Original Article

Pathologic characteristics and management strategies for two categories of prostate cancer patients with low prostate-specific antigen undergoing radical prostatectomy

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Background: Prostate cancer (PCa) with low levels of prostate-specific antigen (PSA) (0–4 ng/mL) includes PCa detected through biopsy and incidental PCa (IPC) in patients with previous prostate surgeries. The study was conducted to compare these two groups of patients undergoing radical prostatectomy (RP), aiming to assess pathological characteristics and suggest strategies for predicting and managing low PSA PCa.

Methods: A retrospective analysis was performed on two categories of low PSA PCa patients. Baseline characteristics, PSA density (PSAD), preoperative multiparametric magnetic resonance imaging (mpMRI) for RP, preoperative and postoperative pathological data, and biochemical recurrence (BCR) were evaluated.

Results: Fifty patients were analyzed. There were 80% of tumors being clinically significant and in early-stage, indicating a favorable prognosis for most low PSA PCa patients, and the use of preoperative androgen deprivation therapy (ADT) treatment may be beneficial for a small subset of patients with advanced tumors. Patients with low PSA and IPC history had lower PSA levels, PSAD, and prostate volume, however, BCR rates did not significantly differ between low PSA patients with and without IPC history. mpMRI and PSAD demonstrated potential in predicting PCa in low PSA cases.

Conclusions: Predicting low PSA PCa remains challenging, but mpMRI and PSAD could be valuable predictors. Both low PSA groups showed a likelihood of clinical significance, with favorable pathological features. Early diagnosis and treatment are crucial, especially for aggressive IPC PCa tumors. Reevaluating PSA thresholds is vital to avoid missed or misdiagnosed low PSA cases.

Keywords: Prostate cancer (PCa); prostate-specific antigen (PSA); incidental prostate cancer (IPC); pathology; radical prostatectomy (RP)

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Introduction

Prostate cancer (PCa) is the most prevalent malignancy in men, currently ranking as the second leading cause of cancer-related deaths in men (1). The traditional diagnostic pathway of PCa starts from an elevated serum prostate-specific antigen (PSA) level and an abnormal digital-rectal examination (DRE) (2,3), followed by a transrectal ultrasound (TRUS), and finally, only prostate biopsy could confirm the suspicion of PCa. However, the detection rate of DRE is quite low in the early stages of the cancer, making diagnosis difficult. PSA levels exceeding 4.0 ng/mL are generally considered to refine prostate biopsy (4). Various studies have suggested that the traditional PSA cut-off may be too high and frequently leads to missed diagnosis of PCa in patients with low PSA levels (<4.0 ng/mL) in clinical practice (4,5). Incidental PCa (IPC) is defined as a tumor that is incidentally diagnosed after benign prostatic hyperplasia (BPH) surgery [transurethral resection of the prostate (TURP)] without any prior suspicion of PCa, or a tumor that is found after autopsy, or a tumor that is incidentally discovered after radical cysto-prostatectomy in patients with bladder cancer (5,6). In the PSA era, the probability of finding IPC after TURP seems to have decreased, however, when a patient with IPC has low PSA levels, it is easy to miss the diagnosis. The optimal clinical management of PCa with low PSA, including IPC, remains controversial.

Previous studies on low PSA have primarily focused on evaluating the characteristics of such patients based on needle biopsy, with no prior studies evaluating the characteristics of low PSA patients who underwent robot-assisted radical prostatectomy (RARP). In patients with low PSA, there can be underlying PCa that is not detected due to PSA abnormalities, as well as IPC in patients with previous TURP. The aim of our study was to evaluate the baseline characteristics, pathological outcomes, and other parameters of two types of low PSA patients who underwent RARP surgery, in order to improve the diagnosis and treatment management strategy for patients with low PSA, including IPC, evaluate potential prediction methods for low PSA, and aim to reduce missed diagnoses, overdiagnosis, and overtreatment of low PSA patients. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-538/rc).

Highlight box

Key findings

- Comparison of radical prostatectomy outcomes between low prostate-specific antigen (PSA) prostate cancer patients detected through biopsy and incidental prostate cancer cases with previous surgeries was conducted.

