Original Article

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Differences Between Patients with and without Persistent PSA after Radical Prostatectomy in Clinically High-risk and/or Locally Advanced Prostate Cancer

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Abstract

Objective: This study aimed to identify preoperative and postoperative factors associated with persistent prostate-specific antigen (PSA) following radical prostatectomy (RP) in patients with clinically high-risk and/or locally advanced prostate cancer. Understanding these factors can guide early postoperative management decisions, including adjuvant treatment strategies.

Materials and Methods: A retrospective analysis was conducted on 183 patients who underwent RP for locally advanced prostate cancer between 2009 and 2023. Patients were divided into two groups: those with persistent PSA at 1 month postoperatively (group 2, n=43), and those without (group 1, n=140). Preoperative and postoperative variables, including PSA levels, clinical stage, biopsy grade group, tumor volume, and pathological findings, were compared between groups.

Results: Patients in group 2 had significantly higher preoperative PSA levels (24.6±19 ng/mL vs. 15±15.5 ng/mL, p<0.001), advanced clinical stage (≥T2B: 52.6% vs. 32.1%, p=0.032), and higher percentage of positive biopsy cores (p=0.011). Postoperative findings demonstrated a higher tumor volume (20.2±14.1 cc vs. 10.7±10.5 cc, p=0.002), tumor density (p=0.005), and positive surgical margins (86% vs. 70%, p=0.025) in group 2. Patients in group 2 had higher rates of lymph node dissection, adjuvant therapy, and early salvage radiotherapy.

Conclusion: Preoperative PSA levels, biopsy grade group, positive surgical margins, and advanced pathological stage are critical predictors of persistent PSA after RP. Early identification of high-risk patients enables personalized management plans, including timely initiation of adjuvant therapies, to improve outcomes. Further prospective studies are needed to refine risk stratification models and personalize treatment strategies.

Keywords: Prostate cancer, persistent PSA, radical prostatectomy, prostate-specific antigen

Introduction

Prostate cancer remains one of the most prevalent malignancies affecting men worldwide. While localized prostate cancer can often be effectively managed with definitive therapies such as radical prostatectomy (RP), the management of locally advanced disease presents significant therapeutic challenges (1). RP, as an initial step in a multimodal treatment approach, plays a pivotal role in these cases. However, persistent prostate-specific antigen (PSA) levels following RP may indicate residual disease and are associated with poorer oncological outcomes (2).

The identification of factors that predict persistent PSA after surgery is critical for optimizing patient management. Understanding these predictors not only facilitates more tailored postoperative surveillance but also informs decisions regarding adjuvant therapies, such as radiotherapy or androgen deprivation therapy, to enhance patient outcomes. Despite improvements in surgical techniques and the availability of effective adjuvant treatments, the incidence of persistent PSA remains a significant concern in patients with locally advanced prostate cancer (3).

In this study, we aimed to identify the preoperative and postoperative factors associated with persistent PSA following

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RP in patients with clinically high risk and/or locally advanced prostate cancer. By clarifying these predictive factors, we aim to contribute to the development of more personalized and effective treatment strategies for this challenging patient population.

Materials and Methods

This study was conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval was obtained from, İzmir Bozyaka Research and Educational Hospital Ethics Committee, reference number 03 (date: 17.01.2018). After obtaining approval from the hospital's ethics committee, we retrospectively evaluated data from 183 patients who underwent open retropubic RP for clinically high risk and/or locally advanced prostate cancer between 2009 and 2023. Patients were included in the study if they had complete data for preoperative and postoperative evaluations, including PSA levels at 1 month post-surgery. Exclusion criteria included incomplete clinical or pathological data, history of prior prostate cancer treatments (such as radiotherapy or androgen deprivation therapy), or the presence of metastatic disease at the time of surgery. Of the 191 eligible patients, only those with available PSA data from the first postoperative month were included in the study.

The postoperative 1-month PSA level was chosen as the threshold for determining persistent PSA based on its widespread use in clinical practice, and its predictive value for identifying residual disease early. Because the half-life of PSA is approximately 3.15 days, serum PSA values of 50 ng/mL should be undetectable within 4 weeks after RP. PSA persistence defined at 1-month postoperatively is strongly associated with adverse oncological outcomes, including biochemical recurrence and metastatic progression. This timeline ensures early detection of residual disease, enabling timely initiation of adjuvant therapies to improve patient outcomes (4).

The patients' demographic characteristics, PSA levels, prostate biopsy findings, RP pathology results, and follow-up data were analyzed. The cohort was divided into two groups: those with no evidence of persistent PSA at 1 month post-RP (group 1) and those with persistent PSA (group 2). The collected data were compared between these two groups. Informed consent was obtained from all individual participants included in the study.

Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) version 23. Descriptive statistics for parametric variables were presented as mean and standard deviation, while non-parametric variables were expressed as median and range (minimum-maximum) or counts and percentages. The normality of distribution for continuous variables was evaluated using the Kolmogorov-Smirnov test. For comparisons of normally distributed quantitative data, the Student's t-test was employed. The Mann-Whitney U test was used for non-normally distributed quantitative variables. Categorical variables were compared using the chi-square and Fisher's exact test. A p-value of less than 0.05 was considered statistically significant within a 95% confidence interval.

Results

The mean age of the 183 patients included in this study was 66.9 years, and the mean preoperative PSA level was 17.3 ng/mL. The clinical and pathological characteristics of the patients are summarized in Table 1. At the 1-month postoperative evaluation, 43 patients were found to have persistent PSA levels, while 140 patients had PSA levels below 0.1 ng/mL. A comparison of the results between the persistent PSA group (group 2, n=43) and the non-persistent PSA group (group 1, n=140) is provided in Table 2.

Preoperative data revealed that the mean PSA level in group 1 (15±15.5 ng/mL) was significantly lower than that of in group 2 (24.6±19 ng/mL) ($p<0.001$). Additionally, patients with clinical stage cT2B or higher were more frequently observed in group 2 compared to group 1 ($p<0.05$). When preoperative transrectal ultrasound-guided biopsy data were analyzed, the biopsy grade group and percentage of positive biopsy cores were significantly higher in patients with persistent PSA (group 2) ($p<0.05$).

Postoperative findings demonstrated that the tumor volume and tumor density (calculated as the ratio of tumor volume to prostate volume) were significantly higher in group 2 ($p<0.05$). Similarly, pathological T-stage and positive surgical margins were more frequently observed in group 2 ($p<0.05$). The rates of lymph node dissection, adjuvant therapy, and adjuvant or early salvage radiotherapy were also higher in this group (Table 3). Key predictors between group 1 and group 2 are summarized in Figure 1, providing a visual comparison of significant variables identified in our analysis.

Discussion

Persistent PSA after RP remains a significant concern in the management of locally advanced prostate cancer. In this study, we identified several preoperative and postoperative factors associated with persistent PSA, aligning with current literature that emphasizes the multifactorial nature of this outcome.

Our finding that higher preoperative PSA levels are predictive

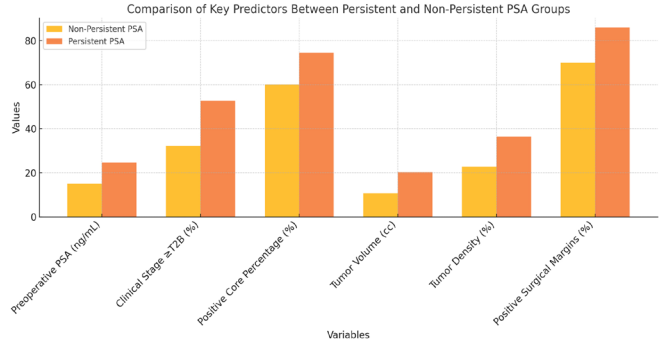

Figure 1. Comparison of key predictors between persistent and non-persistent PSA groups

PSA: Prostate-specific antigen

Table 1. Demographic, clinical, and pathological data of the patients		
		n=191
Age (years)		66.9±6.3 (46-81)
PSA (ng/mL) (n=182)		17.3±16.7 (2.6-100)
Clinical stage, (n=152)	T1C-T2A	95 (62.5%)
	T2B	27 (14.1%)
	≥T2C	30 (19.7%)
Biopsy grade group, (n=185)	1	45 (24.3%)
	2	51 (27.6%)
	3	32 (17.3%)
	4	42 (22.7%)
	5	15 (8.1%)
Number of PCa positive cores (n=155)		5.4±3.6
Percentage of PCa positive cores (n=143)		63.6±30.7%
RP grade group, n	1	14 (7.3%)
	2	45 (23.6%)
	3	55 (28.8%)
	4	44 (23%)
	5	33 (17.3%)
Pathological stage, (n=190)	T3A	103 (54.2%)
	T3B	84 (44.2%)
	T4	3 (1.6%)
Tumor volume (cc)		13.3±12.1
Tumor density		25.9±20.3
Positive surgical margins, n		141 (73.8%)
Lymph node dissection, n		158 (82.7%)
Mean number of LN removed (n=134)		13.8±8.7
Lymph node metastasis, (n=134)		36 (26.9%)
Mean number of positive LNs (n=134)		0.66±1.35
Number of positive LNs, (n=36)	1 LN+	12 (33.3%)
	2 LN+	10 (27.8%)
	≥3 LN+	14 (38.9%)
Follow-up duration (months)		33.4±20.9
Persistent PSA post-RP, (n=183)		43 (23.5%)
Biochemical recurrence, (n=184)		31 (16.8%)
Adjuvant therapy, n		111 (58.1%)
Adjuvant therapy, (n=111)	RT	23 (20.7%)
	RT + LHRH	76 (68.5%)
	RT + LHRH + AA	1 (0.9%)
	LHRH	11 (9.9%)
Radiotherapy, (n=100)	Adjuvant	62 (62%)
	Early salvage	19 (19%)
	Salvage	19 (19%)

