Original Article

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Predictive Value of PSA Density in Pathological Discordance Terms in Patients who Undergo Robotic Surgery for Low-risk Prostate Cancer: An Analytic Cross-sectional Study of a Tertiary Reference Center

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Abstract

Aim: Pathological discordance between biopsy and radical prostatectomy (RP) remains a critical issue in determining appropriate treatment for prostate cancer (PCa). With this study, we aimed to evaluate the role of prostate specific antigen (PSA) density in predicting pathological discordance in low-risk PCa.

Methods: Data from 95 patients who underwent RP for low-risk PCa with Prostate Imaging Reporting and Data System 1-2 on multiparametric magnetic resonance imaging (MRI) were retrospectively analyzed in this cross-sectional study conducted between January and December 2023. The patients were divided into two groups according on biopsy and robotic-assisted laparoscopic prostatectomy pathology. The "compatible group" was defined as patients with no difference in International Society of Urological Pathology grade and tumor stage, other patients were defined as "incompatible group". The cut-off value for PSA density to predict the presence of pathological discordance was calculated by receiver operating-characteristic curve.

Results: Thirty eight (40%) patients were in the compatible group. No difference was found in serum PSA value between the groups (p=0.440), and a significant difference was found in prostate volume and PSA density (p=0.04 and p=0.001, respectively). The predictive cut-off value of PSA density was calculated as 0.088 ng/mL/cc (area under the curve: 0.729) (p<0.001). The sensitivity, specificity, positive and negative predictive values for this 0.088 ng/mL/cc value were 75.4%, 63.2%, 67.2% and 70.3%, respectively.

Conclusion: Prostate specific antigen density was found to have good performance in predicting pathological discordance in low-risk PCa patients with no pathological lesions detected by multiparametric MRI.

Keywords: Biopsy, prostatic neoplasms, prostatectomy, prostate-specific antigen, PSA density, robotics

Introduction

Early diagnosis of prostate cancer (PCa), the most common type of solid organ cancer in men, is important to ensure high treatment rates and local disease control. With the application of prostate specific antigen (PSA) screening for early diagnosis, there has been a dramatic increase in the number of biopsies and the rate of PCa (1,2). This rise also results in detection of tumors that might have no clinical significance and in unnecessary early diagnosis. In the modern era, in addition to imaging techniques, a number of factors are used in order to prevent unnecessary biopsies and unnecessary early diagnosis. Prostate specific antigen density (PSAD), a parameter identified by Benson et al. (3) in the early 1990s, is defined as the ratio of the serum PSA value to the volume of the prostate. This defined PSAD value has become known for its potential applications in the detection of clinically significant PCa and the prediction of high-risk disease, in addition to helping biopsy decisions (4,5).

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Numerous studies have shown the possibility of pathological incompatibility between radical prostatectomy (RP) pathology and the pathology from prostate biopsies (6). Keskin et al. (7) found that compliance was only detected in 56% of the patients, and nearly half of the patients showed pathological non-compliance. The high rate of pathological non-compliance results in half of the patients receiving either inadequate or excessive treatment. In order to predict pathological incompatibility and prevent unnecessary biopsies, current guidelines recommend multiparametric magnetic resonance imaging (mp-MRI) for nearly all patients prior to biopsy (8). Multiparametric magnetic resonance imaging has a good sensitivity in detecting lesions classified as International Society of Urological Pathology (ISUP) grade group 1<. However, the efficacy of mp-MRI in detecting ISUP grade group 1 lesions remains less than 30% (9). Thus, despite the fact that we are in the era of MRI, the significance of other parameters, such as PSAD, remains due to the low success rate of MRI in ISUP grade group 1 lesions.

With this study, we aimed to investigate the role of PSAD value on the prediction of pathological discordance in patients diagnosed with low-risk ISUP grade group 1 PCa who did not have any lesions detected on mp-MRI.

Methods

After receiving ethics committee approval from the University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital Ethics Committee (approval no.: KAEK/12.06.2024.08, date: June 28, 2024), the data of patients who were diagnosed with PCa by biopsy and underwent robot-assisted laparoscopic prostatectomy pathology (RALRP) was retrospectively analyzed with this cross-sectional study between January 2023 and December 2023 in our tertiary reference center.

