4 | 109 | 89.3 | <0.001 |
| ≥10 | 69 | 89.6 | 13 | 10.7 | |
| Deaths | | | | | |
| Total | 4 | 5.2 | 6 | 4.9 | |
| Prostate cancer | 2 | 2.6 | 1 | 0.8 | |
| Mean follow-up (yr) (range) | 5.2 (1.2–7.4) | | 6.1 (1.2–7.9) | | |

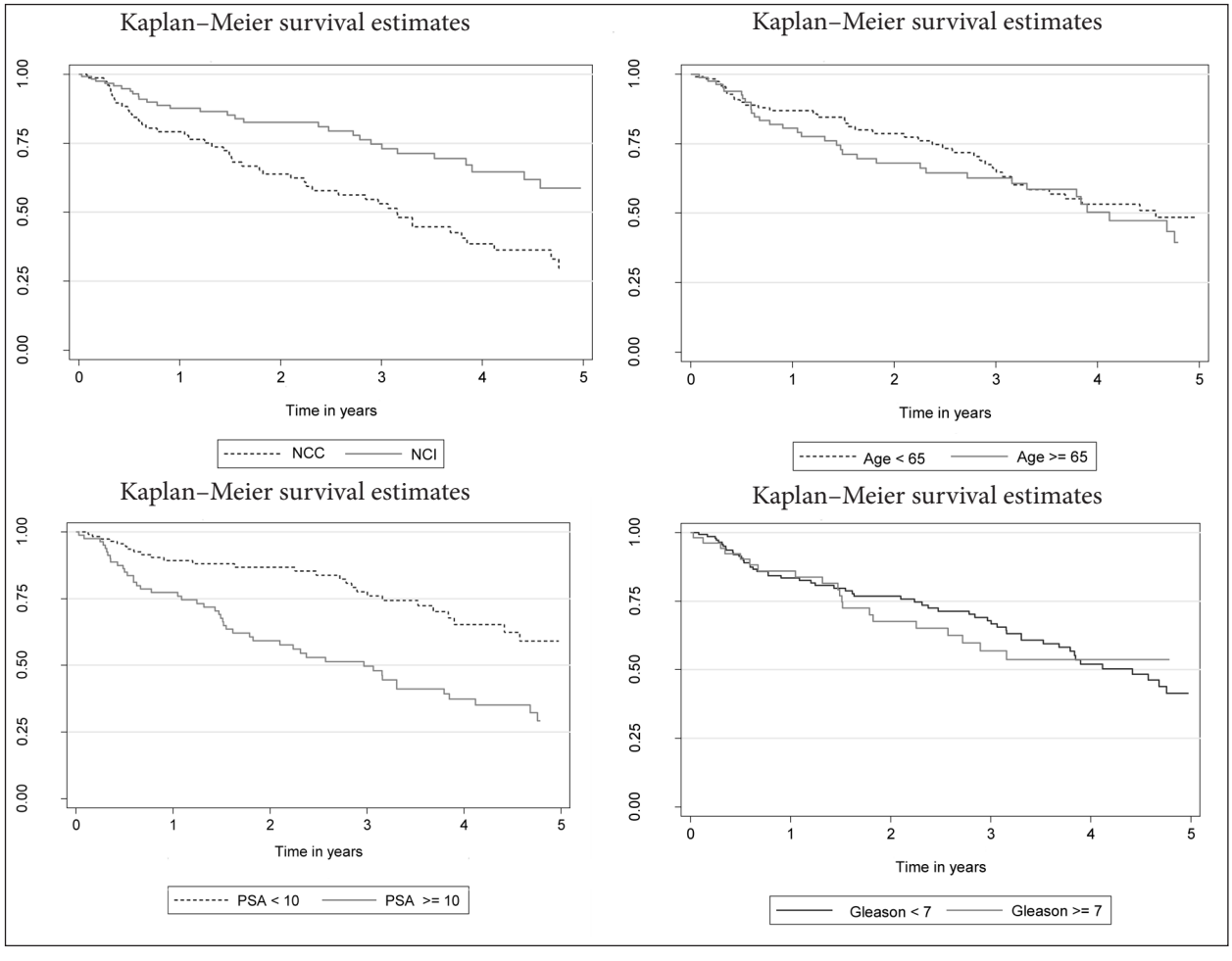


**Figure.** Kaplan–Meier plots representing the bRFS by clinical and pathological characteristics

at NCI had better bRFS than those treated at NCC (p = 0.0007). Better survival was observed in the patients with lower T stage (p = 0.001) and pretreatment PSA < 10 (p = 0.0001). The Kaplan–Meier survival analysis showed no significant differences by age groups (p = 0.69) and by Gleason score (p = 0.79).

