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Feasibility and accuracy of prostate cancer risk calculators in prediction of prostate cancer, extraprostatic extension as well as the risk of lymph nodes metastasis

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Introduction The aim of this article was to evaluate the accuracy of European Randomized study of Screening for Prostate Cancer (ERSPC 4) and Prostate Cancer Prevention Trial (PCPT 2.0) risk calculator on predicting high-grade prostate cancer (HGPCa) and accuracy of Partin and Briganti nomograms on organ confined (OC) or extraprostatic cancer (EXP), seminal vesicles invasion (SVI) and risk of lymph nodes metastasis.

Material and methods A cohort of 269 men aged between 44–84 years, who underwent radical prostatectomy was retrospectively analysed. Based on estimated calculator risk, patients were divided into risk groups: low (LR), medium (MR) and high (HR). Results obtained with calculators were compared to post-surgical final pathology outcome.

Results In ERPSC4, the average risk for HGPC was LR = 5%, MR = 21%, and HR = 64%. In PCPT 2.0, the average risk for HG was: LR – 8%, MR – 14%, and HR – 30%. In the final results, HGPC was observed in: LR = 29%, MR = 67%, and HR = 81%. In Partin, LNI was estimated to occur in: LR = 1%, MR = 2%, and HR = 7.5% and in Briganti: LR = 1.8%, MR = 11.4%, and HR = 44.2% while finally it was found in: LR = 1.3%, MR = 0%, and HR = 11.6%.

Conclusions ERPSC 4 and PCPT 2.0 corresponded well with each other as well as Partin and Briganti. ERPSC 4 was more accurate in predicting HGPC than PCPT 2.0. Partin was more accurate as for LNI than Briganti. In this study group a large underestimation was observed in reference to Gleason grade.

Key Words: prostate cancer ‹› nomograms ‹› risk calculators

INTRODUCTION

Prostate cancer (PCa) is the fifth most common cancerous cause of death in men worldwide and is the neoplasm with the second highest rate of incidence [1]. Risk calculators (RC) were designed to assess the risk of occurrence of prostate cancer, its staging and to help clinicians decide on optimal treatment. Risk prediction models improve the accuracy of prostate-specific antigen (PSA) testing to detect PCa [2].

Nomograms assessing the risk of nodal disease are helpful in everyday practice [e.g Memorial Sloan Kettering Cancer Center (MSKCC) nomogram]. Milionas et al. showed that the MSKCC nomogram demonstrated high discriminative accuracy for prediction of lymph node invasion in men undergoing pelvic lymph node dissection at radical prostatectomy [3].

The aim of this study was comparison and evaluation of the accuracy of the European Randomized study of Screening for Prostate Cancer (ERSPC 4) and Prostate Cancer Prevention Trial (PCPT 2.0) risk calculator on predicting high-grade prostate cancer (HGPCa). Briganti and Partin nomograms

were probed on anticipation of organ confined (OC) or extraprostatic cancer (EXP), seminal vesicle invasion (SVI), and lymph node involvement (LNI).

MATERIAL AND METHODS

Study group

The study sample consisted of a consecutive cohort of 269 men from 44 to 84 years old in a high-volume prostate cancer centre. Database 2017–2018 contains values of PSA, digital rectal examination (DRE), body mass index (BMI), volume of prostate and full pathomorphological evaluation – Gleason score (GS), cTNM and pTNM. Patients were divided into three groups based on d'Amico classification system, as follows: 1) low risk group (n = 87), 2) intermediate (medium) risk group (n = 75), and 3) high risk group (n = 107). Additionally, patients were distributed into 5 Risk Grade Groups: grade group 1 (GS 3+3) – 151, grade group 2 (GS 3+4) – 47, grade group 3 (GS 4+3) – 27, grade group 4 (GS 4+4) – 33, grade group 5 (GS ≥9) – 11 [4]. Overall group characteristics: average age – 65.3 years, average PSA – 15.04 ng/ml, average prostate volume – 45.7 ml, median GS – 7, median of lymph nodes (LNs) removed was 9 [interquartile range (IQR): 6–13]. Low risk d'Amico group: average PSA – 6.29 ng/ml, average prostate volume – 46.7 ml. Intermediate risk d'Amico group: average PSA – 10.5 ng/ml, average prostate volume – 47.9 ml. High risk d'Amico group: average PSA – 25.02 ng/ml, average prostate volume – 43.4 ml. The aforementioned information was used in risk calculators (RC) – Briganti nomogram 2012, PCPTRC 2.0, ERSPC 4 and Partin nomogram. Based on estimated risk conducted by calculators, patients were divided into three groups of risk: low (LR), medium (MR) and high (HR). Conditions of distribution are illustrated in Table 1.

