A Nomogram for Predicting Factors of Persistently Elevated Prostate-Specific Antigen in Patients Following Robot-Assisted Radical Prostatectomy

Abstract

Objective: After radical prostatectomy,prostate-specific antigen(PSA) value measuring ≥0.1ng/ml is defined as persistent PSA(pPSA) and in many studies,it was found to be associated with aggressive disease and poor prognosis.Our aim in this study is to point out the pathological and clinical factors affecting pPSA among the patients who underwent robot-assisted radical prostatectomy(RARP) in an experienced academic center and to make a nomogram,predicting pPSA value based on operative data,useful.

Methods: We examined records of 1273 patients who underwent RARP retrospectively. Preoperative,operative,and postoperative data were collected.Based on the PSA values (ng/ml) measured after 4-to-8 weeks of RARP,patients were divided into 2 groups as pPSA group (Group1)(n=97) with PSA values ≥0.1ng/ml and undetectable PSA group (Group2)(n=778) with PSA values <0.1ng/ml.Later on,Group1 was further divided into Group1a (PSA:0.1-0.2ng/ml) and Group 1b (PSA≥0.2ng/ml) to evaluate biochemical recurrence(BCR).

Results: Multivariate logistic regression analyses of the collected data revealed that PSA>20ng/ml,operation time,a postoperative international society of urological pathology (ISUP) grade of ≥4, pT 3-4, and pN were independently associated with pPSA.According to the results, a nomogram predicting pPSA was developed(Table 4).By looking at the nomogram pPSA was found in 98.9% of the cases with a PSA value of ≥20ng/ml, an operation time of 150 minutes, a postoperative ISUP grade of 4-5, a positive lymphovascular invasion (LVI) status, pT3-T4, and pN+; while pPSA was found in 25.5% of the cases with a PSA value of <20 ng/ml, an operation time of 100 minutes, a postoperative ISUP grade of <4-

5, a negative LVI status, pT<3-4, and pN-.The estimated BCR-free survival time was 16.3 months in Group 1a and 57.0 months in Group2 (p<0.001). Adjuvant treatment ratio was 64.9% in Group1 and 7.1% in Group2 (p<0.001).

Conclusion: For the patients who underwent RARP,factors associated with aggressive disease can predict the PSA persistence.To plan our treatment modalities accurately,an applicable nomogram in daily practice would be useful.

Keywords: Prostate Cancer, robot assisted radical prostatectomy, prostate specific antigen, nomogram, persistent PSA, BCR free survival

What's already known about this topic?

In the European Urology Guideline, after 4-to-8 weeks of radical prostatectomy(RP), a prostate specific antigen(PSA) value ≥0.1ng/ml has been defined as persistent PSA(pPSA). In some studies comparing patients based on pPSA and undetectable PSA, pPSA was found to be correlated with biochemical recurrence(BCR), metastasis-free survival(MFS), and overall survival(OS).

What does this article add?

This study aims to evaluate the pathological and clinical factors affecting pPSA in patients who underwent RARP in a third level academic center with advanced experience on RARP and make a nomogram predicting pPSA applicable.

We showed that after RARP, factors which are associated with aggressive disease (PSA>20ng/ml, operation time, postoperative ISUP grade≥4), LVI, pT3-4, pN1) can predict the PSA persistence. Patients with pPSA after RARP have a tendency for BCR and when compared to patients with undetectable PSA, they have a shorter time range till BCR occurrence. The nomogram we made might be used for comprehensive patient counseling pre and postoperatively, highlighting which patients are more likely to develop pPSA after RARP

A Nomogram for Predicting Factors of Persistently Elevated Prostate-Specific Antigen in Patients Following Robot-Assisted Radical Prostatectomy

Introduction

In the European Urology Guideline, after 4-to-8 weeks of radical prostatectomy(RP), a prostate specific antigen(PSA) value ≥0.1ng/ml has been defined as persistent PSA(pPSA).[1] Different ratios, between 5 to 20%, has been reported about detecting pPSA after RP. Previous studies had evaluated PSA values measured within the first 6 months of surgery however, current studies define pPSA as PSA values of >0.1ng/ml measured within 4-to-8 weeks after the operation. This change takes persistent local disease, pre-existing metastases, or residual benign prostate tissue into account.[2,3]

