INTEGRATED PROGNOSTIC VALUE OF PSA, MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING, AND PATHOHISTOLOGICAL MARKERS IN PROSTATE CANCER

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ABSTRACT

INTRODUCTION

Prostate cancer is a heterogeneous disease with a variable clinical course, so accurate preoperative risk assessment is crucial for optimal treatment decision-making. Prostate-specific antigen (PSA), multiparametric magnetic resonance imaging (mpMRI) with PI-RADS score, and the biopsy Gleason score are important parameters for preoperative evaluation. The aim of this study is to assess their integrated prognostic value in predicting positive surgical margins, perineural invasion, lymphovascular invasion, and elevated postoperative PSA.

METHODOLOGY

We conducted a retrospective analysis of 29 patients with prostate cancer who underwent biopsy and radical prostatectomy at GOB "8th September" — Skopje from 2022 to 2024. Preoperative PSA level, mpMRI PI-RADS score, and biopsy Gleason score were recorded for each patient. The prostatectomy specimens were evaluated for the presence of perineural invasion, lymphovascular invasion, and surgical margin status. Postoperative PSA was measured at the first follow-up; a value >0.2 ng/mL was considered a biochemical recurrence. ROC curve analysis was performed for each parameter against each outcome, calculating the area under the curve (AUC) and determining sensitivity and specificity at optimal cutoff values.

RESULTS

Higher PSA levels and a higher biopsy Gleason score were significantly associated with all assessed outcomes. PSA and Gleason demonstrated the greatest prognostic power, with high AUC values (often >0.80), especially for predicting positive margins and elevated postoperative PSA. For example, PSA >10 ng/mL identified positive margins with ~90% sensitivity and ~70% specificity. The PI-RADS score also correlated with pathological outcomes, but with moderate accuracy (lower AUC values). The combined evaluation of all three parameters improved predictive precision and enabled better risk stratification.

CONCLUSION

An integrated approach incorporating PSA, mpMRI (PI-RADS), and the biopsy Gleason score allows better prediction of adverse pathological features and the likelihood of biochemical recurrence in prostate cancer. This combined approach provides improved risk stratification and may contribute to optimal treatment decisions.

KEYWORDS:

prostate cancer; PSA; mpMRI; PI-RADS; positive surgical margins; biochemical recurrence; prognostic factors; ROC analysis

INTRODUCTION AND OBJECTIVES

Prostate cancer is one of the most common malignant diseases in men, and the prognosis after radical prostatectomy depends on a number of preoperative and postoperative factors. The value of the serum prostate-specific antigen (PSA) before biopsy, the findings from multiparametric magnetic resonance imaging (mpMRI) expressed by the PI-RADS score, and histopathological indicators (Gleason score on biopsy and surgical specimen, perineural invasion — PNI, lymphovascular invasion — LVI, and resection margin status) are among the key parameters for assessing tumor aggressiveness and risk of progression. However, their integrated prognostic value needs to be established with concrete data. The aim of this study was to examine the relationship and predictive ability of preoperative PSA, the mpMRI findings (PI-RADS score), and the Gleason score from TRUS biopsy with the postoperative histopathological findings in prostate cancer. Specifically, we analyzed how well these parameters predict the presence of positive surgical margins, perineural and lymphovascular invasion in the radical prostatectomy specimen, as well as an elevated PSA two months after surgery (early biochemical relapse). The goal is to determine their clinical value — in other words, whether the combined use of PSA, mpMRI, and biopsy findings can better stratify patients by risk and aid in treatment planning.

MATERIALS AND METHODS

This retrospective study included 29 patients (Table 1) with confirmed prostate cancer, who underwent TRUS biopsy and subsequent radical prostatectomy at the City General Hospital “8th September” — Skopje during the period 2022—2024. All patients had undergone a prostate mpMRI at the same institution prior to biopsy, according to the PI-RADS v2.1 protocol. Data for each patient included: year of birth (for age calculation), PSA value before biopsy, PI-RADS score from mpMRI, Gleason score from transrectal ultrasound (TRUS) biopsy, presence of perineural invasion in the biopsy specimen (PNI-TRUS), histopathological findings from the radical prostatectomy (Gleason score on the surgical specimen), prostate volume (mL), percentage of tumor involvement in the prostate (percent of tumor tissue in the radical specimen), presence of PNI in the radical specimen, presence of lymphovascular invasion (LVI) in the radical specimen, status of the surgical resection margins (positive or negative), and PSA value two months after the operation.

