DOI: https://doi.org/10.2298/SARH240318034M
UDC: 616.65-006-089.85

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Unfavorable low-risk factors predict pathologic upstaging and upgrading following radical prostatectomy: evidence for further subclassification of low-risk prostate cancer?

Aleksandar Magdelinić[1], Aleksandar Spasić[2], Marko Vuković[1]

[1]Clinical Center of Montenegro, Urology Clinic, Podgorica, Montenegro;
[2]Military Medical Academy, Urology Clinic, Belgrade, Serbia

SUMMARY

Introduction/Objective We aimed to validate the stratification of low-risk prostate cancer (PCa) into "favorable" and "unfavorable" subgroups of patients undergoing radical prostatectomy (RP), based on the correlation of various biopsy features with high-risk characteristics at final pathology.

Methods The research involved 173 patients who were selected as low-risk PCa. The planned stratification categorized patients into favorable and unfavorable low-risk PCa subgroups, based on their Gleason upgrading (GU) and tumor upstaging (TU) status at final pathology. Unfavorable low-risk PCa was defined by the presence of biopsy results correlating with high-risk characteristics at final pathology, pathological Gleason score (pGS ≥ 4 + 3, or ≥ pT3a, or pN1). Patients were divided into two groups according to the presence of high-risk pathology features: Group 1 (n = 84, favorable) and Group 2 (n = 89, unfavorable).

Results In total, 18 patients from the second group (20.2%) experienced Gleason score upgrading (GS ≥ 4 + 3), and in 94.4% of these cases, their biopsy reports indicated the presence of both perineural invasion (PNI) and lymphovascular invasion (LVI). Furthermore, among patients with upstaging to pT3a or pT3b, both PNI and LVI were observed in 60% and 85.7% of cases, respectively. Multivariate analysis demonstrated that PNI (OR = 3.35; 95% CI: 1.16–7.56; p < 0.001) and LVI (OR = 5.34; 95% CI: 2.02–11.2; p < 0.001) were independently associated with both GU and TU.

Conclusion The presence of PNI and LVI in prostate biopsy samples is associated with both clinically significant GU score and TU following pathologic prostate examination. Therefore, these features represent unfavorable characteristics in biopsy results.

Keywords: prostate cancer; low-risk; unfavorable low-risk; Gleason upgrading; tumor upstaging

INTRODUCTION

Low-risk prostate cancer (PCa) is defined as clinical stage T1/T2a biopsy with a Gleason score (GS) ≤ 6 and a prostate-specific antigen (PSA) level < 10. This is a broad category encompassing a range of pathological characteristics and clinical behaviors [1], within which a small percentage of low-grade cancers progress to high-grade disease [2]. It is well-established that a high incidence of understaging and undergrading on the initial biopsy can occur in this patient group, potentially delaying the initiation of curative treatment [3–6]. Moreover, cancer upgrading is a negative prognostic factor, making the early identification of high-grade cancer in men diagnosed with low-risk disease a priority [2].

The challenge in managing low-risk PCa lies in distinguishing patients with clinically significant cancers who may benefit from radical treatment from the remainder who do not require any intervention [1]. A significant unmet need remains for further stratification of this often-heterogeneous cohort to optimize treatment decisions among the various options available for these patients. It is well-established that low-risk PCa can be classified as very low-risk or low-risk disease based on biopsy and clinical criteria [7]. Nevertheless, this stratification system does not include information regarding several biopsy variables, including perineural (PNI) and lymphovascular invasion (LVI) [5, 6]. Consequently, a more comprehensive clinical model is desirable to identify unfavorable low-risk PCa, which may necessitate a more complex surveillance protocol or early active treatment.

Therefore, our study aims to define the unfavorable biopsy factors that predict a clinically significant form of low-risk PCa, thereby helping to determine which patients may require active, curative interventions rather than deferred treatment.

METHODS

Following approval from the Institutional Review Board, 700 patients underwent radical prostatectomy (RP) between 1995 and 2014. Utilizing databases from two university centers, only those patients meeting the following criteria were included in the analysis: preoperative localized disease, classification as low-risk PCa or International Society of Urological Pathology

Received • Примљено: March 18, 2024
Revised • Ревизија: April 27, 2025
Accepted • Прихваћено: April 29, 2025
Online first: April 30, 2025

Correspondence to:
Aleksandar MAGDELINIĆ
Clinical Center of Montenegro
Department of Urology
Ljubljanska bb
81000 Podgorica
Montenegro
acomgd@yahoo.com

grade I (PSA ≤ 10; cT1–T2a, GS ≤ 6), normal total serum testosterone levels, and no clinical signs of hypogonadism. Each patient had previously declined active surveillance (AS) as an initial treatment option. Exclusion criteria were: intermediate or high-risk grade PCa determined by the initial biopsy (n = 490), unknown surgical margin status, or total serum testosterone level below 12.1 nmol/l (n = 17) [8]. Finally, patients with unknown PSA levels at six weeks post-RP were also excluded (n = 20). Applying these selection criteria resulted in a cohort of 173 patients, who constitute the focus of this analysis.

