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Adverse Pathological Outcomes in Radical Prostatectomy Specimens in Patients with a Serum Prostate-specific Antigen Level ≤3 ng/mL

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Abstract

Objective: To evaluate clinicopathological features of patients with serum prostate-specific antigen (PSA) level of ≤3 ng/mL and diagnosed with prostate cancer (PCa).

Materials and Methods: A total of 34 male patients diagnosed with PCa by either prostate needle biopsy (PNB) or transurethral resection of the prostate (TUR-P) were included in this study between January 2010 and June 2021. Patients whose preoperative serum PSA level was >3 ng/mL and those with missing clinical data were excluded. Preoperative clinical characteristics of the patients and pathological findings of PNB, TUR-P, and radical prostatectomy (RP) specimens were evaluated.

Results: The median age of the patients was 65 (60-69) years. The median preoperative serum PSA level was 1.98 (1.45-2.64) ng/mL. PCa was detected by "systematic prostate biopsy (SBx) only", combined prostate biopsy [SBx following multiparametric magnetic resonance imaging-targeted prostate biopsy (TBx)], and "TUR-P" in 6 (17.6%), 17 (50.0%), and 11 (32.4%) patients, respectively. In combination of both biopsy, PCa was detected in "SBx specimens only", "TBx specimens only", and "both TBx and SBx specimens" in 3 (8.8%), 5 (14.7%), and 9 (26.5%) patients, respectively. Clinically significant (cs) PCa was in 52.9% of the TBx (9/17) and 60.9% of the SBx (14/23) specimen. Twenty (58.8%) patients treated with RP. csPCa in RP specimens was observed in 17/20 (85.0%) patients. Upgrading in RP specimens compared with PNB specimens was observed in 5/11 (45.5%) of the TBx and 9/17 (52.9%) of the SBx specimen. At the final RP pathology, International Society of Urologic Pathology-grade group >3 or non-organ confined disease were observed in 8 (40%) and 8 (40.0%) patients, respectively.

Conclusions: Adverse pathological outcomes in RP specimens are frequent in patients with PCa with a serum PSA level of ≤3 ng/mL at the time of diagnosis, and physicians should be aware of the limitations of pre-set PSA cut-off levels.

Keywords: Pathological outcomes, prostate needle biopsy, prostate-specific antigen, prostate neoplasms, radical prostatectomy, transurethral resection of prostate

Introduction

Prostate cancer (PCa) is the 2nd most common form of cancer in men worldwide, with an estimated 1,276,106 new cases and 358,989 deaths (1). Although several potential etiological risk factors have been reported, such as family history, exogenous/environmental factors, chronic inflammation, geographical region, and dietary habits, the most important factor increasing the incidence of PCa is aging (2,3,4). The prevalence of PCa in the young male population is very low. The estimated mean prevalence of PCa at the of age <30 years is 4%, and it is increased to 49% by age >79 years (2).

Two main indications for prostate needle biopsy (PNB) are elevated serum prostate-specific antigen (PSA) levels and suspicious findings on digital rectal examination (DRE) (3). Currently, multiparametric magnetic resonance imaging (mpMRI) is recommended before a PNB decision, even in biopsy-naïve patients. Transrectal ultrasound-guided systematic prostate biopsy (SBx) (with a minimum of 10 to 12-cores) or SBx + MRI-targeted prostate biopsy (TBx) (when MRI is positive) PNB has been accepted as the standard diagnostic approach for the evaluation of patients with a clinical suspicion for PCa (3). However, the definition of elevated PSA levels is still quite vague and a source of discussion.

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Serum PSA levels of <4 ng/mL was initially defined as "normal" and PNB was recommended for higher serum PSA levels (5,6). However, a significant rate of PCa was reported in men with serum PSA levels of 2.6 to 4.0 ng/mL, and subsequently, PSA levels of ≥2.6 ng/mL were accepted as more appropriate for a PNB indication (7). Nevertheless, the risk of PCa was found to be significantly elevated for patients with PSA levels higher than their age-specific medians (8,9,10). Detection of International Society of Urologic Pathology (ISUP)-grade group ≥2 cancers with a higher frequency is quite possible with very low levels of PSA, and an optimal threshold for PSA in detecting clinically significant (cs) PCa is yet to be established (3,11). Thus, PSA has no "normal" limits, and it would only be logical to consider serum PSA levels higher than age-specific median levels as a possible sign of PCa. In this context, we aimed to evaluate the clinicopathological features of patients who had a serum PSA level of ≤3 ng/mL and were diagnosed with PCa by either PNB or transurethral resection of the prostate (TUR-P).