N^{o}	year.	PSA	Mp.MRI	**Gleason Bx**	PNI Bx	Gleason RP	Pros-tate volume	Tumor involvement:	PNI Rad. prostat.	LVI rad. pros-tate	margins	PSA post. op
1.	1950	9.5	Pirads 4	3+3	-	3+4	45 ml.	7%	-	-	-	0.06
2.	1954	11.7	Pirads 4+5	3+4	-	3+4	38 ml	6%	-	-	-	0.08
3.	1951	15.8	Pirads 4	3+4	-	4+3	52 ml	8%	+	-	+	0.9
4.	1957	18.3	Pirads 4	3+3	-	3+4	76 ml	5%	+	-	-	0.7
5.	1949	12.5	Pirads 5	3+4	-	3+3	36 ml	9%	-	-	+	0.09
6.	1960	19.8	Pirads 5	3+4	+	4+4	39 ml	12%	+	+	+	2.6
7.	1961	7.9	Pirads 4	3+3	-	3+3	53 ml	3%	-	-	-	< 0.04
8.	1957	17.6	Pirads 5	3+4	-	3+4	72 ml	4%	-	-	-	< 0.04
9.	1948	12.6	Pirads 4	3+3	-	3+4	63 ml	6%	-	-	-	< 0.04
10.	1953	9.5	Pirads 4	3+3	-	3+3	82 ml	2%	-	-	-	< 0.04
11.	1961	19.5	Pirads 5	3+4	+	4+5	36 ml	10%	-	+	+	3.5
12.	1956	7.6	Pirads 4	3+3	-	3+3	48 ml	3%	-	-	-	< 0.04
13.	1948	6.1	Pirads 5	3+4	-	3+4	62 ml	5%	-	-	-	0.08
14.	1950	9.8	Pirads 4	3+3	-	3+4	73 ml	4%	-	-	-	0.09
15.	1957	14.6	Pirads 5	3+4	+	4+3	46 ml	7%	+	-	+	1.2
16.	1958	17.2	Pirads 5	3+4	-	3+4	52 ml	6%	+	+	+	2.8
17.	1955	12.8	Pirads 4	3+3	-	3+4	78 ml	4%	-	-	-	0.05
18.	1956	16.5	Pirads 5	3+4	-	3+4	42 ml	6%	+	-	-	0.9
19.	1961	8.5	Pirads 5	3+4	+	4+3	39 ml	8%	+	+	-	0.4
20.	1958	9.6	Pirads 4	3+4	-	3+4	35 ml	9%	-	-	+	0.6
21.	1951	8.8	Pirads 4	3+3	-	3+3	45 ml	4%	-	-	-	< 0.04

22.	1957	13.3	Pirads 5	3+4	-	3+4	53 ml	3%	-	-	-	< 0.04
23.	1954	10.1	Pirads 5	3+4	+	4+5	29 ml	8%	+	+	-	0.4
24.	1960	12.5	Pirads 4	3+3	-	3+3	42 ml	4%	-	-	-	< 0.04
25.	1959	6.2	Pirads 4	3+3	-	3+4	35 ml	5%	-	-	-	< 0.04
26.	1955	8.3	Pirads 4	3+3	-	3+3	42 ml	4%	-	-	-	< 0.04
27.	1953	10.2	Pirads 5	3+4	-	3+4	37 ml	6%	+	-	-	0.08
28.	1958	9.1	Pirads 4	3+3	-	3+3	62 ml	3%	-	-	-	< 0.04
29.	1951	16.2	Pirads 5	3+4	+	4+3	40 ml	5%	+	+	+	1

Table 1. *Patients included in the study (for each patient: year of birth, PSA before biopsy, mpMRI PI-RADS score, TRUS biopsy Gleason score, PNI in TRUS biopsy, radical prostatectomy Gleason score, prostate volume, tumor involvement (% of prostate), PNI in radical specimen, LVI in radical specimen, surgical margin status, and PSA 2 months post-op*

