

Validation of pre- and postoperative nomograms used to predict the pathological stage and prostate cancer recurrence after radical prostatectomy: a multi-institutional study

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Summary

Purpose: To validate the preoperative and postoperative predictive tables of Johns Hopkins hospital, Baltimore, Maryland (JHH) and the prostate nomograms of Memorial Sloan Kettering Cancer Center, New York (MSKCC), most commonly used to predict the pathological tumor stage and postoperative freedom from recurrence, in a mixed cohort of Bulgarian prostate cancer patients.

Methods: Clinical and laboratory data of 282 prostate cancer patients, who underwent radical prostatectomy, were supplied from three different institutions in Bulgaria. Preoperative prostate specific antigen (PSA) values, clinical stage, biopsy Gleason score and the pathological features of the radical prostatectomy specimens were collected from each center and evaluated. Nomogram-predicted probabilities for the presence of unfavorable pathological parameters (extracapsular extension, seminal vesicle invasion/SVI, and lymph node involvement/LNI), and the 5-year freedom from recurrence were compared with actual patient outcomes. Areas under the receiver operating characteristic (ROC) curves (AUC) were determined for each variable to assess the predictive accuracy of the nomograms applied.

Results: The MSKCC prostate cancer nomograms showed superior accuracy for all parameters studied, as compared with the JHH predictive tables. AUC values for organ-confined disease (OCD), SVI and LNI were calculated as 0.763, 0.750, 0.756 and 0.868, 0.787, 0.874 for JHH and MSKCC nomograms, respectively. The AUC values for 5-year freedom from recurrent disease were 0.751, 0.812, 0.813 and 0.894 for pre- and postoperative JHH and MSKCC nomograms, respectively.

Conclusion: Despite the potential for heterogeneity in patient selection and management, most predictions demonstrated high concordance with actual observations. All studied nomograms showed reasonable predictive values for the final pathological features, like OCD, SVI and LNI, and for the 5-year freedom from recurrent disease. This multi-institutional study showed that each of the predictive tools studied could be used in Bulgarian patients with comparable accuracy. Compared with the JHH tables, the MSKCC prostate cancer nomograms showed higher predictive accuracy and should therefore be preferred.

Key words: nomograms, prostate cancer, radical prostatectomy, validation

Introduction

Accurate prediction of pathological stage is of utmost importance for all men newly diagnosed with clinically localized prostate cancer. It is well known that radical prostatectomy is most effective when the disease is confined to the prostate [1-3], while the presence of adverse pathologic features - extraprostatic extension (EPE), SVI and LNI is related to disease aggressiveness and worse oncological outcome [4,5].

Similarly, accurate risk assessment is important for those patients who had already been subjected to radical surgery. The early prediction of recurrent disease helps physicians identify individuals at high risk and thus modulate the surveillance and treatment in the most appropriate way [6].

In the last two decades numerous pre- and postoperative nomograms had been published [7-12]. They are based on multivariate logistic regression analysis of large series of patients with known follow-up. Multiple

clinical variables had been used for the purpose: serum PSA, Gleason score, clinical stage, cancer volume, PSA density, etc.

The extreme popularity of the world-wide-web in recent years facilitated to a great extent the communication and search of information among physicians and patients. Many universities, hospitals and medical centers of excellency uploaded on their web-sites predictive tools and prognostic calculators that are readily available to interested patients and medical specialists.

One of the most commonly used nomogram, the Partin tables, first published in 1993 [13], estimates the pathological stage using a simple combination of clinical variables - the preoperative serum PSA, the clinical stage and the Gleason score. Because of continued stage migration, the Partin tables were periodically updated and validated, most recently in 2007 [14].

This preoperative predictive tool is supplemented by a postoperative nomogram, also developed at the same institution (the so-called Han tables). The latter is used to predict the probability of the first evidence of recurrence (detectable PSA level) following radical surgery [15].

