Prostate Biopsy Results in the PSA Gray Zone: A Five-Year Retrospective Study

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SUMMARY

Our aim was to analyze and compare the diagnostic efficacy of systematic and targeted + systematic prostate biopsies in patients with prostate-specific antigen (PSA) levels of 4–10 ng/mL.

A retrospective study was conducted at University Hospital Centre Zagreb by analyzing biopsy data from 2018 to 2023. A total of 2,466 patients met the inclusion criteria, undergoing either a systematic (n = 1,900) or a combined targeted + systematic biopsy (n = 566). Targeted biopsies were performed for patients with a Prostate Imaging-Reporting and Data System (PIRADS) score ≥ 3 on multiparametric magnetic resonance imaging (mpMRI). Cancer detection rates and Gleason score (GS) distributions were evaluated.

Prostate cancer (PC) was diagnosed in 41% of the study cohort. The detection rate was higher in the targeted + systematic biopsy group (54.7%) than in the systematic biopsy group (38.2%). Among biopsy-naïve patients, targeted + systematic biopsy yielded a detection rate of 72.7%, significantly higher than systematic biopsy alone (42.1%). Clinically significant PC (ISUP ≥ 2) was detected in 35.2% of all cases, with targeted biopsies identifying a higher proportion of clinically significant tumors. Operator bias was observed, as systematic cores in targeted biopsy patients often contained malignant cells.

The combination of targeted and systematic biopsies demonstrated the highest detection rate of clinically significant prostate cancer, particularly in biopsy-naïve patients. Given the increasing use of mpMRI, this approach should be considered the method of choice for patients with elevated PSA levels. Future studies should assess the financial feasibility of widespread mpMRI implementation in prostate cancer diagnostics.

KEYWORDS

Multiparametric magnetic resonance imaging for prostate; *Prostate-specific antigen*; *Prostate biopsy*; *Prostate cancer*

Introduction

Prostate cancer (PC) is a major public health issue worldwide. PC ranks among the most prevalent carcinomas and is the second leading cause of cancer-related mortality in men globally[1]. In 2020, the incidence of prostate cancer in Croatia was 50.2 per 100,000 men (standardized world rate), with a total of 2,299 new cases recorded. Among all male cancer patients, prostate cancer accounted for 19%, making it the most common malignant tumor among men in the Republic of Croatia. In the same year, 785 patients died from prostate cancer, resulting in a mortality-to-incidence ratio of 0.34[2].

Given that there is no single diagnostic test for prostate cancer, doctors rely on combinations of various diagnostic procedures. The most accessible, inexpensive, and also the oldest diagnostic method is digital rectal examination (DRE)[3]. According to research by Naji et al.[4], DRE is not recommended as a screening method for PC. Another diagnostic method, and the one more frequently used, is the measurement of prostate-specific antigen (PSA) levels in men. Combined with the extended lifespan of individuals, this method has resulted in an increased detection of prostate cancer in older men[5]. A PSA level above 4 ng/mL requires further investigation[6]. In patients with PSA levels between 4 and 10 ng/mL, the risk of having PC is approximately 25%[7]. The mentioned PSA values are referred to as the "gray zone"[8]. PSA values above 10 ng/mL increase the risk of having prostate cancer to 50%[7]. However, elevated PSA levels (> 4 ng/mL) can also be found in patients with other conditions, such as prostatitis and benign prostatic hyperplasia (BPH)[9]. Prostate biopsy stands as the gold standard for diagnosing PC[10]. Abnormalities in PSA or its derivatives are currently the most common indication for prostate biopsy[11]. Most patients diagnosed with PC nowadays do not exhibit palpable abnormalities on DRE. In response, transrectal ultrasound-guided biopsies have become more systematic rather than lesion-specific[11,12].