What is known and what is new?

- Findings suggest favorable prognoses for most low PSA prostate cancer patients, especially for early-stage tumors and those receiving neoadjuvant therapy.
- Multiparametric magnetic resonance imaging and PSA density show promise in predicting and managing low PSA prostate cancer cases, highlighting the importance of early diagnosis and reevaluation of PSA cut-off values for accurate clinical management.

What is the implication, and what should change now?

- This suggests that when evaluating the puncture index of prostate cancer, we should not blindly adhere to a certain "threshold". How to accurately diagnose and evaluate early prostate cancer patients and provide appropriate treatment requires a balance between "overtreatment" and "monitoring follow-up" in certain situations.

Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Nanjing Drum Tower Hospital Ethics Committee (No. 2019-253-01) and individual consent for this retrospective analysis was waived. Between July 2018 and June 2023, a retrospective analysis was conducted on a cohort of over 2,000 patients who underwent RARP at a single center. Among these patients, 58 had a PSA level below 4.0 ng/mL and were treated with RARP. Patients with missing data or other tumors were excluded from the study. Ultimately, a total of 50 patients with PCa were included. These patients were divided into two groups based on the causes of PCa findings. The first group, referred to as the Biopsy Patients group, consisted of patients who underwent RARP after a diagnosis of PCa was made through a biopsy. The second group, referred to as the TURP group, primarily comprised patients who were initially misdiagnosed with BPH or other diseases at other hospitals and later referred to our center for RARP after a diagnosis of PCa was made following TURP. The Biopsy group included a total of 26 individuals, of whom 3 received prostate endocrine therapy before RARP. The TURP group consisted of 24 individuals, with 5 of them receiving prostate

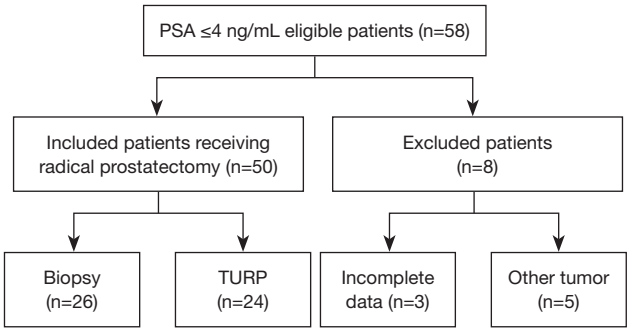

Figure 1 Flow chart of inclusion and exclusion criteria for this study. A total of 50 patients were included in this study. Complete information was recorded for all patients, including mpMRI, TRUS, age, BMI, etc. Prostate volume was collected and PSAD was calculated before prostate biopsy. PSA, prostate-specific antigen; TURP, transurethral resection of the prostate; mpMRI, multiparametric magnetic resonance imaging; TRUS, transrectal ultrasound; BMI, body mass index; PSAD, prostate-specific antigen density.

endocrine therapy before RARP. It is noteworthy that the majority of patients completed RARP within 6 months following TURP. However, two patients experienced a 12-month interval between the two surgeries due to long-term androgen deprivation therapy (ADT) (*Figure 1*).

Basic clinical characteristics

We recorded demographic and baseline data for all 50 patients, including their age at the time of diagnosis by needle biopsy or TURP, hypertension and diabetes status, body mass index (BMI, defined as ≥25 kg/m^2 for obesity in the Asia-Pacific region), smoking and alcohol consumption habits, PSA level before needle biopsy or RARP, prostate volume [measured by TRUS or multiparametric magnetic resonance imaging (mpMRI), calculated as prostate length × width × thickness × 0.52], and PSA density (PSAD). Additionally, we documented the presence of lower urinary tract symptoms (LUTS) prior to RARP and noted if the patients had received ADT before RARP. Furthermore, we collected clinical baseline characteristics before RARP for both groups. For the Biopsy group, we assessed the total number of biopsy needles, the number of biopsy-positive needles, the ratio of positive cores in all biopsies, and the Gleason score (GS). For the TURP group, we obtained the pathological GS after TURP. All patients underwent mpMRI before RARP, and the Prostate Imaging Reporting and Data System (PI-RADS) scores were determined for each patient. In some cases, multiple lesions were detected during mpMRI, and each lesion was assigned a score. However, for lesions that had undergone endocrine therapy or prostate surgery and were difficult to score, they were categorized as "Unable to score".