Materials and Methods

Study Population and Multiparametric Prostate Magnetic Resonance Imaging and Determination of Suspicious Lesions

We retrospectively reviewed the medical records of 346 male patients who were diagnosed with PCa by transperineal PNB or TUR-P (patients with lower urinary tract symptoms unresponsive to medical therapy and diagnosed with incidental PCa at pathology) at Acibadem Mehmet Ali Aydinlar University, Altunizade and Kadıköy Hospitals, Department of Urology between January 2010 and June 2021. The Acibadem Mehmet Ali Aydinlar University Ethics Committee approved the study (decision no: 2021-23/12, date: 03.12.2021). Written informed consent was obtained from all patients.

Demographic characteristics, preoperative clinical characteristics, and pathological findings of PNB, TUR-P, and radical prostatectomy (RP) specimens were noted in detail for each patient. Patients whose preoperative PSA level was >3 ng/mL and those with missing clinical data were excluded. Finally, 34 male patients were included in this study.

Patients who planned to undergo PNB were evaluated with 3-T mpMRI (Magnetom Skyra, Siemens Healthineers, Erlangen, Germany) before PNB. All mpMRI studies were evaluated by the same dedicated radiologist (A.D.), and all prostate imaging-reporting and data system version-2 (PI-RADS) lesions ≥3 were mapped (12). The border of the prostate and lesions were outlined and saved as a biopsy plan using MIM Symphony Dx™ Software Inc. version 6.7 (Cleveland, Ohio, USA). Patients who had ≥PI-RADS-3 lesions in mpMRI underwent combined prostate biopsy (SBx following TBx), whereas patients who had no ≥PI-RADS-3 lesions but with an indication for biopsy underwent SBx only.

Transperineal TBx, SBx, and TUR-P Procedures

All transperineal TBx and SBx procedures were performed under sedoanalgesia in the dorsal lithotomy position. An 18-gauge automatic biopsy gun with a 19 mm sample notch was used in the biopsy procedures (Tru-Core™ II URO Automatic Biopsy Instrument, Argon Medical Devices, Inc. Texas, USA). A single-dose parenteral antibiotic as prophylaxis was administered to all patients during anesthesia induction. Two to four samples were taken from each of the suspicious lesions with a PI-RADS score of ≥3 using a stepper and template grid as previously reported (13). All TUR-P procedures were performed under general anesthesia. All biopsy samples, TUR-P specimens, and whole mount sections after RP were evaluated by a dedicated uropathologist (H.D.) in accordance with the 2014 ISUP criteria (14). csPCa was defined for biopsies [presence of a Gleason score (GS) above 6 or GS-6 disease present in more than 2 cores and/or > 50% of all cores] and prostatectomy specimens (presence of a GS above 6 or GS-6 disease and tumor volume greater than 0.5 cm^3) separately as previously reported (3,15).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 software (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to check the normality of data for quantitative variables. Descriptive data are expressed as median (interquartile range, minimum and maximum), and number and frequency.

Results

The median age of the patients was 65 (60-69) years. Age distributions according to decades were as follows: 3 (8.8%) patients aged 40 to 49 years, 5 (14.7%) patients aged 50 to 59 years, 18 (52.9%) aged 60 to 69 years, and 8 (23.5%) patients aged 70 to 79 years. The median preoperative serum PSA level and prostate volume were 1.98 (1.45-2.64) ng/mL and 46.8 (34.3-57.0) mL, respectively (Table 1). All patients aged 40 to 49 years and 50 to 59 years had serum PSA levels higher than 0.7 and 0.9 ng/mL, respectively. The preoperative demographic and clinical characteristics of the patients and the pathological features of the PNB specimens are summarized in Table 1.

Only 2 (5.9%) patients had suspicious findings on DRE. Five (14.7%) patients had a negative PNB history. Twenty-three (67.6%) patients were evaluated using mpMRI before PNB. The distribution of PI-RADS-3, -4, and -5 lesions on mpMRI was 4/23 (17.4%), 11/23 (47.8%), and 6/23 (26.1%), respectively (Table 1).

PCa was detected by "SBx only", "combination of both biopsy (CBx)", and "TUR-P" in 6 (17.6%), 17 (50.0%), and 11 (32.4%) patients, respectively. In CBx, PCa was detected in "SBx specimens only", "TBx specimens only", and "both TBx and SBx specimens" in 3 (8.8%), 5 (14.7%), and 9 (26.5%) patients, respectively. csPCa was in 52.9% of the TBx (9/17) and 60.9% of the SBx (14/23) specimen. The distribution of cT1a, cT1b, cT1c, and cT2 stages was 8 (23.5%), 3 (8.8%), 21 (61.8%), and 2 (5.9%), respectively.