The clinical variables [age, preoperative PSA, PSA density, and clinical stage (CT)] and all histopathological findings were recorded. All prostate biopsies were performed under transrectal ultrasound [9], and PSA density was calculated based on prostate volume records. The biopsy pathology report included the following variables: (I) PCa grade, (II) percentage of biopsy core involved by PCa (P+), (III) tumor volume (TV), (IV) LVI, (V) perineural invasion (PNI), and (VI) multifocal high-grade intraepithelial neoplasia (hg PIN). The proportion of positive cores (P+) was calculated as the ratio of P+ to the total number [10]. Additionally, PNI was identified according to the previously described principle using the same immunohistochemistry assay [11].

RP was performed using an open retropubic approach, and the entire prostate specimen was subsequently evaluated [12]. In addition, limited lymph node dissection was performed in each patient for the purposes of the study; lymph node specimens were reported as negative (pN0) or positive for cancer (pN1). Seminal vesicle invasion was defined as tumor involvement of the vesicle muscle wall (pT3b). Surgical margins (R) were reported as negative (Ro) or positive for cancer (R1). The pathological GS (pGS) was calculated by summing the two most prevalent tumor patterns [5, 13]. Tumor upstaging (TU) was defined as the detection of pT3 in the final post-prostatectomy pathology or the presence of tumor cell invasion in lymph nodes (pN1). Adverse pathologic features included extraprostatic extension (EPE), ≥ pT3a, R1, GS ≥ 4 + 3, multifocal high-grade PIN, and pN1.

The planned stratification for this study categorized patients with low-risk PCa as either favorable or unfavorable, based on their Gleason upgrading (GU) and TU status at final pathology. Unfavorable low-risk PCa was defined by the presence of biopsy or clinical variables correlating with any of the following high-risk (unfavorable) characteristics at final pathology: pGS ≥ 4 + 3, EPE, ≥ pT3a, or pN1 [14]. This categorization was chosen based on the widely accepted principle that deferred treatment is inappropriate for patients harboring

Table 1. Demographic and clinical characteristics between groups

Parameters	Overall	Group I (favorable)	Group II (unfavorable)	p
Patients, n (%)	173 (100)	84 (49.6)	89 (51.4)	0.32
Mean age, years (SD)	65.4 (6.1)	65 (5.9)	65.9 (4.9)	0.51
Preoperative PSA, ng/ml (SD)	6.7 (3)	6.34 (2.54)	*7.03 (1.7)**	0.03
PSA density, ng/ml/gr (IQR)	0.09 (0.03–0.46)	0.07 (0.02–0.18)	*0.14 (0.03–0.46)**	*0.01*
[a]Clinical T stage, n (%)				
T1	81 (46.8)	*70 (83.3)**	11 (12.3)	*0.04*
T2a	92 (53.2)	14 (16.7)	*78 (87.7)**	*0.007*
[a]Patients with PNI, n (%)	66 (38.1)	6 (7.1)	*60 (67.4)**	*0.001*
[a]Patients with LVI, n (%)	54 (31.2)	1 (1.2)	*53 (59.5)**	*0.001*
[a]Mean percentage of cores involved with PC (P+), %, SD	47.4 (5.2)	40.3 (4.6)	*52.3 (7.2)**	*0.02*
[a]Tumor volume (%), IQR	15 (10–25)	10 (10–20)	*50 (60–10)**	*0.01*
[b]Gleason upgrading, n (%)	104 (60.1)			
GS 3 + 4 (ISUP 2)	86 (49.7)	*61 (72.6)**	25 (27.4)	0.03
GS 4 + 3 (ISUP 3)	9 (5.2)	-	9 (10.1)	-
GS 4 + 4 (ISUP 4)	3 (1.7)	-	3 (3.3)	-
GS 3 + 5 (ISUP 4)	1 (0.5)	-	1 (1.1)	-
GS 4 + 5 (ISUP 5)	5 (2.8)	-	5 (5.6)	-
[b]Tumor upstaging, n (%)	94 (54.3)			
pT2	50 (28.9)	50 (59.5)	-	-
pT3a	30 (17.3)	-	30 (33.7)	-
pT3b	14 (8.1)	-	14 (15.7)	-
[b]Surgical margin positivity, n (%)				
unifocal (R1)	45 (26)	*30 (35.7)**	15 (16.8)	*0.03*
multifocal (R1)	25 (14.4)	8 (9.5)	*17 (19.1)**	*0.04*
[b]Apical involvement, n (%)	34 (19.6)	16 (19)	18 (20.2)	0.6
[b]EPE, n (%)				
Unifocal EPE	14 (8)	-	14 (15.7)	-
Multifocal EPE	17 (9.8)	-	17 (19.1)	-
[b]Positive lymph nodes, n (%)	7 (4)	-	7 (7.8)	-
[b]Multifocal hg PIN, n (%)	70 (40.6)	11 (13)	*59 (66.2)**	*0.02*