Postoperative pathological characteristics

All patients underwent RARP and subsequent pathological examination. The total tumor volume, which is calculated using the ellipsoidal volume formula or maximum tumor diameter, represents the sum of all tumor lesions within an individual. Additionally, the assessable tumor percentage, GS, clinical tumor-node-metastasis (TNM) stage, and GS change were evaluated. Furthermore, based on previous data, patients with a pathologic GS (pGS) of 8–10 and a stage of pT3b or N1 were considered to have 'unfavorable' pathological findings (7). Intraductal carcinoma was also regarded as an unfavorable disease. Insignificant cancer was defined as a total tumor volume of less than 2.5 mL with a GS of 6 or lower and a stage of pT2 (8).

Biochemical recurrence (BCR) was defined as two consecutive rises in PSA levels to over 0.2 ng/mL after RARP, with an upward trend. The specimen was divided into the peripheral zone (PZ) and transitional zone (TZ) based on anatomical considerations. The tumor was then categorized as being either anterior or posterior to the prostatic urethra. Furthermore, the prostate was divided into left and right lobes along its central axis. In cases where the tumor showed some extent of spread, its location was determined based on the area where the tumor was predominantly located (accounting for over 80% of its size). The invasion of more than half a lobe or involvement beyond the prostate was also assessed based on the proportion of the tumor in the respective lobe. Subsequently, the presence of tumor invasion into the seminal vesicles, nerves, or lymph nodes, as well as positive surgical margins (PSM), was evaluated. PSM were considered when tumor cells came into contact with pigment markers on the specimen surface, whereas tumor cells that were merely in proximity to the pigment marker surface were deemed "close" to it. Each RARP sample was examined by two experienced pathologists (*Figure 2*).

Statistical analysis

Qualitative data were analyzed using either the Chi-

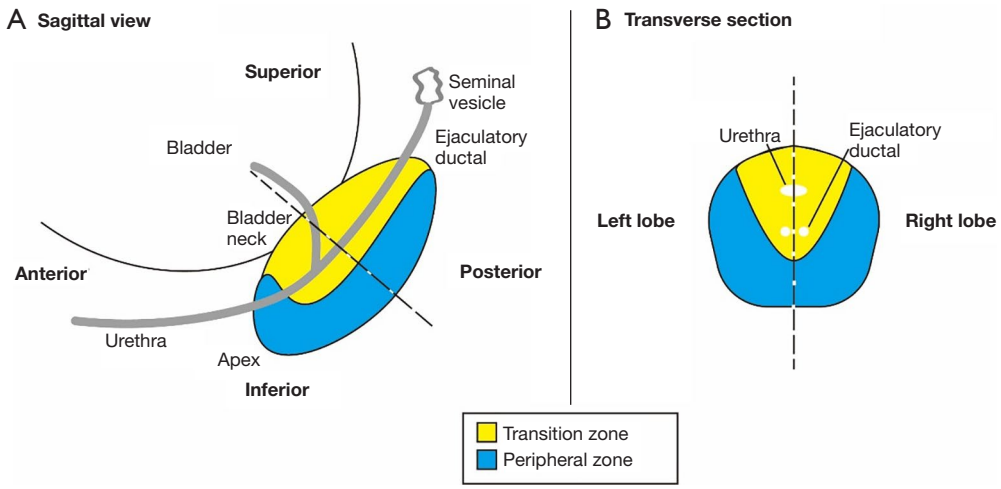

Figure 2 Schematic diagram of the rough anatomical division of the prostate. Describe the location of the left and right lobes, PZ, and TZ. (A) Sagittal view, the dotted line denotes the cutting plane of (B); (B) transverse section, the dotted line serves as the midline for distinguishing between the left and right lobes. PZ, peripheral zone; TZ, transitional zone.

squared test or Fisher's exact test, while the Student's *t*-test was employed for continuous data. The median and interquartile range were used to present follow-up data. Kaplan-Meier analysis was performed to evaluate the survival time of BCR-free survival (BFS), and the log-rank test was utilized to determine the statistical significance of differences. Additionally, multivariate Cox proportional hazards regression analysis was conducted to assess the impact of each parameter and identify independent prognostic factors for BFS. Standard post-RARP follow-up included serum PSA checks every 3 months for a year and every 6 months after that. All statistical analyses were two-sided, with significance set at P<0.05. The SPSS statistical software (version 23.0, Chicago, IL, USA) was utilized for all data analysis.