In 1989, Hodge et al.[13] introduced the traditional sextant biopsy method, which involved collecting six cores. However, this method has later been modified due to its relatively low sensitivity[14]. Today, various biopsy schemes exist with different numbers of cores taken, ranging from the traditional sextant with 6 cores to saturation biopsy with 24 cores[10]. Currently, the most commonly used method for initial PC diagnosis and grading is a 12-core transrectal ultrasound-guided systematic biopsy[15].

According to Eichler et al.[16], a 12-core schematic biopsy, which includes 6 traditional cores and 6 cores from the lateral zone, detects 31% more carcinomas than the traditional sextant method, while balancing carcinoma detection with adverse effects. Biopsy schemes with 18 to 24 cores did not show a statistically significant increase in carcinoma detection[16].

However, systematic biopsy is associated with missed cancer diagnoses and overtreatment of low-grade carcinomas due to concerns that high-grade cancer may have been missed[17]. PSA-based screening has reduced the prostate cancer mortality rate by 20%, but it has been associated with a high risk of overdiagnosis[18]. According to a study by Matoso and Epstein, patients with a Gleason score (GS) of 3 + 3, which includes fewer than two cores and less than 50% of the core sampled, and a PSA density of < 0.15 ng/ml per cm^3, had a minimal risk of clinically significant cancer[19].

Multiparametric magnetic resonance imaging (mpMRI), which integrates morphological assessment from T2-weighted imaging (T2WI) with diffusion-weighted imaging (DWI), dynamic contrast-enhanced imaging (DCE), and magnetic resonance spectroscopic imaging (MRSI), has been extensively studied in recent years[20-23]. Using mpMRI for targeted prostate biopsies has the potential to reduce sampling errors associated with conventional biopsy and provide better disease localization and sampling. MRI-ultrasound fusion-targeted prostate biopsy may improve the identification of clinically significant prostate cancer while limiting

the detection of indolent disease, leading to a more accurate risk stratification[24].

According to the Prostate MR Imaging Study, using mpMRI for triaging men could enable 27% of patients to avoid biopsy, while diagnosing 5% fewer clinically insignificant carcinomas. If subsequent transrectal ultrasound (TRUS) biopsies were guided by mpMRI findings, up to 18% more cases of clinically significant cancer could be detected compared to the standard TRUS biopsy method[25]. Among patients with mpMRI–visible lesions, combined biopsy has led to a better detection of all prostate cancers[17]. Studies have shown that biopsies targeted on mpMRI result in a higher rate of high-grade cancer detection than systematic biopsy[25,26].

However, despite the improved detection of clinically significant cancers with MRI-targeted biopsies, there is ongoing debate about whether MRI-targeted biopsy should replace or be combined with systematic biopsy[21,27-29]. Hansen et al. showed that the combined use of systematic and targeted biopsy was significantly better than targeted biopsies alone in detecting high-grade prostate cancer in patients with GS 7–10 and Prostate Imaging-Reporting and Data System (PIRADS) scores of 4 or 5[30]. Meta-analyses using random-effects models have shown that the positive predictive value for clinically significant prostate cancer was 8% for PIRADS 2, 13% for PIRADS 3, 40% for PIRADS 4, and 69% for PIRADS 5[31].

The European Association of Urology (EAU) recommends performing mpMRI before prostate biopsy in biopsy-naïve men. If there is a positive radiological finding and a PIRADS value ≥ 3, both targeted and systematic biopsy should be performed. In cases of persistent clinical suspicion, it is advisable to perform an mpMRI before repeating the biopsy. If the mpMRI is negative, a systematic biopsy should be conducted, whereas if the mpMRI is positive, only a targeted biopsy is recommended[32].

According to Ahmed et al., mpMRI-targeted biopsy has demonstrated higher sensitivity (87%) compared to ultrasound-guided biopsy (60%) and a greater negative predictive value (72% vs 65%) for detecting Gleason score 3 + 4 prostate cancer and higher. However, a negative mpMRI alone is currently not sufficient to omit prostate biopsy in biopsy-naïve patients, unless they are willing to accept a false-negative rate of 5–10%. Similarly, a positive mpMRI alone cannot currently replace biopsy[25]. The aim of this study was to analyze the results of different types of biopsies in patients with a PSA level of 4–10 ng/ml.

