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ORIGINAL RESEARCH

Medicine Science International Medical Journal

Medicine Science 2019;8(1):211-7

Evaluation of concordance between histopathological prognostic findings from prostate needle biopsy samples and serum prostate-specific antigen levels

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Received 05 Febuary 2019; Accepted 12 Febuary 2019
Available online 04.03.2019 with doi:10.5455/medscience.2019.08.9016

Abstract

Prostate cancer is the most common cancer in men. Although the prostate-specific antigen (PSA) is still used as a diagnostic and screening test, there are some controversies about its performance for the differentiation of high-risk cancer from low-risk cancer at an early stage. The Gleason grading system for the pathological grading of prostatic adenocarcinoma is based on the architectural patterns of prostatic glands and it is one of the major predictors of prostate cancer prognosis and clinical management. This study aimed to investigate the concordance between histopathological prognostic findings from prostate needle biopsy samples and serum PSA levels. This retrospective study included data from 150 patients with histopathologically diagnosed as prostatic adenocarcinoma. All patients underwent multi-core transrectal ultrasound-guided prostate needle biopsy because of elevated PSA. Pathological data were classified as high-grade (≥7, 4+3) and low-grade (≤7, 3+4) based on the Gleason score values. Laboratory data were classified as high-risk (>10 ng/mL) and low-risk (≤10 ng/mL) based on the PSA levels. Ninety three (62%) patients had PSA >10 ng/mL. Seventy patients (46.7%) had Gleason score ≥7 (4+3). Age, tumor volume, PSA levels, and the number of tumor-positive cores were significantly higher in the tumors with Gleason score ≥7 (4+3). Tumor volume, Gleason score, and the number of tumor-positive cores were significantly higher in the tumors with PSA >10 ng/mL. Lymphovascular invasion (LVI) and perineural invasion (PNI) positivity were more often in the high-grade and high-risk tumors. Age, tumor volume, PSA, and the number of tumor-positive cores showed a significant positive correlation with the Gleason score and tumor volume. The cut-off values of PSA (Gleason score ≤7 vs ≥7) was 15.45 ng/mL with AUC=0.882 (95% confidence interval, CI: 0.82 to 0.94), sensitivity was 87% (95% CI: 0.76 to 0.94), specificity was 81% (95% CI: 0.69 to 0.88), and likelihood ratio was 4.4.

Keywords: Biopsy, needle, neoplasm grading, pathology, prostatic neoplasms, prostate-specific antigen

Introduction

Prostate cancer is the most common cancer in men and the second leading cause of cancer death [1]. With the introduction of prostate-specific antigen (PSA) screening programs, prostate cancer incidence increased in recent years. Age, PSA testing, and family history are the most important risk factors for prostate cancer [2].

PSA is a kallikrein-like serine proteinase and an esterase produced by prostatic ductal and acinar epithelial cells. PSA liquefies semen, enhances sperm motility, and dissolves cervical mucus. In the blood, PSA is present in very low concentrations. Serum PSA level increases in prostate cancer, but many benign conditions, including prostate irritation, prostatic infection, and benign prostatic hyperplasia, also cause the elevation in PSA levels [3,4].

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The Gleason grading system for the pathological grading of prostatic adenocarcinoma is based on the architectural patterns of prostatic glands. It is a measure of the degree of differentiation and tumor aggression in prostate cancer. The Gleason grading system was first described by Donald Gleason in1966. As most of the tumors typically had two histologic patterns, a score was created that added the two most common grade patterns in a tumor, with scores ranging from 2 to 10 [5]. In this system, the degree of glandular differentiation and the growth pattern of a tumor in relation to the stroma are evaluated. It is only based on cancer architecture and not influenced by cellular morphology. In course of time, It has undergone various modifications. Although these modifications, the Gleason grading system is still one of the major predictors of prostate cancer prognosis and clinical management [6,7].

Although the PSA is still used as diagnostic and screening test, there is some controversies about its performance for differentiation of high-risk cancer from low-risk cancer at an early stage. It has

been reported that PSA has not shown the ability to discriminate high-risk cancer from low-risk cancer [8]. Furthermore, although current modifications have improved the Gleason grading system, there are differences in interpretation among pathologists. Many of the cancers differently interpreted by multiple pathologists represent borderline cases between 3+3=6 and 3+4=7 or between 3+4=7 and 4+3=7 [9]. Thus, the present study was conducted in order to investigate the concordance between histopathological prognostic findings from prostate needle biopsy samples and serum PSA levels.