Patients who were diagnosed with low-risk PCa according to the D'amico classification using serum PSA value, biopsy pathology [transrectal ultrasound-guided systematic prostate biopsy (12-core)] and digital rectal examinations, and no pathological findings were detected in mp-MRI evaluation [Prostate Imaging Reporting and Data System (PI-RADS) 1 and 2] were included in our study. Patients with intermediate and high risk PCa diagnosis, PI-RADS 2< lesion on mp-MRI, longer than 6 months between the biopsy date and the operation date, parameters that may affect tumor aggressiveness such as the presence of lymphovascular invasion, presence of variant pathology, and cribriform pattern in the biopsy pathology were excluded (Figure 1).

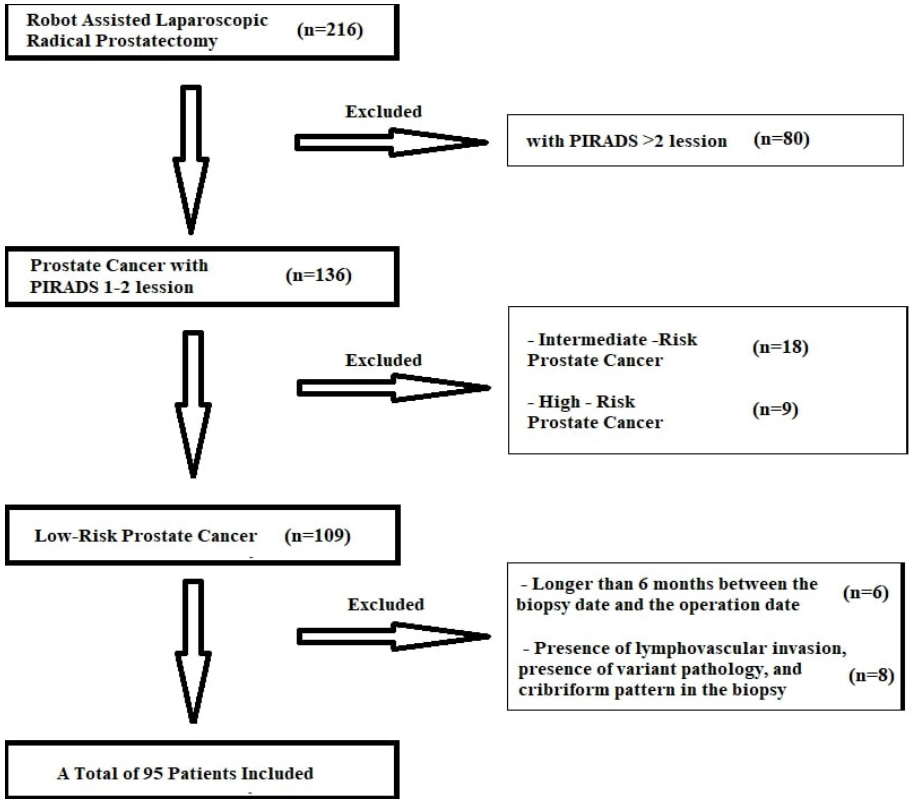

Figure 1. Flowchart of the study
PI-RADS: Prostate Imaging Reporting and Data System

Prostate volume was calculated in cc units by uroradiologists with 5 years of experience using mp-MRI images of the patients. Pathological evaluations of both biopsy and RALRP specimens were performed by uropathologists with at least 5 years of experience. Prostate specific antigen density was calculated in ng/mL/cc unit by dividing the serum PSA value (ng/mL) by the prostate volume (cc).

Gleason scores (GS) in the biopsy and RALRP specimen pathologies of the patients were expressed as ISUP grade scores. An increase in the ISUP grade score in the robot-assisted laparoscopic radical prostatectomy (RYLRP) specimen compared to the biopsy was considered an upgrade. In the pathological examination of the RYLRP specimen, the presence of extracapsular tumor extension, seminal vesicle invasion, and surrounding organ invasion was noted; if at least one of these was present, it was considered a pathological tumor stage increase (upstage).

When compared with the biopsy result, patients in the ISUP grade group and without pathological tumor stage change in the pathology of the RALRP specimen were recorded as the "compatible group", and the other patients were recorded as the "non-compatible group". Within the non-compatible group, patients who have only an elevation in ISUP [upgrade, upgrading patients (UG)] are defined to as "UG only". Similarly, those who alone exhibit an increase in pathological stage [upstage, upstaging patients (US)] are defined as "US only". Lastly, individuals who present both an increase in ISUP and stage are defined as "UG + US".

This study was designed as a retrospective study using only hospital records; informed consent is not obtained.