Results

Robot-assisted radical prostatectomy (RARP) preoperative baseline characteristics

In this study, a total of 50 patients were selected and divided into the Biopsy group and the TURP group for different diagnostic reasons. The mean ages of patients diagnosed with PCa in both groups were 71.9±6.6 and 69.5±5.5 years. Although there were some subtle differences in terms of underlying diseases and lifestyle habits between the two groups, none of these differences were statistically significant. The PSA levels at diagnosis were between 0 and 4 ng/mL, with a mean of 3.06±1.12 ng/mL in the Biopsy group and 0.73±0.56 ng/mL in the TURP group, which was significantly lower than that in the Biopsy group (P<0.001). The measured prostate volumes were 29.8±11.0 and 21.7±7.6 cc under TRUS or mpMRI, respectively. The calculated PSADs were 0.11±0.05 and 0.04±0.04 ng/mL/cc, which were also significantly different (P<0.001). Moreover, 7 patients (26.9%) in the Biopsy group and 20 patients (83.3%) in the TURP group developed LUTS before PCa diagnosis based on inquiry, with the latter having a significantly higher incidence (P<0.001). Finally, based on previous experience, patients who underwent TURP had a higher incidence of perioperative complications of RARP and were also considered a high-risk factor for BCR, with 25% of patients in the TURP group receiving preoperative ADT (*Table 1*).

Additionally, we assessed the clinical T staging before RARP in both groups, with most tumors showing an earlier stage. Notably, in the TURP group, we evaluated the percentage of PCa in tissues. In both groups, a GS score was obtained through biopsy or transurethral resection before RARP. The majority of the scores were ≤7, with 80.8% and 70.8% in the Biopsy group and the TURP group, respectively (P<0.001, P<0.001). However, one case of ductal adenocarcinoma of the prostate (DAP) occurred in the TURP group. There was also a significant difference in preoperative mpMRI between the two groups. In the Biopsy group, most lesions (19 lesions) scored between 3

Table 1 Patients' baseline characteristics

Covariates	Biopsy (n=26)	TURP (n=24)	P value
Age, years	71.9±6.6	69.5±5.5	0.18
Hypertension	13 (50.0)	12 (50.0)	0.61
Diabetes	4 (15.4)	6 (25.0)	0.31
BMI, kg/m^2	24.0±2.6	24.4±3.0	0.57
BMI ≥25 kg/m^2	10 (38.5)	12 (50.0)	0.30
Smoking	4 (15.4)	6 (25.0)	0.31
Drinking	0 (0.0)	3 (12.5)	0.16
PSA, ng/mL	3.06±1.12	0.73±0.56	<0.001
Prostate volume on TRUS/mpMRI, cc	29.8±11.0	21.7±7.6	0.004
PSAD, ng/mL/cc	0.11±0.05	0.04±0.04	<0.001
LUTS	7 (26.9)	20 (83.3)	<0.001
ADT	3 (11.5)	6 (25.0)	0.19

Data are presented as mean ± standard deviation or n (%). TURP, transurethral resection of the prostate; BMI, body mass index; PSA, prostate-specific antigen; TRUS, transrectal ultrasound; mpMRI, multiparametric magnetic resonance imaging; PSAD, prostate-specific antigen density; LUTS, lower urinary tract symptomatology; ADT, androgen deprivation therapy.