Similar nomograms have been created. Some of the most commonly used are the preoperative and postoperative nomograms of the MSKCC in New York.

Using a slightly more sophisticated approach, with an extended range of clinical variables, they also aim to predict the pathological tumor stage [16-19] and the postoperative freedom from recurrence [6].

To be widely used and recommended for clinical application, however, each of these prediction tools should be validated, not only internally, but also externally, to account for the existing apparent differences in men of different ethnicities and socioeconomic status.

Although some of them, e.g. the 1997 and 2001 Partin tables, have been validated in various cohorts from USA, Europe and Asia [20-27], none of these tools has ever been validated in Bulgaria. Without that, the clinical usefulness of these prognostic nomograms in Bulgarian prostate cancer patients remains controversial.

With an aim to validate the pre- and postoperative prognostic tools of two of the biggest and most renowned urological centers in the world, we applied the JHH and MSKCC nomograms in a mixed cohort of Bulgarian prostate cancer patients.

Methods

Clinical data from prostate cancer patients, who underwent radical prostatectomy between 1996 and

2010, were supplied from three different institutions in Bulgaria, located in Varna, Pleven and Sofia. Preoperative serum PSA values, clinical stage, biopsy Gleason score and the pathological features of the radical prostatectomy specimens were collected from each center and evaluated. Patients with missing information about the clinical and pathological parameters and follow up were excluded from the study.

A total of 282 patients finally entered the study: 167 from Varna, 76 from Pleven, and 39 from Sofia (Table 1).

In all cases the diagnosis was made by systematic tru-cut biopsy (6 cores at least). In all three centers, extended pelvic lymphadenectomy was routinely performed prior to radical prostatectomy.

All biopsy specimens were graded by the Gleason scoring system [28]. The percentage of positive cores at biopsy was recorded in all patients. Clinical stage was determined by digital rectal examination. To adapt to the requirements of all nomograms tested, the 1992 TNM staging system was used for clinical and pathological staging [29]. The presence of EPE, SVI, LNI, and positive surgical margins (PSM) was recorded for all prostatectomy specimens. The pathological slides of biopsy and prostatectomy specimens were reviewed by dedicated pathologists at each institution. No central pathological review was provided for the study.

Follow up data were also collected from each institution. To assess the predictive ability of postoperative nomograms immediately after surgery, the number of months without detectable cancer or a rising PSA following radical prostatectomy were marked as 1 in all cases.

Recurrence was defined if 2 consecutive postoperative PSA values rose above the cut-off value of 0.2 ng/ml.

The pre- and postoperative nomograms of JHH and MSKCC were applied to our cohort of patients and the prediction of OCD, EPE, SVI, LNI, as well as the 5-year freedom from recurrence were calculated and compared with the actual patient outcomes. ROC analysis was done to assess the discriminative ability of each of the nomograms applied.

Statistical analysis

All statistical evaluations were 2-sided and done by SPSS 16.0 package program. The power value of ROC curves was calculated by using STATA 10.1 package program. Differences between the probability curves of each institution were evaluated by χ^2 non-parametric test.

Table 1. Clinicopathological characteristics of Bulgarian patients (from Varna, Pleven and Sofia)