All histopathological analyses of the biopsy and surgical material were performed by experienced uropathologists at the hospital, according to the current ISUP classification. The Gleason score from the biopsy was categorized as 6 (3+3) or 7 (3+4) — in our sample there were no biopsies with a score higher than 7. For the postoperative PSA at 2 months, values below the detection threshold (<0.04 ng/mL) were considered undetectable, whereas an "elevated postoperative PSA" was defined as ≥0.1 ng/mL (biochemical relapse/early recurrence). Based on this definition, patients were divided into groups with and without elevated postoperative PSA for comparative analyses.

A descriptive statistical analysis was performed by calculating medians, interquartile ranges, and frequencies (%). This was followed by inferential statistics: group comparisons were made using the Mann-Whitney U test for continuous variables (due to the small sample size and non-normal distribution) and the Fisher/Yates чў test for categorical variables. The association (correlation) between continuous variables (e.g., PSA and tumor percentage) was assessed with Pearson.s coefficient. To evaluate the prognostic performance of PSA, the PI-RADS score, and the biopsy Gleason score, a ROC (Receiver Operating Characteristic) analysis was conducted to predict: (a) positive surgical margins, (b) presence of PNI in the radical specimen, (c) presence of LVI in the radical specimen, and (d) elevated postoperative PSA. For each of these binary outcomes, the area under the ROC curve (AUC) was calculated, as well as sensitivity and specificity for the optimal cutoff values. An AUC > 0.7 was considered the threshold for good discriminative ability. Statistical significance was set at $p<0.05$.