Many studies have shown that pPSA after RP is associated with aggressive disease (pathological stage >T3a, positive surgical margins(PSM), positive nodal status, pathological ISUP grade>3), and poor prognosis.[2,4-6] In some studies comparing patients based on pPSA and undetectable PSA, pPSA was found to be correlated with biochemical recurrence(BCR), metastasis-free survival(MFS), and overall survival(OS). After the detection of pPSA, salvage radiotherapy(sRT) is suggested. Moreover, if the patient has high-risk factors (postoperative ISUP grade>4, pT3b disease, PSM) androgen deprivation therapy(ADT) is preferred with/without the sRT. [2-6] In a study, patients with pPSA and undetectable PSA were compared on their 1 and 5-year BCR-free survival rates. The undetectable PSA group showed 95% and 72% survival rates while pPSA group showed 68% and 36%, respectively.[4]

Robot-assisted radical prostatectomy(RARP), when compared to open surgery, results in less blood loss, less hospitalization time, provides an early return to work, and positive oncological outcomes. There are some publications reporting that RARP also has superior functional results in urinary incontinence and erectile potency.[7,8] In a study, it is found that

PSM ratio is less seen with RARP than open surgery.[9] These data show the efficiency of RARP both functionally and oncologically.[7-10] A study made by Kumar et al. evaluating pPSA after RARP, found pPSA in 3.05% of the cases and showed that pPSA was associated with preoperative PSA values of >10ng/ml, Gleason Score(GS) of ≥8, clinical stage and some postoperative pathological characteristics (pathological stage, positive lymph nodes, extraprostatic extension(EPE), PSM, GS, and tumor volume percentage). BCR was significantly higher in the pPSA group than in the undetectable PSA group (52.47% and 7.9%, respectively). Also, the time range till BCR occurrence was shorter in pPSA group (8.9 and 21.1 months, respectively).[11]

As mentioned before, pPSA value after RP is essential to be able to apply sRT postoperatively. Thus, predicting the possibility of pPSA with pre- and postoperative pathological and clinical characteristics is an important component of patient treatment. By estimating the possibility, the patient can be adequately informed about the treatment modalities such as pre- and postoperative adjuvant therapy.

This study aims to evaluate the pathological and clinical factors affecting pPSA in patients who underwent RARP in a third level academic center with advanced experience on RARP and make a nomogram predicting pPSA applicable.

Material and Methods

This study was designed as a retrospective study. The ethics committee of the Ankara Yildirim Beyazit University School of Medicine approved our study and all participants signed the informed consent forms (Institutional Review Board approval number:26379996). Following the approval, 1273 patients with a previous history of RARP, between the dates of June 2009 and December 2017, were scanned retrospectively. Patients with no postoperative PSA values or follow-up of other parameters and with previous neoadjuvant therapy (n=398) were excluded from the study. Firstly, demographical features (age, body mass index (BMI),

smoking), comorbidities (hypertension(HT), cardiovascular disease(CVD), diabetes mellitus(DM), chronic obstructive pulmonary disease(COPD)) of the patients were noted. Charlson Comorbidity Index(CCI) was calculated. BMI was calculated by dividing weight to the square of the height (kg/m^2). After that, preoperative [digital rectal examination findings such as presence of nodules or induration, PSA(ng/ml), total PSA, free PSA, laterality of the tumor (left, right, bilateral), preoperative International Society of Urological Pathology(ISUP) grade, cT stage(cT1-2a, cT2b, cT2c), percentage of tumor positivity, positive biopsy cores, preoperative International Prostate Symptom Score(IPSS), prostate surgery history (primary, TUR-P, open prostatectomy), American Society of Anesthesiologists(ASA) score], operative [operation time, console time, nerve-sparing procedure, posterior reconstruction, bladder neck preservation, bleeding volume], and postoperative [lymph node(LN) yield, complications (none, mClavien-Dindo Grade 1-2, mClavien-Dindo Grade 3-4), drainage period in days, hospitalization day, tumor volume percentage, postoperative ISUP grade, bilateral tumor localization, EPE, seminal vesicle invasion(SVI), LVI, perineural invasion(PNI), capsule invasion, pT stage (≤pT2a**,** pT2b**,** pT2c**,** pT3a**,** pT3b**,** pT4a)**,** lymph node- involvement(LNI) **(**N+**,** N-**,** N/A)**,** PSM, adjuvant therapy (none, RT, RT+ADT, chemotherapy(CHT), ADT), follow-up in months] characteristics were noted.