Materials and Methods

Data collection

This retrospective study included data from 150 patients with histopathologically diagnosed as prostatic adenocarcinoma at the Department of Pathology of the Education and Research Hospital between 2011 and 2017. The clinic, histopathologic, and laboratory records of patients, who underwent prostate needle biopsy because of elevated tPSA, were collected. All patients underwent multi (≤12)-core transrectal ultrasound (TRUS)-guided prostate needle biopsy. The following inclusion criteria were applied: 1. increased serum tPSA was incidentally found from physical examinations; 2. all pathological results of biopsy specimens were prostatic adenocarcinoma. Patients with missing serum PSA data and no sufficient medical records were excluded from this study. The study was in accordance with the principles outlined in the Declaration of Helsinki. Ethical approval was received from the local Human Non-invasive Clinical Research Ethics Committee. The informed consent was not requested since the study was retrospective and the data were analyzed anonymously.

Study design

The histopathological characteristics of prostate biopsy specimens including tumor volume, Gleason score, total number of core biopsies taken, the number of tumor positive cores, the status of lymphovascular invasion (LVI) and perineural invasion (PNI) were obtained from pathological reports, retrospectively. Pathological data were classified as high (≥7, 4+3) and low (≤7, 3+4) grade tumor based on the Gleason score values [5,10]. Pre-biopsy hematological laboratory data including tPSA were collected from routine laboratory test records. Laboratory data were classified as high-risk (≤10 ng/mL) and low-risk (>10 ng/mL) based on the tPSA levels [11].

Statistical analysis

Statistical analyses were performed using GraphPad Prism version 6.05 (GraphPad Software, Inc., CA, USA). All data sets were tested for normality using the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean ± standard deviation (SD). Not normally distributed data were expressed as median and interquartile range (IQRs). Parametric or non-parametric statistical tests were used according to the distribution of data. The comparisons of continuous variables between groups were analyzed with Mann Whitney-U or two-tailed unpaired student-t test according to the normality of data. For categorical variables, two-tailed Fisher's exact test was used. The correlation analyses were performed using the Spearman's coefficient of rank correlation analysis since data were not normally distributed. In order to detect the sensitivity and specificity of PSA for discriminating of high-grade tumor from the low-grade tumor, the area under the ROC curve was analysed and the cut-off value of tPSA was calculated. A P value <0.05 was considered statistically significant.

Results

Demographic and laboratory parameters of the patients are represented in Table 1. The mean age of the study population was 70.6 ± 8.5. Ninety three (62%) patients had PSA >10 ng/mL. Seventy patients (46.7%) had Gleason score ≥7 (4+3). Lymphovascular invasion was positive in 47 patients (31.3%) and PNI was positive in 77 patients (51.3%).

Table 1. Demographic, histopathological, and laboratory data of patients.

Parameters	n = 150
Age (years)	70.6 ± 8.5
Total Gleason score	7.0 (6.0 – 8.0)
Primary and secondary patterns of Gleason score (n)	
2+2	2
2+3	3
3+2	1
3+3	60
3+4	14
3+5	1
4+3	19
4+4	20
4+5	17
5+3	2
5+4	10
5+5	1
Tumor volume (%)	40 (17 – 75)
Lymphovascular invasion (n)	
Positive	47
Negative	103
Perineural invasion (n)	
Positive	77
Negative	73
Total number of core biopsies taken (n)	12 (10 – 12)
The number of tumor positive cores (n)	5 (2 – 9)
Total PSA (ng/mL)	15.5 (8.1 – 46.4)

*Abbrevations: PSA: Prostate-specific antigen. Normally distributed data are presented as mean ± SD, not normally distributed data are presented as median and interquartile ranges (IQRs).