Materials and methods

In our retrospective study, data were collected from the hospital database on all transrectal prostate biopsies performed at the Department of Urology, University Hospital Centre Zagreb, during the period from January 4, 2018 to October 11, 2023. A total of 3,830 biopsies were conducted during this period, some on multiple occasions for certain patients. Both systematic and targeted biopsies were included in the study. Targeted biopsies were performed – using congnitive fusion targeting – if the lesion on mpMRI, interpreted following PIRADS version 2.1, was equal to or higher than 3 according to PIRADS. Systematic biopsies involved the standard 12-core biopsy technique, while targeted biopsies included a biopsy with 6 targeted cores distributed across up to 3 dominant regions based on the PIRADS lesion identified on mpMRI. Additionally, in targeted biopsies, 12 standard cores were also obtained.

The analyzed data included the biopsy date, patient age, the number of prior biopsies for each patient, the PSA value, biopsy type (targeted or systematic), the PIRADS score, the histopathology report, the positivity of targeted biopsies, the positivity of systematic biopsies, and the highest Gleason score.

The inclusion criterion was a PSA value between 4 and 10 ng/mL. Data were collected and analyzed using Microsoft Excel.

Results

Out of the 3,830 patients included in our study, 2,466 (64.4%) had a PSA value between 4 and 10, which was our inclusion criterion. Out of these, 1,900 (77%) underwent systematic biopsy, while 566 (23%) underwent targeted + systematic biopsy. Overall, 1,033 (42%) patients from the observed group (PSA 4–10) were diagnosed with prostate cancer, 552 of which had clinically significant prostate cancer (ISUP 2 or higher).

In the systematic biopsy group, prostate cancer was diagnosed in 38.2% of the patients (Figure 1). In the targeted + systematic biopsy group, prostate cancer was diagnosed in 54.7% of the patients (Figure 1). Among the 558 biopsies in the targeted + systematic group, 272 (48.7%) had PIRADS 3, 204 (36.6%) had PIRADS 4, and 82 (14.7%) had PIRADS 5 lesions on mpMRI. Of these, 38.7% of PIRADS 3, 61.9% of PIRADS 4, and 86.3% of PIRADS 5 biopsies were positive (Figure 2).

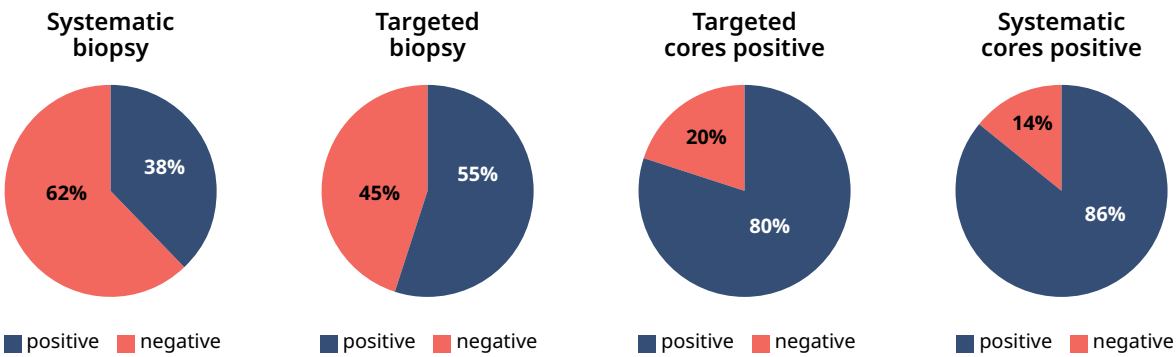

Fig. 1. Positivity rates of systematic and targeted biopsies, and positivity rates of targeted and systematic cores in targeted biopsies