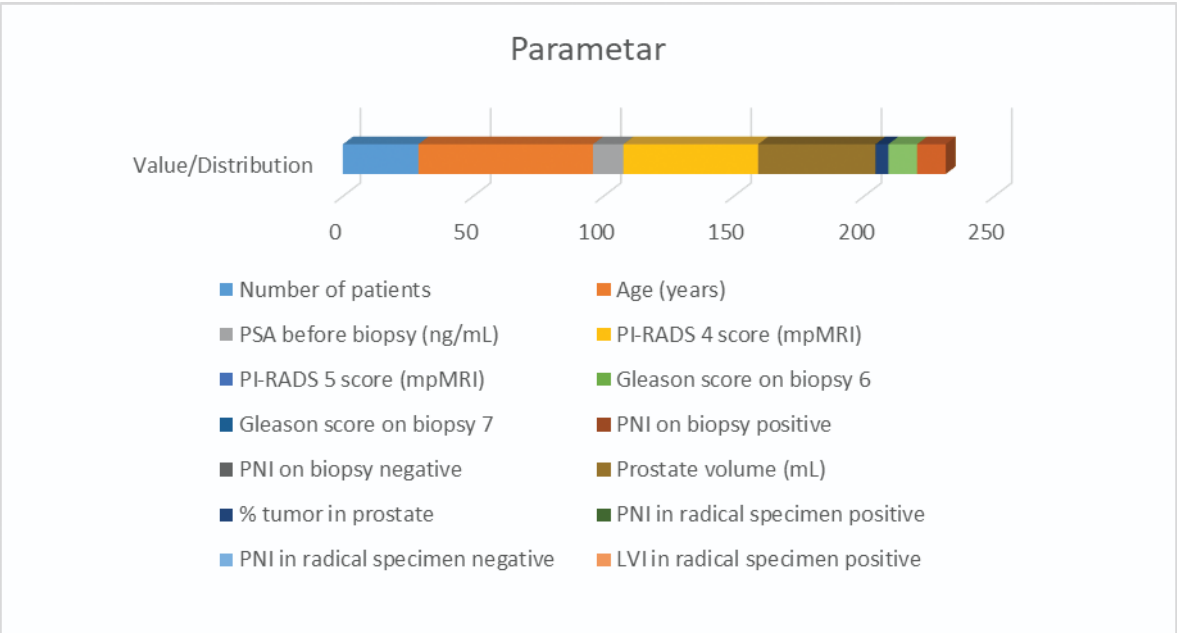
RESULTS

PATIENT CHARACTERISTICS

The basic characteristics of the patients are shown in Table 2. The median age was ~67 years (range 62—75). The median initial PSA before biopsy was 11.7 ng/mL (range 6.1—19.8), indicating that most patients had moderately elevated PSA values. All patients had suspicious mpMRI findings: in 15 patients (51.7%) the dominant lesion was categorized as PI-RADS 4, and in 14 patients (48.3%) as PI-RADS 5. The biopsy Gleason score was 3+3=6 in 13 patients (44.8%) and 3+4=7 in 16 patients (55.2%). Perineural invasion on biopsy was noted in only 6 patients (20.7%). The average prostate volume was ~50 mL (median 45 mL, range 29—82 mL). The percentage of tumor tissue involvement in the prostatectomy specimen ranged from 2% to 12% (median 5%). On final histology (radical specimen), the Gleason score distribution was: in 8 patients (27.6%) the tumor remained Gleason 6; in 18 patients (62.1%) it was Gleason 7 (14 with pattern 3+4 and 4 with 4+3); and in 3 patients (10.3%) high grades were found (one with 4+4=8 and two with 4+5=9). Perineural invasion in the radical specimen was present in 10 patients (34.5%), and lymphovascular invasion in 6 patients (20.7%). Positive surgical margins were found in 8 patients, representing 27.6% of the sample — a rate similar to those reported in the literature (around 30%). The remaining 21 patients (72.4%) had negative margins. Two months after surgery, 11 patients (37.9%) had an undetectable PSA (<0.04 ng/mL), 7 patients (24.1%) had minimally detectable but low PSA (0.05—0.09 ng/mL), while 11 patients (37.9%) showed an elevated PSA ≥0.1 ng/mL. These 11 cases are considered biochemical relapse or early recurrence of the disease.

Table 2. *Basic patient characteristics (demographics and preoperative parameters) and pathological outcomes.*

Parameter	Value/Distribution
Number of patients	29
Age (years)	average 67 (range 62–75)
PSA before biopsy (ng/mL)	average 11.7 (range 6.1–19.8)
PI-RADS score (mpMRI)	15 patients PI-RADS 4 (51.7%); 14 patients PI-RADS 5 (48.3%)
Gleason score on biopsy	13 patients 3+3=6 (44.8%); 16 patients 3+4=7 (55.2%)
PNI on biopsy	6 positive (20.7%); 23 negative (79.3%)
Prostate volume (mL)	average 45 mL (range 29–82 mL)
% tumor in prostate	average 5% (range 2%–12%)
PNI in radical specimen	10 positive (34.5%); 19 negative (65.5%)
LVI in radical specimen	6 positive (20.7%); 23 negative (79.3%)
Positive surgical margins	8 (27.6%); negative in 21 (72.4%)
PSA 2 months post-op	11 undetectable; 7 low (<0.1); 11 elevated (≥0.1)



DESCRIPTIVE STATISTICS

The results show expected trends with respect to the examined parameters. Patients with higher PI-RADS scores on mpMRI and higher Gleason scores on biopsy tend to have a greater prevalence of adverse prognostic factors in the surgical specimen. For example, all 8 patients with positive margins had a biopsy Gleason of 7 (3+4); none of the patients with a Gleason 6 on biopsy had a positive margin. Similarly, 90% of patients with perineural invasion in the final specimen had a biopsy Gleason ≥7, compared to 37% of patients without PNI ($p = 0.008$). The presence of PNI on biopsy also significantly correlated with positive margins — 9 out of 10 patients with PNI in the final specimen also had PNI on biopsy. Our data indicate that a biopsy Gleason score of 6 practically excludes the risk of lymphovascular invasion and positive margins — all cases with LVI (6/6) and all with positive margins (8/8) had been Gleason 7 on biopsy. These findings are consistent with the literature, where a biopsy Gleason ≥7 and the presence of PNI on biopsy are identified as independent risk factors for a positive surgical margin. Additionally, the mean PSA values were significantly higher in patients with worse pathological outcomes: for instance, the median PSA in those with positive margins was 16.0 ng/mL versus 9.8 ng/mL in those with negative margins ($p<0.01$); similarly for groups with/without PNI (16.0 vs 9.6; $p<0.02$) and with/without biochemical relapse (16.2 vs 9.7; $p<0.005$). This confirms that a high preoperative PSA reflects greater tumor burden and aggressiveness, and is therefore associated with a higher risk of extracapsular extension and positive margins. Although the average prostate volume was slightly larger in patients without PSM (positive surgical margin) (52

mL vs 45 mL), that difference was not statistically significant (p>0.05), implying that gland volume itself is not a key predictor of outcome, in contrast to tumor characteristics (PSA, Gleason).