Significant differences were observed between groups categorized as high and low-grade based on the Gleason score values for age, tumor volume, tPSA, the number of tumor positive cores, LVI, and PNI (P=0.0002, P<0.0001, P<0.0001, P<0.0001, P<0.0001, P < 0.0001, respectively) (Table 2). The results of the study revealed that age, tumor volume, the number of tumor positive cores, and tPSA values were significantly higher in the tumors with Gleason score ≥7 (4+3) compared to the tumors with Gleason score ≤7 (3+4). LVI and PNI positivity were more often in the high-grade tumors (Figure 1).

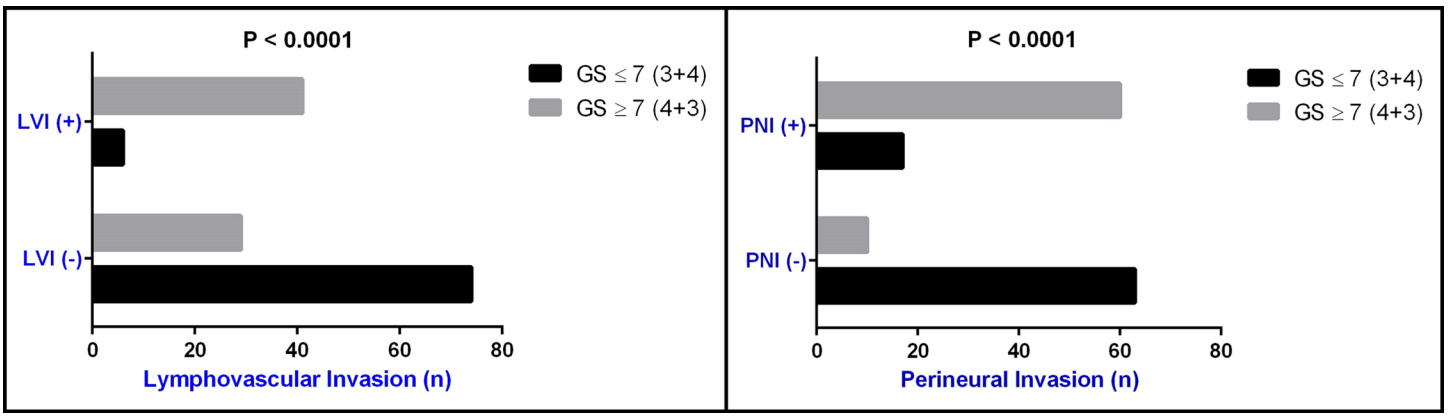

Figure 1. The distribution of the status of LVI and PNI in low-grade and high-grade tumors

Table 2. The comparisons of prognostic variables between low-grade (Gleason Skor ≤7, 3+4) and high-grade (Gleason Skor ≥7, 4+3) tumor groups

	Gleason Skor ≤ 7 (3+4) (n=80)	Gleason Skor ≥ 7 (4+3) (n=70)	p
Age (years)	68 (62-74)	75 (67-81)	0.0002*
Tumor volume (%)	17 (9.5 - 30)	75 (48.8 - 90)	< 0.0001*
Total PSA (ng/mL)	9.4 (6.9 - 14.4)	47.5 (19.4 - 100)	< 0.0001*
The number of tumor positive cores (n)	3 (2 – 5)	8 (6 – 10)	< 0.0001*
Lymphovascular invasion (n)			< 0.0001*
Positive	6	41	
Negative	74	29	
Perineural invasion (n)			< 0.0001*
Positive	17	60	
Negative	63	10	

*Abbrevations: PSA: Prostate-specific antigen. Normally distributed data are presented as mean ± SD, not normally distributed data are presented as median and inter-quartile ranges (IQRs). Normally distributed data were tested using the two-tailed Student-t test. Not normally distributed data were tested using the Mann–Whitney U-test. A P-value < 0.05 was considered statistically significant.

Significant differences were found for tumor volume, Gleason score, the number of tumor positive cores, LVI, and PNI between groups categorized as high and low risk based on tPSA levels (P <0.0001, P <0.0001, P <0.0001, P=0.046, P <0.0001, respectively) (Table 3). As illustrated in Figure 2, LVI and PNI positivity were significantly higher in the tumors with tPSA >10 ng/mL.