Characteristics	Varna	Pleven	Sofia	Total
Number of cases, n	167	76	39	282
Age, years, mean (range)	64.8 (46-78)	64.5 (49-76)	69.5 (54-76)	65.3 (46-78)
Initial PSA, ng/ml, n (%)				
0-4.0	15 (8.9)	–	–	15 (5.3)
4.1-10.0	44 (26.3)	15 (19.7)	15 (38.5)	74 (26.2)
10.1-20.0	45 (26.9)	39 (51.3)	16 (41.0)	100 (35.5)
20.1-100.0	58 (34.7)	20 (26.3)	4 (10.2)	82 (29.1)
>100.0	5 (3.0)	2 (2.6)	4 (10.2)	11 (3.9)
Clinical stage (1992), n (%)				
T1 /a,b,c/	24 (14.4)	6 (7.9)	–	30 (10.6)
T2 /a,b,c/	113 (67.7)	52 (68.4)	23 (58.9)	188 (66.7)
T3 /a,b,c/	30 (17.9)	18 (23.7)	16 (41.0)	64 (22.7)
Biopsy Gleason Sum, n (%)				
5-6	67 (40.1)	12 (15.8)	28 (71.8)	107 (37.9)
7 (3+4)	28 (16.8)	25 (32.9)	5 (12.8)	58 (20.6)
7 (4+3)	20 (11.9)	25 (32.9)	2 (5.1)	47 (16.7)
8-10	52 (31.1)	14 (18.4)	4 (10.2)	70 (24.8)
% Positive biopsy cores, n (%)				
0-25	43 (25.7)	19 (25.0)	6 (15.4)	68 (24.1)
26-50	77 (46.1)	42 (55.3)	25 (64.1)	144 (51.1)
51-75	33 (19.8)	13 (17.1)	8 (20.5)	54 (19.1)
76-100	14 (8.4)	2 (2.6)	–	16 (5.7)
Gleason sum at surgery, n (%)				
5-6	58 (34.7)	9 (11.8)	24 (61.5)	91 (32.3)
7 (3+4)	36 (21.6)	20 (26.3)	2 (5.1)	58 (20.6)
7 (4+3)	21 (12.6)	11 (14.5)	3 (7.7)	35 (12.4)
8-10	52 (31.1)	36 (47.4)	10 (25.6)	98 (34.7)
RP pathological details, n (%)				
OCD	87 (52.1)	36 (47.4)	19 (48.7)	142 (50.4)
EPE	63 (37.7)	32 (42.1)	14 (35.9)	109 (38.6)
SVI	48 (28.7)	23 (30.3)	8 (20.5)	98 (34.8)
LNI	43 (25.7)	16 (21.0)	8 (20.5)	70 (24.8)
PSM	29 (17.4)	19 (25.0)	12 (30.8)	60 (21.3)
5-yr disease-free survival, n (%)	120 (71.8)	52 (68.4)	24 (61.5)	196 (69.5)

OCD: organ-confined disease, EPE: extraprostatic extension, SVI: seminal vesicles invasion, LNI: lymph nodes involvement, PSM: positive surgical margins, RP: radical prostatectomy, yr: year, PSA: prostate specific antigen

Results

Patient characteristics

Patient age ranged from 46 to 78 years (mean 65.3).

Most patient and tumor parameters showed values indicating an aggressive tumor potential, placing those patients at high risk for disease recurrence (Table 1).

Less than one third of the patients - 89 (31.6%) - had preoperative serum PSA value < 10.0 ng/ml. In 93 cases (33.0%) the initial serum PSA exceeded 20 ng/ml (even 100 ng/ml in 11 cases), making these patients unfavorable candidates for radical surgery, according to the standards accepted in most American and European institutions.

This was also valid for the clinical stage: only 30 (10.6%) patients came for surgery with clinical (c) cT1 stage, while the stage 64 patients (22.7%) had been ini-

tially clinically determined as cT3. The highest clinical stage was found in the series from Sofia, where 16 patients (41%) were staged clinically as cT3 stage.

Favorable Gleason score was registered in 107 (37.9%) patients, while 70 patients of the entire cohort had highly aggressive, low-differentiated tumors (Gleason score > 7). Surprisingly, the highest proportion of low-grade tumors was found in the Sofia series - 28 patients (71.8%), not corresponding to the higher clinical stage of this patient subset.

Almost one fourth of our patients had < 25% positive cores at biopsy, the highest proportion - 144 patients (51.1%) - being within the range of 26-50% positive cores.

There was a slight upgrading after prostatectomy - the low grade tumors (Gleason sum 5-6) had decreased slightly - 91 cases (32.3%), while the high grade tumors (Gleason sum > 7) increased - 98 (34.7%).

