RETROSPECTIVE ANALYSIS

The use of European Randomized study of Screening for Prostate Cancer calculator as a diagnostic tool for prostate biopsy indication

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ABSTRACT

BACKGROUND: It is a well-known fact, that too many men are having prostate biopsy performed with negative biopsy results. The decision to undertake prostate biopsy is usually based on prostate specific antigen (PSA) level and digital rectal examination (DRE). A risk-based strategy may reduce the numbers of unnecessary prostate biopsies.

METHODS: Retrospective statistical analysis of data from 195 men undergoing their initial prostate biopsy from 1.1.2015 to 31.12.2015 based on elevated PSA ≥ 4.0 ng/ml and/or abnormal DRE were included. Subsequent risk stratification using the European Randomized study of Screening for Prostate Cancer calculator (ERSPC) was used with the intent to calculate the accuracy of ERSPC with the aim to avoid unnecessary (negative) prostate biopsies.

RESULTS: The specific values of sensitivity and specificity in this cohort were 94.34 % and 24.72 %. In direct comparison of PSA and ERSPC calculator, the differences between sensitivity, specificity, negative predictive value and false omission rate as negative were statistically insignificant, but the positive predictive value was on the edge of statistical significance (p = 0.054), slightly in favor for ERSPC calculator.

CONCLUSION: PSA still remains the single most predictive factor for identifying men with an increased risk of prostate cancer to be detected on prostate biopsy, but using other risk factors included in ERSPC can considerably reduce the numbers of unnecessary biopsies on initial screening *(Tab. 4, Fig. 2, Ref. 23)*. Text in PDF *www.elis.sk*.

KEY WORDS: prostate, biopsy, risk, antigen.

Introduction

Prostate cancer is the most common malignant disease of other origin than skin cancer in elderly men (over 70 years of age) in Europe (1). Globally, it is the second most commonly diagnosed malignant disease and the sixth most common cause of death for malignancy in men, while 14 % of newly diagnosed malignant diseases worldwide and 6 % of cancer related deaths are due to prostate cancer (2, 3).

Prostate cancer has variable course from indolent forms to an extremely aggressive disease. At present, we are expecting a breakthrough in early diagnostics of clinically significant tumors, which could secure an early treatment before advanced stages of the disease develop. In general, two approaches are valid options for early diagnostics: screening of every man of certain age or se-

lective screening based on the risk group. Mass screening is not recommended at present, even though the number of evidence increases in favor of such screening (4, 5).

The third analysis of mortality due to prostate cancer in ERSPC study, published in Lancet, august 2014 (4) showed an absolute benefit in prolonging the observing interval to 13 years (2 more years added in comparison with the previous report). ERSPC is the largest randomized trial of prostate cancer, involving 162 388 men and 900 prostate cancer related deaths. Screening during this study was based on PSA testing every 2–4 years in the intervention arm and no screening was provided to patients in the control arm. ERSPC initially proved a significant reduction of prostate cancer related death after 9 and 11 years of follow up (4, 5, 6). The most recent published results of prolonged survival with two more years added up to 13 years showed a reduction of absolute prostate cancer related death in the screening arm with a ratio of the total number of men needed to be invited to the screening – 781 (NNI) to 27 diagnosed carcinomas of prostate (number needed to detect (NND)) in prevention of single death related to prostate cancer. These ratios were significantly lower after 13 years than the ratios published in the previous results after 9 (NNI 1410, NND 48) and 11 years (NNI 979, NND 35) (Tab. 1) (4). This showed a significant benefit over the previous results, but the main insuffi-

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Tab. 1. Numbers of patients needed to be invited and numbers needed to be diagnosed in the prevention of single death related to prostate cancer from ERSPC (3).

Years of surveillance	NNI	NND
9	1419	48
11	979	35
13	781	27

NNI – numbers of patients needed to be invited, NND – numbers needed to be diagnosed

ciency of the screening is the diagnosis of clinically insignificant carcinomas and these results were inadequate to introduce across the board screening, because we still need quantification of risks related to over-diagnosing and connected treatment.