PSA – prostate-specific antigen; PNI – perineural invasion; P+ – percentage of positive cores; PC – prostate cancer; GS – Gleason score; ISUP – the International Society of Urological Pathology; EPE – extraprostatic extension; LVI – lymphovascular invasion; R1 – positive surgical margin; hg PIN – high-grade intraepithelial neoplasia; IQR – interquartile range
*statistically significant difference between two groups ($p < 0.05$);
[a]pathologic data on initial biopsy specimen;
[b]pathologic data on prostatectomy specimen

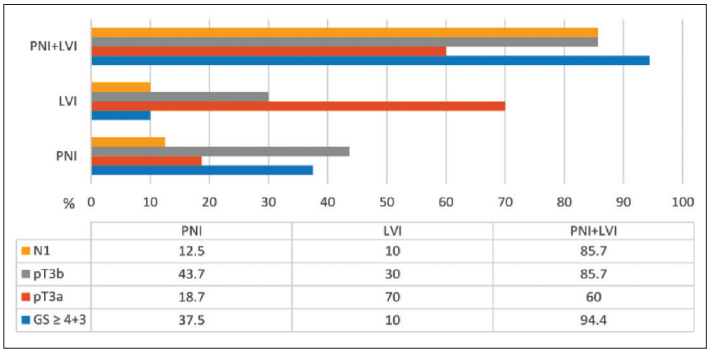

Figure 1. Association between individual and combined biopsy features (predictors of both, Gleason upgrading and tumor upstaging) and high-risk characteristics at final pathology

PNI – perineural invasion; LVI – lymphovascular invasion; GS – Gleason score; pT3a – pathological tumor stage 3a; pT3b – pathological tumor stage 3b

such features [15]. Group 1 (favorable) consisted of patients without high-risk characteristics on final histology, while Group 2 (unfavorable) included patients with at least one unfavorable feature at final pathology.

The primary objective of the study was to determine the correlation between clinical and biopsy determinants with high-risk characteristics at final pathology, thereby defining unfavorable low-risk PCa. Moreover, research aimed to establish the incidence of upgrading and upstaging, as well as adverse pathologic features on postsurgical specimens.

Statistical analysis

Continuous variables are presented as mean ± SD, and differences between groups were analyzed using the Mann–Whitney U test. Categorical variables are presented as counts and percentages. Non-parametrically distributed continuous variables are presented using the median, minimum, and maximum values. Finally, the relationship between biopsy determinants and GU/TU at final pathology was examined using multivariable logistic regression analysis. All analyses were performed using IBM SPSS Statistics for Windows, Version 23.0. (IBM Corp., Armonk, NY, USA).

Ethics: All patients provided written consent prior to their enrollment in the study. The treatment protocol was approved by the Ethics Committee of the Clinical Centre of Montenegro (No. 03/01-9360/2). The study was conducted in accordance with the principles of the Declaration of Helsinki of the World Medical Association.

RESULTS

Overall, 173 patients met the low-risk criteria defined by the study. The average patient age was 65.4 ± 6.1 years, and the median preoperative PSA was 6.7 ± 2.2 ng/ml. GU was detected in 104 (60.1%) patients: 86 (49.7%) to 3 + 4, nine (5.2%) to 4 + 3, three (1.7%) to 4 + 4, and five (2.8%) to 4 + 5 PCa. In RP specimens, 50 patients (28.9%) were staged as pT2b-c, 30 patients (17.3%) were staged as pT3a, and 14 patients (8.1%) were referred as T3b at final pathology (Table 1). No statistically significant differences were observed between the two groups regarding the number of patients ($p = 0.6$), mean patient age ($p = 0.4$), and apical involvement on surgical specimens ($p = 0.09$) between the two groups. In Group 2, preoperative PSA (0.04), PSA density ($p = 0.03$), clinical stage T2a ($p = 0.01$), PNI ($p < 0.01$), LVI ($p < 0.01$), TV ($p = 0.03$) and P+ ($p = 0.04$) were statistically higher than in Group 1. Furthermore, multifocal surgical margin positivity (19.1% *vs.* 9.5%, $p = 0.03$) and multifocal high-grade PIN (66.2% *vs.* 13%; $p = 0.01$) were found to be significantly higher in Group 2.