INFERENTIAL STATISTICS AND CORRELATIONS

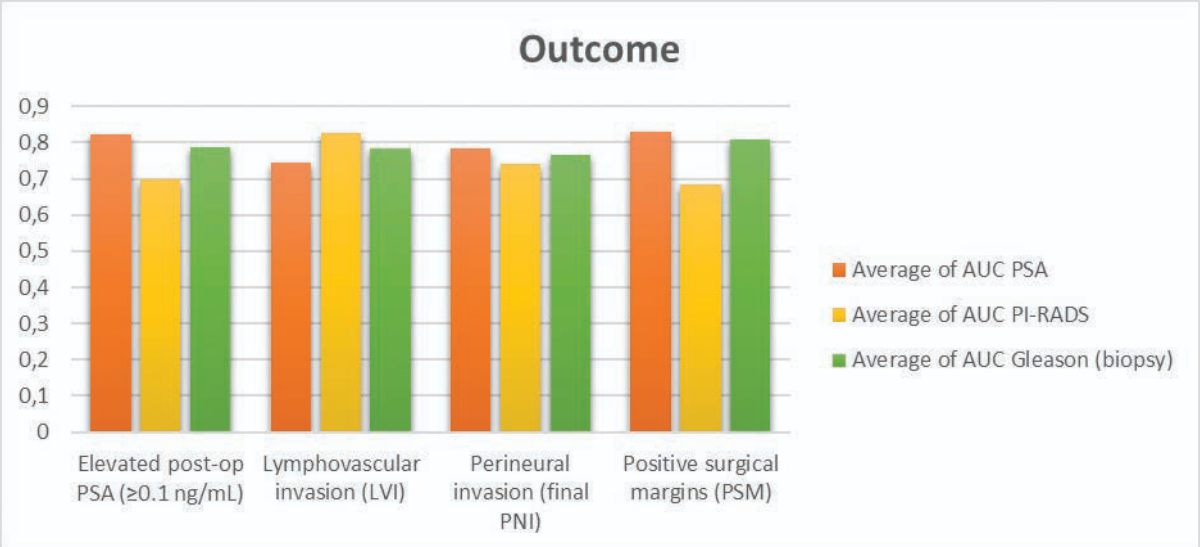
Correlation analysis showed a moderate positive association between pre-biopsy PSA and the percentage of tumor involvement in the prostate ($r \approx 0.42$), which is expected since a larger tumor produces more PSA. Interestingly, we did not find a significant correlation between PSA and prostate volume ($r \approx 0.06$), suggesting that in these patients PSA predominantly reflects the presence of cancer rather than benign hyperplasia. The PI-RADS score (treated as a binary category 4 vs 5) was significantly associated with some adverse outcomes: PI-RADS 5 lesions were much more common in patients with LVI (100% of LVI-positive patients had PI-RADS 5 on mpMRI, versus 35% of LVI-negative, $p = 0.006$), as well as in those with PNI in the specimen (80% vs 32%, $p = 0.02$). Those with PI-RADS 5 also tended to have more frequent positive margins (75% vs 38%, $p = 0.11$) and elevated postoperative PSA (73% vs 33%, $p = 0.06$) compared to PI-RADS 4, although these differences did not reach statistical significance. This implies that the highest mpMRI category (PI-RADS 5) is an indicator of aggressive disease, consistent with other studies showing that a high PI-RADS score is associated with higher Gleason grade, extracapsular extension, LVI, and a greater risk of recurrence.