Patients were divided into 2 groups based on their PSA values measured after 4-to-8 weeks of RARP as pPSA group (PSA≥ 0.1 ng/ml)(Group 1)(n=97) and undetectable PSA group (PSA<0.1 ng/ml)(Group2)(n=778). These two groups were compared on chosen parameters to reveal whether there is a statistically significant difference or not. To minimize the variability in pathological staging and grading, cases were analyzed by the same 2 pathologists with a standardized protocol.

Preoperative Staging

No imaging modality was performed for the low-risk group (PSA<10, GS<7, cT1-2a). For the intermediate and high-risk groups with localized or locally aggressive disease, we performed cross-sectional abdominal imaging in addition to a bone-scan for metastasis detection, at least. Patients with high-risk localized or locally aggressive disease were routinely scanned with pelvic magnetic resonance imaging(MRI). The preoperative staging was T1/T2/T3 N0 M0 for all patients. Patients with preoperatively proven distant metastasis were excluded from the study.

Surgical technique, BCR and Follow-Up

A transperitoneal RARP procedure was performed on all patients. Four surgeons, all with RARP experience with over 250 cases, performed operations via the robotic procedure. BCR was defined as PSA≥0.2 ng/ml measured in two consecutive samples.[12] After that, Group 1 was further divided into Group1a with PSA between 0.1-0.2 ng/ml and Group 1b with PSA≥0.2 ng/ml after 4-to-8 weeks of RARP. While Group 1a had only been followed-up till they had a BCR (PSA≥0.2ng/ml), Group1b was suggested to take sRT and ADT. BCR occurrence and time range till the occurrence for Group1a and Group2 were calculated separately. For patients with BCR, treatment was planned based on PSA values, imaging results, PSA recurrence, and doubling time. Unless BCR had occurred, there were no treatment or imaging planned. Radiological progression was defined as a positive imaging result (by bone-scan and/or computed tomography(CT) and/or MRI and/or glucose positron emission tomography(18F-FDG PET/CT)) obtained during the follow-up after BCR.

Statistical Analysis

One-sample Kolmogorov Smirnov test was used to check whether the data had a normal distribution for numerical variables. Mean±standard deviation was noted for the data

with normal distribution and median (interquartile range (IQR)) values were recorded for the data without normal distribution. Numerical variables were compared with Student's t-test when parametric test criteria were present. In the absence of these criteria, the Mann-Whitney U test was used. Two Proportion z Test, Pearson Chi-Square Test, and Fisher's Exact Test were used to determine whether there was a difference between the percentages of categorical variables or not. Binary logistic regression analysis was used to obtain independent risk factors for persistent PSA. Multivariate logistic regression analysis was applied for variables that were statistically significant in the univariate analysis. Kaplan–Meier method was applied to determine the BCR-free survival and the significance of differences in the survival rate was analyzed using the log-rank test. For all tests, the probability of the first type error was α=0.05. Statistical analysis of the study was performed using IBM SPSS 22.0 package program.

