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Evaluation of Risk Groups for the Prediction of Biochemical Progression in Patients Undergoing Radical Prostatectomy

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What's known on the subject? and What does the study add?

According to previous studies, preoperative and postoperative prostate specific antigen level measurements, pathological stage, Gleason score, extraprostatic extension, positive surgical margins and seminal vesicle invasion could be the predictors of biochemical progression and biochemical progression-free survival in prostate cancer patients undergoing radical prostatectomy. In our study, we showed that postoperative prostate specific antigen level higher than ≥0.2 ng/dL is the most important predictor of biochemical progression and biochemical progression-free survival in prostate cancer patients undergoing radical prostatectomy.

Abstract

Objective: The aim of this study was to investigate the potential relationship between biochemical progression and prognostic risk factors in patients with prostate cancer (PCa) patients undergoing radical prostatectomy (RP).

Materials and Methods: After inclusion/exclusion criteria were applied, 216 patients who underwent RP were included in this study. Follow-up protocol included prostate specific antigen (PSA) measurements; every 3 months for the first year, every 6 months for the second year, and an annual check after 2 years. Preoperative and postoperative PSA measurements, pathological stage, Gleason score (GS), extraprostatic extension, positive surgical margins and seminal vesicle invasion were evaluated. Uni- and multivariable analyses were used to detect the relationship between biochemical progression, biochemical progression-free survival (BPFS) and prognostic risk factors.

Results: Median follow-up was 29 months. Biochemical progression was observed in 39 (18.1%) patients, in 18 (9.7%) of 185 patients with first postoperative PSA level of <0.2 ng/dL, and 21 (67.7%) of 31 patients with first postoperative PSA level of ≥0.2 ng/dL. Patients with first postoperative PSA level of ≥0.2 ng/dL had a statistically significant higher risk of biochemical progression and shorter BPFS (odds ratio: 2.41; 95% confidence interval: 1.84-3.10; p<0.001), in univariate and multivariate analyses. Patients with GS ≥8 or T3-4 or positive surgical margins had a statistically significant higher risk of biochemical progression (p<0.001, p=0.003, p<0.001).

Conclusion: Postoperative PSA level higher than ≥0.2 ng/dL was the most important predictor of biochemical progression and BPFS after RP. GS ≥8, T3-4 stages, and positive surgical margins are also related to biochemical progression.

Keywords: Prostate cancer, radical prostatectomy, biochemical progression

Introduction

Prostate cancer (PCa) is the most frequent malignancy and the fifth leading cause of cancer-related death in men worldwide (1). In 2016, 30.000 deaths occurred in the United due to PCa (2). Currently, the gold standard treatment for localized PCa is radical prostatectomy (RP) (3). Prostate specific antigen (PSA) levels are commonly used for the early detection of disease progression after RP.

In the urology guidelines (4,5), biochemical progression is defined as a PSA-level increase above 0.2 ng/mL in two

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consecutive determinations with a minimum two-week interval in PCa patients who underwent RP. Additionally, in a 10-year follow-up study, biochemical progression could occur in up to 30% of PCa patients (6). Preoperative and postoperative PSA measurements, pathological stage, Gleason score (GS), extraprostatic extension (EPE), positive surgical margins, and seminal vesicle invasion (SVI) are considered prognostic factors related to biochemical progression (7,8).

We hypothesized that prediction and early detection of biochemical progression might help clinicians be able to prevent and/or delay disease progression and thereby decrease PCa-specific mortality (9). Therefore, we investigated the biochemical progression status, predictors of biochemical progression and the potential relationship between biochemical progression and prognostic risk factors in PCa patients who underwent RP.

Materials and Methods

Between May 2007 and August 2017, 245 localized PCa patients who underwent RP, were evaluated retrospectively.

This study was approved by our institutional medical ethical committee (2018/145).

Patients with secondary malignancy (5 patients) missed postoperative PSA records (18 patients), and incomplete pathological data (6 patients) were excluded. Consequently, a total of 216 patients were included in the study. Also, none of the patients received neoadjuvant therapy, and surgical procedures were performed the open retropubic method.