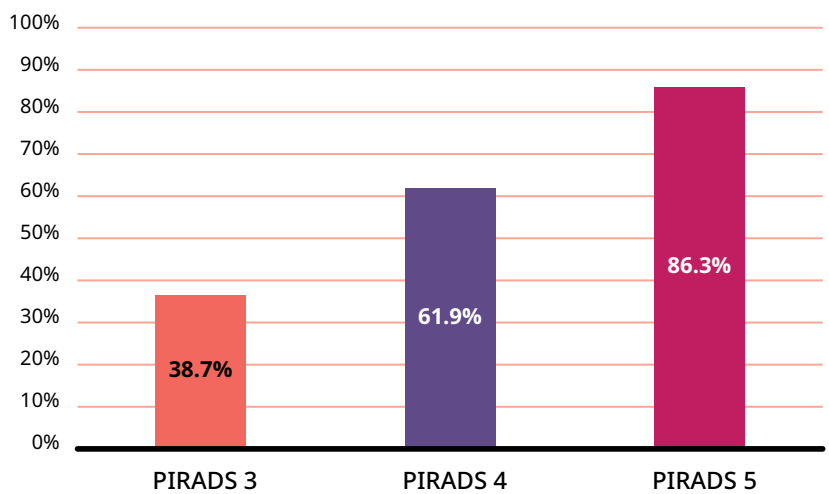

Fig. 2. Positivity dependent on PIRADS scores

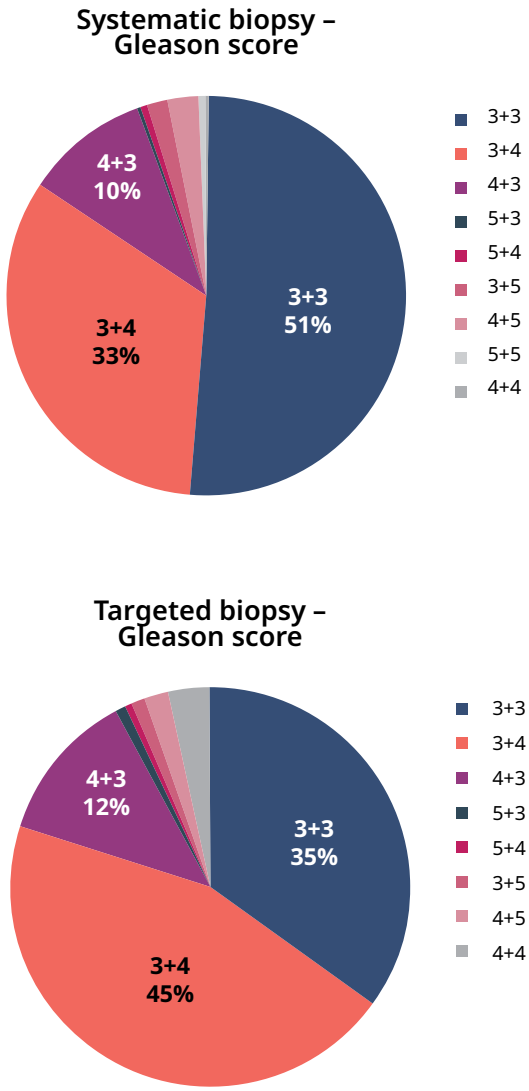

Fig. 3. Gleason score distribution in systematic versus targeted biopsy

Of the 309 patients diagnosed with cancer via targeted + systematic biopsy, 249 (80.5%) had a positive finding on targeted cores (Figure 1), and 268 (86.7%) had a positive finding on systematic cores (Figure 1). In the group of patients diagnosed with cancer via targeted + systematic biopsy, 60 (19.4%) had positive findings on systematic cores without positive targeted cores, while 41 (13.3%) had positive targeted cores without positive systematic cores.

