# Predictive factors for biochemical recurrence in radical prostatectomy patients

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**Introduction** Radical prostatectomy (RP) is considered the best treatment for the management of localized prostate cancer in patients with life expectancy over 10 years. However, a complete recovery is not guaranteed for all patients who received/underwent RP treatment. Biochemical recurrence is frequently observed during the post-operative follow-up period. The main objective in this study is to evaluate the predictive factors of biochemical recurrence in localized prostate cancer patients who underwent RP surgery

**Material and methods** The study included 352 patients with prostate cancer treated by RP at a single institution between February 2004 and June 2014. Detailed pathological and follow-up data of all patients were obtained and analyzed to determine the results.

**Results** Mean follow-up duration was 39.7 months. 83 patients (23%) experienced biochemical recurrence (BCR) during the follow-up period. Mean BCR duration range was 6.56 (1–41) months. In multivariate logistic regression analysis, Gleason score (GS), PSA and extra-capsular tumour spread (ECS) variables were found to be statistically significant as BCR predictive factors.

**Conclusions** According to our study results, it is thought that PSA, GS and ECS can all be used for guidance in choosing a treatment modality for post-RP biochemical recurrence and metastatic disease as predictive factors. However, there is no consensus in this matter and it is still debated.

**Key Words:** prostate cancer ‹› radical prostatectomy ‹› recurrence ‹› Gleason score

## INTRODUCTION

In today's world, cancer incidence rates are on a rise due to the aging population, longer life expectancy and changes in people's lifestyles [1, 2, 3]. Prostate cancer is the most commonly observed solid tumour in Europe with a rate of 214 cases out of 1000 [2]. In addition, it is the second most common cause of death in male cancer patients [4]. Radical prostatectomy (RP) is considered the golden standard for treatment in patients with localized prostate cancer with a life expectancy of over 10 years. However, a complete cure is not guaranteed for all RP patients. Biochemical recurrence (BCR) is observed in 35% of these patients during the follow-up period [5].

In this sense, it is important to predict the recurrence risks for both treatment and follow-up. In our study, we evaluated the patients with a clinical diagnosis of localized prostate cancer who underwent RP and attempted to determine the predictive factors of biochemical recurrence.

## MATERIAL AND METHODS

### Patient selection criteria

Data of 419 prostate cancer patients treated with radical prostatectomy between February 2004 and June 2014 was retrospectively reviewed. 67 patients were excluded from the study due to positive lymph node

metastases, receiving active surveillance or lost to follow-up. Thus, 352 patients were enrolled for evaluation. In accordance with the EAU Guidelines on Prostate Cancer, the follow-up was conducted on the 3rd, 6th and 12th month after prostatectomy during the first year, and every six months in the second year and thereafter with annual PSA level and digital rectal exam results. PSA level ≥0.20 ng/mL by two subsequent measurements was defined as biochemical recurrence [6].

## Method

Age, PSA values prior to transrectal ultrasound-guided biopsy, digital rectal examination (DRE) findings, TRUS-Bx Gleason score, RP date, RP specimen, pathological data, postoperative PSA values, the date of biochemical recurrence and the duration of follow-up period were recorded.

A thorough physical exam, digital rectal exam, PSA and hemogram evaluations and TRUS-Bx were performed prior to the operation. TNM 2009 classification was used for clinical staging.

Computerized tomography and bone scintigraphy was used on patients with +20 ng/mL serum PSA value and/or a total of +7 TRUSB Gleason scores and/or bone pain.

A Radical Prostatectomy specimen was obtained primarily from the distal (apical) and proximal (bladder neck) surgical margin and the bottom of vesicula seminalis. Later, the entire prostate; sliced in 3 mm spaces from distal (apex) to proximal (bladder neck) surgical margin and were coded from distal to proximal. Each slice was then sent to pathology for analysis. The tumour's primary origination zones, location, perineurial invasion (PNI), prostate capsular invasion (PCI), seminal vesicle invasion (SVI) of the tumour, extra-capsular tumour spread (ECS), high-grade PIN existence, condition of non-neoplastic prostate, positive surgical margin (PSM), integrity of prostatic capsule and lymph nodes' conditions were all found in pathology reports.