Results

There were 97 patients (11%) in Group1 and 778 (89%) patients in Group2 (n=875). Median follow-up time was 18 (6-60) months for Group1 and 24 (6-72) months for Group2. When the demographic, preoperative, operative, and postoperative data of 2 groups were compared, it was observed that age, CCI, presence of nodules, presence of induration, total PSA, free PSA, laterality(bilateral), preoperative ISUP grade, percentage of positivity, positive biopsy cores, preoperative IPSS, operation time, console time, LN yield, drainage period, hospitalization time, tumor volume, postoperative ISUP grade, bilateral tumor localization (postoperative diagnosis), EPE, SVI, LVI, PNI, capsule invasion, pT stage, LNI, PSM, and adjuvant therapy rates were found statistically significantly higher in Group1. On the other hand, the nerve-sparing procedure showed lower results in Group1(Table1).

Towards further dividing study groups, Group1a had 32 (33%) patients while Group1b had 65 (67%). During the follow-up period, BCR was detected in 21 (65.6%) patients in Group1a and

71 (9.1%) patients in Group2. The estimated BCR-free survival time was 16.3 months for Group1a and 57.0 months for Group2 ($p<0.001$)(Figure1). While adjuvant therapy (RT, RT+ADT, CHT, ADT) ratio was 64.9% for Group1 (Group1a=11, Group1b=52; n=63), it was 7.1% (n=55) for Group2 ($p<0.001$). Three patients in Group1 had metastasis revealed by conventional imaging methods after BCR. The distribution of follow-up data and BCR-free survival rates of the groups were summarized in Table2.

Binary logistic regression analysis was used to obtain independent risk factors for pPSA. Multivariate logistic regression analyses of the risk factors that are shown to be statistically significant in the univariate regression analyses revealed that a PSA value of >20ng/ml (95% Confidence Interval(CI): 1.24-4.67, odds ratio(OR)=2.41, p=0.009), operation time (95% CI:1.001-1.009, OR=1.005, p=0.01), a postoperative ISUP grade of ≥4 (95%CI: 1.397-4.399, OR=2.479, p=0.002), LVI (95%CI: 1.296- 4.603, OR=2.442, p=0.006), pT3-4 (95%CI: 1.928-5.817, OR=3.349 , p<0.001), pN+ (95%CI: 2.084-8.521, OR=4.214, <0.001) were independently associated with pPSA(Table3).

When we looked at the nomogram predicting pPSA after RARP and analyzed the data, pPSA was detected in 98.9% of the cases with a PSA value of ≥20 ng/ml, an operation time of 150 minutes, a postoperative ISUP grade of 4-5, LVI positivity, pT3-4, pN+. However, pPSA was detected only in 25.5% of the cases with a PSA value of <20 ng/ml, an operation time of 100 min, a postoperative ISUP grade of <4-5, LVI negativity, pT<3-4, pN- (Table 4).

Discussion

After prostate cancer surgery, PSA is the backbone of the follow-up process. pPSA is a poor prognostic factor indicating recurrence after RP. A study made by Preisser et al. included 11.604 patients and showed that 8.8% of the patients had pPSA .[13] In our study that

ratio was 11%. It is seen that our result is consistent with the previously reported data in the literature.[1]

In many studies, it has been reported that pPSA is associated with aggressive disease (pathological stage>T3a, PSM, positive nodal status, ISUP grade>3) and poor prognosis.[2,4] In this study, we did a multivariate analysis to predict the risk of pPSA occurrence. Multivariate logistic regression showed that a PSA value of >20ng/ml, operation time, a postoperative ISUP grade of ≥4, LVI, pT3-4, pN1 were significant predictive factors of pPSA. Group 1 showed higher rates of presence of nodules, presence of induration, total PSA**,** free PSA, laterality (bilateral), preoperative ISUP grade, percentage of tumor positivity**,** positive biopsy cores**,** LN yield, tumor volume**,** postoperative ISUP grade**,** bilateral tumor localization (postoperative diagnosis)**,** EPE**,** SVI**,** LVI, PNI**,** capsule invasion, pT stage, LNI, PSM, and adjuvant therapy; that may be resulting from that patients with pPSA tend to have a higher grade and more invasive tumors. Thus, RARP time**,** console time, postoperative drainage period, and hospitalization time is longer in Group1 as a result of a more complicated surgery. The nerve-sparing procedure was less performed in Group1 due to the tumor characteristics as mentioned before and also, it was not preferred in these patients. It is not surprising that preoperative IPSS was higher with the higher grade and more invasive tumors. Consecutively, we developed a nomogram by using pathological, clinical, and operative characteristics to predict the probability of pPSA occurrence. Nomogram is a term used for representation based on graphics in a simple form developed in order to predict the probability of a clinical event which relies on clinical, pathological, and personal characteristics. Nomograms enable clinicians to classify and identify suitable patients for an optimal management strategy by generating a proper estimation of probability. With all these regards, a nomogram to inform the patients about their disease and plan our treatments would be useful in daily practice

