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Outcomes and predictors of clinically significant prostate cancer detection by transperineal computer fusion biopsy during active surveillance

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Introduction Active surveillance (AS) is an option for management of low-risk and selected intermediate prostate cancer (PC) patients. Pathological progression confirmed on prostate biopsy (PB) is the most common reason for transitioning to radical treatment. The role and timing of repeat PB during AS is a topic of ongoing debate.

The aim of the study was to determine the detection rate of clinically significant PC (csPC) during AS protocol by transperineal computer fusion PB in low-risk PC patients enrolled based on results of transrectal systematic PB, and to identify predictors that may impact csPC detection.

Material and methods The study involved 95 patients with low-risk PC enrolled in AS, who underwent confirmatory or follow-up PB, proceeded by mpMRI.

Results The reclassification rate to csPC was 38.9% and 43.9% for confirmatory and follow-up biopsies, respectively. Patients with csPC differed significantly from those without csPC in the following parameters: prostate-specific antigen (PSA) 10.5 ng/ml vs 7.3 ng/ml (p = 0.029), PSA density (PSAD) 0.27 ng/ml^2 vs 0.18 ng/ml^2 (p = 0.006), age – 68 years vs 66.5 years (p = 0.024), lesion size 16 mm vs 14 mm (p = 0.042), and PIRADS score (p = 0.004). Multivariable regression models showed that PIRADS score each one-category increase hazard ratio (HR) – 3.615 (1.599–8.172), PSAD >0.20 ng/ml^2; HR – 2.760 (1.065–7.149) and age; HR – 1.085 (1.011–1.164) were independent factors increasing the probability of csPC detection in PB.

Conclusions Confirmatory and repeat transperineal PB detect a significant rate of csPC in low-risk PC patients on AS. Higher PIRADS score and PSAD >0.20 ng/ml^2 increase the csPC detection rates during AS and should prompt immediate PB.

Key Words: active surveillance ‹› prostate fusion biopsy ‹› prostate cancer ‹› multiparametric magnetic resonance

INTRODUCTION

Active surveillance (AS) is the preferred management option in prostate cancer (PC) patients with low-risk of disease progression and an expected survival of at least 10 years [1]. The undisputed benefit associated with AS is primarily the possibility of avoiding radical treatment, which carries the risk of complications and impacts the quality of life [2, 3]. Results of prospective studies with a 10-year observation time indicate, that AS protocol was associated with a slightly higher risk of distant metastases compared to radical treatment (6% vs 2%), but no significant difference in PC-specific survival was observed [4]

Current criteria for qualification for AS include prostate biopsy (PB) results (Gleason score, number

of positive cores, or the maximum percentage core involvement), clinical stage, baseline PSA level, and multiparametric magnetic resonance (mpMRI) findings [5, 6]. To minimize the risk of progression, it is recommended to qualify for AS protocol based on a combined PB result, including targeted and systematic PB with computer fusion technique [7]. Justification for performing combined fusion PB lies in the possibility of inadequate sampling of PC foci in standard PB, which may result in underestimation of PC volume or Gleason score (sampling error) [8]. Therefore, in cases where AS strategy is initiated based solely on standard systematic PB results, it is recommended to perform confirmatory PB within a year, and it should be a combined computer fusion PB based on repeated mpMRI scans [9]. The AS protocol involves regular patient monitoring for PC to exclude any disease progression [10]. Within the AS protocol, periodic measurements of PSA levels, repeat DRE examinations and repeat mpMRI scans should be performed. Urological society guidelines recommend that follow-up biopsies should be performed roughly every 3 years or immediately if any abnormalities are found in follow-up examinations. However, there are no clearly defined criteria for qualification for immediate PB [11]. For example, there is no guidance on how to proceed in cases of biochemical progression (an increase in PSA level) with a stable mpMRI scan. Moreover, performed studies indicate a significant proportion of PC patients, ranging from 30% to 40%, who discontinued the AS in favor of radical treatment within a 3–5 year period due to Gleason score progression confirmed in follow-up PB [12, 13].

The aim of the study was to determine the detection rate of clinically significant PC (csPC) during AS protocol by transperineal computer fusion PB in low-risk PC patients, who were enrolled based on results of transrectal systematic PB, and to identify potential factors obtained before the procedure which may impact clinically csPC detection.

MATERIAL AND METHODS

Study population

We retrospectively analyzed patients, who underwent MRI ultrasound fusion PB at the ECZ Hospital Otwock, Poland, between November 2016 and June 2021. Finally, the study involved 95 patients enrolled in AS with low-risk PC (cT1a–cT2a, PSA <10 ng/ml, ISUP 1) who underwent confirmatory PB or follow-up PB. The results of PB and the following parameters obtained before PB were analyzed: PSA, PSA density (PSAD), prostate volume, PIRADS score, MRI lesion diameter, lesion location, and DRE status. CsPC was defined as ISUP 2 or more.