Table 2 Preoperative baseline

Variables	Biopsy (n=26)	TURP (n=24)	P value
Preoperative T stage			0.79
≤T2	23 (88.5)	20 (83.3)	
T3a	2 (7.7)	2 (8.3)	
T3b–T4	1 (3.8)	2 (8.3)	
Percentage of prostate cancer in tissues			<0.001
≤5% (cT1a)	–	19 (79.2)	
>5% (cT1b)	–	5 (20.8)	
GS			<0.001
≤6	8 (30.8)	9 (37.5)	
7	13 (50.0)	8 (33.3)	
8–10	5 (19.2)	7 (29.2)*	
PI-RADS			<0.001
≤2	1 (3.8)	2 (8.3)	
3	5 (19.2)	2 (8.3)	
4	14 (53.8)	3 (12.5)	
5	6 (23.1)	5 (20.8)	
Unable to score	0 (0.0)	12 (50.0)	

Data are presented as n (%). *, contains DAP. TURP, transurethral resection of the prostate; GS, Gleason score; PI-RADS, Prostate Imaging Reporting and Data System; DAP, ductal adenocarcinoma of the prostate.

and 4, with all lesions providing clear scores. On the other hand, in the TURP group, some lesions (12 lesions) were difficult to score, and others (8 lesions) scored between 4 and 5 (P<0.001) (*Table 2*).

Pathological characteristics after RARP

Both groups underwent RARP and pathological examination to confirm the presence of prostatic malignancies in all tumors. The measurable total tumor volume did not differ significantly between the two groups, however, the TURP group (9 cases) had a significantly greater number of lesions that were difficult to measure compared to the Biopsy group (2 cases) (P=0.01). On the other hand, the Biopsy group had a significantly larger prostate volume of 34.3±16.4 cc compared to the TURP group with 22.4±8.8 cc (P=0.003). For the postoperative pathological GS score, a more detailed classification was used to distinguish between 3+4 and 4+3 tumors. In the Biopsy group, nearly half of the tumors had a score of 3+4, while the remaining scores were distributed, and no tumors other than prostate adenocarcinoma were observed. In the TURP group, almost half of the tumors had a score =6, and tumors were also distributed across other scores. Although the GS score seemed higher in the Biopsy group than in the TURP group, this difference was not statistically significant (P=0.09). Notably, tumors in the TURP group that were diagnosed as DAP before RARP were identified as PCa intraductal carcinoma (IDC-P) upon pathological examination after RARP. Regarding the T stage, the majority of tumors in both groups were T2 stage. There were fewer advanced tumors (≥ T3b) in both groups. Furthermore, there was no statistically significant difference in the N stage between the two groups. Additionally, there were no significant differences between the two groups in terms of lymphadenectomy, the positive lymph node rate, the changes in GS scores before and after RARP and the number of cases of unfavorable diseases between the two groups (*Table 3*). During a median follow-up of 35.9 and 34.9 months, 4 and 3 patients in the Biopsy and TURP groups, developed BCR events. However, there was no significant difference in the BCR rate between the two groups (*Figure 3*). It is important to highlight that we have

Table 3 Postoperative pathological characteristics

Characteristics	Biopsy (n=26)	TURP (n=24)	P value
Total tumor volume			
Not evaluable	2 (7.7)	9 (37.5)	0.01
Evaluable, cc	2.4±2.5	2.6±4.5	0.90
Prostate volume, cc	34.3±16.4	22.4±8.8	0.003
% of evaluable tumor	8.3±8.9	13.5±21.0	0.37
Pathologic GS			0.09
6	5 (19.2)	10 (41.7)	
3+4	12 (46.2)	6 (25.0)	
4+3	5 (19.2)	1 (4.2)	
8	2 (7.7)	1 (4.2)	
≥9	2 (7.7)	5 (20.8)	
IDC-P	0 (0.0)	1 (4.2)	
Pathologic T stage			0.41
T2	22 (84.6)	17 (70.8)	
T3a	2 (7.7)	2 (8.3)	
T3b–T4	2 (7.7)	5 (20.8)	
Pathologic N stage			0.60
Nx	16 (61.5)	16 (66.7)	
N0	8 (30.8)	8 (33.3)	
N1	2 (7.7)	0 (0.0)	
Lymph node dissection	10 (38.5)	8 (33.3)	0.77
Lymph node positive	2 (7.7)	0 (0.0)	0.48
Changes in GS			0.07
Downgrade	7 (26.9)	2 (8.3)	
No change	14 (53.8)	20 (83.3)*	
Upgrade	5 (19.2)	2 (8.3)	
Insignificant cancer	3 (11.5)	7 (29.2)	0.11
Unfavorable disease	2 (7.7)	5 (20.8)	0.18
BCR	4 (15.4)	3 (12.5)	0.55
The follow-up period, months	35.9 (22.3–49.3)	34.9 (24.0–49.0)	0.82