The Cox univariate and multivariate survival analysis determined the bRFS prognostic value for the significant clinical and pathological features (Table 2). The independent factors predicting bRFS pre-operatively were the T stage and PSA level. In the multivariate analysis difference between treatment centres has changed after adjustment of other characteristics: the patients treated at NCI had an insignificantly higher bRFS rate, but the observed difference was not significant.

Information on surgical margins and perineural invasion was available for 122 prostate cancer patients, all treated at NCI. The results of univariate and multivariate analysis are shown in Table 3. Both surgical margins and perineural invasion, as well as pretreatment PSA were independent predictive factors for bRFS. Interestingly, the T stage became in-

**Table 2.** Univariate and multivariate analysis of pathological factors predicting bRFS in RP only treated high-risk prostate cancers

| Parameter | Univariate | | | | Multivariate | | | |
|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | | p value | HR | 95% CI | | p value |
| Treatment centre | | | | | | | | |
| NCC | 1 (ref.) | – | – | | 1 (ref.) | – | – | |
| NVI | 0.46 | 0.29 | 0.73 | 0.001 | 1.14 | 0.54 | 2.4 | 0.74 |
| T stage | | | | | | | | |
| T2b-T2c | 1 (ref.) | – | – | | 1 (ref.) | – | – | |
| T3 | 2.07 | 1.31 | 3.27 | 0.002 | 1.92 | 1.19 | 3.09 | 0.008 |
| Gleason score | | | | | | | | |
| <7 | 1 (ref.) | – | – | | 1 (ref.) | – | – | |
| ≥7 | 1.07 | 0.66 | 1.75 | 0.785 | 1.15 | 0.69 | 1.91 | 0.591 |
| PSA level | | | | | | | | |
| <10 | 1 (ref.) | – | – | | 1 (ref.) | – | – | |
| ≥10 | 2.50 | 1.58 | 3.96 | 0.000 | 2.72 | 1.28 | 5.71 | 0.009 |

**Table 3.** Univariate and multivariate analysis of pathological factors predicting bRFS in RP only treated high-risk prostate cancers

| Parameter | Univariate | | | | Multivariate | | | |
|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | | p value | HR | 95% CI | | p value |
| T stage | | | | | | | | |
| T2b-T2c | 1 (ref.) | – | – | | 1 (ref.) | – | – | |
| T3 | 2.4 | 1.14 | 5.05 | 0.02 | 1.899 | 0.8 | 4.5 | 0.1 |
| Gleason score | | | | | | | | |
| <7 | 1 (ref.) | – | – | | 1 (ref.) | – | – | |
| ≥7 | 1.06 | 0.51 | 2.23 | 0.9 | 0.4722 | 0.19 | 1.15 | 0.1 |
| PSA level | | | | | | | | |
| <10 | 1 (ref.) | – | – | | 1 (ref.) | – | – | |
| ≥10 | 2.67 | 1.06 | 6.74 | 0.04 | 3.4138 | 1.31 | 8.91 | 0.01 |
| Positive surgical margins | | | | | | | | |
| No | 1 (ref.) | – | – | | 1 (ref.) | – | – | |
| Yes | 3.78 | 1.78 | 8.04 | 0.001 | 3.232 | 1.48 | 7.07 | 0.003 |
| Perineural invasion | | | | | | | | |
| No | 1 (ref.) | – | – | | 1 (ref.) | – | – | |
| Yes | 2.78 | 1.33 | 5.79 | 0.006 | 2.6178 | 1.12 | 6.12 | 0.03 |

significant after adjustment for post-operative parameters (resection margins and perineural invasion).