The pathological review of the prostatectomy

specimens showed that only half of the patients had OCD. The percentage of EPE, SVI and LNI was 38.6, 34.8, and 24.8%, respectively. Positive surgical margins were detected in 60 patients (21.3%) from the entire cohort. This percentage varied between the three institutions - it was lowest in Varna (17.4%), and highest in Sofia (30.8%).

A total of 196 patients (69.5%) of the whole series had undetectable (<0.2 ng/ml) serum PSA values in the first 5 years after surgery. This number also included patients operated between 2006-2010 who were obviously free of disease for a period < 5 years, which is a potential bias and limitation of the study.

Nomogram evaluation

The MSKCC nomograms showed superior accuracy for all parameters studied, as compared with the JHH predictive tables, although the difference was not statistically significant in all cases.

Thus, AUC values for OCD, EPE, SVI, and LNI were calculated as 0.763 and 0.868 ($p < 0.001$) (Figure 1); 0.704 and 0.823 ($p < 0.001$) (Figure 2); 0.750 and 0.787 ($p = 0.067$) (Figure 3); 0.756 and 0.874 ($p < 0.001$) (Figure 4) for JHH and MSKCC nomograms, respectively. These numbers show that the only time when the Partin tables can be used with comparable predictive accuracy, as the preoperative MSKCC prostate

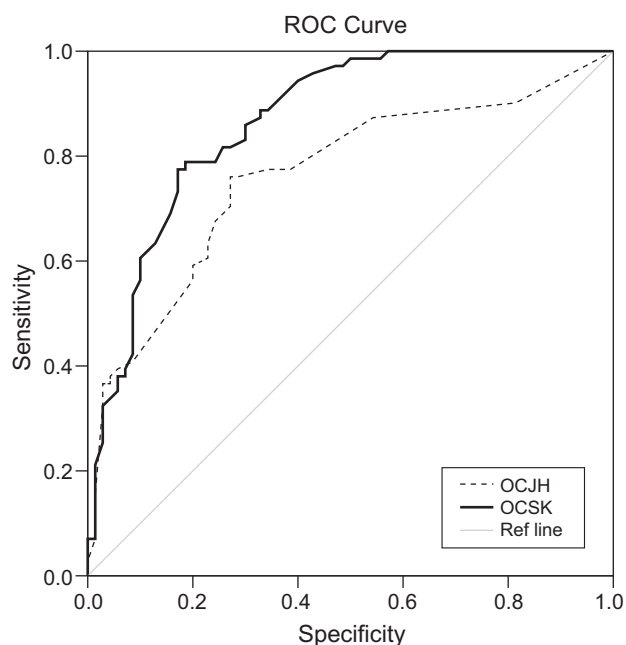


Figure 1. ROC curve analysis comparing predicted probabilities of organ confinement (OC) by the preoperative JHH nomogram (Partin tables) [$AUC^{JHH} = 0.763$ (95% CI 0.706-0.819)] and the preoperative MSKCC nomogram [$AUC^{MSKCC} = 0.868$ (95% CI 0.826-0.909)], p -value < 0.001.