Statistical Analysis

The data obtained from the patients were analyzed via Statistical Package Program for Social Sciences 22.0. Numbers and percentages were used for descriptive statistics for categorical variables. The mean, minimum, and maximum values were used to describe numerical variables. The distribution of the data was tested using the Kolmogorov-Smirnov test for normality. T-test was used for parameters to compare groups with normal distribution. The cut-off value for PSA density indicating pathological discordance was calculated with the receiver operating-characteristic curve. P-value was considered <0.05 within the 95% confidence interval.

Results

Data from 95 patients were used in our study. The mean PSA value, PSA density and prostate volume (cc) of all patients were calculated as 5.7±1.6 ng/dL, 0.09±0.03 ng/mL/cc and 66.1±34 cc, respectively. All patients (100%, n=95) were found to have PI-RADS<3 lesions on mp-MRI and biopsy pathology was ISUP 1 (GS 3+3=6). The clinical and pathological stages and RALRP pathological datas of the patients were shown in Table 1. Only 40% (n=38) of the patients were found to be in the compatible group. Analysis of the data from patients in the non-compatible group compared to all patients showed that 37.9% (n=36) had only UG, 1.1% (n=1) had US, and 21% (n=20) had both UG and US.

Table 1. Demographic and pathological data

	All patients (n=95)
	Mean±SD
Age	62.5±5.5
BMI (kg/m²)	27.3±2.8
PSA value (ng/dL)	5.7±1.6
PSA density (ng/mL/cc)	0.09±0.03
Prostate volume (cc)	66.1±34
	n (%)
Clinical T-stage	
T1c	73 (76.8%)
T2a	22 (23.2%)
Pathological results of RALRP	
Gleason score	
3+3	40 (42.1%)
3+4	39 (41.1%)
4+3	9 (9.5%)
4+4	1 (1.1%)
4+5	5 (5.3%)
5+3	1 (1.1%)
ISUP grade	
1	40 (42.1%)
2	39 (41.1%)
3	9 (9.5%)
4	2 (2.1%)
5	5 (5.3%)
Pathological T-stage	
T2	74 (77.9%)
T3a	17 (17.9%)
T3b	4 (4.2%)
Compatible group	38 (40%)
Non-compatible group	57 (60%)
UG only	36 (37.9%)
US only	1 (1.1%)
UG + US	20 (21%)

BMI: Body mass index, ISUP: International Society of Urological Pathology, PI-RADS: Prostate Imaging Reporting and Data System, PSA: Prostate specific antigen, PALRP: Robot assisted laparoscopic radical prostatectomy, SD: Standard deviation, UG: Upgrading patients, US: Upstaging patients

There was no difference in PSA values (p-value=0.440) between the patients in the non-compatible group (UG group, US group, and US + UG group) and the patients in the compatible group, but there was a statistically significant difference in prostate volumes and PSA densities (p-value=0.04 and 0.001, respectively) (Table 2).

The cut-off value for PSA density in predicting pathological discordance was calculated as 0.088 ng/mL/cc (area under the curve: 0.729) (p<0.001). For the value of 0.088 ng/mL/cc, sensitivity, specificity, and positive and negative predictive values were calculated as 75.4%, 63.2%, 67.2%, and 70.3%, respectively (Table 3, Figure 2).

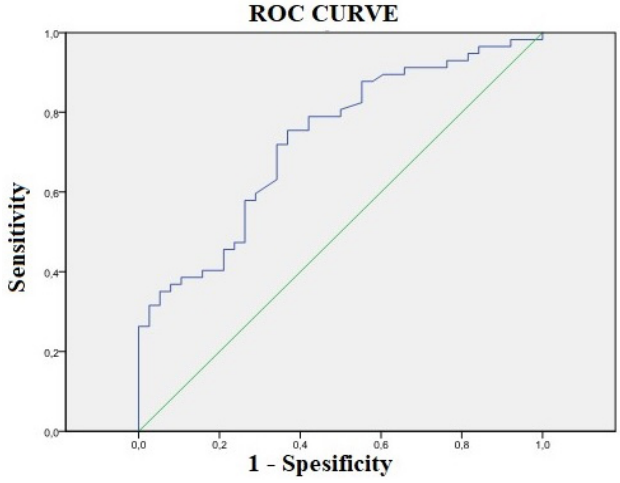

Figure 2. Receiver operating characteristic curve of PSA density predicting pathological progression (area under the curve: 0.729)
PSA: Prostate specific antigen, ROC: Receiver operating characteristic curve