Data are presented as n (%), mean ± standard deviation or median (interquartile range). *, contains one IDC-P. TURP, transurethral resection of the prostate; GS, Gleason score; BCR, biochemical recurrence; IDC-P, prostate cancer intraductal carcinoma.

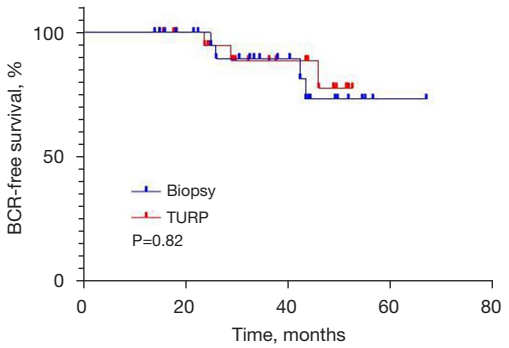

Figure 3 Kaplan-Meier estimates BFS according to confirmed PCa causes. BCR, biochemical recurrence; TURP, transurethral resection of the prostate; BFS, BCR-free survival; PCa, prostate cancer.

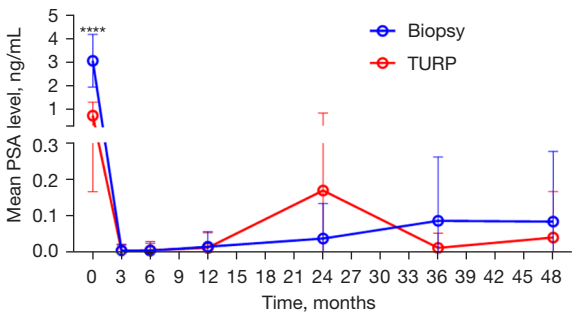

Figure 4 Mean PSA value across time by group. ****, P<0.0001. PSA, prostate-specific antigen; TURP, transurethral resection of the prostate.

included further details on the trends in PSA during the follow-up period. Our analysis revealed no significant differences in the mean PSA values over time between the two groups, with the exception of the values recorded at month 0 (*Figure 4*).

Tumor location

There was no significant difference in tumor location between the two groups. In general, most lesions were located in the PZ, with a smaller proportion in the TZ in both the left and right lobes. However, it is worth noting that while the two groups did not differ significantly in terms of tumor volume, there was a statistically significant difference in tumor invasion (P=0.03). Tumors in the TURP group appeared to invade more easily compared to those

Table 4 Tumor location and invasion

Characteristics	Biopsy (n=26)	TURP (n=24)	P value
Tumor location			0.87
LPZ	16 (61.5)	12 (50.0)	
RPZ	15 (57.7)	13 (54.2)	
LTZ	7 (26.9)	4 (16.7)	
RTZ	6 (23.1)	5 (20.8)	
Not evaluable	3 (11.5)	5 (20.8)	
Tumor invasion			0.03
<1/2 LL	16 (61.5)	8 (33.3)	
<1/2 RL	18 (69.2)	7 (29.2)	
≥1/2 LL	5 (19.2)	9 (37.5)	
≥1/2 RL	4 (15.4)	10 (41.7)	
EPE	4 (15.4)	5 (20.8)	
Not evaluable	2 (7.7)	5 (20.8)	
SVI	1 (3.8)	4 (16.7)	0.15
Perineural invasion	11 (42.3)	9 (37.5)	0.48
PSM	6 (23.1)	4 (16.7)	0.42
LNI	2 (7.7)	0 (0.0)	0.27

Data are presented as n (%). TURP, transurethral resection of the prostate; LPZ, left peripheral zone; RPZ, right peripheral zone; LTZ, left transition zone; RTZ, right transition zone; LL, left lobe; RL, right lobe; EPE, extraprostatic extension; SVI, seminal vesicle invasion; PSM, Positive surgical margin; LNI, lymph node involvement.

in either the left or right lobe of the Biopsy group, whereas the extent of invasion was more limited in the Biopsy group. There were no statistically significant differences observed in seminal vesicle invasion (SVI), nerve invasion, positive margins, and lymph node involvement (LNI) between the two groups (*Table 4*).