In total, 18 patients from Group 2 (20.2%) were upgraded to a GS ≥ 4 + 3, and in 94.4% of these cases, the biopsy report revealed both PNI and LVI. Moreover, TU was detected in 49.4% of patients from Group 2, with 33.7%, and 15.7% of patients exhibiting pT3a or pT3b, respectively. Biopsy reports were positive for both PNI and LVI in 60% of patients with pT3a upstaging and in 85.7% of patients with pT3b upstaging on final histology. Additionally, six out of seven patients (85.7%) with positive lymph nodes after surgery had both PNI and LVI on prostate needle biopsy pathology (Figure 1).

Table 2. Multivariable analysis of clinical/biopsy variables and high-risk (unfavorable) characteristics at final pathology

Biopsy and clinical variables	Multivariable	
	OR (95% CI)	p
Model 1 – upgrading on final histology (GS ≥ 4 + 3)		
Preoperative PSA	0.95 (0.88–2.11)	0.09
Clinical T-stage (1–2a)	1.69 (0.96–2.99)	0.1
Tumor volume	13.6 (4.5–31.2)	0.3
PNI	4.97 (2.16–9.67)	< 0.01
LVI	3.51 (1.13–8.71)	0.03
P+ (>50%)	1.13 (1.03–1.31)	0.04
PSA density	1.24 (0.99–1.55)	0.06
Multifocal high-grade PIN	*1.4 (1.25–1.58)*	*0.04*
Model 2 – upstaging on final histology (≥ pT3, N+)		
Preoperative PSA	1.00 (0.98–1.03)	0.7
Clinical T-stage (cT2a)	0.93 (0.67–1.31)	0.8
Tumor volume	0.76 (0.64–1.51)	0.3
PNI	3.35 (1.16–7.56)	< 0.01
LVI	5.34 (2.02–11.2)	< 0.01
P+ (>50%)	0.96 (0.94–1.02)	0.2
PSA density	1.47 (0.98–2.2)	0.07
Multifocal hg PIN	0.88 (0.11–2.31)	0.09

GS – Gleason score; PSA – prostate-specific antigen; PNI – perineural invasion; LVI – lymphovascular invasion; hg PIN – high-grade intraepithelial neoplasia

Multivariate logistic regression analysis revealed that PNI (OR = 4.97; 95% CI: 2.16–9.67; $p = 0.001$), LVI (OR = 3.51; 95% CI: 1.13–8.71; $p = 0.01$), percentage of P+ (OR = 41.5; 95% CI: 4.82–283.16; $p = 0.02$), and multifocal high-grade PIN (OR = 1.77; 95% CI: 0.87–2.56; $p = 0.031$) were independently associated with GU, while PNI (OR = 3.35; 95% CI: 1.16–7.56; $p < 0.001$) and LVI (OR = 5.34; 95% CI: 2.02–11.2; $p < 0.001$) were identified as independent predictors of TU. Although not statistically significant, the association of PSA density (OR = 1.24; 95% CI: 0.99–1.55; $p = 0.057$ and OR = 1.47; 95% CI: 0.98–2.2; $p = 0.07$) was notable (Table 2).

DISCUSSION

AS is a convenient therapeutic approach for PCa as it avoids overtreatment of patients with clinically inapparent disease while offering curative therapy to patients with progressive disease [16]. Nevertheless, during treatment of low-risk PCa, clinical predictors associated with GU or TU on surgical pathology should be strongly considered to identify subsets of patients who may have more aggressive disease and require more appropriate treatment [10]. Previous studies have documented that independent predictors of TU in low-risk PCa are associated with older age and higher PSA [14, 17], a higher proportion of P+ [10] and tumor involvement greater than 50% in each core [14]. Moreover, PNI appears to be a strong predictor of GU (over four-fold) in low-risk PCa [5, 6] with a previously

established correlation to biochemical failure [5, 11]. The present research indicated that a higher proportion of P+, multifocal high-grade PIN, and the presence of LVI and PNI were independent predictors of GU in the surgical specimen with the latter two showing a stronger association (3.51- and 4.97-fold) than the former (1.13- and 1.77-fold). In addition, LVI and PNI independently increased the risk of TU on final histology (3.35- and 5.34-fold), identifying them as the most reliable unfavorable predictors of both GU and TU. The risk of GU was even higher for patients with combined PNI and LVI in the same biopsy specimen, with 94.4% having pGS ≥ 4 + 3 and 85.7% having pT3b or pN1 disease, which are both considered very high-risk factors [18, 19]. Thus, many patients with PNI and LVI on biopsy specimens have occult high-risk disease that may go undetected prior to surgery. Therefore, additional evaluation is mandatory in these patients to improve risk classification. Zumsteg et al. [19] reached a similar conclusion for intermediate-risk PCa, where two or more unfavorable intermediate-risk factors on a biopsy specimen led to a 41% incidence of high-risk features on final pathology (Gleason pattern 5, pT3b-T4, pN1).