Discussion

Tumor stage (as defined by the tumor-node-metastasis classification) and grade, GS, and ISUP grade classification have been accepted to be useful and reliable factors in predicting the prognosis of PCa. In PCa, tumor stage is determined by digital rectal examination and radiological imaging, and tumor grade is also determined by pathological examination of biopsy cores. Using these parameters, which are indicators of tumor aggressiveness, in addition to the PSA value, patients are classified as low, intermediate, or high risk, and treatment is planned according to this risk classification. Pathological results from biopsies are used to classify patients' risks and plan their treatment, but there can be pathological discordance between the specimen from a RP and the pathology of biopsies from patients who had a RP, depending on the risk class chosen based on the biopsy result. Upgrading is detected at a rate of approximately 30% in RP pathology, depending on the biopsy grade (10). In an another study, the upgrading and upstaging rates were found 42% and 24%, respectively (11).

Considering that more conservative treatment protocols, such as active surveillance, are predominantly applied to low-risk patients, this high pathological discordance rate becomes more clinically important. Failure to determine the correct PCa aggressiveness may lead to inadequate treatment and inappropriate follow-up of aggressive tumors. Since, it appears that some of the low-risk patients who are considered to be in the clinically localized disease group actually have a more aggressive malignancy. Various parameters have been investigated to predict this discordance, and a recent meta-analysis identified age, prostate volume, PSA value, PSAD, number and percentage of positive cores, PI-RADS score, clinical

Table 2. Comparison of pathologically compatible and non-compatible groups

	Compatible group (n=38)	Non-compatible group (n=57)					
		UG only (n=36)	p-value	US only (n=1)	p-value	US + UG (n=20)	p-value
PSA value (ng/dL)	5.65±1.5	5.71±1.9	0.880*	5.6	n/a	5.97±1.2	0.440*
Prostate volume (cc)	78.8±39.0	61.6±31.5	**0.041***	35	n/a	51.7±16.8	**0.004***
PSA density (ng/mL/cc)	0.081±0.028	0.103±0.034	**0.004***	0.16	n/a	0.124±0.044	**0.001***

Bold values refer to statistical significance. *t-test
PSA: Prostate specific antigen, UG: Upgrading patients, US: Upstaging patients

Table 3. Cut-off value of PSA density in predicting pathological discordance

	Cut-off value	Sensitivity (%)	Specificity (%)	PPV	NPV	AUC (95% CI)	p-value
PSA density (ng/mL/cc)	0.088	75.4%	63.2%	67.2%	70.3%	0.729	<0.001

AUC: Area under the curve, NPV: Negative predictive value, PPV: Positive predictive value, PSA: Prostate specific antigen, CI: confidence interval

T-stage, surgical margin status, and pathological T-stage as independent factors predicting upgrading following RP (6).

Several research have been published in the literature to reduce high rates of upgrading. It has been shown in the literature that the upgrading rate decreases as the number of sample cores taken in the biopsy increases. King et al. (12) showed that extended biopsy reduced GS upgrading from 66.7% to 36.8% in patients with a biopsy GS of 6. Capitanio et al. (13) study also showed that taking more than 18 core biopsy samples in low-risk PCa patients reduced the GS upgrading rate from 47.9% to 23.5%. Since the question of what the optimal number of biopsy cores should be for any biopsy technique is still unclear, Chambó et al. (14) recommend that at least 10 biopsy samples be obtained in patients with low-risk PCa. The European Urology Association guideline recommends that taking samples from more than 12 cores does not have an additional contribution to diagnosis and suggests a systematic 12-core biopsy for patients with suspicions of PCa who don't have any lesions on MRI (PI-RADS 1-2) (15). For this reason, it is even more important to predict pathological discordance in patients who have no lesion detected on MRI (PI-RADS 1-2) and who undergo systematic 12-core biopsy with suspicion of PCa. It seems that several parameters are needed other than increasing the number of cores to predict pathological compatibility and reduce possible non-compatible, especially in this patient group. We designed our analysis to include only patients who had a systematic 12-core biopsy in order to analyze the importance of the parameters in this group. Some studies in the current literature have shown that the percentage of positive cores among the all the sampled cores may affect the pathological concordance between biopsy and RP. A few studies have shown that an increase in the number of positive cores is associated with an increase in the GS upgrading rate, but there are also studies in the literature showing that there is no relationship between them (11,16). Since there is still no clear information on this issue, we did not evaluate the effect of positive core rate on compliance in this study.