The data were analyzed using Spearman's coefficient of rank correlation to evaluate the possible association of prognostic variables with Gleason score and tumor volume in 150 patients (Table 4). Age, tumor volume, tPSA, and the number of tumor positive cores showed significant positive correlation with the Gleason score (r=0.336, P <0.0001; r=0.787, P <0.0001; r=0.667, P <0.0001; r=0.716, P <0.0001, respectively). Correlations between tumor volume, age, tPSA, and the number of tumor positive cores were also analyzed (Table 4). Age, tPSA, and the number of tumor positive cores showed significant positive correlation with the tumor volume (r=0.254, P=0.0017; r=0.736, P <0.0001; r=0.786, P <0.0001, respectively).

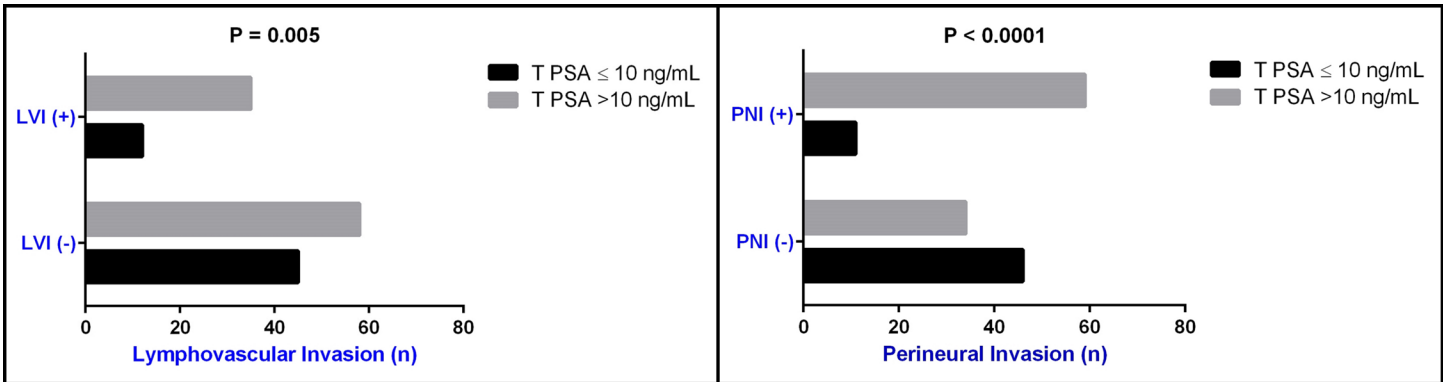

Figure 2. The distribution of the status of LVI and PNI in low-risk and high-risk

Table 3. The comparisons of prognostic variables between low-risk (tPSA ≤10.0 ng/mL) and high-risk (tPSA >10.0 ng/mL) tumor groups

	tPSA ≤ 10.0 ng/mL (n=57)	tPSA > 10.0 ng/mL (n=93)	p
Age (years)	70 (62-74)	71 (65-79)	0.154
Tumor volume (%)	15 (8 - 25)	60 (25 – 81.5)	< 0.0001*
Gleason Score	6 (6 - 6)	7 (6 - 8)	< 0.0001*
The number of tumor positive cores (n)	3 (1 – 4)	6 (3 – 9)	< 0.0001*
Lymphovascular invasion (n)			0.046*
Positive	12	35	
Negative	45	58	
Perineural invasion (n)			< 0.0001*
Positive	11	59	
Negative	46	34	

*Abbrevations: PSA: Prostate-specific antigen. Normally distributed data are presented as mean ± SD, not normally distributed data are presented as median and inter-quartile ranges (IQRs). Normally distributed data were tested using the two-tailed Student-t test. Not normally distributed data were tested using the Mann–Whitney U-test. A P-value < 0.05 was considered statistically significant.

Table 4. The associations of prognostic variables with Gleason score and tumor volume

n = 150	Gleason Score	
	r	P
Age (years)	0.336	< 0.0001*
Tumor volume (%)	0.787	< 0.0001*
tPSA (ng/mL)	0.667	< 0.0001*
The number of tumor positive cores (n)	0.716	< 0.0001*
n = 150	**Tumor Volume**	
	r	P
Age (years)	0.254	0.0017*
Gleason Score	0.787	< 0.0001*
tPSA (ng/mL)	0.736	< 0.0001*
The number of tumor positive cores (n)	0.786	< 0.0001*

*Abbrevations: PSA: Prostate-specific antigen. Data were tested using the Spearman's coefficient of rank correlation analysis since data were not normally distributed.. A P value less than 0.05 was considered statistically significant.