## Statistics

Windows Statistical Package for Social Sciences (SPSS) version 22.0 package program was used for the statistical analysis. A chi-square test was used to group the parameters and for evaluation

**Table 1.** *Summary of the single and multivariate logistic regression analysis data of all variables*

| | | BCR(+) (n) | BCR(+) (%) | BCR(-) (n) | BCR(-) (%) | Total | Univariate analysis | Multivariate analysis |
|---|---|---|---|---|---|---|---|---|
| Age (year) | | 69.1 | | 65.3 | | 67 | 0.014 | 0.893 |
| PSA (ng/mL) | | | | | | | <0.0001 | 0.001 |
| | <10 | 29 | 12.9 | 195 | 87.1 | 224 | | |
| | 10.1-20 | 29 | 32.5 | 60 | 67.5 | 89 | | |
| | >20 | 25 | 64.1 | 14 | 35.9 | 39 | | |
| Gleason | | | | | | | <0.0001 | 0.005 |
| | 6 | 13 | 8.7 | 135 | 91.3 | 148 | | |
| | 7 | 32 | 20.8 | 126 | 79.2 | 158 | | |
| | 8 | 24 | 92.3 | 2 | 7.7 | 26 | | |
| | 9 | 14 | 70 | 6 | 30 | 20 | | |
| PSM | | | | | | | 0.003 | 0.101 |
| | + | 34 | 34.3 | 65 | 67.7 | 99 | | |
| | - | 49 | 19.3 | 204 | 80.7 | 253 | | |
| PNI | | | | | | | 0.009 | 0.458 |
| | + | 43 | 30.9 | 96 | 69.1 | 139 | | |
| | - | 40 | 18.7 | 173 | 81.3 | 213 | | |
| SVI | | | | | | | <0.0001 | 0.394 |
| | + | 24 | 52.1 | 22 | 47.9 | 46 | | |
| | - | 59 | 19.2 | 247 | 80.8 | 306 | | |
| ECS | | | | | | | <0.0001 | 0.004 |
| | + | 51 | 44.7 | 63 | 55.3 | 114 | | |
| | - | 32 | 13.4 | 206 | 86.6 | 238 | | |
| PCI | | | | | | | <0.0001 | 0.484 |
| | + | 55 | 32.9 | 112 | 67.1 | 167 | | |
| | - | 28 | 15.1 | 157 | 84.9 | 185 | | |
| pT stage | | | | | | | <0.0001 | 0.003 |
| | T2 | 8 | 4.1 | 184 | 95.8 | 192 | | |
| | T3 | 75 | 46.8 | 85 | 53.2 | 160 | | |

BCR – biochemical recurrence, PSA – prostate specific antigen, PN – perineurial invasion, PCI – prostate capsular invasion, SVI – seminal vesicle invasion, ECS – extracapsular tumor spread, PSM – positive surgical margin

of clinical evidence. Effect of independent variables on recurrence was examined using univariate and multivariate logistic regression analysis. Each parameter was analyzed for statistical significance. "p" values below 0.05 were deemed as statistically significant.

