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Factors determining biochemical recurrence in low-risk prostate cancer patients who underwent radical prostatectomy

Radikal prostatektomi yapilan düşük risk prostat kanserli hastalarda biyokimyasal rekürrensi öngören faktörler

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ABSTRACT

Objective: This study was conducted to research the factors determining biochemical recurrence (BCR) in low-risk localized prostate cancer patients who underwent radical prostatectomy (RP).

Material and methods: We retrospectively analyzed the data of 504 patients who had undergone RP between 2003 and 2013 at our clinic. One hundred and fifty-two patients who underwent RP for low-risk prostate cancer were included in the study.

Results: The mean follow-up period for patients was 58.7 (21–229) months. The mean age of the patients was 63.7±7.2 years (49–79). The mean prostate specific antigen (PSA) value was 5.25±4.22 ng/mL (3.58–9.45). The BCR rate after the operation was 25% (38/152). In the univariate analysis, recurrence determining factors were shown to include extracapsular involvement (ECI) (p=0.004), capsular invasion (CI) (p=0.001), age (p=0.014), and tumor size (p=0.006). However, only CI was found to be significant in multivariate analysis (p=0.001).

Conclusion: Capsular invasion is an independent risk factor in low-risk prostate cancer patients who underwent RP for BCR.

Keywords: Biochemical recurrence; low-risk; radical prostatectomy.

ÖZET

Amaç: Bu çalışmada düşük riskli lokalize prostat kanseri nedeniyle radikal prostatektomi (RP) operasyonu yapılan hastalarda biyokimyasal rekürrensi (BKR) öngören faktörleri araştırdık.

Gereç ve yöntemler: Kliniğimizde 2003 ile 2013 tarihleri arasında RP operasyonu yapılan 504 hastanın verileri retrospektif olarak tarandı. Bu hastalar içerisinde düşük riskli prostat kanseri nedeniyle radikal prostatektomi yapılan 152 hasta çalışmaya dahil edildi. İstatistiksel analizde SPSS 15.0 windows versiyon programı kullanıldı. P<0,05 olması anlamlı kabul edildi.

Bulgular: Hastaların ortalama takip süresi 58,7 (21-229) ay, yaş ortalaması 63,7±7,2 yıl (49-79), prostat spesifik antijen (PSA) ortalaması 5,25±4,22 ng/mL (3,58-9,45) idi. Ameliyat sonrası BKR oranı %25 (38/152) idi. Rekürrensi öngören faktörler tekli analizde, ekstrakapsüler yayılım (EKY) (p=0,004), kapsüler invazyon (p=0,001), yaş (p=0,014), tümör hacmi (p=0,006) iken, çoklu analizde ise sadece kapsüler invazyon (Kİ) anlamlı olarak bulunmuştur (p=0,001).

Sonuç: Kİ düşük riskli prostat kanserli hastalarda radikal prostatektomi sonrası bağımsız bir risk faktörüdür.

Anahtar kelimeler: Biyokimyasal rekürrens; düşük risk; radikal prostatatektomi.

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Introduction

Prostate cancers (PC) are the most frequently diagnosed solid tumors in European males.[1] It is also reported to be the second reason for cancer-related deaths in males according to a study conducted in USA.[2] Radical prostatectomy (RP) is the standard form of treatment in low-risk localized PC patients. The patients who benefit the most from radical surgery are the patients within low-risk group.[3] The most important advantage of RP is the potential of cure without damaging the surrounding tissues and a better chance of tumor staging

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because the organ is completely removed. However, not all RP patients are completely cured. Biochemical recurrence (BCR) is diagnosed in 22% of follow-up low-risk patients[4] who require additional treatments. Therefore, determining BCR is important in treatment and follow-up plans. In our study, our main purpose was to review the low-risk localized PC patients that developed BCR after RP and to define the factors that determine the recurrence.

Material and methods

We retrospectively analyzed the data of 504 patients who had undergone RP between 2003 and 2013 at our clinic. All surgeries were performed by two surgeons who were experienced in RP. One hundred and fifty-two patients who underwent RP for low-risk PC were included in the study. Patients with clinical term ≤T2a, Gleason score ≤6, and prostate-specific antigen (PSA) ≤10 were defined as low-risk localized PC patients. All patients' ages, preoperative prostate-specific antigen (PSA) values, RP specimen pathology data, Gleason score (GS), perineural invasion (PNI), capsule invasion (CI), extracapsular extension (ECE), seminal vesicle invasion (SVI), positive surgical margins (PSM), and postoperative PSA values were recorded. All patients were followed with 3-month visits in the first, 6-month visits in the second and third, and yearly visits after the third year of operation. BCR was defined as a single PSA value over 0.2 ng/mL or high PSA values during the postoperative period.[5]

Statistical analysis

All statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) 15.0 for Windows. Chi-square test was used to group and to define clinical parameter importance. Independent risk factors were determined by employing univariate and multivariate Cox regression analysis. P values below 0.05 were considered statistically significant.