Diagnostic value and clinical usefulness of tPSA for discrimination of a high-grade tumor (GS ≥7, 4+3) from the low-grade tumor (GS ≤7, 3+4) were evaluated by analysing area under the ROC curve. The cut-off values of tPSA was 15.45 ng/mL with AUC=0.882 (95% confidence interval, CI: 0.82 to 0.94; standard error, SE: 0.03, P <0.0001), sensitivity was 87% (95% CI: 0.76 to 0.94), specificity was 81% (95% CI: 0.69 to 0.88), and likelihood ratio was 4.4 (Figure 3).

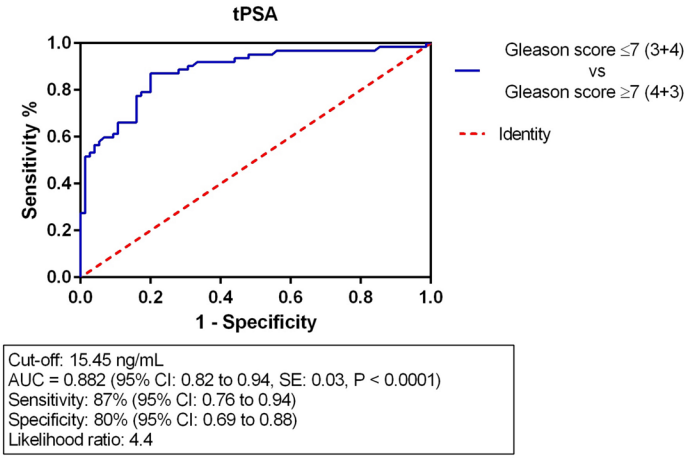

Figure 3. The area under the ROC curve analysis of PSA as diagnostic test for discriminating of high-grade tumor from the low-grade tumor (Gleason score ≤7 vs ≥7)

Discussion

Current screening and diagnostic procedures in prostate cancer recommended by European Association of Urology (EAU) - European Society for Radiotherapy & Oncology (ESTRO) - International Society of Geriatric Oncology (SIOG) Guidelines are based on PSA measurements and digital rectal examination (DRE) or TRUS. For pathological analysis, the Gleason score is recommended to evaluate tumor grade [12]. The Gleason score and other clinical variables are commonly used to create risk stratification for patient management. The most common risk stratification procedures for prostate cancer is the National Comprehensive Cancer Network (NCCN) and D'Amico classification system. It classifies prostate cancer as low risk (Gleason score: 2–6, PSA ≤10), intermediate risk (Gleason score: 7, PSA >10–20), and high risk (Gleason score: 8–10, PSA >20)

according to the serum PSA level and the Gleason score both 3+4=7 and 4+3=7 is considered the same within the intermediate risk group [13,14]. There is considerable disagreement in the literature regarding Gleason score grouping. Some studies have reported that Gleason 7 tumors should be further subdivided, with most of them suggesting a categorization into Gleason 3+4 and Gleason 4+3 tumors depending on the predominant Gleason pattern seen in cancer [15-17]. Despite the confirmed prognostic value of Gleason score in prostate cancer, Gleason score 7 tumors exhibit a heterogeneous clinical outcome. Several studies have shown that Gleason score 4+3=7 demonstrates worse pathological stage and biochemical recurrence rates than 3+4=7. This could be explained by the presence of both moderately (Gleason pattern 3) and moderately to poorly (Gleason pattern 4) differentiated elements with various proportions in GS 7 tumors. [15,18,19]. In this study, prostatic adenocarcinomas with Gleason 7 score were grouped as 3+4 and 4+3 based on the modified International Society of Urological Pathology (ISUP) 2014 Gleason grading system [10].