Currently, even though the meaning of diagnostic multi-parametric magnetic resonance imaging (mpMRI) is increasing, the main indication for prostate biopsy relates to PSA evaluation and digital rectal examination. Abnormal digital rectal examination remains an absolute indication to prostate biopsy, but with normal "benign" finding, PSA evaluation remains as a not quite accurate tool. In the past, the generally accepted limit PSA value was 4 ng/ml (7), but this accepted value was decreased by the same science team after six years to the recommended value of 2.5 ng/ml (8). At present, the generally accepted values are limited between 2.5–3.0 ng/ml, mainly in young men. The number of false positive patients and thus unnecessary biopsies remains an ongoing problem. If only PSA is applied as a biopsy indicator (PSA ≥ 3.0 ng/ml), almost 76 % of these biopsies are negative in the result (6). Data from Prostate Cancer Prevention Trial (PCPT) study showed that there is no limiting value for PSA, because of the specificity and sensitivity of the PSA test, but it is a continual spectrum of prostate cancer risk amongst practically any PSA value. If we consider Gleason score over 7 as a parameter of prostate cancer aggression, by using limiting value of 4 or 2, 59.6 % and 25.4 % of aggressive cancers would be missed (9).

ERSPC calculator

ERSPC calculator is not a single calculating tool, but a set of calculators for different clinical and diagnostic situations. Calcula-

tors 1 and 2 are meant for the general public and take into account values as age, family history, International Prostate Symptom Score (IPSS), PSA. Calculators 3–6 are meant for urologic professionals and have a different usage. Calculators 3 and 4 were by origin separate modules, which were then joined into a single module. Calculator 3 was formerly meant to evaluate the risk of prostate cancer in previously not biopsied men and calculator 4 for men, who already underwent prostate biopsy with a negative finding. These two calculators were joined together and a new module was added, which took into account the Prostate Health Index (PHI) value. The result is 4 modules for professionals and their review is described in Table 2.

External validation of ERSPC calculator reached the area under curve (AUC) values between 0.71 and 0.8 (10, 11). Direct correlation between ERSPC and PCPT calculator was in the favor of ERSPC (11) with AUC 0.71 for ERSPC calculator and 0.63 for PCPT model.

Patients and methods

To evaluate the risk, we used ERSPC calculator – simplified module 3 and 4, because of higher achieved values of AUC in validation. As the target group, men with newly diagnosed elevation of PSA, who underwent their first biopsy of prostate between 1.1.2015 -31.12.2015 in our department were chosen. We analyzed the retrospective data from medical documentation of 221 patients. Men with biopsy findings of atypical small acinar proliferation (ASAP) and high-grade prostatic intraepithelial neoplasia (HG-PIN) were excluded from the study. Also men with PSA > 50, "men on active surveillance" and men with previous prostate biopsy in the last 5 years were not included in this study. The limiting value of PSA to indicate biopsy prostate was 4.0 in men below 60 years; with positive family history, the limiting value of PSA was 2.5. After the fulfillment of the aforementioned criteria, 195 patients were included in the study.

Statistical analysis

Retrospectively, risk was evaluated using online ERSPC calculator by implementing the required values of this cohort. Basic statistical analysis was performed with calculation receiver op-

Tab. 2. Review of modules of ERSPC calculator.

	ERSPC Calculator 3 and 4 (united)	ERSPC Calculator 3 and 4 (united) with PHI	ERSPC Calculator 5	ERSPC Calculator 6
Use	Calculating the risk of prostate cancer detection by biopsy	Calculating the risk of prostate cancer detection by biopsy considering the value of PHI	Calculating the chance of indolent prostate carcinoma, which does not require immediate treatment	Calculating the future risk in the next 4 years
Used values	PSA, previous biopsy, DRE finding, TRUS volume of prostate, TRUS structure	PSA, previous biopsy, DRE finding, TRUS volume of prostate, TRUS structure, PHI	Gleason score, mm of carcinoma in biopsy samples from prostate, mm of healthy tissue in biopsy samples from prostate, TRUS volume of prostate, PSA	Age, PSA, DRE finding, Family history, TRUS volume, Previous biopsy

ERSPC – European Randomized study of Screening for Prostate Cancer, PSA – prostate specific antigen, DRE – digital rectal examination, TRUS – transrectal ultrasound, PHI – prostate health index

erating characteristic values (ROC) for risk calculator and also PSA for the whole group. The cohort was divided into 16 groups according to evaluated risk. Given that, from the clinical point of view, the most important risk group was between 10–40 % (13), closer analysis was done by comparison of sensitivity, specificity, positive and negative predictive value and false omission rate (FOR). All evaluations were implemented to biopsy samples with limiting value of PSA 4 ng/ml. Thus, the results were relative.

Results

195 patients out of 221 fulfilled the aforementioned criteria for analysis. Prostate carcinoma was diagnosed in 105 patients (54.36 %) after the first prostate biopsy. 74 (69.81 %) out of this group had Gleason score ≥ 7. Closer cohort characteristics are mentioned in Table 3.