All data were obtained from the patient file records of our urology and radiation oncology departments and the institutional electronic database. Preoperative and postoperative PSA measurements, prostate biopsy pathology findings, and RP pathology reports were considered.

Follow-up protocol included PSA measurements; every 3 months for the first year, every 6 months for the second year, and an annual check after 2 years. Biochemical progression was defined as a PSA-level increase above 0.2 ng/mL in two consecutive determinations. Preoperative and postoperative PSA measurements, pathological stage, GS, EPE, positive surgical margins, and SVI were evaluated with univariate and multivariate analyses in patients who had biochemical progression. Disease-free survival and overall survival were defined as the period between the date of operation and progression and the date of diagnosis and last follow-up or mortality, respectively.

Statistical Analysis

Descriptive analyses were performed using the frequencies for the sociodemographic variables. The chi-square test was used to analyze the relationship between parametric values in comparison with categorical data, and Fisher's exact test was chosen to compare two nonparametric groups. The Mann-Whitney U test was used in the analysis of variables that did not show normal distribution. Kaplan-Meier analysis was used to calculate survival probabilities. Logistic regression analysis was applied to the independent variables affecting the dependent variable. The results were analyzed within the 95% confidence interval. A p-value of ≤0.05 was considered statistically significant. All statistical analyses were conducted using SPSS 24.0 for Windows (IBM, Chicago, IL, USA).

Results

The mean age of our patients was 63.1 years (range 47-75). The pathological T-stage was pT1c in 7 (3.2%) patients, pT2a in 9 (4.2%) patients, pT2b in 2 (0.9%) patients, pT2c in 92 (42.6%) patients, pT3a in 32 (14.8%) patients, pT3b in 73 (33.8%) patients and pT4a in 1 (0.5%) patient. 22 (10,2%) patients underwent lymph node dissection. Only 5 (2.3%) patients had lymph node metastasis. The median preoperative and postoperative PSA levels were 12.0 and 0.3 ng/mL, respectively. Pathological and biochemical characteristics are summarized in Table 1.

When classified according to the D'Amico risk classification, 7 (8.4%) of 83 low-risk patients, 21 (22.6%) of 93 medium-risk patients and 11 (27.5%) of 40 high-risk patients had biochemical progression.

The median follow-up was 29 months (range 7.1-128.9 months). The mean survival time for the whole population was 89.6 months, and the 3-year overall survival probability was 87.9%. The mean disease-free survival time was 22.9 months, and the 1-year and 2-year BPFS probabilities were 42.5% and 31.9%, respectively (Figure 1).

No significant correlation was found between overall survival and prognostic risk factors like GS, PNI, EPE, SVI, positive surgical margins, and postoperative first PSA levels. However, patients with first postoperative PSA level of <0.2 ng/dL had significantly longer BPFS than those with the first postoperative PSA level of ≥0.2 ng /dL in both univariate and multivariate analyses (hazard ratio: 2.41; 95% confidence interval: 1.84-3.10; p<0.001).

The first postoperative PSA level was <0.2 ng/dL in 185 (85.6%) patients and ≥0.2 ng/dL in 31 (14.4%) patients. Biochemical progression was observed in 39 (18.1%) patients. Of those, 18 (9.7%) patients had a first PSA level <0.2 ng/dL, and 21 (67.7%) patients had a first PSA level ≥0.2 ng/dL. The mean survival time was 99.2 months and 36.3 months for patients with first postoperative PSA level of <0.2 ng/dL and ≥0.2 ng/dL, respectively. Patients with the first postoperative PSA level of ≥0.2 ng/dL had a significantly higher risk of biochemical

progression compared to those with the first postoperative PSA level of <0.2 ng/dL (p<0.001) (Table 2). Patients with GS ≥8 or T3-4 or positive surgical margins had a statistically significant higher risk of biochemical progression (p<0.001, p=0.003, p<0.001). Mean survival time and biochemical progression according to different pathological risk factors are also shown in Table 2.