Targeted biopsy most commonly diagnosed Gleason score 3+4 prostate cancer at 42.7%, followed by Gleason score 3+3 at 36.2%, and Gleason score 4+3 at 12%. The most common Gleason score in systematic biopsy was 3+3 at 50.9%, followed by 3+4 at 33.3%, and 4+3 at 9.5% (Figure 3).

Out of the 1,461 biopsy-naïve systematic biopsies, prostate cancer was detected in 615 patients, or 42.1% cases (Figure 4). In the 210 biopsy-naïve targeted biopsies, prostate cancer was detected in 152 patients, or 72.7% cases (Figure 4). In 436 patients who underwent repeat systematic biopsy,

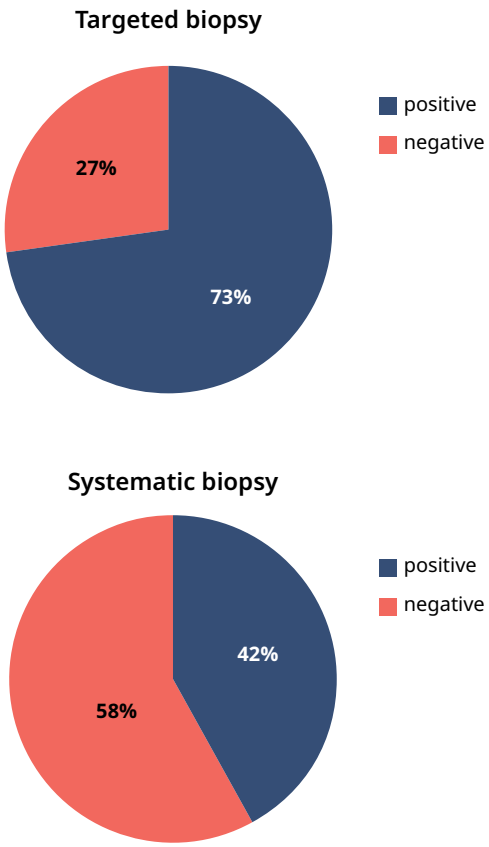

Fig. 4. Positivity rates of targeted and systematic biopsies in biopsy-naïve patients