Prostate biopsy

Each PB was proceeded by mpMRI and assessed on the PIRADS 2.1 scale. If more than one lesion was present at mpMRI, the index lesion was defined as the highest PI-RADS assessment category or the largest lesion in case of more than one within the same category. PB was performed by a transperineal approach using Trinity Koelis® navigation system (Koelis, France) under local anesthesia. Biopsies involved: two-three targeted cores from mpMRI lesion, and twelve systematic cores from the non-targeted area. CsPC was defined as ISUP 2 or more.

Statistical analysis

The outcomes of this study were the detection rates of csPC (ISUP 2 or more). Non-normally distributed continuous variables were reported as medians (Me) with the interquartile range (IQR) and compared using the Mann–Whitney U test. PSAD was calculated using PSA divided by the MRI-derived prostate volume (ellipsoid method). Youden's index (sensitivity + specificity-1) for identification of the optimum cut-off point for PSAD was used as a predictor of csPC detection. Categorical variables were reported as frequencies and proportions. Differences in rates were tested by the chi-square test. Univariable and multivariable regression models were performed to evaluate predictors of csPC detection in SB and TB. Odds ratio (OR), 95% confidence interval (95% CI) of odds ratio, and p-values were recorded. The receiver operating characteristic (ROC) curves for diagnosis of csPC by PSA and PSAD were analyzed. A p-value of < 0.05 was considered significant. SPSS© software (SPSS statistics 25) was used for statistical analysis.

Bioethical standards

The study did not require approval from the bioethics committee.

RESULTS

Characteristics of the group and comparison of clinical data – non-clinically significant vs clinically significant prostate cancer

CsPC was diagnosed in 41% (39/95) of cases (Table 1). The rate of reclassification to csPC was 38.9% (21/54) for confirmatory PB and 43.9% (18/41) for follow-up PB, respectively. Patients with csPC differed

statistically significantly from those without csPC in the following parameters: PSA level – 10.5 ng/ml vs 7.3 ng/ml (p = 0.029), PSAD – 0.27 ng/ml^2 vs 0.18 ng/ml^2 (p = 0.006), age – 68 years vs 66.5 years (p = 0.024), lesion size 16 mm vs 14 mm (p = 0.042) and PIRADS score (p = 0.004). There were no significant differences between the above groups in: DRE results (p = 0.35), the zone location of the dominant lesion – peripheral vs non-peripheral (p = 0.68), MRI prostate volume – 39 ml vs 41 ml (p = 0.435) and PB history: confirmatory vs follow up (p = 0.677). The AUC for diagnosis of csPC via PSAD was 0.692 (95% CI: 0.585–0.798, p = 0.002). The highest Youden's index was at a PSAD level of 0.20 ng/ml^2. At this point, the diagnosis of csPC had 67% sensitivity and 59% specificity.

Clinical factors impacting the detection of clinically significant prostate cancer

In univariable regression analysis, it was shown that: age (lineal): hazard ratio (HR) – 1.076 (1.008–1.150), categorized PSAD level >0.20 ng/ml^2: HR – 2.417 (1.024-5.703), PI-RADS score (increase each one category) HR – 3.377 (1.589–7.178), and maximal diameter of index lesion in mpMRI (lineal): HR – 1.060 (1.001–1.122) were significant factors increasing the probability of csPC detection in PB (Table 2). In multivariable regression analysis it was shown that PIRADS score (increase each one category); HR – 3.615 (1.599–8.172), PSAD >0.20 ng/ml^2; HR – 2.760 (1.065–7.149) and age; HR – 1.085 (1.011–1.164) were independent factors increasing the probability of csPC detection in PB.

DISCUSSION

The study's objective was to determine the detection rate of csPC during an AS protocol using transperineal computer fusion PB. Additionally, the goal was to identify pre-procedural factors that could impact the detection of csPC. Current study revealed that among 95 men on AS, the rate of reclassification to csPC was 38.9% (21/54) for confirmatory PB and 43.9% (18/41) for follow-up PB, respectively. Patients with csPC and those without csPC showed a statistically significant difference in the PIRADS score (p = 0.004). In the multivariable regression analysis, it was revealed that for each one-category increase in the PIRADS score, the HR was 3.615 (1.599–8.172). Similar group sizes, study design were present in research of Osses et al. The reclassification rate to csPC