ROC curves for PSA, calculated ERSPC risk, age, and transrectal ultrasound (TRUS) measured volume in correlation with positive histological finding of carcinoma were evaluated. As we can see in the Figure 1, the results for ROC curves were in favor of ERSPC calculator, but these were evaluated out of all possible calculated risk groups, not only from concrete clinically significant risk interval. The usage of high limiting risk > 30–40 % did

Tab. 3. Cohort characteristics.

	Cohort	Negative biopsy	Positive biopsy
Total number (%)	195 (100)	89 (45.64)	106 (54.36)
Age, median (range)	66 (46–83)	65 (50–79)	67(46–83)
Age, Number (%)			
< 50	2 (1.03)	0 (0.00)	2 (1.89)
50–59	32 (16.41)	20 (22.47)	12 (11.32)
60–69	92 (47.18)	41 (46.07)	51 (48.11)
70–79	67 (34.36)	28 (31.46)	39 (36.79)
≥ 80	2 (1.03)	0 (0.00)	2 (1.89)
PSA, median (range)	9.63 (0.5–48)	7.16 (0.5–39.82)	11.91 (4.6–48)
PSA value, Number (%)			
< 2.5 ng/ml	3 (1.54)	3 (3.37)	0 (0.00)
2.5–4.0 ng/ml	4 (2.05)	3 (3.37)	1 (0.94)
4.01–10.00 ng/ml	102 (52.31)	59 (66.29)	43 (40.57)
10.01–20.00 ng/ml	58 (29.74)	21 (23.60)	37 (34.91)
> 20 ng/ml	28 (14.36)	3 (3.37)	25 (23.58)
DRE, Number (%)			
Normal	115 (58.97)	61 (68.54)	54 (50.94)
Abnormal	80 (41.03)	28 (31.46)	52 (49.06)
TRUS, Number (%)			
Normal	178 (91.28)	86 (96.63)	92 (86.79)
Abnormal	17 (8.72)	3 (3.37)	14 (13.21)
TRUS volume, median (range) ml	45 (11–200)	55 (11–150)	43 (21–200)
TRUS volume, Number (%)			
< 30 ml	30 (15.38)	11 (12.36)	19 (17.92)
30–59 ml	104 (53.33)	42 (47.19)	62 (58.49)
60–89 ml	42 (21.54)	22 (24.72)	20 (18.87)
90–119 ml	9 (4.62)	7 (7.87)	2 (1.89)
≥ 120 ml	10 (5.13)	7 (7.87)	3 (2.83)

PSA – prostate specific antigen, DRE – digital rectal examination, TRUS – transrectal ultrasound
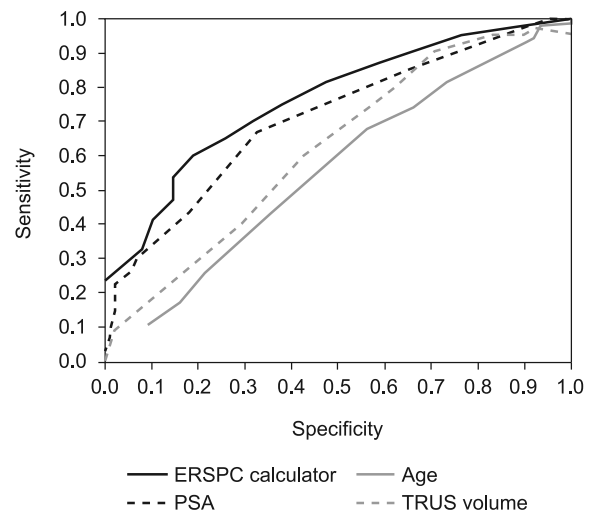
Fig. 1. Receiver operating characteristic curves for ERSPC calculator, PSA, Age and TRUS volume.
ERSPC – European Randomized study of Screening for Prostate Cancer; PSA – prostate specific antigen; TRUS – transrectal ultrasound
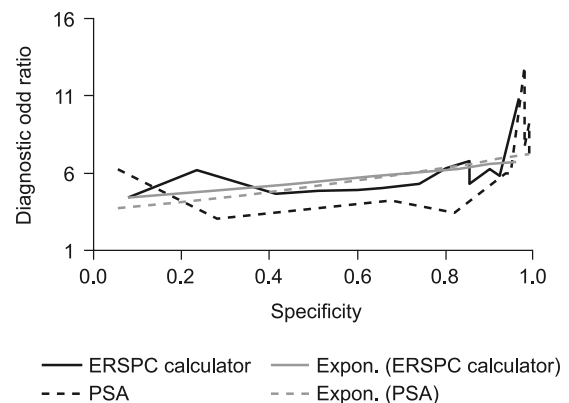
Fig. 2. Graphic representation of diagnostic odd ratio for ERSPC and PSA showing an evident benefit of ERSPC in the lower specificities.
ERSPC – European Randomized study of Screening for Prostate Cancer; PSA – prostate specific antigen