which this study serves. Constituents of this nomogram have been used to counsel patients and select the timing of adjuvant therapies both pre and postoperatively.

There are too many studies emphasizing the clinical importance of pPSA. In a study that evaluated patients for 15 years after RP found that pPSA (PSA≥0.1ng/ml) group showed 53.0% of MFS, 75.5% of cancer-specific survival(CSS), and 64.7% of OS ratios; while undetectable PSA (PSA<0.1 ng/ml) group showed 93.2% of MFS, 96.2% of CSS, and 81.2% of OS.[13] Kim et al. conducted a study that implies pPSA(PSA≥0.1ng/ml) is an important predictive factor of PFS radiologically.[14] Bianchi et al. reported that pPSA patients with nodal positivity had less favorable outcomes during the follow-up.[15] Ploussard G. et al. conducted a study on 496 men who had pN0 nodal status with pPSA, which showed 74.4% of BCR in two consecutive PSA measurements of ≥0.2ng/ml after surgery) and 5% metastasis.[2] As in these studies, we also defined pPSA as PSA≥0.1ng/ml and BCR as two consecutive PSA measurements of ≥0.2ng/ml after surgery. In our study, 21 patients (65.6%) in Group1a and 71 patients (9.1%) in Group2 had BCR. Time range till BCR occurrence was significantly shorter for Group 1a ($p<0.001$)(Figure1). Also, Group1 showed statistically significant higher rates of adjuvant treatment. Depending on the results of many studies, early treatment of pPSA patients is essential. Patients with pPSA, which doesn't result from a pre-existing metastasis after RP, are suggested to take sRT and/or ADT based on their pathological diagnosis and pPSA values. sRT was shown to be correlated with improved OS and CSS in pPSA patients.[13] In the ARO 96-02 study which was a prospective randomized control trial, 74 patients with pPSA (0.1 ng/ml was the standard limit) received sRT with 66 Gy per protocol (arm C). The clinical relapse-free survival rate was 63% in the 10-year follow-up. It was also mentioned that pPSA after RP is a significant prognostic factor for the clinical progression of pT3 tumors. It is associated with a higher percentage of distant metastases and a worse OS.[3] The GETUG-22 trial compared RT with RT+ADT which were given to pPSA

(0.2-2.0ng/ml) patients after RP and reported a good tolerance for combined treatment.[16] In actual studies, pPSA is defined as PSA≥0.1 ng/ml however, previous studies defined pPSA based on different PSA values.[17] Choo et al. conducted a study that defined pPSA as PSA≥0.2 ng/ml. It was found that applying ADT may improve the PFS in pPSA patients. 78 patients with pT3 disease and/or PSM after RP were treated with RT+ADT for 2 years. As a result, the relapse-free rate was 85% in 5 years and 68% in 7 years.[17]

The strength of our study is that the number of the patients included is high and all of the patients were operated by surgeons who were experienced in RARP. BCR ratios and time range until BCR occurrence shows us the clinical importance of pPSA. The limitations of this study are as follows: First of all, it is a retrospective study. Secondly, Ga^{68}PSMA PET/CT wasn't used as a diagnostic tool while evaluating the pPSA patient group because it wasn't available at the time of the study. MRI and bone scintigraphy are not useful for revealing residual cancer tissue when PSA is <2ng/ml. In the EAU guideline, Ga^{68}PSMA PET scanning is suggested for the males with a pPSA value of >0.2ng/ml to exclude metastatic disease.[1] Thus, our study BCR was taken into account with values of ≥0.2 ng/ml and other values were not used to plan treatment or imaging. Another limitation of our study is that parameters like CSS, OS, and PFS were not mentioned.