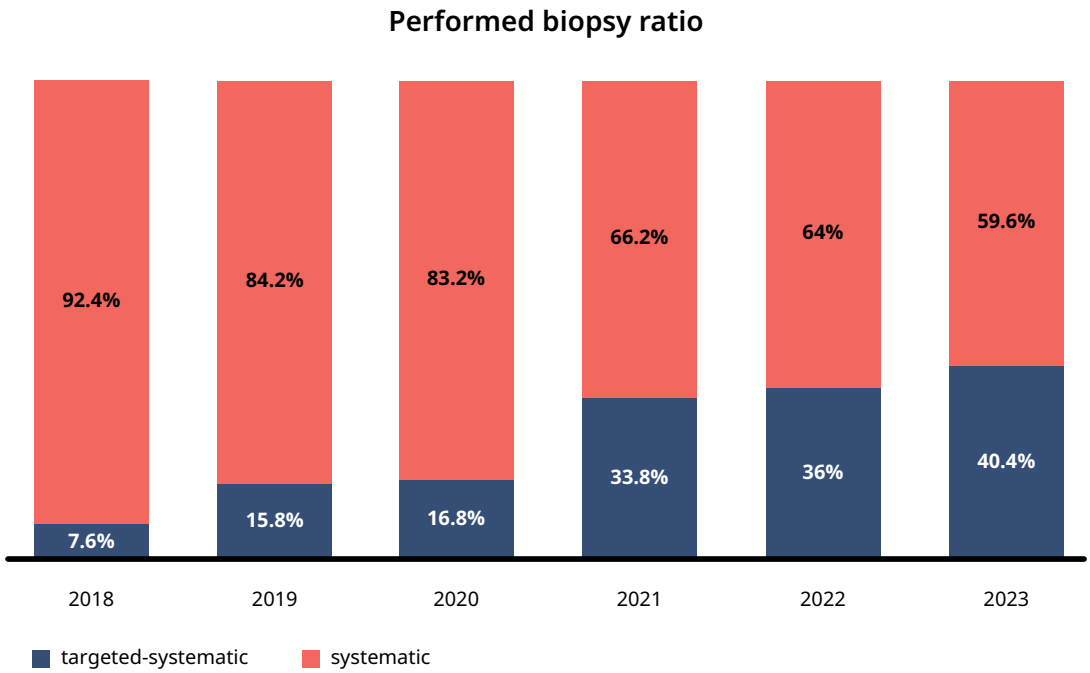

Fig. 5. Distribution of targeted and systematic biopsies over a six-year period

prostate cancer was detected in 233 (53.4%), while in 356 patients whose repeat biopsy was targeted, prostate cancer was diagnosed in 157 (44.1%) cases.

Regarding clinically significant prostate cancer, 197 out of 309 cases were detected via targeted biopsy, and 355 out of 724 cases via systematic biopsy.

Discussion

Systematic biopsy has been the cornerstone of prostate cancer diagnosis for the last 30 years. However, it is associated with significant limitations leading to missed clinically significant carcinomas and an overdetection of clinically insignificant forms of cancer, resulting in overtreatment[33]. Furthermore, although tumors in the anterior zone are less common than in the peripheral zone, the relative inaccessibility of anterior zone biopsy represents a clear limitation of TRUS[34].

As a result, targeted prostate biopsies have emerged as a valuable tool in diagnosing prostate cancer. At University Hospital Centre Zagreb, the use of targeted biopsies has seen a significant increase, rising from 7.6% in 2018 to 40.4% in 2023, reflecting a notable upward trend (Figure 5). The combination of targeted and systematic biopsies resulted in a higher percentage of prostate cancer detection in patients undergoing their first biopsy; 72.7% compared to 42.1% when only systematic biopsies were used (Figure 4).

However, the study may have been influenced by selection bias due to the limited availability of mpMRI. This raises questions about the financial feasibility of adopting mpMRI-targeted biopsies as the standard practice in our country, despite recommendations from the European Association of Urology (EAU). Still, Cheng et al. conducted a study

in Singapore where the use of mpMRI-targeted biopsies proved to be cost-effective[35]. Furthermore, the use of mpMRI can reduce unnecessary biopsies in patients with PIRADS 1 and PIRADS 2.

Consistent with our expectations, our study demonstrated that targeted prostate biopsies detect a higher number of clinically significant prostate cancers than systematic biopsies. Although there was a higher percentage of cancers detected using targeted biopsy, especially in biopsy-naïve patients, there was also a high percentage of positive systematic cores observed in those patients. This has also been observed in other studies, and has been explained by operator bias[36]. When performing targeted biopsy, operators typically sample the targeted core first, and perform systematic biopsy after that. During systematic biopsies, the operator, deliberately or not, may direct systematic cores towards suspicious areas identified on mpMRI, in an attempt to compensate for imprecision and to increase the chance of diagnosis.

A recent study called FUTURE found no significant differences in detection rates of clinically significant prostate cancers between cognitive fusion, software fusion, and MR in-bore biopsies[37]. Stabile et al. showed that fusion biopsy has a higher detection rate than cognitive biopsy for clinically significant prostate cancer. Moreover, operator expertise is significantly associated with higher detection rates of clinically significant prostate cancer[38]. Ideally, the optimal biopsy technique should have the highest detection rate for clinically significant prostate cancer, while minimizing the detection of clinically insignificant disease. Currently, there is no consensus on which type of MRI-targeted biopsy performs better in a given setting[39].