not have a real clinical impact and thus a selective evaluation of high-risk group was removed from the following analysis.

Concerning graphic representation of diagnostic odd ratio between PSA and ERSPC calculator, the evident benefit of ERSPC calculator is shown in the lower specificities, which did correlate with the usage of lower limiting risk values (i.e. value of 12.5 % recommended by Rotterdam group of prof. Schröder) (Fig. 2).

In decision about the indication for prostate biopsy, the limiting risk values recommended by prof. Schröder to consider prostate biopsy were in range of 12.5–20 % as relative indication, and value over 20 % for absolute biopsy indication (13).

In applying risk between 5–40 % relative values of sensitivity for ERSPC calculator were found as 65.09 % (for used limiting risk of ≥ 40 %) – 99.06 % (for used limiting risk ≥ 5 %) in PSA limit of 4 ng/ml. Gained values of specificity for ERSPC calculator usage were in range from 6.74 % (for limiting risk ≥ 5 %) –

Tab. 4. Gained relative statistical parameters of ERSPC calculator in different limiting risk values in comparison with PSA ≥ 4.0 ng/ml.

Limiting value	Sensitivity (%)	Specificity (%)	PPV (%)	FOR (%)
≥ 5%	99.06	6.74	55.85	1.12
≥ 12.5%	94.34	24.72	59.88	6.74
≥ 20%	83.96	42.70	63.57	19.10
≥ 40%	65.09	79.78	79.31	41.57
PSA ≥ 4.0	99.06	5.62	55.56	1.12

PSA – prostate specific antigen, PPV – positive predictive value, FOR – false omission rate

79.78 % (for limiting risk ≥ 40 %). By using the limit ≥ 4 ng/ml, PSA gained a value of relative sensitivity 99.06 % and specificity 5.62 % in this cohort (Tab. 4).

By using the lowest recommended 12.5% value as an instrument for prostate biopsy indication, the specific values of sensitivity and specificity in this cohort were 94.34 % and 24.72%. In direct comparison of PSA and ERSPC calculator, the differences between sensitivity, specificity, negative predictive value and false omission rate as negative were statistically insignificant, but the positive predictive value was on the edge of statistical significance (p = 0.054), slightly in favor for ERSPC calculator.

Discussion

As concluded by our results, it is not possible to clearly demonstrate the benefit of ERSPC calculator limited by PSA value 4.0 ng/ml. However, it is probable that it would be possible to show the benefit of ERSPC calculator in lower limiting PSA values of 3.0–3.5 ng/ml, which could lead to a decreased number of unnecessary prostate biopsies. A limiting value of PSA 4 ng/ml seems quite high, which testifies to the high number of carcinomas of prostate in our cohort. A study using lower limiting values of PSA (PSA ≥ 3.0) would be needed in order to prove the benefit of a risk calculator.

In the recent cohort, we could actually avoid 26 prostate biopsies (13.3 %) by using the calculated risk of 12.5 % as a limit for prostate biopsy indication. Yet in this case, the problem would be the remaining 5 prostate carcinomas, which would be missed and undetected using this calculator. Out of these 5 cases, 3 would be low risk disease with Gleason 3 + 3 and would not undergo immediate treatment, while 2 patients with intermediate risk Gleason 3 + 4 would be missed (after diagnosis, they underwent radiotherapy). All 5 undetected patients had „"arger" prostates (70–120 ml), while the middle value of prostate volume was 45 ml in the entire group.

Under evaluation of real risk was as well shown in the comparative study of PCPT and ERSPC calculators (12), published in European Urology 2010, which showed the under evaluation of real risk by ERSPC calculator and, on the other side, over evaluation of real risk by PCPT calculator. In usage of ERSPC calculator, it was an under evaluation only in calculated risk over 35 %. The under evaluation of real risk might have been reported due to the fact, that the results of ERSPC study were based on sextant prostate biopsy, while at present, the number of samples taken was commonly higher (10–12) (13).