The high sensitivity and low specificity of PSA testing in the diagnosis of prostate cancer is a problem in clinical practice. Despite this disadvantage, PSA is still a clinically useful tumor marker for the early detection of prostate cancer. In general, an increased PSA may indicate the presence of prostate carcinoma and higher PSA levels may reflect the greater risk of prostate cancer. However, data from several studies have shown that this relationship is not valid as previously thought [2,20,21]. Thus, diagnostic performance and clinical usefulness of tPSA for distinction of a high-grade tumor from the low-grade tumor were investigated in this study. In addition, it was examined whether an agreement between serum tPSA levels and histopathological prognostic parameters.

Several factors were assessed for potential association with prostatic adenocarcinoma in the present study. It was observed that advanced age and increased tPSA levels had a significant association with prostatic adenocarcinoma. Age and tPSA levels showed a significant positive correlation with the Gleason score. When data were grouped as high and low-grade tumor based on the Gleason score values, tPSA levels were significantly higher in the tumor with the Gleason score ≥7. Furthermore, when data were classified as low and high risk based on tPSA levels, the Gleason scores were higher in the group with tPSA >10 ng/mL. These findings are consistent with several studies in the literature [22-25]. Bright and colleagues reported that advanced age and elevated serum PSA levels were found to be predictive of incidentally diagnosed prostatic carcinoma [22]. Gunda et al. found that incidental prostatic carcinoma was independently associated with age of 70–80 years and PSA levels >10ng/mL [23]. In another study, PSA level and Gleason score contributed significantly to the prediction of pathological stage [24]. Guimaraes and colleagues also found a positive correlation between high-grade Gleason score and higher preoperative PSA [25]. On the other hand, contrary results were obtained by Antunes et al. In their study, while advanced age was significantly associated with the finding of prostatic carcinoma, the PSA levels did not have any significant association with incidental prostatic carcinoma [26]. Pai et al. found no significant correlation between tumor grade by Gleason score and pre-operative levels of PSA [27]. In another study, PSA and age were not found to significantly correlate with the Gleason score [28].

In this study, increased tPSA levels were also significantly associated with tumor volume. Tumor volume values were higher in the group with tPSA levels >10 ng/mL. At the same time, tumor volume values were positively correlated with Gleason score values. Consistent with the findings of this study, Kato et al. found positive correlations between the serum PSA levels and the tumor volume [29]. In a study by Carvalhal et al, it has been found that PSA had a significant correlation with prostate size only at a prostate weight ≥ 54.6 gm (P=0.01). Regardless of prostate size, PSA had a more strong correlation with tumor volume than with prostate size (P<0.0001). Authors suggested that PSA was significantly correlated with prostate size only in the largest prostate glands, but was significantly associated with tumor volume in small, medium, or large prostates. Thus, PSA continues to be a better marker for tumor volume than for prostate size [30]. Although higher grade and larger volume tumors produce less PSA per cell as compared to lower grade tumors, poorly differentiated tumors are associated with higher PSA levels as these tumors tend to be larger and of more advanced stage [31]. In contrast to findings of the present study, Stamey and colleagues reported a decrease in the association of PSA with tumor volume. In a series of 1300 radical prostatectomies performed from 1993 to 2003, Stamey et al. divided the cases into four 5-year time intervals. The association between PSA and tumor volume decreased over time. The authors suggested that the loss of correlation with tumor volume may compromise the current usefulness of PSA for early prostate cancer detection [32].

It was found that LVI and PNI were prognostic factors in prostatic adenocarcinoma in this study. Lymphovascular invasion and PNI positivity were more often in high grade and high-risk groups. This is similar to the findings of Miyake et al. Their study included 959 patients diagnosed as GS 7 prostate cancer. They grouped patients as Gleason score 3+4 and 4+3. They found significant differences in the PSA level, LVI, and PNI between these 2 groups [33]. Cheng et al. found a significant association between LVI and higher serum PSA, advanced pathological stage, higher Gleason score, and PNI [34]. Liu et al. reported that LVI and PNI indicated a worse prognosis in patients with prostate cancer [35]. Jiang et al. observed that LVI was correlated with Gleason score, higher pathological stage, positive surgical margin, and seminal vesicle invasion. Authors suggested that LVI in histopathology is associated with advanced clinicopathological features in prostate cancer patients and could serve as a poor prognostic factor in patients who underwent radical prostatectomy [36]. In a study by Kang et al., it has been found that patients with PNI or LVI had higher rates of advanced biopsy and pathological Gleason score (≥7), and higher proportions of advanced clinical and pathological T stage ≥3. Researchers suggested that PNI and LVI are adverse pathologic parameters and independent predictors for prostate cancer, and the concurrent presence of PNI and LVI resulted in poorer outcomes in prostate cancer patients who underwent radical prostatectomy [37].