Results

The patients' mean follow-up period was 58.7 (21–229) months, mean age was 63.7±7.2 years (49–79), and mean PSA value was 5.25±4.22 ng/mL (3.58–9.45). Thirty-eight (25%) patients were diagnosed with BCR. The average recurrence period was 22.5 months. When RP specimen pathological results were reviewed, 18 (11.8%) patients had PSM, 20 (13.2%) had CI, 30 (19.7%) had ECE, 18 (11.8%) had SVI, and 50 (32.9%) had PNI. Table 1 summarizes the clinical and pathological properties of the patients.

In univariate analysis, there was a significant relationship between BCR and ECE (p=0.004), age (p=0.014), tumor volume (p=0.006), and CI (p=0.001). There was no relation between recurrence and PNI (p=0.548), SVI (p=0.118), and PSM (p=0.086). In multivariate analysis, the only significant relationship was found between CI and BCR (p=0.001). Table 2 summarizes the values.

Table 1. Clinical and pathological properties of RP patients

Patients (n)	**152**
Age	63.7±7.2 years
PSA	5.25±4.22 ng/mL
Tumor volume	14.4±12.9 mL
PNI	32.9% (50/152)
SVI	11.8% (18/152)
ECE	19.7% (30/152)
CI	13.2% (20/152)
PSM	11.8% (18/152)
BCR	25% (38/152)

PSA: prostate-specific antigen; PNI: perineural invasion; SVI: seminal vesicle invasion; ECE: extracapsular extension; CI: capsule invasion; PSM: positive surgical margins; BCR: biochemical recurrence

Table 2. Factors affecting biochemical recurrence

	Biochemical recurrence (+)	**Biochemical recurrence (-)**	**Univariate analysis p values**	**Multivariate analysis p values**
Mean age (years)	67.2±8.5	62.5±6.4	0.014	0.154
Mean tumor volume (mL)	21.4±15.3	12.0±11.2	0.006	0.496
ECE	16/38 (42.1%)	14/114 (12.3%)	0.004	0.574
PNI	12/38 (31.6%)	38/114 (33.3%)	0.548	-
CI	16/38 (42.1%)	4/114 (3.5%)	0.001	0.001
PSM	8/38 (21.0%)	10/114 (8.4%)	0.086	-
SVI	7/38 (18.4%)	11/114(9.6%)	0.118	-

ECE: extracapsular extension; PNI: perineural invasion; CI: capsule invasion; PSM: positive surgical margins; SVI: seminal vesicle invasion

Discussion

Prostate cancer is a disease that requires long-term treatment and a good follow-up plan. Regardless of the first curative therapy administered, 16%–35% of the patients require a secondary treatment within 5 years after the initial treatment.[6-10] RP is one of the most commonly used treatments for PC and allows very good cancer control. The main goal in RP is to remove the cancer completely while it is still limited to the prostate gland. However, because of errors in clinical staging, specimens of 30%–40% of localized prostate patients who underwent RP showed extraprostatic involvement.[11,12] In addition, 35% patients develop BCR within 10 years following the operation.[13-15] Because of the superior sensitivity of PSA, recurrence of the disease can be diagnosed during the early term. There is a long time between BCR and localized relapse or far metastases for the previous reason. During this period, patients may require additional secondary treatments. There is still a controversy about which treatments should be administered to which patients. Considering this fact, determining BCR factors following the operation is very important. Many factors were found to affect the post-RP results.

One of the most known factors is the PSA value during initial diagnosis. Many authors who published predictor studies for BCR following RP reported PSA as a strong preoperative indicator in both univariate and multivariate analysis.[16-20] In addition, GS of the RP specimen is also an independent strong predictor for BCR in univariate and multivariate analysis.[16-20] Because we included only low-risk localized PC patients in our study, we disregarded those parameters.

Seminal vesicle invasion is a bad prognostic parameter with 5%–60% biochemical progression-free rates.[21,22] In our study, we did not find a relationship between SVI and BCR in univariate analysis. We think that because we worked with low-risk patients, SVI patient numbers were lower than those in the literature.