Discussion

Our study showed that a postoperative PSA level higher than ≥0.2 ng/dL was the most significant predictor of biochemical progression and BPFS after RP. This result can be interpreted as indicating that adjuvant radiotherapy can be considered for patients with a measurable postoperative PSA value in multidisciplinary councils, and patients can benefit from adjuvant radiotherapy rather than salvage radiotherapy. However, in a recent randomized phase 3 GETUG-AFU 17 study, no difference was shown in terms of progression-free survival between adjuvant and early salvage radiotherapy after RP, and side effects were more common in the adjuvant radiotherapy arm (10). But it should be kept in mind that this study was limited by the lack of statistical power to reach conclusions about efficacy. Therefore, it is still not wrong to say that uncertainties remain regarding the question of which patients can benefit from adjuvant radiotherapy or salvage radiotherapy after RP.

Currently, administering strict postoperative follow-up protocols, discussing these patients in multidisciplinary uro-oncology councils, and collaboration with urologists, especially

Table 1. Patients' characteristics

Parameter	**Value**
Patients	216
Median preoperative PSA (ng/mL)	12.0±15.2
Median postoperative PSA (ng/mL)	0.3±1.5
Biopsy GS	**n (%)**
≤6	127 (59.9%)
7	55 (25.9%)
8	18 (8.5%)
9-10	12 (5.7%)
Pathological GS	**n (%)**
≤6	97 (44.9%)
7	71 (32.9%)
8	22 (10.2%)
9-10	26 (12%)
Pathological tumour stage	**n (%)**
pT1	7 (3.2%)
pT2	103 (47.7%)
pT3	105 (48.6%)
pT4	1 (0.5%)
Surgical margin status	**n (%)**
Positive	111 (51.4%)
Seminal vesicle invasion	**n (%)**
Positive	36 (16.7%)
Perineural invasion	**n (%)**
Positive	159 (73.6%)
Lymph node metastasis	**n (%)**
Positive	5 (2.3%)
BCP	**n (%)**
Positive	39 (18.1%)
Time to BCP (months)	
From diagnosis	22.9
From operation day	19.6

PSA: Prostate specific antigen, pT: Pathological tumour stage, BCP: Biochemical progression, GS: Gleason score