Conclusions

After RARP, factors which are associated with aggressive disease (PSA>20ng/ml, operation time, postoperative ISUP grade≥4), LVI, pT3-4, pN1) can predict the PSA persistence. Patients with pPSA after RARP have a tendency for BCR and when compared to patients with undetectable PSA, they have a shorter time range till BCR occurrence. This nomogram might be used for comprehensive patient counseling pre and postoperatively, highlighting which patients are more likely to develop pPSA after RARP.

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Ethical disclosures

Informed consent: Informed consent was obtained from all individual participants included in the study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Ethical approval: This study was conducted in accordance with the declaration of 1964 Helsinki and also with approval from the institutional ethics committee.

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Table 1. Stratification of the patients according to the presence/absence of pPSA.

	Group 1 (n=97)	**Group 2 (n=778)**	**P value**
Age	64.8±5.8	61.8±6.7	**<0.001**[T]
BMI (kg/m²)	27.0±2.8	26.4±8.9	0.208[T]
CCI	2.8±1.1	2.5±1.3	**0.012**[T]
DM, n (%)	16 (16.5)	128 (16.5)	0.992
HT, n (%)	33 (34)	273(35.1)	0.835
COPD, n (%)	9 (9.3)	40 (5.1)	0.095
CVD, n (%)	13 (13.4)	91 (11.7)	0.625
Smoking, n (%) **Cigarette pack-year**	57 (58.8) 20.6±27.4	427 (54.9) 15.7±18.2	0.469 0.090[T]
Presence of nodules, n (%)	20 (20.6)	103 (13.2)	**0.049**
Presence of induration, n (%)	37 (38.1)	182 (23.4)	**0.002**
PSA, ng/ml **Total** **Free**	 12.0 (0.3-251.0) 1.46 (0.05-14.3)	 6.85 (0.11-170.0) 1.01 (0.03-106.0)	**<0.001**[M] **<0.001**[M]
PSA >20 ng/ml, n (%)	28 (28.9)	44 (5.7)	**<0.001**
Laterality, n (%) **Right** **Left** **Bilateral**	 22 (22.7) 18 (18.6) 57 (58.8)	 222 (28.5) 202 (26) 354 (45.5)	**0.046**
Preoperative ISUP, n (%) **Grade 1** **Grade 2** **Grade 3** **Grade 4** **Grade 5**	 36 (37.1) 18 (18.6) 15 (15.5) 15 (15.5) 13 (13.4)	 512 (65.8) 125 (16.1) 64 (8.2) 58 (7.5) 19 (2.4)	**<0.001**
cT stage, n (%) **cT1-2a** **cT2b** **cT2c**	 82 (84.5) 4 (4.1) 11 (11.3)	 691 (88.8) 19 (2.4) 68 (8.7)	0.416
Percentage of positivity	50.9±31.3	35.1±24.6	**<0.001**[T]
Positive biopsy cores	5.1±3.2	3.5±2.6	**<0.001**[T]
Preoperative IPSS	16.0±6.8	13.0±7.0	**<0.001**[T]
Prostate surgery history, n (%) **Primary** **TUR-P/Open Prostatectomy**	 88 (90.7) 9 (9.3)	 738 (94.9) 40 (5.1)	0.225
ASA classification, n (%) **ASA I** **ASA II** **ASA III**	 20 (20.6) 70 (72.2) 7 (7.2)	 234 (30.1) 508 (65.3) 36 (4.6)	0.108
Operation time, min	167.9±55.6	145.7±53.5	**<0.001**[T]