According to Ziayee et al., less experienced physicians missed a relevant proportion of clinically significant prostate cancers with mpMRI[40]. Implementing mpMRI before biopsy in patients who have not yet undergone biopsy may improve the detection of clinically significant prostate cancer, but it does not appear to eliminate the need for systematic biopsy[27]. Kuliš et al. performed targeted prostate biopsies by directing a targeted biopsy with 6 cores toward the suspicious lesion, as previously indicated by mpMRI. Subsequently, a standard systematic biopsy with 12 cores was conducted. In cases where more than one suspicious lesion was identified on mpMRI, three cores were sampled from each of the two most suspicious lesions[41]. On the other hand, avoiding systematic biopsy in favor of MRI-targeted biopsy for screening and early detection in individuals with elevated PSA levels reduced the risk of overdiagnosis by half, but at the cost of delaying the detection of intermediate-risk tumors in a small subset of patients[42].

Conclusion

Ultimately, the combination of targeted and systematic biopsies has proven to be the method with the highest rate of detecting clinically significant prostate cancer, especially in biopsy-naïve patients. This approach should be considered the method of choice for patients with elevated PSA levels.

DISCLOSURE OF CONFLICT OF INTEREST The authors would like to acknowledge the ERDF fund through the project PRONOBIS – Robotic navigated prostate biopsy (project code: NPOO.C3.2.R3-I1.04.0181).

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SAŽETAK

Rezultati biopsija prostate u PSA sivoj zoni: petogodišnja retrospektivna analiza

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Cilj nam je bio analizirati i usporediti dijagnostičku učinkovitost shematske i ciljane + shematske biopsije prostate u pacijenata s razinama prostata-specifičnog antigena (PSA) 4-10 ng/mL.

Provedena je retrospektivna studija u Kliničkom bolničkom centru Zagreb, analizirajući podatke o biopsijama od 2018. do 2023. godine. Ukupno 2.466 pacijenata ispunjavalo je kriterije uključivanja te su podvrgnuti ili shematskoj biopsiji (n = 1.900) ili kombiniranoj ciljanoj + shematskoj biopsiji (n = 566). Ciljane biopsije provedene su kod pacijenata s Prostate Imaging-Reporting and Data System (PIRADS) ocjenom ≥ 3 na multiparametrijskoj magnetskoj rezonanci (mpMRI). Procijenjene su stope otkrivanja raka i distribucija Gleasonova zbroja.

Rak prostate dijagnosticiran je u 41 % ispitanika. Stopa detekcije bila je viša u skupini s ciljanom + shematskom biopsijom (54,7 %) u usporedbi sa skupinom sa samo shematskom biopsijom (38,2 %). Među pacijentima koji prethodno nisu bili podvrgnuti biopsiji, ciljana + shematska biopsija imala je stopu detekcije od 72,7 %, što je značajno više od same shematske biopsije (42,1 %). Klinički značajan rak prostate (ISUP ≥ 2) otkriven je u 35,2 % svih slučajeva, pri čemu su ciljane biopsije identificirale veći udio klinički značajnih tumora. Primijećena je pristranost operatera, budući da su shematski uzorci u pacijenata podvrgnutih ciljanoj biopsiji često sadržavali zloćudne stanice.

Kombinacija ciljane i shematske biopsije pokazala je najveću stopu otkrivanja klinički značajnog raka prostate, osobito kod pacijenata koji prethodno nisu bili podvrgnuti biopsiji. S obzirom na sve veću primjenu mpMRI-ja, ovaj pristup treba smatrati metodom izbora za pacijente s povišenim PSA razinama. Buduće studije trebale bi procijeniti financijsku isplativost široke primjene mpMRI-ja u dijagnostici raka prostate.

KLJUČNE RIJEČI

Multiparametrijska magnetska rezonanca prostate; *Prostata specifični antigen*; *Biopsija prostate*; *Rak prostate*