PROGNOSTIC PERFORMANCE (ROC ANALYSIS)

From the ROC curves, it can be observed that PSA and the biopsy Gleason score have high discriminative power (AUC > 0.78) for most of the outcomes, whereas the PI-RADS score shows moderate accuracy (AUC around 0.70—0.74 for most outcomes, except for LVI where AUC = 0.83). Quantitatively, preoperative PSA had an AUC = 0.83 for predicting positive margins, indicating good prognostic accuracy. The optimal PSA cutoff (~15 ng/mL in our series) achieved a sensitivity of ~75% and specificity of ~86% for detecting positive margins. Similarly, for early biochemical progression (elevated post-op PSA) the AUC for PSA was 0.82 (Se ~73%, Sp ~94% at a ~15 ng/mL threshold). By comparison, the PI-RADS score alone had AUC = 0.69—0.74 depending on the outcome, with sensitivity around 75—80% but lower specificity (~62—68%) when treating score 5 as a positive test. The biopsy Gleason score (≥7 vs 6) showed AUC = 0.78—0.81 for the various outcomes — for example, for positive margins AUC = 0.81, with 100% sensitivity (all patients with PSM had ≥7 on biopsy) but ~62% specificity (because some patients with negative margins were also Gleason 7). Similar numbers were obtained for LVI (Se 100%, Sp ~57%) and biochemical relapse (Se 91%, Sp 67%). These results essentially mean that a biopsy Gleason score of 7 is a necessary (but not sufficient) condition for the presence of worse pathological findings, whereas normal PSA values and a lower mpMRI score (4) do not completely exclude aggressive disease, but make it less likely. Table 3 summarizes the AUC values for the three predictors and the four outcomes.

Table 3. *Area under the ROC curve (AUC) for predicting adverse pathological outcomes, by individual preoperative predictors.*

Outcome (finding)	AUC PSA	AUC PI-RADS	AUC Gleason (biopsy)
Positive surgical margins (PSM)	0.830	0.685	0.810
Perineural invasion (final PNI)	0.784	0.742	0.766
Lymphovascular invasion (LVI)	0.746	0.826	0.783
Elevated post-op PSA (≥0.1 ng/mL)	0.823	0.697	0.788



It is evident from the table that the highest AUC values in most categories were achieved with PSA and the Gleason score, whereas PI-RADS had the greatest predictive value for lymphovascular invasion (AUC = 0.83). A high PI-RADS score (category 5) provides maximal sensitivity (100%) for LVI — in our series all cases with LVI were PI-RADS 5 — but at the cost of weaker specificity (since a significant portion of PI-RADS 5 cases did not have LVI). On the other hand, high values of PSA and Gleason offer a balanced sensitivity and specificity, and relatively high AUCs, which make them useful for preoperative risk stratification.

DISCUSSION

This study highlights the importance of an integrated assessment of PSA, mpMRI findings, and biopsy histopathological characteristics for predicting surgical outcomes in prostate cancer. Our results are in agreement with previous research and established knowledge in urologic oncology.

First, the strong prognostic role of pre-biopsy PSA is confirmed — high PSA levels are significantly associated with extracapsular tumor extension and a higher risk of positive surgical margins. This is expected because PSA directly correlates with tumor mass and degree of differentiation: tumors that infiltrate beyond the prostate often secrete more PSA. Our positive margin rate (27.6%) is in line with the reported range of 25—35% in the literature, indicating that our sample is representative and that surgical techniques and criteria for PSM in our institution are similar to those of other centers.

Second, the mpMRI findings and PI-RADS score proved useful, but not sufficient on their own, for assessing aggressiveness. All patients in this series had suspicious lesions (PI-RADS 4 or 5) since they were selected for biopsy and surgery — in other words, lower-score lesions were absent. This limits the evaluation of the value of lower PI-RADS categories, but makes the difference between 4 and 5 significant. In our data, PI-RADS 5 was a clear indicator of higher risk of extensive disease: these patients more often had PNI, LVI, and positive margins (although for some outcomes the difference was not statistically significant due to small numbers). This aligns with the multicenter study by Kəzəlay et al. (2020) which showed that the PI-RADS score significantly correlates with Gleason score, extracapsular extension, seminal invasion, and LVI — in other words, a high PI-RADS score is a good indirect indication of more aggressive pathology. However, MRI has its limitations: as noted by Xu et al. (2023), the PI-RADS score alone does not fully capture all spatial characteristics of the tumor (e.g., the length of contact with the capsule, apical location, etc.) that are important for predicting a positive margin. Therefore, contemporary approaches often combine multiple MRI parameters and clinical data in nomograms or scoring systems to better predict PSM. Our findings support this — mpMRI is a valuable tool, but it functions best in combination with the other parameters.