There is growing evidence demonstrating the importance of proper grading and staging of PCa on initial biopsy and prior to treatment decision. A large randomized study by Bill-Axelson et al. [20] reported seven men with initially low-risk disease who died from PCa after surgery. In six of these patients, tumors were upgraded to GS 7 or 8 at prostatectomy, leading to the conclusion that PCa-related death in men with low-risk disease often results from unrecognized high-grade disease [20, 21]. These findings suggest that high-grade disease on surveillance biopsies likely represents misclassification at diagnosis rather than true disease progression [20, 21, 22]. Therefore, developing a clinical predictive model to identify unfavorable biopsy features associated with advanced disease on RP is crucial.

Studies have emphasized the discordance between biopsy and RP specimens with a high incidence of tumor upgrading on final histology. Despite the adoption of second-opinion pathology reviews, the accuracy rate in evaluating RP specimens remains low [23, 24]. Our study corroborates these findings, with GU detected in 60.1% of final pathology specimens and the International Society of Urological Pathology grade 2 being the predominant one (49.7%).

Some authors suggested that pGS of at least 4 + 3 = 7, pT3b, and pN1 are the strongest predictors of long-term outcomes after surgery [14, 18, 19]. Therefore, we selected grade group 3 and pT3a as the pathologic threshold for defining high-risk characteristics at final pathology in order to identify unfavorable biopsy features. Although several biopsy and clinical variables were selected as predictors of tumor upgrading and upstaging, a clear definition of favorable and unfavorable predictive factors for low-risk PCa is still lacking, unlike the established definitions for intermediate-risk cancer [25]. Porcaro et al. [10] proposed a stratification system for low-risk PCa, based on PSA value and the proportion of P+ on prostate biopsy, but they did not include a biopsy report of PNI and LVI, which were significant predictors of advanced prognostic features in our study. Additionally, the "DETECTIVE" study [26] identified LVI and PNI in needle biopsy as exclusion criteria for AS, supporting our earlier finding that these variables likely represent significant baseline features associated with high-risk tumors on final pathology. Moreover, multiple studies have demonstrated a higher risk of biochemical recurrence (BCR) after RP, progression to metastatic disease, and cancer-specific mortality when PNI is seen in the biopsy tissue [27, 28]. Nevertheless, the clinical significance of PNI in low-risk PCa remains to be fully established.

PNI has been shown to be associated with an increased risk of both pathological [hazard ratio (HR) 2.21, 95% CI: 0.92–5.33, p = 0.076] and clinical progression (HR 2.39, 95% CI: 1.1–4.94, p = 0.019) among PCa patients on AS [13]. Furthermore, Cohn et al. [29] observed that PNI was associated with a higher rate of exclusion from AS due to biopsy-confirmed disease progression, aligning with the findings of the aforementioned "DETECTIVE" trial [26]. These conclusions corroborate the results from our study, where PNI was found to be the strongest predictor of tumor upgrading and the second most prominent predictor of disease upstaging on final histology. In contrast to the aforementioned studies, our research also identified LVI as an unfavorable biopsy prognostic factor for both GU and TU on final pathology. Considering these findings, we propose stratifying low-risk PCa into unfavorable (presence of PNI and LVI, with or without multifocal high-grade PIN and P+ on prostate biopsy) and favorable (absence of these variables) categories based on biopsy specimens.

On the other hand, it should be emphasized that only a few recent studies have investigated the potential significance of PNI or LVI in GU and TU in these patients. In one such recently published study, the authors used univariate Cox regression models and reported that lymphovascular or PNI correlated with a higher BCR rate [30]. However, after considering standard pathologic tumor features, lymphovascular or PNI were not statistically associated with a higher BCR as the Gleason grade group and pathologic tumor stage were strongly associated with PNI and LVI [30].

Although our study was not designed to focus on limitations, several should be acknowledged. Primarily, its retrospective nature and the small sample size are significant limitations. Furthermore, the absence of data from advanced imaging (such as multiparametric magnetic resonance imaging) or biomarkers (e.g., Genomic Prostate Score or Decipher) is a drawback. This study also did not address the outcomes of subsequent adjuvant or salvage treatment during follow-up, as it was outside the scope of our research. Finally, we did not estimate cancer-specific deaths or progression-free survival rates between the two groups, thus the definitive prognostic value of PNI, LVI, and P+ remains incomplete. Despite these limitations, our study provides significant findings that can assist physicians in making effective decisions regarding optimal patient treatment modalities.