Table 1. *Characteristics of the groups*

Total n (%) or median (IQR)	Total (n = 95)	Non-csPC (n = 56)	csPC (n = 39)	Non-csPC vs csPC p-value
Age (years) median (IQR)	67.0 (62–71)	66.5 (61–69)	68 (64–73)	**0.024**
PSA [ng/ml] median (IQR)	8.5 (5.7–13.1)	7.3 (5.3–9.5)	10.5 (7.2–15.0)	**0.029**
PSAD [ng/ml^2] median (IQR)	0.23 (0.12–0.38)	0.18 (0.1–0.27)	0.27 (0.17–0.49)	**0.006**
DRE, n (%) Normal Abnormal	 84 (88.4) 11 (11.6)	 51 (91.1) 5 (8.9)	 33 (84.6) 6 (15.4)	0.350
Prostate volume [mm] median (IQR)	40.0 (32–58)	41 (32–59)	39 (28–55)	0.435
Maximal diameter of IL in mpMRI [mm] median (IQR)	16.0 (13–23)	14.0 (12–22)	16.0 (14–25)	**0.042**
mpMRI zone location, n (%) Peripheral zone Non-peripheral zone	 46 (48.4) 49 (51.6)	 26 (46.4) 30 (53.6)	 19 (48.7) 20 (51.3)	0.681
Pirads score, n (%) 3 4 5	 9 (9.5) 39 (41.5) 47 (49.5)	 8 (14.3) 28 (50.0) 20 (35.7)	 1 (2.6) 11 (28.2) 27 (69.2)	**0.004**
Biopsy Confirmatory Follow up	 54 (56.8) 41 (43.2)	 33 (58.9) 23 (41.1)	 21 (53.8) 18 (46.2)	0.677

csPC – clinically significant prostate cancer; DRE – digital rectal examination; mpMRI – multiparametric magnetic resonance; Non-csPC – non-clinically significant prostate cancer; PSA – prostate-specific antigen; PSAD – prostate-specific antigen density

Table 2. *Univariate and multivariate logistic regression model*

Parameter	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (lineal)	1.076 (1.008–1.150)	0.028	1.085 (1.011–1.164)	0.023
PSA (lineal)	1.051 (0.999–1.105)	0.053		
DRE Normal (ref) Abnormal (1)	1.855 (0.523–6.571)	0.339		
PSAD [ng/ml^2] <0.20 (ref) >0.20 (1)	2.417 (1.024–5.703)	0.044	**2.760 (1.065–7.149)**	**0.037**
Index lesion diameter (lineal)	1.060 (1.001–1.122)	0.047		
PIRADS (Increase of each category)	3.377 (1.589–7.178)	0.002	**3.615 (1.599–8.172)**	**0.002**

DRE – digital rectal examination; PIRADS – Prostate Imaging–Reporting and Data System; PSA – prostate-specific antigen; PSAD – prostate-specific antigen density

during AS in men with positive mpMRI findings was 48% (30/63), significantly higher than 10% (5/48) observed in those with negative mpMRI results [14]. Among mpMRI-positive men, 23% (7 of 30) experienced upgrading through targeted PB alone, while 33% (10/30) underwent upgrading solely through systematic PB. In another study individuals with PI-RADS 4 and 5 lesions exhibited a greater probability of GG ≥2 compared to patients with PI-RADS 1-3 lesions [15]. In the PRIAS study, a significant number of patients underwent reclassification to GG 2 and 3 during AS [16]. This change was observed in 30 (6%) and 5 (1%) patients with negative mpMRI results, and in 296 (29%) and 101 (10%) patients with PIRADS ≥3, respectively. In fact, PIRADS 5 was associated with 4.95 (95% CI: 3.25–7.56) higher fold of GG reclassification in comparison to negative mpMRI. In this study, several prognostic factors were mentioned; however, it was emphasized that the mpMRI result was the strongest among them. The results of the PRIAS study were consistent with ours, despite significant differences between this study and ours.

Another study by Doan et al. supports our results and indicates that mpMRI findings were significant predictors for PC progression [17]. In the study by Beksac et al. the obtained HR regarding the detection of csPCa for PIRADS 4 and 5 was 4.11 (95% CI: 1.79–9.44, p = 0.0009) [18]. Despite significant differences in the populations studied, these results are similar to our study. Patients in the Beksac et al. study were younger (62.1 years old), with, on average, lower PSA levels (5.0 ng/ml) and PSAD (0.09 ng/ml^2) compared to our cohort. However, like our study, it was demonstrated that a higher PIRADS score was an independent prognostic factor for csPC detection. On the other hand, in the study of Chesnut et al., the PIRADS score increased in 48 (23%) cases, decreased in 27 (13%) cases, and remained unchanged in 132 (64%) cases [19]. The progression of the PIRADS score was not linked to the risk of reclassification from PC to csPC. As a conclusion, performing PB solely based on a progression of the PIRADS score would lead to missing a substantial amount of csPC.