The relationship between preoperative serum PSA value and GS upgrading also varies in the literature, similar to other parameters. Moussa et al. (18) showed that PSA level was a statistically significant determinant of GS upgrading, since the studies of Mian et al. (17), Jin et al. (11), and King et al. (12) did not show any relationship. In our study, no significant relationship was found between PSA level and GS upgrading.

Increased prostatic volume has been shown to lower the risk of GS upgrading (19). The relationship between prostatic volume and upgrading has been tried to be explained by the fact that the presence of a small prostate volume is an indicator of low *in vivo* androgenicity and that PCa, an androgen-dependent cancer, can develop despite this low *in vivo* androgenicity. This may indicate that cancer cells developing in the small-volume prostate may be a more aggressive tumor (20). Jin et al. (11) showed that patients with upgrading had significantly lower prostate volume, but in the same study, this low volume was not shown to be a predictor for upgrading in regression analysis. In this study, we found that patients with upgrading had lower prostate volume, similar to the literature. The choice of tool for calculating prostate volume affects the reliability of PSAD. Ultrasonography (USG) and MRI are the most commonly used methods. Transabdominal measurements generally yield higher prostate volumes than transrectal USG, which tends to underestimate prostate volume compared to mp-MRI. Additionally, mp-MRI-based PSAD calculations have shown a higher detection rate for PCa than transrectal USG (21,22). In our study, to minimize this bias, we used prostate volume calculated from mp-MRI for all measurements.

The PSAD was initially introduced as a more accurate predictor of PCa than PSA, but its use has been inconsistent in daily practice over the years. However, it was found to be associated not only with cancer detection but also with cancer aggressiveness (23). Several studies on PSAD-based upgrade prediction have been published in the literature. Corcoran et al. (24) showed that 58.3% of patients diagnosed with low-risk PCa increased to higher GS in RP pathology and that PSA density was a significant predictor of upgrading in ISUP group 1 patients. Similar results were shown by Kojima et al. (25) and Magheli et al. (26). Jin et al. (11) found 0.13 ng/mL as a significant predictive value for PSAD, with a sensitivity and specificity rate of 40% and 92%, respectively, to predict upgrading, and in the same study, they recommend using PSAD together with other predictive factors, considering the complexity of PCa. Sfoungaristos et al. (27) determined this value as 0.15 ng/mL. However, in the current study by Ozkaya et al. (28), the PSAD value was 0.18 ng/mL in the upgraded group and 0.16 ng/mL in the non-upgraded group, with no significant difference observed between the two, contrary to these previous studies. Our study showed a significant predictive value in predicting pathological discordance for 0.088 ng/mL, with a higher sensitivity of 75.4% and a lower specificity of 63.2%, contrary to the literature.

Study Limitations

There are some limitations in our study. First of all, the retrospective design of our study and the low number of patients are the main limitations of our study. In addition, the presence of more than one uroradiologist and uropathologist in both the evaluation of MRI images and pathological examination may lead to interobserver

differences, and this is considered another important limitation of our study. There is no clear period in the literature to prevent changes in tumor stage and grade between biopsy and RP operation in PCa patients. Therefore, in our study, we limited this period to 6 months, depending on our high clinical patient load. Yet, it is predictable that different outcomes may arise within shorter or longer periods. Hence, this duration interval between two processes acts as a further limitation in our study. Despite these limitations, using only MRI for prostate volume calculation is a strength of our study.

Conclusion

Our study highlights the ongoing significance of PSAD in predicting the consistency between biopsy and RP material in patients diagnosed with low-risk ISUP grade 1 PCa, particularly when mp-MRI detects no pathological lesion. Prostate specific antigen density is easy to use and calculable; despite recent technological developments, its significance remains valuable and it is a good predictor for upgrading and upstaging in PCa.

Footnote

Ethics Committee Approval: The study was initiated after receiving approval from the University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital Ethics Committee (approval no.: KAEK/12.06.2024.08, date: June 28, 2024).

Informed Consent: This study was designed as a retrospective study using only hospital records; informed consent is not obtained.

Authorship Contributions

Surgical and Medical Practices: E.T.K., O.C., Y.C.F., H.O., M.S., A.S., H.L.C., Concept: E.T.K., O.C., A.S., H.L.C., Design: E.T.K., A.S., H.L.C., Data Collection or Processing: E.T.K., Analysis or Interpretation: E.T.K., O.C., Y.C.F., H.O., M.S., Literature Search: E.T.K., Writing: E.T.K., O.C., Y.C.F., H.O., M.S.

Conflict of Interest: No conflicts of interest were declared by the authors.

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