CONCLUSIONS

Approximately one in three men with low-risk PCA on biopsy who undergo RP are found to have undesirable pathologic features. While stratifying low-risk patients into favorable and unfavorable categories is a positive step, traditional clinical and pathological criteria have not proven effective in identifying the unfavorable subset. Future large, prospective studies integrating clinical, pathological, and imaging modalities into a comprehensive prognostic model are needed to draw definitive conclusions. Meanwhile, the presence of both PNI and LVI in biopsy specimens may serve as a useful clinical predictor of TU or upgrading and an important tool in the treatment strategy for low-risk PCa patients. Furthermore, multifocal high-grade PIN or more than 50% P+ on biopsy may enhance this prognostic accuracy.

Conflict of interest: None declared.

REFERENCES

1. Karpinski MJ, Hüsing J, Claassen K, Möller L, Kajüter H, Oesterling F, et al. Combining PSMA-PET and PROMISE to re-define disease stage and risk in patients with prostate cancer: a multicentre retrospective study. Lancet Oncol. 2024;25(9):1188–201. [DOI: 10.1016/S1470-2045(24)00326-7] Erratum in: Lancet Oncol. 2024;25(12):e626. [DOI: 10.1016/S1470-2045(24)00635-1] [PMID: 39089299]
2. Ploussard G, Fiard G, Barret E, Brureau L, Créhange G, Dariane C, et al. French AFU Cancer Committee Guidelines - Update 2022–2024: prostate cancer - Diagnosis and management of localised disease. Prog Urol. 2022;32(15):1275–372. [DOI: 10.1016/j.purol.2022.07.148] [PMID: 36400483]
3. Sequeira JP, Salta S, Freitas R, López-López R, Díaz-Lagares Á, Henrique R, et al. Biomarkers for Pre-Treatment Risk Stratification of Prostate Cancer Patients: A Systematic Review. Cancers (Basel). 2024;16(7):1363. [DOI: 10.3390/cancers16071363] [PMID: 38611041]
4. Krilaviciute A, Kaaks R, Seibold P, de Vrieze M, Lakes J, Radtke JP, et al. Risk-adjusted Screening for Prostate Cancer-Defining the Low-risk Group by Data from the PROBASE Trial. Eur Urol. 2024;86(6):493–500. [DOI: 10.1016/j.eururo.2024.04.030] [PMID: 38749854]
5. Ola IO, Talala K, Tammela T, Taari K, Murtola TJ, Kujala P, et al. Long-term Risk of Prostate Cancer Mortality Among Men with Baseline Prostate-specific Antigen Below 3 ng/ml: Evidence from the Finnish Randomized Study of Screening for Prostate Cancer. Eur Urol Oncol. 2024:S2588-9311(24)00272-4. [DOI: 10.1016/j.euo.2024.11.010] [PMID: 39643505]
6. Finati M, Davis M, Stephens A, Chiarelli G, Cirulli GO, Morrison C, et al. The Role of Baseline Prostate-specific Antigen Value Prior to Age 60 in Predicting Lethal Prostate Cancer: Analysis of a Contemporary North American Cohort. Eur Urol Oncol. 2024;7(6):1535–42. [DOI: 10.1016/j.euo.2024.06.014] [PMID: 38991891]
7. Schroeder DW, Foster BR, Young DJ, Coakley FV. Targeted biopsy of the prostate. Abdom Radiol (NY). 2025;50(1):261–71. [DOI: 10.1007/s00261-024-04452-z] [PMID: 38976055]
8. Lunenfeld B, Mskhalaya G, Zitzmann M, Corona G, Arver S, Kalinchenko S, et al. Recommendations on the diagnosis, treatment and monitoring of testosterone deficiency in men. Aging Male. 2021;24(1):119–38. [DOI: 10.1080/13685538.2021.1962840] [PMID: 34396893]
9. Lokeshwar SD, Nguyen J, Rahman SN, Khajir G, Ho R, Ghabili K, et al. Clinical utility of MR/ultrasound fusion-guided biopsy in patients with lower suspicion lesions on active surveillance for low-risk prostate cancer. Urol Oncol. 2022;40(9):407.e21-407.e27. [DOI: 10.1016/j.urolonc.2022.06.005] [PMID: 35811206]
10. Porcaro AB, Siracusano S, de Luyk N, Corsi P, Sebben M, Tafuri A, et al. Low-Risk Prostate Cancer and Tumor Upgrading in the Surgical Specimen: Analysis of Clinical Factors Predicting Tumor Upgrading in a Contemporary Series of Patients Who were Evaluated According to the Modified Gleason Score Grading System. Curr Urol. 2017;10(3):118–25. [DOI: 10.1159/000447164] [PMID: 28878593]