Third, the Gleason score from the biopsy was confirmed as perhaps the strongest individual predictor of aggressiveness — a fact already well known in urology. In our series, a biopsy Gleason 7 was present in all patients with extracapsular

extension (indirectly assessed via PSM, PNI, LVI or post-op PSA). Those with a biopsy Gleason 6 rarely had adverse findings: about half of them were upgraded to Gleason 7 in the final specimen, but interestingly none of those initially low-risk patients developed LVI or PSM. This suggests that patients with Gleason 6 on biopsy have a very low risk of extensive disease, which is significant for clinical decision-making — they could be candidates for more rigorous nerve-sparing surgery or even active surveillance if other parameters are favorable. On the other hand, the presence of Gleason 7 (or higher) on biopsy should alert clinicians to potential microscopic extension. This is supported by meta-analyses — high Gleason, PNI on biopsy, as well as a greater percentage of positive biopsy cores are consistently identified as independent factors for a positive margin and faster biochemical progression. Our study quantitatively demonstrates the same relationships in our local population.

The main limitation of this study is the relatively small sample (n = 29) from a single center, which reduces statistical power and the possibility of multivariate analyses. Some differences (e.g., for PI-RADS 5) did not reach significance, likely due to lack of statistical power, even though the trends are clear. Furthermore, all patients had suspicious mpMRI, so we have no data for PI-RADS 1—3, which would be interesting for a complete evaluation of the negative prognostic value of mpMRI. Despite these limitations, the findings provide an important insight into the profile of our patients and are in line with global trends.

CONCLUSION AND RECOMMENDATIONS

Conclusion: The integration of preoperative findings — PSA, mpMRI (PI-RADS), and the biopsy Gleason score — provides significant prognostic information on the course of prostate cancer. High PSA (>15 ng/mL), lesions with PI-RADS 5, and a Gleason score ≥7 on biopsy are associated with a greater likelihood of periprostatic tumor extension, positive surgical margins, perineural and vascular invasion, as well as early biochemical progression after prostatectomy. In particular, the biopsy Gleason score stands out as a strong predictor — patients with low grade (Gleason 6) have a very low risk of aggressive pathological findings, whereas the presence of a higher grade (Gleason 7) indicates the need for more careful treatment and follow-up. Similarly, extremely high PSA values and PI-RADS 5 findings should alert the team to the possibility of extracapsular disease.

Recommendations for clinical practice: The results of this study underscore the need for a multidisciplinary approach in evaluating patients with prostate cancer. Preoperatively, the combined consideration of PSA, mpMRI findings, and biopsy histopathology provides the best picture of disease extent. For example, a patient with PSA 18 ng/mL, a PI-RADS 5 lesion and biopsy Gleason 3+4 should be managed as high-risk for incomplete resection — an aggressive surgical approach is recommended (more extensive excision of peri-prostatic tissue, possibly extended lymphadenectomy) with preparedness for adjuvant therapy. In contrast, a patient with PSA 7 ng/mL, PI-RADS 4 and biopsy Gleason 6 has a high chance of organ-confined tumor; for him a nerve-sparing technique can be considered, and the chances of needing adjuvant therapy are low. This information is invaluable for precise patient counseling and planning the surgical strategy. In the future, it would be useful to develop nomograms or scoring systems specific to our population that integrate these parameters (and possibly others, such as percentage of positive biopsies, PSA density, etc.) to predict certain outcomes. In this way, each new patient could be profiled preoperatively on an individual basis, and the team (urologist, radiologist, oncologist) could make the correct decision for optimal treatment. With the modern trend toward personalized medicine, such models of integrated assessment will contribute to better oncological outcomes and preservation of patient quality of life.

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