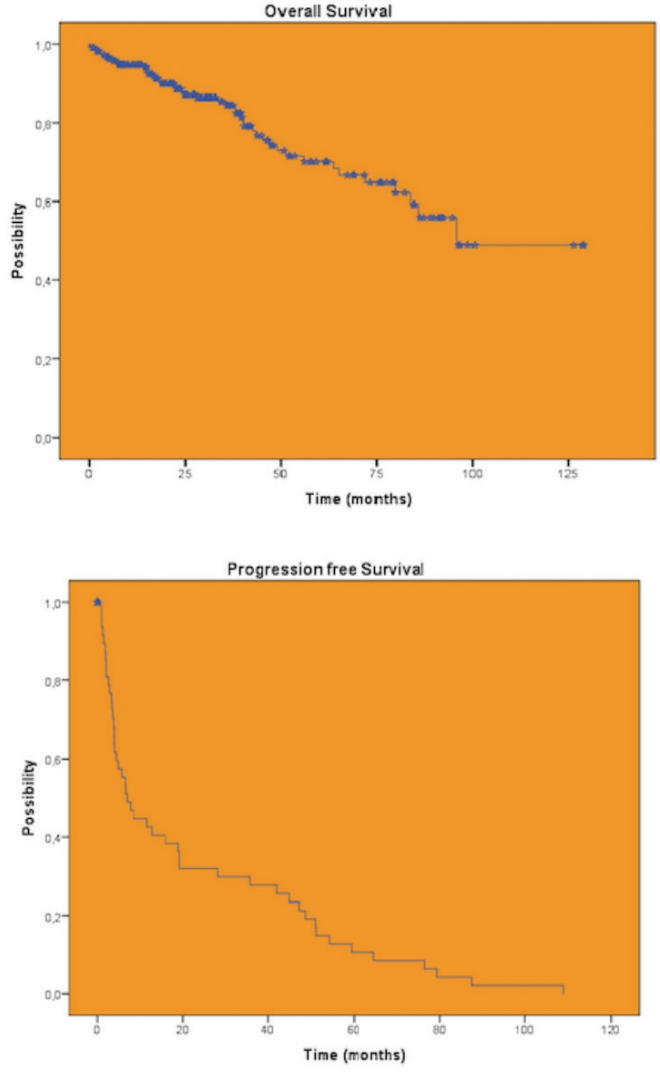

Figure 1. Kaplan-Meier survival analysis

with radiation oncologists, seem to be the most important strategies in daily clinical practice. The long-term outcomes of randomized phase 3 studies with strong statistical power may reduce uncertainties in this regard. Previous studies reported biochemical progression rates ranging from 8% to 30% after RP (11-13). In our study, a biochemical progression rate of 18.1% was found after RP, which is consistent with the literature.

Recent studies with median follow-up times between 15.7 and 26 months reported 2-year BPFS rates ranging between 79.6-86.5% after RP (14,15). Compared to both studies, despite the longer median follow-up time (29 months) that can be considered a strong aspect, we found a lower rate of 2-year BPFS for the whole study population. However, we believe that the high percentage of patients with positive surgical margins, detectable postoperative PSA level and/or pT3-4 disease, and who did not receive adjuvant radiotherapy may explain the low BPFS rate. Because of late recurrence risk, long-term follow-up can be required, especially for the patients with high-risk PCa (16).

In their study including 200 PCa patients who underwent RP, Doherty et al. (17) reported that biochemical progression was directly related to postoperative PSA levels, which should optimally undetectable. Our study, which included a similar number of patients, showed that having a first postoperative PSA level of <0.2 ng/dL was significantly associated with better progression-free survival and progression risk compared with having the first postoperative PSA level of ≥0.2 ng/dL (p<0.001). Additionally, a postoperative PSA level higher than ≥0.2 ng/dL was the most important predictor of biochemical progression and BPFS after RP compared to other parameters. Therefore, these results support the importance of regular PSA measurements after RP.

Epstein et al. (18) showed significant variability in recurrence rates regarding GS of 7, 8, and 9. The prognostic role of GS and the new group grade system was illustrated by Mathieu et al. (19) in a large series of 27,122 PCa patients. According to the new group grading system, the 4-year predicted BPFS rates of PCa patients with grades 1, 2, 3, 4, and 5 were 96.1%, 86.7%, 67.0%, 63.1%, and 41.0%, respectively. In our study, GS was not directly associated with overall survival, but patients with a total GS of ≥8 had a higher risk of biochemical progression compared to those with total GS of ≤7, which correlates with the literature. High total GS can be a predictor of biochemical progression and can be interpreted as the importance of the required collaboration between urologists and radiation oncologists in terms of recurrence and early treatment in PCa patients with high GS or new group grade.

Ball et al. (20) investigated the effect of EPE on biochemical progression and showed that EPE had a negative impact on recurrence-free survival. They also divided EPE into two groups as focal and non-focal, which can be determinants of BPFS. Compared to our findings, although we did not subdivide patients according to EPE, we could not find any correlation between EPE and BPFS. Although the incidence of pT3b cases may decrease with early diagnosis and treatment, it has been shown that SVI could be a precursor for progression (21). On the other hand, Freedland et al. (22) signified that SVI is not a predictor of poor prognosis and cancer-free survival alone without considering other risk factors. In this study, we found that patients with stage pT3-4 have a higher risk of biochemical progression than those with stage pT1-2. Therefore, EPE and SVI were interpreted as risk factors for biochemical progression. Nevertheless, BPFS and overall survival were not directly related to EPE or SVI.