Discussion

In this study, we examined patients with low PSA who underwent RARP surgery and categorized them into the Biopsy and TURP groups based on different preoperative PCa diagnostic methods. Before RARP, the TURP group exhibited significantly lower levels of serum PSA, PSAD, and prostate volume. This discrepancy can be attributed to the fact that PSA is primarily secreted by the prostate, and in the TURP group, TURP surgery was performed prior to RARP, resulting in the removal of a portion of the prostate. This surgical stress likely led to lower PSA levels, smaller prostate size, and reduced PSAD compared to the Biopsy group. It is important to note that in the TURP group, a large majority of patients had previously been diagnosed with BPH at another hospital, which explains the significantly higher odds of LUTS compared to the Biopsy group. Some studies have demonstrated that the prevalence of PCa is not low in individuals with a PSA level below 4 ng/mL (9-11), that is why they dedicated to investigating tools and risk factors for predicting PCa in patients with low PSA. For instance, a retrospective study of 158 prostate biopsies from patients with low PSA revealed that 20.3% of men with low PSA were diagnosed with PCa, with the PI-RADS score on MRI being the sole independent predictor (12). Many studies now suggest that PSA thresholds can be lowered to enable early detection and treatment of clinically significant but less aggressive localized tumors, thereby preventing tumor progression before detection and improving the cure rate of PCa (13,14). Numerous novel tools and indicators for predicting PCa, such as PSAD, free to total PSA (f/tPSA), PSA-TZ, prostate health index (PHI) and PI-RADS score, have been proposed (12,15,16). These tools and indicators are utilized to forecast PCa occurrence in patients with low PSA. In our study, we gathered data on PSAD and PI-RADS and found that both factors played a role in predicting PCa. Therefore, we recommend including additional tests such as mpMRI, TRUS, and free PSA (fPSA) in routine physical examinations for elderly men with low PSA, particularly those experiencing LUTS. Furthermore, calculations involving PSAD and f/tPSA can provide further insights into the likelihood of PCa and aid in accurately distinguishing between benign and malignant conditions. If there is a high suspicion of PCa or difficulty in differentiating BPH based on the PI-RADS score, a biopsy examination should be performed to determine the diagnosis. This study emphasizes that while the number of identified cancer cases in the low PSA range may be small, the majority of them are clinically significant lesions that require prompt diagnosis and early treatment. Among them, some are high-grade tumors with potential invasiveness and recurrence. Therefore, patients with low PSA should receive attention in clinical practice.

We conducted an analysis of the pathological features following RARP in both groups. Due to the previous treatment of the TURP group, it was difficult to measure tumor volume and the prostate volume was smaller. These