PSA: Prostate-specific antigen, PCa: Prostate cancer, RP: Radical prostatectomy, LN: Number of positive lymph node, RT: Radiotherapy, LHRH: Luteinizing hormone-releasing hormone, AA: Androgen ablation

of persistent PSA is consistent with previous studies. For instance, Preisser et al. (4) found that elevated preoperative PSA, alongside other clinical variables such as advanced T-stage, significantly increased the likelihood of biochemical persistence (2). Additionally, the percentage of positive biopsy cores was also highlighted as, a crucial predictor, a finding corroborated by Milonas et al. (5), who demonstrated that patients with a higher proportion of positive cores were at greater risk for PSA persistence (3).

Surgical margin status was another key postoperative factor linked to PSA persistence. This relationship is well-established in the literature. Wiegel et al. (6) showed that positive margins, particularly in combination with extracapsular extension and seminal vesicle invasion, significantly increase the risk of biochemical recurrence and PSA persistence (2,3). Similarly, Shiota et al. (7) observed that patients with positive margins are more likely to benefit from early salvage radiotherapy, underscoring the importance of identifying these high-risk patients early (3).

Pathological stage, particularly ≥pT3b disease, was also a strong predictor of persistent PSA in our cohort, consistent with studies by Fossati et al. (8) and Bartkowiak et al. (9), which highlighted the prognostic impact of advanced pathological stage on the likelihood of PSA persistence and long-term oncologic outcomes (3). These findings emphasize the need for more aggressive adjuvant treatment strategies in patients with advanced stage disease.

Our findings have significant implications for clinical decision-making, particularly regarding adjuvant and salvage radiotherapy strategies. Adjuvant radiotherapy (RT) involves treating some patients who might never develop recurrent cancer, potentially exposing them to unnecessary side effects. On the other hand, salvage RT, which is reserved for patients with confirmed recurrence, may delay treatment in high-risk patients, increasing the risk of progression to metastatic disease. Although the ARO 96-02 trial showed that early salvage radiotherapy improves relapse-free and overall survival in patients with persistent PSA, especially in clinically high-risk and/or locally advanced prostate cancer, as an indicator of residual disease, has been strongly associated with worse oncological outcomes, emphasizing the importance of earlier and individualized intervention (6-8,10).

Pre-operative predictors such as high PSA levels and advanced clinical stage could guide pre-surgical counseling and decision-making. For patients identified as high risk for persistent PSA, discussions regarding alternative treatment modalities, such as primary RT combined with androgen deprivation therapy, or multimodal treatment may be warranted. This approach could avoid the risks associated with delayed adjuvant interventions. Additionally, the early identification of high-risk patients may streamline decisions for immediate adjuvant RT and androgen deprivation therapy in the postoperative period, allowing these treatments to be initiated without waiting for biochemical recurrence (5,7,10,11).

Postoperative factors like positive surgical margins and advanced pathological stages further highlight the need for aggressive management in patients at high risk of persistent PSA levels. In such cases, the integration of imaging modalities like PSMA

PET/CT may be bypassed to expedite the initiation of adjuvant therapy, particularly in settings where PSA monitoring indicates a high likelihood of disease progression. Recent studies have shown that timely adjuvant RT, particularly when combined with androgen deprivation therapy, significantly improves metastasis-free survival and reduces biochemical recurrence. This approach could benefit patients with pathological risk factors, irrespective of early postoperative PSA levels, ensuring better long-term outcomes (7,9,11,12).