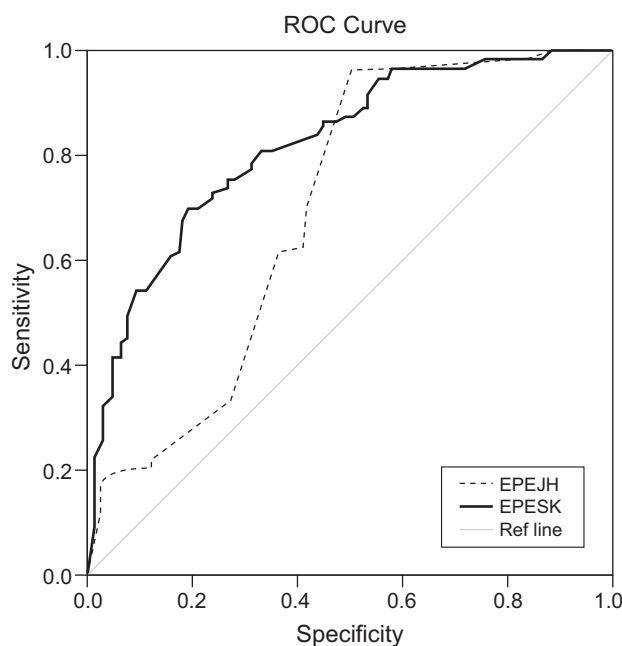


Figure 2. ROC curve analysis comparing predicted probabilities of extraprostatic extension (EPE) by the preoperative JHH nomogram (Partin tables) [$AUC^{JHH} = 0.704$ (95% CI 0.642-0.765)] and the preoperative MSKCC nomogram [$AUC^{MSKCC} = 0.823$ (95% CI 0.775-0.871)], p -value < 0.001.

cancer nomogram, is in assessing the predictive probability of SVI.

The AUC values for 5-year freedom from recur-

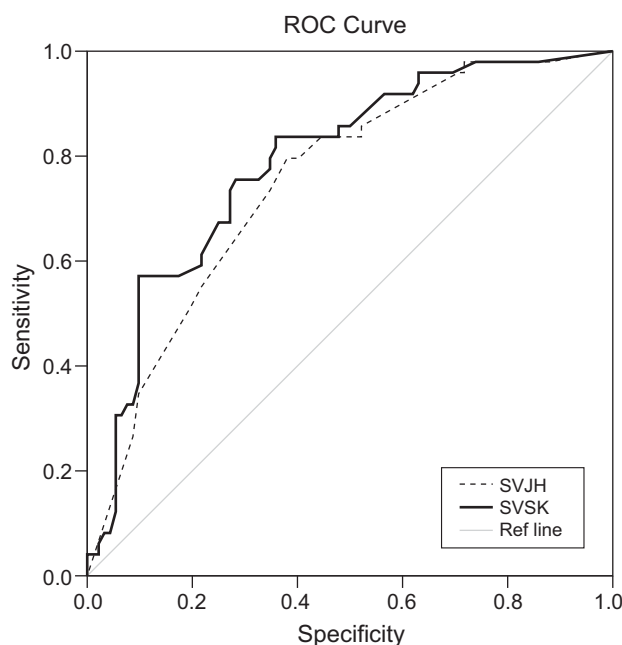


Figure 3. ROC curve analysis comparing predicted probabilities of seminal vesicle invasion (SVI) by the preoperative JHH nomogram (Partin tables) [$AUC^{JHH} = 0.750$ (95% CI 0.692-0.808)] and the preoperative MSKCC nomogram [$AUC^{MSKCC} = 0.787$ (95% CI 0.732-0.842)], p -value = 0.067.