Table 1. *Conditions of distribution into risk groups*

Groups	ERSPC 4	PCPT 2.0	Partin	Briganti
Low risk	<10%	<11%	OC ≥75%	≤5%
Medium risk	10–40%	11–18%	OC 74–50%	6–20%
High risk	>40%	>20%	OC <50%	>20%

ERSPC 4 – European Randomized study of Screening for Prostate Cancer; PCPT 2.0 – Prostate Cancer Prevention Trial; Partin, Briganti – prostate cancer risk calculators; OC – organ confined

Prostate cancer risk calculators used in this study

The Briganti calculator is used to evaluate probability of metastases in lymph nodes and requires: PSA, clinical T-stage, primary and secondary Gleason grade, and percentage of positive cores [5]. The Partin calculator requires PSA, Gleason score and clinical T-stage to predict whether the tumour will be confined to the prostate – tendency to be in one of the four pathological stages: organ confined, extraprostatic extension, seminal vesicle invasion or lymph node invasion [6, 7]. PCPT 2.0 requires data of six clinical risk factors: PSA, DRE, age, race, family history, and biopsy history. This calculator is applicable to men who are at least 50-years-old, have no previous diagnosis of prostate cancer and have recent DRE and PSA results (examination performed less than 1 year before) [8]. ERSPC 4 is designed to determine the likelihood of cancer in the repeat biopsy and grade of cancer (high-grade cancer defined as Gleason score ≥7 and/or cT >T2b). It requires PSA, DRE or transrectal ultrasonography (TRUS) and biopsy history [9].

Study protocol

All of the above mentioned prostate cancer risk calculators were used to compare the predictions with an actual outcome of the full final pathology results after prostate resection.

In case of PCPT 2.0 and ERSPC 4 basing on findings of calculators, outcome of biopsy and the full final pathology results after radical prostatectomy, Gleason grade of patients was upgraded and downgraded. Comparing outcome of biopsy and the full final pathology after radical prostatectomy Gleason grade was upgraded or downgraded. Percentage of upgrading and downgrading was used to show accuracy of PCPT 2.0 and ERSPC 4 in predicting HGPCa in different risk groups computed by nomograms.

Table 2. *Effectivity of Partin nomogram in predicting local advancement*

Groups	OC		EXP		SVI	
	Partin estimation	Histopath outcome	Partin estimation	Histopath outcome	Partin estimation	Histopath outcome
LR	80%	62%	17%	3.7%	3%	1.2%
MR	71.5%	48%	20.5%	21.5%	6%	8.9%
HR	40%	21%	36%	71.2%	15.5%	25.8%

OC – organ confined; EXP – extraprostatic extension; SVI – seminal vesicle invasion; LR – low risk; MR – medium risk; HR – high risk; histopath – histopathological

Statistical analysis

Statistical methods consisted of a couple steps. Initially, the specificity, sensitivity, negative and positive predictive value of nomograms were assessed. The second step was external validation of nomograms. The discrimination accuracy of the models to predict HGPCa or OC, EXP, SVI and LNI was quantified using the receiver operating characteristic – derived area under the curve, where 100% indicates perfect prediction and 50% is considered equivalent to the toss of a coin. The extent of overestimation or underestimation of the histologically confirmed versus the nomogram predicted HG PCa or OC, EXP, SVI and LNI rates was shown in Tables.

Table 3. *Comparison of Partin and Briganti nomograms in predicting lymp node involvement*

Groups	Partin estimation	Briganti estimation	Histopath outcome
LR	1%	1.8%	1.3%
MR	2%	11.4%	0%
HR	7.5%	44.2%	11.6%

LR – low risk; MR – medium risk; HR – high risk, histopath – histopathological

Table 4. *Comparison of ERPSC 4 and PCPT 2.0 in predicting HG PCa*

Groups	ERSPC 4	PCPT 2.0	Histopath outcome
LR	5%	8%	29%
MR	21%	14%	67%
HR	64%	30%	81%

ERSPC 4 – European Randomized study of Screening for Prostate Cancer; PCPT 2.0 – Prostate Cancer Prevention Trial (prostate cancer risk calculators); LR – low risk; MR – medium risk; HR – high risk, histopath – histopathological

Table 5. *Upgrading and downgrading in different risk groups as for ERSPC 4 and PCPT 2.0*

Groups	Upgrading in comparison to biopsy		Downgrading in comparison to biopsy	
	ERSPC 4	PCPT 2.0	ERSPC 4	PCPT 2.0
LR	23%	28%	8%	23%
MR	31%	46%	15%	26%
HR	33%	41%	16%	30%

ERSPC 4 – European Randomized study of Screening for Prostate Cancer; PCPT 2.0 – Prostate Cancer Prevention Trial (prostate cancer risk calculators); LR – low risk; MR – medium risk; HR – high risk

RESULTS

Prostate cancer stage assessment (T stage in TNM classification)

Local advancement was calculated using the Partin nomogram. Chance of OC tumour was 80% for LR group, 71.5% for MR group, and 40% for HR group, while according to full final pathology outcome organ confined disease was observed in LR = 62%, MR = 48% HR = 21%. EXP was estimated to occur in LR = 17%, MR = 20.5%, HR = 36%, but in the final result it was found in LR = 3.7%, MR = 21.5%, and HR = 71.2%. SVI was appraised to be in LR = 3%, MR = 6%, and HR = 15.5%, although in final outcome it was detected in LR = 1.2%, MR = 8.9%, and HR = 25.8% (Table 2).