Our findings also underline differences in adjuvant treatment preferences between groups, with the persistent PSA group demonstrating significantly higher rates of adjuvant therapy,

Table 2. Comparative results of clinicopathological data in patient groups with and without postoperative persistent PSA

		No persistent PSA (n=140)	Persistent PSA (n=43)	p-value
Age (years)		66.7±6.1	67.9±6.2	0.372
PSA (ng/mL)		15±15.5	24.6±19	**<0.001**
Clinical stage, n (n=147)	**T1C-T2A**	74 (67.9%)	18 (47.4%)	**0.032**
	T2B	15 (13.8%)	12 (31.6%)	
	≥ T2C	20 (18.3%)	8 (21%)	
Biopsy grade group, n (n=178)	**1**	40 (29.6%)	3 (7%)	**0.025**
	2	36 (26.7%)	12 (27.9%)	
	3	23 (17%)	8 (18.6%)	
	4	26 (19.3%)	15 (34.9%)	
	5	10 (7.4%)	5 (11.6%)	
Number of PCa positive cores (n=151)		5.1±3.7	6.3±3.3	0.054
Percentage of PCa positive cores (n=139)		60.1±30.8	74.4±28.1	**0.011**
RP grade group, n	**1**	10 (7.1%)	2 (5%)	0.490
	2	35 (25%)	7 (17.5%)	
	3	41 (29.3%)	13 (32.5%)	
	4	29 (20.7%)	14 (35%)	
	5	25 (17.9%)	7 (17.5%)	
Pathological stage, (n=182)	**T3A**	83 (59.7%)	14 (32.6%)	**0.003**
	T3B	53 (38.1%)	29 (67.4%)	
	T4	3 (2.1%)	0 (0%)	
Tumor volume (cc)		10.7±10.5	20.2±14.1	**0.002**
Tumor density		22.8±17.9	36.4±25.3	**0.005**
Positive surgical margins, n		98 (70%)	37 (86%)	**0.025**
Lymph node dissection, n		110 (78.6%)	41 (95.3%)	**0.006**
Positive lymph node metastasis, n		24 (17.1%)	12 (27.9%)	0.120
Mean number of positive LNs (n=129)		0.54±1.05	1.02±1.9	0.351

PSA: Prostate-specific antigen, PCa: Prostate cancer, LNs: Number of positive lymph nodes

Table 3. Adjuvant therapy status in patients with and without persistent PSA

		No persistent PSA (n=140)	Persistent PSA (n=43)	p-value
Adjuvant therapy, n		70 (50%)	38 (88.4%)	**<0.001**
Adjuvant therapy, (n=108)	**RT**	16 (22.8%)	6 (15.8%)	0.399
	RT + LHRH	48 (68.6%)	26 (68.4%)	
	RT + LHRH + AA	0 (0%)	1 (2.6%)	
	LHRH	6 (8.6%)	5 (13.2%)	
Radiotherapy (n=97)	**Adjuvant RT**	37 (57.8%)	22 (66.7%)	**0.04**
	Early salvage RT	10 (15.6%)	9 (27.3%)	
	Salvage RT	17 (26.5%)	2 (6%)	

PSA: Prostate-specific antigen, RT: Radiotherapy, LHRH: Luteinizing hormone-releasing hormone, AA: Androgen ablation

including adjuvant RT (88.4% vs. 50%, p<0.001). This reinforces the role of persistent PSA as a decisive factor in postoperative management, supporting a more proactive approach in initiating adjuvant therapies. By incorporating persistent PSA predictors into routine practice, clinicians can better stratify patients for adjuvant treatments, optimize the timing of interventions, and potentially improve oncological outcomes.

Study Limitations

This study has several limitations. First, its retrospective design may introduce selection and recall biases, potentially impacting the generalizability of the findings. Second, the data were obtained from a single institution, which may limit the applicability of the results to broader populations. Additionally, some variables, such as genetic markers, were not included; their inclusion could provide a more comprehensive risk stratification in predicting persistent PSA.

Conclusion

Our findings are consistent with existing literature, reinforcing that both preoperative and postoperative factors, such as preoperative PSA levels, the percentage of positive biopsy cores, positive surgical margins, and advanced pathological stage, are critical in predicting persistent PSA after RP. Early identification of these high-risk patients is essential for tailoring postoperative management strategies, including the timely use of salvage radiotherapy and adjuvant treatments. Further prospective studies are warranted to refine risk stratification models and optimize individualized treatment pathways.

Ethics

Ethics Committee Approval: Ethical approval was obtained from University of Health Sciences Türkiye, İzmir Bozyaka Research and Educational Hospital Ethics Committee, reference number 03 (date: 17.01.2018).

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

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Ç., M.Ç., M.H.D., M.M., B.K., T.Ç., İ.H.B., B.G., T.D., Concept: A.E., B.K., Design: S.Ç., T.Ç., Data Collection or Processing: A.E., M.M., Analysis or Interpretation: A.E., S.Ç., Literature Search: M.H.D., İ.H.B., Writing: A.E., M.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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