GS of 6 (3+3), 7 (3+4), and 7 (4+3) tumors were observed in 6 (35.3%), 6 (35.3%), and 2 (11.8%) patients in TBx specimens (n=17), and their distribution was 9 (39.1%), 5 (21.7%), and 4 (17.4%) in SBx specimens (n=23), respectively.

Twenty (58.8%) patients were treated with RP, while 2 (5.9%) of them underwent radiotherapy. One patient (2.9%) who had

only one tumor foci in TBx specimens with a GS of 6 (3+3) received focal ablative interstitial laser thermotherapy. Eleven (32.4%) patients were managed with active surveillance (AS). None of the AS patients required active treatment due to any cause, with a median follow-up period of 16 (8-24) months.

pT2a, pT2c, pT3a, and pT3b diseases were observed in 5 (25.0%), 7 (35.0%), 6 (30.0%), and 2 (10.0%) patients who underwent RP (n=20), respectively (Table 2). csPCa in prostatectomy specimens was observed in 17/20 (85.0%) patients. Surgical margin positivity was observed in 2/20 (10.0%) patients. Extended pelvic lymph node dissection was performed in 4/20 (20.0%) patients, and regional lymph node metastasis was observed in 1/20 (5.0%) patients (Table 2). The pathological features of RP specimens are summarized in Table 2.

GS of 6 (3+3), 7 (3+4), 7 (4+3), and 9 (5+4) diseases were observed in 3 (15.0%), 9 (45.0%), 6 (30.0%), and 2 (10.0%) prostatectomy specimens (n=20), respectively. In patients who underwent RP, 8 (40.0%) were diagnosed by "SBx specimens only", 2 (10.0%) by "TBx specimens only", 7 (35.0%) by "both TBx and concomitant SBx specimens", and 3 (15.0%) "TUR-P", respectively. Upgrading in prostatectomy specimens compared with PNB was observed in 5/11 (45.5%) and 9/17 (52.9%) patients who underwent TBx and SBx, respectively (Table 3).

Table 1. Demographic and clinical characteristics of patients and pathological features of prostate biopsy specimens

Variables		**Median (IQR)**
Age (year)		65 (60-69)
Preoperative prostate specific antigen level (ng/mL)		1.98 (1.45-2.64)
Prostate volume (mL)		46.8 (34.3-57.0)
Digital rectal examination (n, %)	Benign	32 (94.1%)
	Suspicious	2 (5.9%)
Previous negative prostate needle biopsy history (n, %) (yes)		5 (14.7%)
PI-RADS-3 lesion in mpMRI (n=23) (n, %) (yes)		4/23 (17.4%)
PI-RADS-4 lesion in mpMRI (n=23) (n, %) (yes)		11/23 (47.8%)
PI-RADS-5 lesion in mpMRI (n=23) (n, %) (yes)		6/23 (26.1%)
Total number of suspicious lesions in mpMRI		2 (0-3)
Number of sampled cores in targeted prostate biopsy		12 (7-13)
Number of sampled cores in a systematic prostate biopsy		12 (12-13)
Total number of sampled cores in prostate biopsy		23 (12-25)
Number of tumor-positive cores in targeted prostate biopsies		1 (1-1)
Number of tumor-positive cores in systematic prostate biopsies		2 (1-4)

IQR: Interquartile range, PI-RADS: Prostat imaging-reporting and data system, mpMRI: Multiparametric magnetic resonance imaging

Table 2. Pathological features of radical prostatectomy specimens (n=20)

Variables		**n, %**
Pathological (pT) Stage	pT2a	5 (25.0%)
	pT2b	0
	pT2c	7 (35.0%)
	pT3a	6 (30.0%)
	pT3b	2 (10.0%)
ePLND (yes)		4 (20.0%)
Total number of lymph nodes excised in ePLND [median (IQR)]		30 (25-34)
Pathological regional lymph node (pN) stage	pNx	16 (80.0%)
	pN0	3 (15.0%)
	pN1	1 (5.0%)
Surgical margin (positive)		2 (10.0%)
Tumor volume in prostatectomy specimens (mL) [median (IQR)]		2.6 (0.7-7.0)
Tumor volume ratio in prostatectomy specimens (%) [median (IQR)]		5.9 (1.4-15.0)
Clinically significant prostate cancer in radical prostatectomy (yes)		17 (85.0%)
Estimated blood loss during surgery (mL) [median (IQR)]		100.0 (50.0-200.0)

ePLND: Extended pelvic lymph node dissection, IQR: Interquartile range

Table 3. Gleason score concordance between prostate biopsy techniques and radical prostatectomy specimens (n=20)		
Variables		**n, %**
Targeted prostate biopsy	Same grade	6 (54.5%)
	Up grade	5 (45.5%)
Systematic prostate biopsy	Same grade	8 (47.1%)
	Up grade	9 (52.9%)