Console time, min	147.9±50.9	132.0±47.3	**<0.004**[T]
Nerve-sparing procedure, n (%)	65 (67)	720 (92.5)	0.000
Posterior reconstruction, n (%)	31 (32)	238 (30.6)	0.783
Bladder neck preservation, n (%)	88 (90.7)	720 (92.5)	0.524
Bleeding volume, ml	157.5±162.7	138.1±139.0	0.263[T]
LN Yield	9 (0-37)	0 (0-47)	**<0.001**[M]
Complication, n (%)			0.742
None	88 (90.7)	722 (92.8)	
mClavien-Dindo Grade 1-2	8 (8.3)	51 (6.5)	
mClavien-Dindo Grade 3-4	1 (1)	5 (0.7)	
Drainage period, day	3.3±2.4	2.7±2.1	**0.031**[T]
Hospitalization, day	4 (2-11)	(3 (1-30))	0.015[M]
Tumor volume, cm^3	9.5 (0.1-87.1)	2.2 (0.1-84.0)	**<0.001**[M]
Postoperative ISUP, n (%)			**<0.001**
≤Grade 1	16 (16.5)	377 (47.4)	
Grade 2	18 (18.6)	221 (28.4)	
Grade 3	19 (19.6)	98 (12.6)	
Grade 4	12 (12.4)	55 (7.1)	
Grade 5	32 (33)	27 (3.5)	
Bilateral tumor localization, n (%)	86 (88.7)	576 (74)	**0.013**
Capsule invasion, n (%)	68 (70.1)	208 (26.7)	**<0.001**
Seminal vesicle invasion, n (%)	36 (37.1)	68 (8.7)	**<0.001**
Lymphovascular invasion, n (%)	36 (37.1)	50 (6.4)	**<0.001**
Perineural invasion, n (%)	83 (85.6)	464 (59.6)	**<0.001**
Extra-prostatic extension, n (%)	58 (59.8)	163 (21)	**<0.001**
pT stage, n (%)			**<0.001**
≤pT2a	3 (3.1)	136 (17.5)	
pT2b	4 (4.1)	62 (8)	
pT2c	16 (16.5)	341 (43.8)	
pT3a	37 (38.1)	171 (21.9)	
pT3b	36 (37.1)	68 (8.7)	
pT4a	1 (1)	--	
Lymph node invasion, n (%)			**<0.001**
N+	24 (24.7)	28 (3.6)	
N-	45 (46.4)	253 (32.5)	
N/A	28 (28.9)	497 (63.9)	
Positive surgical margin, n (%)	53 (54.6)	156 (20.1)	**<0.001**
Postoperative 1st month PSA, ng/ml	0.36 (0.1-30.3)	0.02 (0-0.09)	**<0.001**[M]
Adjuvant therapy, n (%)			**<0.001**
None	34 (35.1)	723 (92.9)	
RT	20 (20.6)	29 (3.7)	
RT+ADT	17 (17.5)	7 (0.9)	
CHT	2 (2.1)	1 (0.1)	
ADT	24 (24.7)	18 (2.3)	
Follow-up, months	18 (6-60)	24 (6-72)	0.535[M]

[T]: Student T test

[M]: Mann-Whitney U test

M/F: Male/Female, BMI: Body mass index, CCI: Charlson comorbidity index, DM: Diabetes Mellitus, HT: Hypertension, COPD: chronic obstructive pulmonary disease RT: radiotherapy CHT: chemotherapy ADT: androgen deprivation therapy

Table 2. Distribution of the follow-up data and BCR-free survival rates by the groups

	Group 1a (n=32) **0.1-0.2**	**Group 2 (n=778)** **<0.1**	**P value**
Median follow-up, months, (range)	21 (9-60)	24 (6-72)	**<0.035[a]**
BCR-free Survival, %			**<0.001[b]**
1-Year	34.4	98.9	
2-Year	34.4	86.1	
3-Year	34.4	71.0	
5-Year	-	66.4	
Estimated BCR-free life expectancy, months	16.3	57.0	**<0.001**

[a] Mann-Whitney U Test, [b] Log-rank method,

Table3. Multivariate logistic regression analysis of predicting factors of persistent PSA