The SR and meta-analysis by Rajwa et al. analyzed 15 studies on 2,240 patients [20]. The pooled rate of PC progression, encompassing histological progression to Gleason grade 2 or higher, was 27%. Depending on PC progression prevalence, the pooled negative predictive value for serial prostate mpMRI ranged from 0.81 (95% CI: 0.73–0.88) to 0.88 (95% CI: 0.83–0.93). Even with a high negative predictive value, mpMRI lacks sufficient precision to definitively rule out PC progression during AS. Therefore, it should not be the sole trigger for PB but must be considered alongside with other clinical factors in the decision-making process. According to the current EAU guidelines: during AS follow-up, individuals with mpMRI findings of PI-RADS 1–2 and a low PSAD (<0.15) may be spared from undergoing repeat PB. Nevertheless, it's important to note that the recommendation's strength is weak. This indicates a lack of sufficient robust data in the literature regarding this issue. In the SR of Willemse et al., a limited number of the included studies (14%) specified the utilization of mpMRI in their protocols.

Apart from the PIRADS score, various other potential predictors of upgrading PC to csPC are being explored. These include PSA, PSAD, DRE status, lesion location, and prostate volume. The EAU guidelines mention a low PSAD as a possible factor contributing to a low progression rate; however, no direct recommendations regarding PSAD are es-

tablished [1]. In our study, in the non-csPC group, the median PSAD was 0.23, while in the csPC group, it was 0.37. PSAD >0.2 was associated with 2.417 (1.024–5.703) higher risk of csPC detection during AS. Our results are consistent with recent literature results. In SR of Rajwa et al. the PSAD falls within the range of 0.06 to 0.27 [20]. Author suggests that the addition of PSAD to mpMRI may support the decision process. In the study of Blute [21], populations of AS from Johns Hopkins University and the University of Wisconsin were analyzed, including risk factors for reclassification. In these patients, the PSAD HR was 1.28 (95% CI: 1.06–1.56) for Johns Hopkins University and 3.38 (95% CI: 1.45–7.84) for the University of Wisconsin. PSAD was used as one of the components of the nomogram without taking into account the MRI result. The inclusion criteria for the study were more stringent (PSA <10 ng/ml, ≤2 positive cores on transrectal prostate biopsy) than in our study. In another study mentioned above, the prognostic significance of PSAD for the detection of csPCa was also demonstrated. The obtained HR was 1.09 (95% CI: 1.05–1.13, p <0.0001), notably lower than in our study. This difference could be attributed to variations in the mean PSAD values within each group: non-upgrading 0.08 vs 0.23 and up-grading 0.12 vs 0.37 (Beksac vs Milecki) [18].

The EAU guidelines indicate that low PSAD might be linked to a lower progression rate. Moreover, individuals with PI-RADS 1–2 findings on mpMRI and a PSAD below 0.15 may be spared from undergoing a repeat PB [1]. Similarly, the AUA guidelines make a similar statement, but they emphasize the continuous nature of risk associated with the spectrum of PSAD values. They also advise against relying solely on threshold values [22]. Nevertheless, cutoff thresholds are extremely helpful and desirable in everyday clinical practice and decision-making. Currently, there is a lack of data in the literature regarding the ranges of PSAD values and the associated risk of reclassification. Correlating this information with other risk factors could significantly help in decision-making about when to perform a repeat PB in a patient.

Surprisingly, DRE did not play a significant role. Frequent DRE during AS is still recommended [10]. However, recently, it has become a subject of debate. According to the expert panel, performing DRE is unnecessary when mpMRI or other routine imaging (e.g. transrectal ultrasonography) is conducted during AS [23]. The literature lacks robust data regarding the significance of DRE during AS.

The limitations of this study include, firstly, its retrospective nature. Secondly, patients were enrolled in AS based on systematic PB, which is a suboptimal option. Thirdly, the study involved a small group of participants, including the absence of patients with PIRADS 1–2 results. Fourthly, the examination did not assess changes in parameters over time from the initiation of AS. Fifthly, mpMRI results were obtained from various imaging facilities and were assessed by different radiologists. However, it can be considered a partial limitation. This situation better reflects real-world clinical practice, where access to radiologists specialized primarily in uro-radiology is not always guaranteed. Sixthly, the study did not take into account the genetic predispositions to prostate cancer. This factor was also not considered in the vast majority of the aforementioned studies, although it is an element of undeniable significance and certainly warrants further research [24, 25]. On the other hand, access to genetic testing is also very limited in many centers.

CONCLUSIONS

Confirmatory and repeat TP fusion computer PB has a significant detection rate of csPC in low-risk PC patients enrolled in AS based on transrectal systematic PB. PIRADS scores emerged as robust indicators, with higher scores associated with an elevated risk of reclassification. The incorporation of pre-procedural factors such as PSAD and the patient's age further contributed to the nuanced decision-making process. These findings emphasize the clinical relevance of our approach in identifying and managing patients at higher risk of progression, highlighting the potential for more targeted and effective interventions during AS.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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