## RESULTS

The mean age of participants was 67 (60–74) years and mean preoperative total PSA concentration was 11.34 (3.1–24.3) ng/mL. Mean follow-up duration was 39.7 months. 83 patients (23%) experienced BCR during the follow-up period. Mean BCR duration (range) was 6.56 (1–41) months. Preoperative PSA value was <10 ng/mLin 224 (63.6%), between 10–20 ng/mL in 89 (25.2%) cases and over >20 ng/mL in 39 patients (11.1%). The majority of patients had pathological stage T2 (54.5%) disease and a Gleason score of 7 (44.9%).Gleason score distribution of the patients was; 148 (42%) with 6, 158 (44.9%) with 7, 26 (7.4%) with 8 and 20 (5.7%) with a total GS of 9. Table 1 summarizes the relationship between RP pathology, Gleason score (GS) distribution and BCR

Moreover, Table 1 summarizes the univariate and multivariate logistic regression analysis data of all variables. According to the data from univariate analysis, PSA, GS, SVI, PSM, ECS, PCI, PNI and age were found to be statistically significant in the prediction of postoperative BCR (p<0.05) while the multivariate logistic regression analysis of the same variables showed that only GS, PSA and ECS variables were statistically significant; BCR prediction "p" values were 0.006, 0.0001 and 0.004 respectively for this variables

## DISCUSSION

Prostate cancer is a type of cancer that requires long-term treatment, proper follow-up and additional treatments when necessary. Regardless of the treatment given, 16–35% of the patients require a secondary treatment within 5 years after their first curative treatment [7–11]. Radical prostatectomy (RP) is one of the most preferred treatment approaches for management of prostate cancer. However, due to drawbacks in clinical staging, 30–40% of clinically localized prostate cancer patients reveal extraprostatic disease in RP specimens [12, 13]. PSM existence can be affected by the preferred surgery method and surgeon's experience [14, 15]. In the first 10 years after operation, 35% of the patients experience biochemical recurrence [16, 17]. Disease recurrence can be detected before

clinical symptoms become apparent, thanks to PSA sensitivity. Therefore, there is a long time period between BCR and exhibition of clinical symptoms such as local recurrence or distant metastasis. Patients may receive secondary treatments during that period. It is still debated which patients should receive treatment and/or in which time period these treatments should be used. The main concern is the possible side-effects of secondary treatments. Therefore, determination of the predictive factors in post-op BCR has gained importance and numerous factors were shown to have an effect on post radical prostatectomy outcomes.

PSA values during diagnosis is one of the most well-known factors with such function.

Numerous authors of studies about predicting post radical prostatectomy biochemical recurrence state that PSA value during diagnosis is a strong preoperative indicator both in univariate and multivariate analyses [18–22]. In accordance with previous results, our study detected PSA value calculated during diagnosis as an independent predictor for biochemical recurrence.

According to numerous studies conducted on the subject, the total value of the radical prostatectomy specimen's Gleason score is a strong independent predictor of biochemical recurrence both in univariate and multivariate analysis [18–21]. These results are more conclusive in patients with a total Gleason score value of +7. The same outcome was reached in our study in multivariate analysis as an independent predictor. No statistical difference is found in terms of the biochemical recurrence in total Gleason score values up to 6 when the studies regarding the subject were examined in general.

PSM is directly associated with biochemical recurrence after RP and PSM is seen in 6–41% of all radical prostatectomy specimens [23]. The difference between the given ratios is based on the experience of the surgeon. These rates decrease with surgeon's experience [14, 15]. In our study, this rate was detected as 28.1%. Existence of PSM is an undesirable event in various oncological surgery fields as well as radical prostatectomy. Some studies showed a relationship between PSM existence and biochemical recurrence [24, 25, 26], while others revealed no such association [27, 28]. Distinctively, Stephenson et al. in a multivariate analysis, detected that PSM number (≥1) and common PSM existence is significant in prediction of biochemical recurrence [29]. Again, in their study of 932 patients who underwent radical prostatectomy, risk of biochemical recurrence changed between 20% and 47% in a mean 5 year of follow-up period [31, 32]. In our study, this value was found to be 28.1% during

our follow-up period. The biochemical recurrence rate was found to be 19.3% in NSM patients. Despite the statistical significance revealed by univariate analysis, multivariate analysis showed that PSM is not an independent predictor in terms of biochemical recurrence.