11. Vukovic M, Kavaric P, Magdelinic A, Nikomanis P, Tomovic S, Pelicic D. Perineural invasion on biopsy specimen as predictor of tumor progression in aging male treated with radical prostatectomy. Could we use it for pre-surgical screening? Aging Male. 2020;23(5):720–5. [DOI: 10.1080/13685538.2019.1581758] [PMID: 30843451]
12. Hekman L, Barrett A, Ross D, Palaganas E, Giridhar P, Elumalai T, et al. A Systematic Review of Clinical Trials Comparing Radiation Therapy Versus Radical Prostatectomy in Prostate Cancer. Clin Genitourin Cancer. 2024;22(5):102157. [DOI: 10.1016/j.clgc.2024.102157] [PMID: 39084158]
13. Moreira DM, Fleshner NE, Freedland SJ. Baseline Perineural Invasion is Associated with Shorter Time to Progression in Men with Prostate Cancer Undergoing Active Surveillance: Results from the REDEEM Study. J Urol. 2015;194(5):1258–63. [DOI: 10.1016/j.juro.2015.04.113] [PMID: 25988518]
14. Valdez-Vargas AD, Sánchez-López HM, Badillo-Santoyo MA, Maldonado-Valadez RE, Manzo-Pérez BO, Pérez-Abarca VM, et al. Recurrence rate of localized prostate cancer after radical prostatectomy according to D'amico risk classification in a tertiary referral hospital: association study. Cir Cir. 2021;89(4):520–7. [DOI: 10.24875/CIRU.200007601] [PMID: 34352860]
15. Hu X, Miao J, Huang J, Qian L, Zhang D, Wei H. Influence of Active Surveillance on Gleason Score Upgrade and Prognosis in Low- and Favorable Intermediate-Risk Prostate Cancer. Curr Oncol. 2022;29(10):7964–78. [DOI: 10.3390/curroncol29100630] [PMID: 36290907]
16. Ruane-McAteer E, Prue G. Psychological aspects of active surveillance. World J Urol. 2022;40(1):9–13. [DOI: 10.1007/s00345-020-03553-w] [PMID: 33388921]
17. Zhang H, Doucette C, Yang H, Bandyopadhyay S, Grossman CE, Messing EM, et al. Risk of adverse pathological features for intermediate risk prostate cancer: Clinical implications for definitive radiation therapy. PLoS One. 2021;16(7):e0253936. [DOI: 10.1371/journal.pone.0253936] [PMID: 34264975]
18. Kawamura N, Hayashi T, Nagahara A, Nakai Y, Nakayama M, Ikawa T, et al. Outcomes in patients with high- and very high-risk localized prostate cancer treated with definitive IMRT and long-term hormone therapy. Jpn J Clin Oncol. 2024;54(3):346–51. [DOI: 10.1093/jjco/hyad178] [PMID: 38146119]
19. Zumsteg ZS, Chen Z, Howard LE, Amling CL, Aronson WJ, Cooperberg MR, et al. Number of Unfavorable Intermediate-Risk Factors Predicts Pathologic Upstaging and Prostate Cancer-Specific Mortality Following Radical Prostatectomy: Results from the SEARCH Database. Prostate. 2017;77(2):154–63. [DOI: 10.1002/pros.23255] [PMID: 27683213]
20. Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med. 2011;364(18):1708–17. [DOI: 10.1056/NEJMoa1011967] [PMID: 21542742]
21. Berenguer CV, Pereira F, Câmara JS, Pereira JAM. Underlying Features of Prostate Cancer-Statistics, Risk Factors, and Emerging Methods for Its Diagnosis. Curr Oncol. 2023;30(2):2300–21. [DOI: 10.3390/curroncol30020178] [PMID: 36826139]
22. Sorce G, Flammia RS, Hoeh B, Chierigo F, Hohenhorst L, Panunzio A, et al. Grade and stage misclassification in intermediate unfavorable-risk prostate cancer radiotherapy candidates. Prostate. 2022;82(10):1040–50. [DOI: 10.1002/pros.24349] [PMID: 35365851]
23. Maehara T, Sadahira T, Maruyama Y, Wada K, Araki M, Watanabe M, et al. A second opinion pathology review improves the diagnostic concordance between prostate cancer biopsy and radical prostatectomy specimens. Urol Ann. 2021;13(2):119–24. [DOI: 10.4103/UA.UA_81_20] [PMID: 34194136]
24. Maruyama Y, Sadahira T, Araki M, Mitsui Y, Wada K, Rodrigo AGH, et al. Factors predicting pathological upgrading after prostatectomy in patients with Gleason grade group 1 prostate cancer based