Prostate cancer lymph node involvement

Lymph node invasion according to Partin nomogram was estimated to occur in LR = 1%, MR = 2%, and HR = 7.5%. Lymph node invasion according to Briganti nomogram was assessed to exist in LR = 1.8%, MR = 11.4%, and HR = 44.2%. In final examination, it was discovered in LR = 1.3%, MR = 0%, and HR = 11.6% (Table 3).

Prostate cancer grading

In ERPSC 4, average risk for high-grade (HG) cancer, defined as Gleason grade ≥7, was LR = 5%, MR = 21%, and HR = 64%. In PCPT 2.0, average risk for HG was LR = 8%, MR = 14%, and HR = 30%. In final pathology results, HG was observed in LR = 29%, MR = 67%, and HR = 81% (Table 4).

Misguiding of prostate cancer grade

As for ERSPC 4 upgrading of Gleason score in accordance to prior biopsy outcome was overall 29% and in groups: LR = 23%, MR = 31%, and HR = 33%. Downgrading of Gleason score was overall 13%, LR = 8%, MR = 15%, and HR = 16%.
As for PCPT 2.0 upgrading of Gleason score in accordance to prior biopsy outcome was overall 38% and in groups: LR = 28%, MR = 46%, and HR = 41%. Downgrading of Gleason score was overall 26%, LR = 23%, MR = 26%, and HR = 30% (Table 5).

DISCUSSION

PSA is thought to be the best marker for detecting early PCa [10]. However, elevated levels of PSA are not a characteristic feature only for PCa, but can

also be caused by prostate inflammation, bigger prostate volume or after ejaculation (for about 24 hours) [11, 12]. It is of high importance to perform PCa screening as a considerable reduction in PCa mortality associated with PSA testing has been confirmed [12]. Risk calculators can be used as a more accurate method of diagnosis of PCa than PSA by itself because in addition to PSA levels they also include other factors such as prostate volume, age or family history which leads to better accuracy of results.

Published trials show various results regarding the impact of PCa screening on mortality. There are suggestions in the literature that screening leads to overdetection and overtreatment of some patients [10]. Overdiagnosis and overtreatment are associated with treatment-related side effects [13]. Unfortunately, the role of screening is unclear and performed studies are heavily biased. Clinicians and patients regarding PSA based screening need to consider if benefits overbalance potential short and long term adverse effects of that procedure [14]. Proper usage of calculators might be helpful in that field. Applying additional factors results in bigger precision of outcomes than PSA level alone. There is a place for calculators in the process of screening and planning therapy, however the effectiveness of risk calculators still needs to be improved. This is an effort worth making as a study shows that a simple risk stratification tool combined with a highly sensitive pathologic biopsy classification might result in a considerable decrease of unnecessary biopsies and overdiagnosis of potentially indolent disease [15]. On the other hand, high score of ERSPC 4 and PCPT 2.0 correlates with higher incidence of HGPCa so this may be an indication to perform such biopsy, especially since an abnormal DRE is associated with an increased risk of higher GS [16].

One of the limitations of this study might be use of transrectal ultrasound-guided biopsy.

It is the most common method of obtaining prostate samples [17]. Yet it does have major disadvantages as it is not obtained from specific lesions, since the majority of prostate tumours are not possible to depict or have non-specific appearances on ultrasound [18]. Targeted biopsy through magnetic resonance imaging (MRI) guidance or MRI-ultrasound fusion offers a way to localize and sample suspected cancers with precision [19]. Owing to this fact, use of fused MRI biopsy would lead to decrease of up- and downgrading percentage among patients. Combination of MRI targeted biopsy and risk calculators can be a great option for clinicians in planning therapeutic management. That is probably the way that development and usage of estimators should go.

Partin nomogram can help with deciding on further therapeutic options as it can anticipate local advancement and metastasis in lymph nodes [20]. Assessing the risk decreases the risk of overtreatment and possible complications. Briganti and Partin nomograms might be used to identify patients who should be qualified to an extended pelvic lymph node dissection (ePLND). Their involvement shall help in avoiding unnecessary ePLND in patients that will not benefit from this procedure [21]. The Briganti calculator has been documented to have a high precision in predicting LNI but as opposed to the study by Walz et al., was less accurate in our study population [22]. Nevertheless, it was proven to have a clinical significance. Hansen et al. performed a study proving that updated Briganti nomogram is applicable and accurate for different European cohorts [23]. Also, the outcome of the Hinev et al. study demonstrates prevalence of Briganti over other similar nomograms [24].

CONCLUSIONS

Our results are comparable to previously conducted studies. All the analysed calculators showed positive correlation with risk increase in every examined parameter. ERPSC 4 and PCPT 2.0 calculators corresponded well with each other. ERPSC 4 was more accurate in predicting high-grade prostate cancer among our study population than PCPT 2.0. Partin and Briganti nomograms corresponded well with each other. Partin nomogram was more accurate in our study population as for lymph node invasion than Briganti calculator.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DECLARATION

Approval was obtained from the ethics committee of Bioethics Committee of the Nicolaus Copernicus University in Toruń functioning at Collegium Medicum in Bydgoszcz. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Informed consent was obtained from all individual participants included in the study.

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