The presence of positive surgical margins is known as a determining factor for recurrence, but it is not obvious that it increases the risk of cancer-specific mortality (23). A recent meta-analysis investigating the relationship between positive

Table 2. Results of uni- and multivariate analyzes in patients with biochemical progression

Variables	n: Patients number	Biochemical progression positive n (%)	Mean survival in months	Univariate analyzes OR (95% CI) p-value	Multivariate analyzes OR (95% CI) p-value
PSA <0.2 PSA ≥0.2	n=185 n=31	18 (9.7%) 21 (67.7%)	99.2 36.3	3.41 (1.81-6.10) <0.001	6.65 (2.16-21.96) <0.001
GS <8 GS ≥8	n=168 n=48	21 (12.5%) 18 (37.5%)	94 68.6	2.66 (1.24-5.48) <0.001	5.57 (1.77-14.42) <0.001
pT1-2 pT3-4	n=110 n=106	10 (9.1%) 29 (27.4%)	103.6 77.3	1.17 (1.08-1.28) 0.003	1.19 (1.08-1.33) 0.003
PSM- PSM+	n=105 n=111	8 (7.6%) 31 (27.9%)	95.4 77.8	2.44 (1.17-5.02) <0.001	5.11 (1.52-12.9) <0.001
PNİ- PNİ+	n=57 n=159	8 (14%) 31 (19.5%)	101.3 83.7	1.01 (0.97-1.07) 0.099	-

GS: Gleason score, pT: Pathological tumor stage, PSA: Prostate specific antigen, PSM: Positive surgical margin, PNI: Perineural invasion, OR: Odds ratio, CI: Confidence interval

surgical margins and biochemical progression showed that the presence of positive surgical margins was an independent risk factor for progression (24). Moreover, in a recent study, Lian et al. (25) reported that the location of positive surgical margins was a significant independent predictor of biochemical progression. Similarly, we found that the presence of positive surgical margins was significantly associated with a higher risk of biochemical progression, both in univariate and multivariate analyses. However, we did not investigate the relationship between biochemical progression and the positive surgical margin location.

The literature contains conflicting results regarding the effect of PNI on survival in patients who underwent RP. Merrilees et al. (26) observed that the presence of PNI does not predict biochemical progression. Similarly, Reeves et al. (27) reported that PNI is not an independent predictor of biochemical progression, whereas Loeb et al. (28) revealed that PNI was a dependent risk factor for biochemical progression. The authors stated that PNI should be evaluated with other risk factors like PSA, GS, and stage, together, as a predictor of progression. Our study also did not show any significant correlation between PNI and biochemical progression. Therefore, we agree that PNI, as a single parameter, might not be adequate to predict biochemical progression.

Study Limitations

The limitations of this study are as follows. Firstly, it was a retrospective study with a relatively small number of patients. Secondly, we did not consider/investigate factors such as PSA doubling time, PSA velocity, and PSA density, which can also help physicians be able to determine biochemical progression. Another limitation of our study is the limited number of lymph node dissections.

Conclusion

In conclusion, postoperative PSA level higher than ≥0.2 ng/dL is the most important predictor of biochemical progression and BPFS in PCa patients after RP. Besides, GS ≥8, T3-4 stages and positive surgical margins are also related to biochemical progression. However, further research with longer follow-up and larger sample sizes must evaluate more specific and precise predictors of biochemical progression.

Ethics

Ethics Committee Approval: This study was approved by our institutional medical ethical committee (Trakya University Faculty of Medicine Scientific Research Ethics Committee - 2018/145).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.M., G.T., E.A., V.Y.Ç., U.K., Concept: S.M., G.T., E.A., V.Y.Ç., U.K., Design: S.M., G.T., E.A., V.Y.Ç., U.K., Data Collection or Processing: S.M., G.T., E.A., V.Y.Ç., U.K., Analysis or Interpretation: S.M., G.T., E.A., V.Y.Ç., U.K., Literature Search: S.M., G.T., E.A., V.Y.Ç., U.K., Writing: S.M., G.T., E.A., V.Y.Ç., U.K.

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