Discussion

Patients with a low serum PSA level may harbor life-threatening cancers and should not be ruled out without proper evaluation. In 1994, Catalona et al. (6) compared the efficacy of DRE and serum PSA in the early detection of PCa. In this multicenter, prospective clinical trial, 6.630 male volunteers were assessed, and quadrant prostate biopsies were performed on patients who had a PSA level of greater than 4 ng/mL and/or suspicious DRE findings for PCa. The PCa detection rate was 3.2% for DRE, 4.6% for PSA, and 5.8% for the 2 methods combined (6). According to their findings, the authors recommended using PSA in conjunction with DRE to enhance early PCa detection. They recommended a PSA cut-off value of 4 ng/mL as a trigger for PNB (6). Subsequently, they investigated the detection rate of PCa in a screening population of men with serum PSA levels of 2.6 to 4.0 ng/mL and normal DRE findings (7). The authors reported a significant PCa prevalence (22%) in this population, and most cancers detected appear to be clinically important. Thus, they suggested that detecting PCa in men with these serum PSA levels may help reduce PCa mortality and morbidity rates (7).

PSA is a serine protease produced by the epithelial cells of normal, hyperplastic, and cancerous prostatic tissue (16) and has a high false positive rate when used as a screening tool because of its non-specific nature for possible malignancy. PSA levels may also increase with aging, mainly because of increased prostate volume due to benign prostatic hyperplasia (8,17). In this context, several studies have been conducted to determine age-specific reference ranges of PSA in different populations (8,9,18,19,20). The major concerns in all of these studies were both identifying high-risk PCa and reducing the number of unnecessary PNBs. However, the possibility of missing a csPCa was the major problem. In their pioneering work, Oesterling et al. (20) recommended different reference ranges for PSA for men based on their age (i.e, for 40 to 49 years 0-2.5 ng/mL; 50 to 59 years 0-3.5 ng/mL; 60 to 69 years 0-4.5 ng/mL; and 70 to 79 years 0-6.5 ng/mL) (8). The authors claimed that age-specific reference ranges have the potential to make PSA a more discriminating tumor marker for detecting csPCa in older men (by increasing specificity) and to find more potentially curable cancers in younger men (by increasing sensitivity) (8). A few years later, Morgan et al. (9) determined the age-specific reference ranges of PSA in black men with and without PCa. According to sensitivity analyses, they recommended that using age-specific reference ranges can improve the clinical value of screening and recommended the following reference ranges: 0 to 2.0 ng/mL for men in their 40s, 0 to 4.0 ng/mL for men in their 50s, 0 to 4.5 ng/mL for men in their 60s, and 0 to 5.5 ng/mL for men in their 70s (9). In the following years, in a PCa screening study, the median serum PSA level was reported as 0.7 ng/mL for men aged 40 to 49 years and 0.9 ng/mL for men aged 50 to 59 years (10). In this study, baseline serum PSA values between age-specific median and 2.5 ng/mL in high-risk men in their 40s were associated with a 14.6-fold increased risk of later PCa diagnosis and a 7.6-fold increased risk for men in their 50s. Because of these findings, the authors warned clinicians that they should no longer regard men younger than 60 years with a serum PSA level of less than 2.5 ng/mL as "normal" (10). Although there were only 3 and 5 patients aged 40 to 49 years and 50 to 59 years, respectively, in our study, all had higher serum PSA levels than the age-specific medians determined by Loeb et al. (10). Patients in this study who had a serum PSA level of ≤3 ng/mL at the time of diagnosis revealed csPCa in 85.0% of the RP specimens, and adverse pathological findings such as grade group 3 or higher tumors or extraprostatic disease extension were also common (40% and 40% respectively). Surgical margin positivity and regional lymph node metastasis were observed in 10.0% and 5.0% of the cases, respectively. Finally, upgrading in prostatectomy specimens ranged from 45.5% to 52.9% according to the PNB technique. All these findings suggest that a comprehensive diagnostic approach should be considered in patients with a PSA value of ≤3 ng/mL but higher than their age-specific median levels.