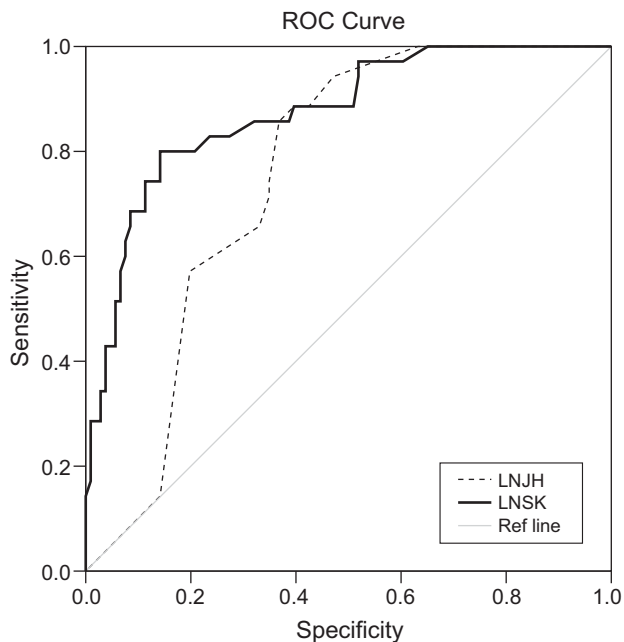


Figure 4. ROC curve analysis comparing predicted probabilities of lymph node involvement (LNI) by the preoperative JHH nomogram (Partin tables) [$AUC^{JHH} = 0.756$ (95% CI 0.701-0.811)] and the preoperative MSKCC nomogram [$AUC^{MSKCC} = 0.874$ (95% CI 0.827-0.920)], p -value < 0.001.

rent disease were 0.751, 0.812, 0.813 and 0.894 for pre- and postoperative JHH and MSKCC nomograms, respectively. Again, both MSKCC nomograms (the pre- and postoperative one) predicted more accurately the occurrence of recurrent disease, as compared with the respective (pre- and postoperative) Han tables of JHH ($p < 0.001$; $p < 0.001$, respectively) (Figure 5A, 5B).

Discussion

The world-wide-web made the access to specialized information much easier than before. Currently, many Bulgarian patients and their treating urologists use the predictive tools and prognostic calculators of world renowned institutions (like JHH and MSKCC) that are readily available in Internet, for counseling and taking treatment decisions. However, to be officially applied and widely used, with convincing accuracy, an external validation of these nomograms, particularly on a Bulgarian cohort of patients, is a must.

To assess the ability of the prognostic tools of JHH and MSKCC to discriminate the 4 pathological categories of interest and the 5-year freedom from recurrent disease, detailed clinico-pathological data from 3 different urological institutions located in Western (Sofia), Middle (Pleven), and Eastern Bulgaria (Varna) were collected and analyzed. Various ROC curves were con-

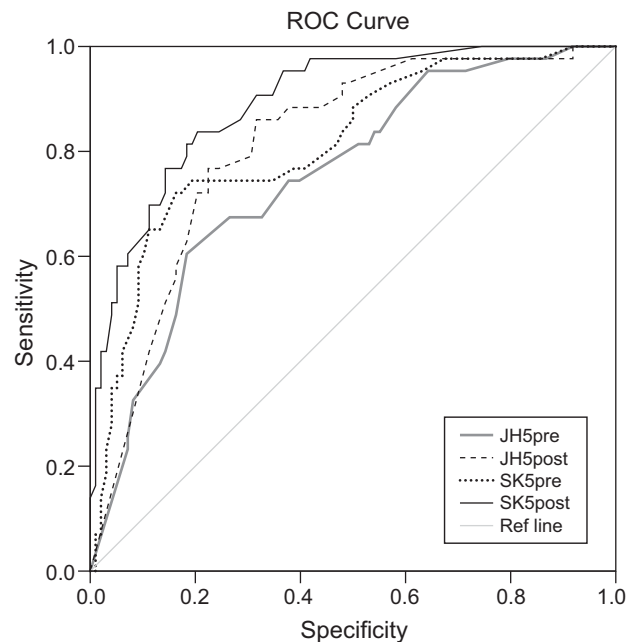


Figure 5. ROC curve analysis comparing predicted probabilities of 5-year freedom from recurrent disease by: **A/** the preoperative JHH nomogram (Han tables) [$AUC^{JHH} = 0.751$ (95% CI 0.691-0.811)] (medium weight line) and the preoperative MSKCC nomogram [$AUC^{MSKCC} = 0.813$ (95% CI 0.758-0.869)] (dotted line), $p < 0.001$; and **B/** the postoperative JHH nomogram (Han tables) [$AUC^{JHH} = 0.812$ (95% CI 0.759-0.864)] (dashed line) and the postoperative MSKCC nomogram [$AUC^{MSKCC} = 0.894$ (95% CI 0.856-0.932)] (black line), $p < 0.001$.

structed and the respective AUC were calculated and compared.