Early reports by Partin et al. and D'Amico et al. defined important PSA cut-off points of <10, 10.1–20, and >20 ng/mL that are still used to define prostate cancer risk stratification groups [13,14,24]. In a study by Catalona et al., cancer was found in 26% of the men

with a PSA level of 4.0 to 10.0 ng/mL. 72% of these tumors were confined to the prostate. Cancer was found in 66% of patients with a serum level >10.0 ng/mL. While 77% of these cancers were clinically localized, only 33% of the patients had a prostate-confined cancer. Thus, PSA levels of 4 to 10 ng/mL will detect cancer pathologically confined to the prostate, but if the level is >10 ng/mL, patients will have locally advanced cancer according to the findings of the study by Catalona et al [38]. In the present study, ROC curve was analysed and the cut-off value of tPSA was calculated to detect the sensitivity, specificity, and diagnostic performance of PSA for distinction of a high grade (Gleason score ≥7, 4+3) tumor from the low grade (Gleason score ≤7, 3+4) tumor. It was found that the cut-off values of tPSA was 15.45 ng/mL with AUC = 0.882 (95% CI: 0.82 to 0.94), sensitivity was 87% (95% CI: 0.76 to 0.94), specificity was 81% (95% CI: 0.69 to 0.88), and likelihood ratio was 4.4. According to these findings, tPSA values higher than 15.45 ng/mL indicated poorly differentiated and high graded tumors. Lojanapiwat et al. found similar results with the present study. They studied the correlation and diagnostic performance of the PSA level with cancer diagnosis and aggressiveness of prostate cancer (Gleason score >7) in 1.116 patients who underwent TRUS and prostate biopsy. A positive biopsy result was found in 395 patients and these patients were grouped based on baseline PSA level. A significant correlation was found between the PSA level and tumor diagnosis and tumor aggressiveness. AUC was 0.82 for the diagnosis of prostate cancer and 0.78 for Gleason score >7. The sensitivity and specificity of PSA level of 4.1–10, 10.1–20, 21.1–50, 50.1–100, and >100 ng/mL in the diagnosis prostate cancer was 98.0% and 9.3%, 81.5% and 55.5%, 65.8% and 87.5%, 47.8% and 98.2%, 34.4% and 99.7%, respectively. Lower sensitivity was found at higher PSA levels, whereas the specificity was elevated when the PSA level was higher. The sensitivity and specificity of PSA level of 4.1–10, 10.1–20, 21.1–50, 50.1–100, and >100 ng/ for tumor aggressiveness (tumor with Gleason score >7) was 97.8% and 1.99%, 91.6% and 36.4%, 83.2% and 62.8%, 66.5% and 79.3%, 52% and 87.8%, respectively. Authors suggested that the chance of prostate cancer diagnosis was more than that of benign prostatic hyperplasia and the chance of detection of prostate cancer was about 50% when the biopsy was performed when the PSA level was higher than 20 ng/mL [39].

Conclusion

The correct diagnosis and grading of prostate cancer are very important for a patient's prognosis, clinical management, and therapeutic options. The findings of this study reveal that there is a well correlation between serum PSA levels and Gleason score, tumor volume, the number of tumor positive cores, LVI, and PNI. Tumors with high-grade Gleason score show an associaton with more increased PSA level, more extensive tumor volume, more often LVI, PNI positivity, and advanced age. As mentioned above, although PSA has relatively a low specificity, with high sensitivity, it can be used in urologic practice for discrimination of a low-grade tumor from the high-grade tumor. Consequently, both PSA and Gleason grading system is a clinically useful diagnostic and prognostic tool for the management of prostate cancer.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Ethical approval was received from the local Human Non-invasive Clinical Research Ethics Committee.

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