on opinion-matched biopsy specimens. Mol Clin Oncol. 2020;12(4):384–9. [DOI: 10.3892/mco.2020.1996] [PMID: 32190323]
25. Preisser F, Cooperberg MR, Crook J, Feng F, Graefen M, Karakiewicz PI, et al. Intermediate-risk Prostate Cancer: Stratification and Management. Eur Urol Oncol. 2020;3(3):270–80. [DOI: 10.1016/j.euo.2020.03.002] [PMID: 32303478]
26. Lam TBL, MacLennan S, Willemse PM, Mason MD, Plass K, Shepherd R, et al. EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel Consensus Statements for Deferred Treatment with Curative Intent for Localised Prostate Cancer from an International Collaborative Study (DETECTIVE Study). Eur Urol. 2019;76(6):790–813. [DOI: 10.1016/j.eururo.2019.09.020] [PMID: 31587989]
27. Teramoto Y, Numbere N, Wang Y, Miyamoto H. Clinical Significance of Perineural Invasion by Prostate Cancer Detected on Needle Core Biopsy. Am J Clin Pathol. 2023;159(2):116–9. [DOI: 10.1093/ajcp/aqac142] [PMID: 36494055]
28. Teramoto Y, Wang Y, Miyamoto H. Risk Stratification by Quantification of Perineural Cancer Invasion on Prostate Needle Core Biopsy: Should It Be Counted? J Urol. 2023;210(4):639–48. [DOI: 10.1097/JU.0000000000003618] [PMID: 37433144]
29. Cohn JA, Dangle PP, Wang CE, Brendler CB, Novakovic KR, McGuire MS, et al. The prognostic significance of perineural invasion and race in men considering active surveillance. BJU Int. 2014;114(1):75–80. [DOI: 10.1111/bju.12463] [PMID: 24106869]
30. Siech C, Wenzel M, Grosshans N, Cano Garcia C, Humke C, Koll FJ, et al. The Association Between Lymphovascular or Perineural Invasion in Radical Prostatectomy Specimen and Biochemical Recurrence. Cancers (Basel). 2024;16(21):3648. [DOI: 10.3390/cancers16213648] [PMID: 39518086]

Неповољни фактори код болесника са нискоризичним карциномом простате предвиђају патолошко погоршање и напредовање након радикалне простатектомије: докази за даљу подкласификацију?

Александар Магделинић[1], Александар Спасић[2], Марко Вуковић[1]

[1]Клинички центар Црне Горе, Клиника за урологију, Подгорица, Црна Гора;
[2]Војномедицинска академија, Клиника за урологију, Београд, Србија

САЖЕТАК

Увод/Циљ Циљ истраживања је био да се потврди стратификација нискоризичног карцинома простате (*PCa*) на „повољне“ и „неповољне“ подгрупе болесника који су подвргнути радикалној простатектомији, према корелацији различитих карактеристика биопсије са карактеристикама високог ризика на коначној патологији.

Методе У ову студију су укључена 173 болесника која су у време операције изабрана као кохорте са ниским ризиком од *PCa*. Планирана стратификација укључивала је повољан и неповољан *PCa* ниског ризика, у складу са повећањем Глисоновог степена и статусом повећања стадијума тумора код крајње патологије. Неповољан *PCa* ниског ризика дефинисан је као присуство резултата биопсије који корелирају са високоризичним карактеристикама у коначној патологији [патолошки Глисонов скор ≥ 4 + 3, или ≥ *pT3a*, или *pN1*)]. Болесници су подељени у складу са присуством високоризичних обележја у коначној патологији у Групу 1 ($n = 84$, повољно) и Групу 2 ($n = 89$, неповољно).

Резултати Осамнаест болесника из Групе 2 (20,2%) има Глисонов скор ≥ 4 + 3, а у 94,4% случајева њихови биопсијски извештаји су открили и перинеуралну инвазију (ПНИ) и лимфоваскуларну инвазију (ЛВИ). Штавише, болесници са напредовањем *pT3a* или *pT3b* показали су и ПНИ и ЛВИ у 60% и 85,7% случајева, респективно. Мултиваријантна анализа је показала да су ПНИ (*OR* = 3,35; 95% *CI*: 1,16–7,56; $p < 0,001$) и ЛВИ (*OR* = 5,34; 95% *CI*: 2,02–11,2; $p < 0,001$) независно повезани и са повећањем Глисоновог степена и са повећањем стадијума тумора.

Закључак Докази о ПНИ и ЛВИ у биопсији простате повезани су и са клинички значајним напредовањем и са преокретом после патолошког прегледа простате, што представља неповољне карактеристике биопсије.

Кључне речи: рак простате; низак ризик; неповољан низак ризик; Глисонов скор; раст тумора