The effect of age on recurrence after RP is still debated. Poor prognosis is reported with advanced age.[23,24] However, some studies did not find any effect at all.[25,26] In another meta-analysis study, age was not found to be a prognostic factor.[27] In our study, age was significant in univariate (p=0.014) but insignificant in multivariate (p=0.154) analysis.

The relationship between tumor volume in RP specimens and recurrence is not clear. However, most studies did not find a relationship between them.[28,29] Our study results were also similar. Although it was significant in univariate (p=0.006) analysis, it was insignificant in multivariate (p=0.496) analysis.

Positive surgical margins are observed in 6%–41% of the RP cases.[30] The main reason for the difference between those values is the surgical experience. With the increasing surgical experience, those rates decrease.[31,32] In our study, this rate was 11.8%. Because we included only low-risk cases in our study, those rates were low. PSM is an unwanted and worrying situation for surgeons that perform oncological surgeries including RP. Although this term means that there are still live cancer cells within the patients' body, the prognostic importance of PSM in PC is still debated. Although some studies reported that PSM was related to higher BCR rates,[33-35] some did not show such a relationship.[36,37] On the other hand, Stephenson et al's[38] multivariate analysis showed that PSM number (≥1) and widespread PSM were significant in predicting BCR. In addition, Ahyai et al's[39] study on 932 RP patients showed that only 20% of the patients with PSM developed BCR, and adjuvant treatments administered to selected patients would decrease the overtreatment risk. BCR risk of PSM changes between 20% and 47% in a mean 5-year follow-up period.[40,41] In our study, this value was found to be 21.0%. BCR rate in patients with negative SM was 7% in our study. Although recurrence is more frequent in PSM patients, it was not found to be statistically significant (p=0.086).

The relationship between the tumor and prostate capsule is also an important factor affecting prognosis. Epstein et al's[42] 1993 study reported the importance of capsular invasion and the degree of capsular invasion in prognosis. Moreover, Wheeler et al's[43] 688 patient series study reviewed the relationship between cancer prognosis and CI grade and level using multivariate analysis. According to this study, patients with only CI had a 13% BCR rate, whereas patients with localized ECE had a 27% BCR rate in a 5-year follow-up after RP. The same study reported the BCR rate of widespread ECE patients to be 58%, stating that widespread ECE was an independent predictor for BCR. Theiss et al's[44] study showed a 10-year BCR rate in patients without CI as 21%, patients with CI as 35.3%, and 61.5% in ECE patients. The authors recommended that CI should be differentiated from ECE. In our study, BCR rate in patients without CI was 3.5% and 42.1% in CI patients. Those rates were found to be 42.1% in ECE and 12.3% in non-ECE patients. In univariate analysis, CI and ECE were found to be significant factors (p=0.001-0.004); however, in multivariate analysis, only CI was found to be an independent risk factor (p=0.001).

The clinical importance of PNI found in RP specimens is still questionable. D'Amico et al.[45] reported PNI as an independent prognostic factor in BCR. However, the studies that show no correlation between PNI and BCR are more common.[46-48] Jeon et al.[49] also reported that patients with PNI have higher GS, ECI, SVI, and PSM. Lee et al's[50] 2010 study showed that PNI

Turkish Journal of Urology 2015; 41(2): 61-6
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presence was related to lymph node invasion, higher GS, PSM, higher tumor volume, and late-term PC; however, PNI was not an independent risk factor for BCR in multivariate analysis. Our study results were similar to the ones in the literature that show no relation between PNI and BCR (p=0.548).

One must not forget while reviewing all those studies that, as previously mentioned, PC manifestations vary greatly from geographical and racial factors. The effect of dietary customs as well as African race present with a higher risk of more aggressive PC may help explain these different results. A study conducted in Turkey also clearly showed that patients who underwent RP have higher grade tumors.[51]

One of the weak points in our study is its retrospective nature and limited patient numbers. In addition, more detailed pathological results could have been obtained, such as the extent and number of positive surgical margins, whether extracapsular involvement is focal or extended, which could have been added to the variables, thereby producing better results.

In our study, 25% of patients who underwent RP for localized PC developed BCR in an average follow-up period of 58.7 months. In univariate analysis, age, average tumor volume, capsule invasion, and extracapsular involvement were all significant for BCR. PNI and PSM were not statistically significant. In multivariate analysis, the only independent predictor for BCR was found to be CI. In these times where the adjuvant therapies administered to the patients during the period between BCR after RP and metastatic disease is still controversial, CI presence may show us a way for treatment. Although ECE and PSM were not found to be independent predictors in this study, wider series with longer follow-up periods and more detailed pathological data may solve the dilemmas in those areas.

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