## DISCUSSION

The research of prostate cancer predictions is booming, with more than 100 predictive tools published by 2008 (7). The most widely used tools are the D'Amico prostate cancer risk groups, CAPRA scale and nomograms (e. g. Kattan's nomogram). The basis for these predictive models is preoperative parameters, most importantly tumor size (T stage), pretreatment PSA level and biopsy Gleason score. Postoperative parameters are also investigated, and although few models have been externally validated, they seem to add up to the predictive power of the pre-operative tools (8).

Most of the predictive tools for RP outcomes use a small set of repeatedly validated parameters. Some of the standard parameters are T stage, pretreatment PSA and Gleason score, less frequently they are patient age, % of biopsy cores positive. Postoperative parameters investigated include pathologic Gleason score, surgical margins, extracapsular extension, perineural invasion, seminal vesical and lymph node invasion (8). In a particular predictive model a few of these variables could be excluded or granted different predictive weight – but the essential structure of the models is comparable.

A possible reason for this prolific variation is that the tools have been validated in different populations, with different prevailing prostate cancer characteristics. Locally developed tools require external validation to ensure that they could be applied to other populations. This is particularly relevant in distinct regions and populations (e. g. Europe and Asia) (9, 10). Thus, predictive models should be adjusted to suit locally.

In this study we examined high-risk prostate cancer biochemical recurrence after RP in two cancer centers in Lithuania and Belarus. In our study, we found that the pretreatment PSA and T stage were independent preoperative predictors of bRFS. The Gleason score had only a minimal impact and was statistically insignificant. Additional independent post-operative predictors also were positive surgical margins and perineural invasion.

An intriguing finding was that the T stage was no longer an independent predictive factor in the multivariate model when adjusted for positive surgical margins and perineural invasion. A minimal role of the clinical stage for risk stratifying has already been shown by Reese et al. (11). The T stage could be less important than that established by D'Amico or other widely used risk groupings. This does not necessarily mean that the tumor extent is completely irrelevant. Alternative ways to evaluate the local tumor spread include the index tumor volume (12) and maximum tumor diameter (13). The exact predictive role of the tumor size and volume will have to be specified in further research.

The T stage may not correlate with prostate cancer prognosis very well as the pre-operative staging is frequently incorrect. Reese et al. (14) found that after RP, the clinical stage was changed for 35% of patients. Patients who were downgraded after RP (as the tumor extent was found to be smaller than that established previously) were also shown to have better prognosis (15). However, even the updated and corrected T stage was not predictive of biochemical recurrence.

Originally, the T stage is a cornerstone of the most popular prostate cancer risk grading scales, such as D'Amico et al. (16). This study used a high-risk prostate cancer definition published by the National Comprehensive Cancer Network (17) – similar to D'Amico. A simple stratification of prostate cancer to low, intermediate and high risk is already predictive itself of the outcome. Preoperative risk groups are the key for primary prostate cancer risk assessment but the risk should be revised after the RP procedure. Results of our study show that postoperative criteria (such as perineural invasion and positive surgical margins) may lead to risk relocation.

Positive surgical margins were strongly predictive of biochemical recurrence in this study. Similar results were found in other studies (7, 18–20). Godoy et al. (21) found that even the exact site of positive surgical margins – namely, anterior and basilar – was important and correlated with biochemical recurrence even more than the number of positive margins.

Surgical margins are closely related to the RP surgery technique. RP can be performed in a few different ways: classical open RP, laporoscopic or robot assisted laporoscopic. The robot assisted laparoscopic RP is associated with fewer positive surgical margins and subsequently less use of adjuvant therapy (22). However, a few studies have shown that the outcomes (in terms of biochemical recurrence) are related not to the operation itself, but

rather to other predictive parameters – including positive surgical margins (23, 24).

We found that perineural invasion was also an independet biochemical recurrence predictor. In other studies, this is sometimes confirmed (19), and sometimes perineural invasion is merely associated with (and thus predictive through) positive surgical margins, and only relevant in low-risk prostate cancer (25).