findings are consistent with the conclusions obtained from preoperative examinations, we believe that this may be related to TURP. Most of the diseases were organ-confined, and there were few insignificant cancers in both groups. The majority of the lesions had clinical significance and required treatment. Additionally, there were few cases of unfavorable disease, so most of the tumors had a good prognosis and a lower BCR rate after RARP. Interestingly, none of the high-grade tumors treated with ADT before surgery developed BCR during follow-up, and none of the patients who developed BCR received ADT before surgery. In the TURP group, we identified a unique case where the tumor was initially pathologically diagnosed as prostatic ductal adenocarcinoma after TURP, but was diagnosed as prostatic intraductal carcinoma after receiving RARP. Therefore, we did not classify it according to the GS score, as IDC-P in RARP specimens is known to be an aggressive pathological pattern (17-19). This case was also treated with ADT before RARP and during follow-up, we closely monitored it and there were no instances of BCR. There is a growing body of evidence suggesting that preoperative ADT is beneficial for patients. This approach is linked to reduced surgical challenges, improved treatment efficacy, and fewer postoperative complications. Consequently, ADT with treatment intensification is strongly recommended for patients especially with metastatic castration-sensitive PCa (20,21). Previous studies have indicated that TURP is an independent risk factor for BCR after radical prostatectomy (RP) for PCa, implying that individuals who have undergone TURP are more likely to experience BCR after RARP (22,23). Additionally, patients with a history of TURP had worse perioperative outcomes compared to those without a history of TURP, including higher positive margin rates, bladder neck reconstruction rates, total complication rates, and lower nerve preservation rates (24). In our study, there were no significant differences in extraprostatic extension (EPE), SVI, perineural invasion (PNI), PSM, or LNI between the two groups. There was also no significant difference in BCR between the two groups. We believe that the main reason for this is that a higher proportion of patients in the TURP group received ADT before RARP, effectively preventing the occurrence of BCR events, particularly in high-risk PCa cases. Therefore, we propose that the history of TURP should not be considered a contraindication for RARP, while preoperative ADT may be beneficial. Additionally, the lack of significant difference in BCR may be due to the small number of cases enrolled in the cohort. Therefore, a multicenter and large cohort study is needed to validate the key determinants of BCR in PCa patients with a history of TURP.

In our study, we aimed to evaluate potential predictive tools and pathological characteristics of PCa patients with a PSA level between 0 and 4 ng/mL. This study is the first to assess various clinical parameters in PCa patients with low PSA who underwent RARP surgery, based on the cause of diagnosis. However, there are limitations to this study. Firstly, it was retrospective in nature and the data analyzed came from selected patients undergoing RARP at a single institution, which introduces inherent selection bias. Additionally, for some equivocal PCas, RARP is necessary to confirm their pathological features, making selection bias difficult to avoid. Secondly, drawing epidemiological conclusions from our study is challenging due to the rarity of patients with low PSA levels and missing data resulting from referrals. This led to a smaller number of cases being included in the study. Finally, we focused primarily on preoperative baseline characteristics of RARP, postoperative pathological characteristics, and BCR without longer follow-up to assess PCa-specific mortality, which may be more crucial in evaluating the true clinical impact of cancer in the cohort. Additionally, we lack data on the social and psychological status and physical activity of these patients, which may be related to a reduced risk of PCa, improved PCa-specific survival rates, enhanced functional outcomes, and a reduction in adverse events associated with ADT (25-27). Overall, there is currently insufficient attention given to PCa patients with low PSA levels. Increasing evidence suggests that PCa with low PSA does not necessarily indicate low-grade, insignificant disease. This population is more challenging to detect tumors in compared to those with PSA levels >4 ng/mL, as physicians often relax their vigilance for men who do not reach PSA cutoffs, allowing tumors to progress undetected. High-grade PCa with low PSA is more aggressive, carries a higher risk of disease progression, and has worse survival and treatment outcomes (28,29), which is a concerning trend. Therefore, we recommend that future research focus on identifying more sensitive screening indicators than PSA and incorporate novel imaging technologies to enhance the early detection of patients with low PSA levels. Subsequently, prospective clinical trials and other methodologies should be employed to explore the most appropriate diagnostic, treatment, and management strategies for these patients.

Conclusions

PCa cases with low levels of PSA are generally rare. It

is crucial to note that most tumors with low PSA levels carry clinical significance, favorable pathological features, and a positive prognosis, underscoring the importance of early diagnosis and prompt treatment. However, a subset of patients in this group may exhibit higher malignancy and worse prognosis, preoperative ADT treatment may be beneficial. While predicting PCa with low PSA levels poses challenges, employing mpMRI and PSAD can facilitate accurate prognostication. Reevaluation of the cut-off value for low PSA levels is recommended to reduce the risk of missed or incorrect diagnoses. In cases of suspected PCa that pose diagnostic challenges, conducting supplementary examinations is advised to confirm the diagnosis and determine the necessity for further procedures like biopsies.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-538/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-538/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Nanjing Drum Tower Hospital Ethics Committee (No. 2019-253-01) and individual consent for this retrospective analysis was waived.

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