Nevertheless, the optimum trigger value for PSA is still unclear. Bosch et al. (17) created a model for the prediction of "normal" changes in serum PSA levels over time in individual men based on age and initial serum PSA levels in a community-based European male without PCa. The major aspect of "Krimpen study" was that longitudinal changes in PSA were evaluated (17). In a recent study, Gilbert et al. (21) developed a new age-specific PSA threshold based on "Krimpen study" for detecting PCa. In this study, the authors compared the ability of their age-specific PSA thresholds to discriminate between high- and no/low-risk PCa with 2 other existing thresholds: (i) PSA threshold of 3 ng/mL for all agesand (ii) National Institute of Clinical Excellence guidelines dependent on age-group thresholds (21). The authors found that a simple threshold of PSA 3 ng/mL for all ages identified more PCa at a high risk of progression than either of the other two methods, resulting in fewer missed PCa, and more men received unnecessary PNB. Moreover, while age-dependent thresholds were more discriminatory, too many PCa at high risk of progression were missed (21). In contrast, we demonstrated that adverse pathological outcomes in RP specimens can be observed in patients with a serum PSA level of ≤3 ng/mL. Therefore, we consider that patients with serum PSA levels higher than age-specific medians should be evaluated at least by mpMRI.

In addition to the pathological characteristics specific to PCa, the different features and inherent risks of current biopsy approaches may influence the discordant histopathological results. One of the important findings of our study was the increased frequency of csPCa and upgrading in GS in RP specimens compared with that in PNB specimens. A recent Cochrane meta-analysis comparing mpMRI with template biopsies in biopsy-naïve and repeat biopsy settings reported that mpMRI-targeted biopsies were a more favorable diagnostic test than SBx in all men with

suspected csPCa (22). However, Westhoff et al. (23) reported that TBx detected significantly less PCa without being superior to SBx in detecting csPCa, except in men with previous negative biopsies, and they concluded that a combination of TBx and SBx was the single approach for csPCa detection. Thus, even the most current approach is still far from perfect, as we demonstrated previously, where the frequency of csPCa was much lower in TBx and SBx specimens than in RP specimens (24). In this study, CBx performed better in predicting the ultimate RP pathology, missing csPCa in 4.3% of cases (24). Several studies have shown that biopsy concordance with RP samples ranges from 37% to 58% using SBx alone (25,26,27). There are also significant differences in the literature regarding the ability of TBx to better predict the GS of RP (28). The concordance ratios of the GS between biopsy and RP specimens for TBx and SBx were reported as 91.5% vs. 53.8%, respectively (29). In this study, patients with a negative SBx history underwent TBx (29). Alshak et al. (30) recently reported ISUP grade group upgrading and downgrading ratios between TBx and RP samples 25% and 22.1%, respectively. Similarly, in the present study, we observed that the frequency of upgrading in RP specimens was 45.5% in TBx specimens and reached 52.9% in SBx specimens.

Study Limitations

Our study has several limitations that need to be considered. First, the retrospective and non-randomized nature of our study introduces the possibility of selection bias. Second, the major limitation was the small sample size of our study cohort, and only 20 patients were treated with RP. On the other hand, we demonstrated that adverse pathological outcomes in RP specimens can be observed in patients with a serum PSA level of ≤3 ng/mL. Therefore, we believe that our study results may contribute to the body of knowledge on this specific patient population. Further investigations with larger cohorts that were treated with RP are needed to confirm our study results.

Conclusion

In conclusion, adverse pathological outcomes in RP specimens are frequent in patients with a serum PSA level of ≤3 ng/mL. Physicians must be aware of blanket recommendations suggesting the absence of csPCa below certain thresholds of PSA, and a comprehensive diagnostic approach for the possible presence of PCa should be considered, especially in young patients with PSA above their age-specific median level. Further prospective investigations with larger patient populations are required to confirm our study results.

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Ethics

Ethics Committee Approval: The Acibadem Mehmet Ali Aydinlar University Ethics Committee approved the study (decision no: 2021-23/12, date: 03.12.2021).

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Authorship Contributions

Concept: B.Ö., H.D., L.T., Design: B.Ö., H.D., L.T., Data Collection or Processing: N.K., Analysis or Interpretation: N.K., M.B.Ö., Literature Review: N.K., M.B.Ö., Critical Review: B.Ö., A.D., L.T., Supervision: B.Ö., A.D., L.T., Writing: N.K., M.B.Ö.

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