Another important factor effective in prognosis is the relation of tumour with prostate capsule. In their study in 1993, Epstein et al. reported that capsular invasion and the extent of this invasion are prognostically significant [33]. Again, in their 688 patient series study, Wheeler et al. assessed the relationship between the degree and level of prostatic capsule invasion (PCI) and cancer prognosis in a multivariate analysis. According to their results, 13% of the PCI(+) patients experienced biochemical recurrence in 5 years, whereas this rate was 27% in ECS(+) patients [34]. In another study, Theiss et al. reported that in 10 years the biochemical recurrence rate was 21% in PCI(-) patients, 35.3% in PCI(+) and 61.5 in ECS(+) patients [35]. Authors suggest that PCI and ECS should be distinguished. In our study, single-variable analysis showed significance in PCI and ECS in terms of recurrence, while multivariate analysis detected PCI as a non-predictor, and, ECS as an independent risk factor.

Clinical importance of PNI in radical prostatectomy specimens is still debated. D'Amico et al. showed that PNI is an independent prognostic factor for BCR [36]. However, the studies showing that PNI is not correlated with BCR are in majority [37, 38, 39]. Lee et al., in their 2010 study, detected that PNI existence is related to lymph node invasion, high Gleason score, surgical margin positivity, high tumour volume and advanced prostate cancer. However, the same study showed in multivariate analysis of PNI that it is not an independent factor for biochemical recurrence [40, 41]. In our study, PNI[+] did not significantly affect the BCR in multivariate analysis.

Seminal vesicle invasion is an insufficient prognostic parameter with biochemical progression- free rates varying between 5–60% [42, 43]. Bloom et al. showed the relation between SVI and post radical prostatectomy high BCR levels which later developed distant metastasis [44]. Freedland et al. reported significantly higher PSA values in patients with SVI, advanced pathological stage, advanced tumours and accompanying extra-capsular spread and/or positive surgical margins.

However, the same study detected better prognosis in patients with SVI, low Gleason score, negative surgical margins and advanced age. This study concluded that SVI does not necessarily mean nega-

tive prognosis all the time [45]. In our study, biochemical recurrence probability in patients with SVI was detected on a high level (52.1%), similar to literature. This factor showed significance for BCR in single-variable analysis but did not significantly affect the BCR in multivariate analysis.

Another variable that might have an impact on biochemical recurrence is the age of the patient during diagnosis. Inga et al. evaluated patients that underwent radical prostatectomy due to prostate cancer and the effect of age on tumour characteristic, oncologic and functional results [46].

According to the results of this study no significant outcome was revealed regarding the total of advanced age survival rate, disease specific survival and biochemical recurrence-free survival. However, a significant increase was seen in RP Gleason scores of patients in advanced age. In our study, single-variable analysis showed significance but multivariate analysis did not reveal the same outcome.

Kordan et. al reported that surgical margin, preoperative PSA values and the Gleason score are significant predictors for biochemical recurrence-free survival in stage pT2 [47]. In our study, this evaluation couldn't be performed due to the limited number of biochemical recurrence patients in the pT2 group.

Despite the parameters discussed in the study, a definitive parameter predicting BCR could not be found. One must keep in mind that, as mentioned previously, prostate cancer shows major differences based on geographical and racial context. Presence of black race with different dietary habits as well as a more aggressive prostate cancer risks can be useful in explaining the variation of results. In a study carried out in Turkey, radical prostatectomy patients were seen to possess more advanced stage cancer [48].

Our study had drawbacks in that it was retrospective, had a relatively short follow-up period compared to literature and limited number of participants.

## CONCLUSIONS

To sum up, according to our study results, it is thought that PSA, GS and ECS can all be used for guidance in choosing a treatment modality for post-RP biochemical recurrence and metastatic disease as predictive factors. However there is still no consensus on this matter and it is still being debated.

**CONFLICTS OF INTEREST**
The authors declare no conflicts of interest.

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