To avoid the under evaluation of real risk by ERSPC calculator and to avoid false negative findings, we would consider decreasing the limit risk as indicator for prostate biopsy.

By using the PSA as the main indicator for prostate biopsy, its low specificity and related number of false positive results with „unnecessary" prostate biopsies remains a problem.

Using ERSPC calculator might help to reduce the amount of unnecessary biopsies and is recognized as a recommended diagnostic tool in European Association of Urology (EAU) Guidelines 2016 (14), according to which the risk evaluation in asymptomatic men with PSA 2–10 ng/ml recommended before the prostate biopsy is one of following tools:

risk calculator,

other blood tests, urine sampling (PHI – prostate cancer antigen 3) or imaging methods.

Out of imaging methods, mpMRI is on the rise, which is recommended mostly before repeated prostate biopsies. In MRI, the main problem remains in the evaluation of mpMRI prostate slides, because of significant interpersonal variability. Implementing of Prostate Imaging Reporting and data System score (PIRADS) limits these interpersonal differences in the results, but is still an issue for consideration (15).

The problem in using SWOP (ERSPC) calculator remains in the amount of non-diagnosed prostate carcinomas in the recommended limit for prostate biopsy indication 12.5 %. There were 5 detections of evaded prostate carcinomas in this cohort, out of which minimally in the two it would be clinically significant. On the other hand, an evasion of diagnosis could also be caused by using only PSA and DRE evaluation, because PSA, if used with lower limit values, is not 100 % sensitive (16). The problem of decreasing the limit of PSA is obviously its correlation with a decrease of specificity as well as an increase of false positive tests with "unnecessary" prostate biopsies. It is also possible that the sensitivity of SWOP calculator could be higher in some clinical scenarios than sensitivity of PSA and DRE; mainly in cases of small prostate volume and low level of PSA.

In future, it would certainly be interesting to focus on the usage of calculator, particularly in cases of specific prostate volumes, where the usage of calculator might be wider and potentially with a higher sensitivity and specificity than PSA.

Furthermore, the usage of module 5 and 6 are potentially interesting. Module 5 – to detect indolent carcinomas – will hopefully receive validation in the ongoing PRIAS study. PRIAS study is aimed at men with potentially indolent disease on active surveillance. Healthy men with the ability to undergo active treatment PSA < 10 ng/ml, PSA density < 0,2, positivity of 1–2 samples in prostate biopsy, Gleason score 3+3 and DRE in correlation with T1c or T2 were included in this program.

Module 6 – a module to predict the future risk – might be helpful in planning following the screening evaluations in men (17), but this must be a topic in an external validation.

The problem of low specificity can be, on the other hand, solved by using new technologies such as: mpMRI-TRUS fusion biopsy, either transrectal or transperineal (18). Also, the importance of pre-bioptic mpMRI and following fusion mpMRI-TRUS

biopsy, or cognitive lead biopsy is increasing (19). Recent results comparing the mpMRI-TRUS fusion biopsies with histological results of samples after radical prostatectomies showed that mpMRI only identified 92 % of lesions, and a combination of focused and systematic biopsy confidently identified 97 % of lesions (18). The disadvantage of this approach is an increased detection of clinically insignificant prostate carcinomas

Diagnostic accuracy of mpMRI was proven by the recent PROMIS study published in The Lancet, which showed that 1/4 of unnecessary prostate biopsy can be avoided based on a negative finding on mpMRI and thus prevent possible side effects resulting from the biopsy (20). The disadvantage of this approach might be an issue with availability and capacity of mpMRI, mostly in regional departments, where using the calculator might help. The economic impact of overall usage of pre-bioptic MRI is not known.

In conclusion, PSA persists as the most important single predictive factor of prostate carcinoma mainly in men with no other risk factors (21, 22). Even though the previous retrospective data (13) referred to the usage of a strategy based on risk in indication for prostate biopsy, other results, such as the amount of unnecessary over diagnosed clinically, non-significant prostate cancers and impact on mortality reduction remains unclear (23).

When using SWOP calculator risk, it is required to think of possible risk under evaluation because this calculator was developed on a basis of histological samples of sextant biopsies. Caution is required in larger prostates, but usage of the calculator can in fact lead to a decreased number of unnecessary prostate biopsies. This is important not only because of unpleasant intervention for men, but also because of an increased antibiotic microbial resistance and possible septic complications after transrectal prostate biopsies.

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