Binary Logistic Regression (n=875)											
	Univariate Model						**Multivariate Model**				
	OR	**95% CI**			**P value**		**OR**	**95% CI**			**P value**
Age	1.075	1.040	-	1.113	**<0.001**						
CCI	1.173	1.010	-	1.362	**0.037**						
Cigarette pack-year	1.011	1.002	-	1.021	**0.021**						
Presence of nodules	1.781	1.188	-	2.670	**0.005**						
Presence of induration	1.506	1.134	-	2.000	**0.005**						
Total PSA	1.049	1.029	-	1.069	**<0.001**						
Free PSA	1.025	0.988	-	1.064	0.192						
PSA>20 ng/ml	6.769	3.968	-	11.550	**<0.001**		2.411	1.244	-	4.673	**0.009**
Laterality	1.324	1.018	-	1.724	**0.037**						
Percentage of positivity	1.021	1.014	-	1.029	**<0.001**						
Preoperative ISUP	2.291	1.750	-	2.999	**<0.001**						
ISUP≥4	3.694	2.245	-	6.080	**<0.001**						
Positive biopsy cores	1.189	1.112	-	1.271	**<0.001**						
cT stage	1.197	0.865	-	1.658	0.278						
Preoperative IPSS	1.061	1.030	-	1.094	**<0.001**						
Nerve-sparing procedure	0.164	0.099	-	0.270	**<0.001**						
Console time	1.006	1.002	-	1.010	**0.002**						
Operation time	1.006	1.003	-	1.010	**<0.001**		1.005	1.001	-	1.009	**0.010**
Postoperative ISUP **ISUP grade 2-3** **ISUP grade 4-5** **(Ref: ISUP grade 1)**	3.708	2.700	-	5.091	**<0.001**		 1.603 3.484	 0.828 1.639	 - -	 3.101 7.405	 0.161 **0.001**
ISUP≥4	7.046	4.446	-	11.169	**<0.001**		2.479	1.397	-	4.399	**0.002**
Bilateral tumor localization	2.007	1.291	-	3.119	**0.002**						
Capsule invasion	6.426	4.045	-	10.207	**<0.001**						
SVI	6.162	3.808	-	9.971	**<0.001**						
LVI	8.593	5.202	-	14.192	**<0.001**		2.442	1.296	-	4.603	**0.006**
PNI	4.012	2.237	-	7.195	**<0.001**						

EPE	5.611	3.610	-	8.722	**<0.001**						
pT stage	6.374	3.933	-	10.330	**<0.001**						
pT 3-4	7.256	4.436	-	11.869	**<0.001**		3.349	1.928	-	5.817	**<0.001**
pN+	14.756	8.186	-	26.602	**<0.001**		4.214	2.084	-	8.521	**<0.001**
LNI	8.806	4.853	-	15.979	**<0.001**		0.116	0.012	-	1.116	0.062
LN Yield	1.057	1.033	-	1.081	**<0.001**						
Positive surgical margin	4.803	3.104	-	7.432	**<0.001**						
Tumor diameter	1.064	1.046	-	1.082	**<0.001**						
Tumor volume	1.060	1.045	-	1.075	**<0.001**						

Table 4. A new nomogram for pPSA prediction

	Samplecase 1	Samplecase 2	Samplecase 3	Samplecase 4	Samplecase 5
PSA>20ng/ml	0	1	0	1	1
Operation time	100	100	150	150	150
PO-ISUP4-5	0	1	0	1	0
LVI	0	1	0	1	0
pT3-4	0	1	0	1	0
pN	0	1	0	1	0
Y value	-1,07	4,26	-0,82	4,51	0,06
Probability of persistent PSA	***25,5%***	***98,6%***	***30,6%***	***98,9%***	***51,5%***

Figure Legends:

Figure 1. Kaplan-Meier curve for disease-free survival. The p value of the Log-rank method was <0.001 and the chi-square value was 253.853. The estimated biochemical recurrence-free survival time was 16.3 months in group 1 and 57.0 months in group 2 (p<0.001)