A few limitations may undermine our results. Our sample size (199 patients for a preoperative factors analysis, and 122 for a postoperative one) is quite small, and differences that we have found insignificant may turn out significant with a larger sample. This could explain why we found only a minimal predictive role of the Gleason score. We also do not claim our list of possible predictive factors to be exhaustive. Postoperative factors (positive surgical margins and perineural invasion) rendered the T stage insignificant in the multivariate analysis. Addition of further parameters could change the situation still – for example, genetic parameters (26), comorbidities (27) and BMI (28) may be associated with RP outcomes as well.

It is complicated to compare our results with results from similar studies (and results among other studies themselves) straightforwardly. Researchers use slight variants of high-risk prostate cancer definitions, study populations are heterogenous (especially if selected according to the popular d'Amico risk groups criteria) and different sets of parameters are used for a multivariate analysis. Our study adds to the growing volume of evidence in the field. Hopefully, this will eventually lead to an unambiguous and prognostically valid definition of high-risk prostate cancer itself and more focused care for these patients.

## CONCLUSIONS

Pretreatment PSA, positive surgical margins and perineural invasion were independent predictors of biochemical recurrence after radical prostatectomy in high-risk prostate cancer patients, while the T stage became insignificant after adjusting for postoperative parameters. Further research will settle the predictive factors more clearly and will lead to a better definition of high-risk prostate cancer.

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## DIDELĖS RIZIKOS PROSTATOS VĖŽYS: PROGNOSTINIAI BIOCHEMINIO RECIDYVO VEIKSNIAI PO RADIKALIOS PROSTATEKTOMIJOS

*Santrauka*

**Įžanga / tikslas.** Prognostiniai veiksniai padeda numatyti didelės rizikos prostatos vėžio atsinaujinimą po radikalios prostatektomijos ir galėtų padėti atrinkti pacientus, kuriems būtų reikalingas adjuvantinis ar multimodalinis gydymas. Šio tyrimo tikslas buvo nustatyti didelės rizikos prostatos vėžio biocheminio recidyvo po radikalios prostatektomijos iki ir pooperacinius prognostinius veiksnius.

**Metodai.** 2005–2009 m. duomenys apie didelės rizikos prostatos vėžiu sergančius pacientus buvo retrospektyviai surinkti dviejuose gydymo centruose: Nacionaliniame vėžio institute (Vilnius, Lietuva) ir N. N. Aleksandrovo nacionaliniame vėžio centre (Minskas, Baltarusija). Tyrimo grupę sudarė 199 pacientai. Ikioperaciniai nepriklausomi kintamieji buvo naviko išplitimas T pagal TNM klasifikaciją, PSA koncentracija prieš radikalią prostatektomiją ir Gleason skalės įvertis. Papildomai įvertintas 122 pacientų operacijos radikalumas ir perineurinė invazija. Analizuotas išgyvenamumas iki biocheminio progresavimo ir bendrasis išgyvenamumas. Vidutinis stebėjimo laikas buvo 5,8 metų.

**Rezultatai.** Pirminio naviko išplitimas (T) ir mažesnė PSA koncentracija prieš gydymą buvo susiję su geresniu išgyvenamumu ($p = 0,001$ ir $p = 0,0001$ atitinkamai). Daugiaveiksnėje ikioperacinių veiksnių analizėje didesnis naviko išplitimas ($p = 0,008$) ir didesnė PSA koncentracija prieš gydymą ($p = 0,009$) buvo susiję su didesne biocheminio recidyvo rizika. Į daugiaveiksnę analizę įtraukus ir pooperacinius veiksnius, tik PSA koncentracija prieš gydymą ($p = 0,01$), teigiami (neradikalūs) chirurginiai kraštai ($p = 0,003$) ir perineurinė invazija ($p = 0,03$) liko nepriklausomais biocheminio recidyvo prognostiniais veiksniais.

**Išvados.** Didelės rizikos prostatos vėžiu sergančių pacientų PSA koncentracija prieš gydymą, teigiami (neradikalūs) chirurginiai kraštai ir perineurinė invazija yra nepriklausomi biocheminio recidyvo rizikos veiksniai. Pirminis naviko išplitimas, į analizę įtraukus pooperacinius veiksnius, buvo nereikšmingas.

**Raktažodžiai:** didelės rizikos prostatos vėžys, radikali prostatektomija, biocheminis recidyvas