An AUC of 1 indicates perfect discrimination and an AUC of 0.5 indicates no discrimination. The larger the AUC, the better its discrimination ability is. Generally, $AUC \geq 0.70$ indicates that the model has good discriminative value, 0.6 - 0.7 represents moderate discrimination and < 0.60 represents poor discrimination [27].

The extreme popularity and wide use of the Partin tables may be explained by its simplicity and inclusiveness with accurate prediction based on the three most commonly available preoperative variables: serum PSA, clinical stage and Gleason score.

Our results confirmed those of previous validation studies [20-27] that the Partin tables are able to predict the pathological stage with good discriminative ability, as the AUC of all studied parameters always exceeded 0.70. We also proved that the preoperative and postoperative Han tables, developed at the same institution, can be used to predict with comparable accuracy ($AUC > 0.70$) the 5-year freedom from recurrences.

The major limitation of JHH prognostic tables is the lack of other analyzed covariates. Other potentially important factors not included in the Partin and Han tables have been recently implicated as predictors of more

aggressive disease. The results of these contemporary studies confirmed that the inclusion of new variables, such as percentage of positive biopsy cores, surgical margin status, etc. in the preoperative and postoperative nomograms can significantly increase their predictive accuracy [30]. Thus, updated nomograms, incorporating a larger number of prognostic variables, have been created in big institutions like MSKCC and have been offered free to public access by Internet [16-19]. However, the number of studies, externally validating these nomograms, is limited.

Our study confirmed the predictive ability of the MSKCC pre- and post-treatment prostate cancer nomograms. Moreover, it convincingly proved their superiority as compared to the JHH prognostic tables. There was a significant difference ($p < 0.001$) between the respective ROC curves with regard to most of the parameters studied, the only exemption being the prediction of SVI, where the difference between the JHH and MSKCC nomograms was not statistically significant ($p = 0.067$).

Our study, however, has several limitations that might lead to biases when interpreting the results.

Firstly, it comprised a limited number of cases ($n = 282$), with uneven distribution among the three institutions involved (Varna - 167, Pleven - 76, and Sofia - 39 patients enrolled).

Secondly, there was a big difference and a large heterogeneity observed among the tumor and patient characteristics between the three centers.

Besides, there was a significant difference between the tumor and patient characteristics in our study and those in other American, European and Asian studies on post radical prostatectomy patients [20-27]. Generally, the majority of our patients might be classified as a high risk patient subset, showing more aggressive features of their tumors - higher values of initial serum PSA; higher clinical stage; higher Gleason score, etc., as compared to other studies, and the historical and the contemporary Partin cohorts, in particular.

Our study was also limited by the lack of central pathological review, implying that there might be considerable variations in the interpretation of the radical prostatectomy specimens between the three centers.

Another difference from many published studies, this time favoring the patient outcome, is the routine use of extended lymph node dissection in all three Bulgarian institutions. This fact might explain why, despite the exclusively high proportion of LN positive cases in our series - 24.8%, the 5-year PSA-free survival is relatively good: 5 years after surgery 196/282 (69.5%) of our patients are still with undetectable (< 0.2 ng/ml) PSA levels.

Despite all these differences, the study showed that

all prognostic tools are adequate in predicting the final pathological features and the oncologic outcome, and might be used in Bulgarian patients as well. The differences observed in some of the clinical and pathological parameters reflect the national differences with regard to the patient's attitude to screening, the availability and the routine use of serum PSA testing and the current strategy of treating localized prostate cancer in Bulgaria.

Conclusion

Despite the potential for heterogeneity in patient selection and management, most predictions demonstrated high concordance with actual observations. All studied nomograms showed reasonable predictive values for the final pathological features, like OCD, EPE, SVI and LNI, and for the 5-year freedom from recurrent disease. This multi-institutional study proved that each of the predictive tools studied could be used in Bulgarian patients. Compared with the JHH tables, the MSKCC prostate cancer nomograms showed higher predictive accuracy and should be therefore preferred.

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