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ORIGINAL PAPER

The factors predicting biochemical recurrence in patients with radical prostatectomy

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Summary ***Objective: The main objective of this study was to evaluate the factors predicting recurrence in patients who underwent radical prostatectomy (RP) for localized prostate cancer.***
Materials and Methods: A total of 275 patients who underwent RP between 2000 and 2012 years in our clinic were evaluated retrospectively and 238 patients who met our criteria were included in the study. The effect of PSA values at diagnosis in addition the histopathological variables on the risk of recurrence was evaluated. Biochemical recurrence (BCR) is defined as "an increase of > 0.2 ng/ml or more in the serum total PSA count". The statistical analysis of this study was done using SPSS for Windows Version 15.0 package program. Values below p < 0.05 are accepted as statistically significant.
Results: The mean follow up, age and PSA of patients were 37,2 months, 66,01 ± 6,85 years and 11,12 ng/ml, respectively. BCR rate was 28% (68/238). Univariate analysis revealed that PSA levels during initial diagnosis (p < 0.0001), Gleason score (GS) (p < 0.0001), prostatic capsule involvement (p < 0.005), extracapsular extension (p = 0.0001), seminal vesicle involvement (p < 0.003) and surgical margin positivity (p < 0.014) were significant factors in predicting recurrence, while multivariate analysis showed that PSA at initial diagnosis (p = 0.002) and GS (p = 0.003) were independent prognostic factors. PSA > 10 ng/ml and Gleason score > 7 are considered as the risk factors for BCR.
Conclusion: Our study results showed that PSA value during initial diagnosis as well as Gleason score were independent factors in predicting BCR following radical prostatectomy.

KEY WORDS: Prostate cancer; Biochemical recurrence; Radical prostatectomy.

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INTRODUCTION

Prostate cancer is the most common solid tumor encountered in men, with an incidence of 214 cases in 1000 men in Europe (1). According to a study conducted in USA, it is the second leading cause of cancer deaths among men. In the same study, the occurrence rate of clinical prostate cancer was 16%, whereas the rate of death due to this disease was 3% (2). Radical prostatectomy (RP) is recognized as the golden standard in treatment of patients with localized prostate cancer and a life expectancy beyond 10 years. The most important advantage of radical prostatectomy is the curing potential without damaging adjacent tissues. It also provides accurate staging because of total removal of the organ. However, a total cure is not achieved in all the patients with RP. Biochemical recurrence (BCR) is observed in 35% of the patients after the operation (3). These patients require further treatment. In this sense it is essential to predict recurrence for treatment and follow-up. In this study, our main aim was to evaluate the localized prostate cancer patients treated by RP who developed BCR in order to determine predicting recurrence factors.

MATERIALS AND METHODS

The data of 706 cases diagnosed with prostate cancer in *Izmir Tepecik Education and Research Hospital Urology Clinic* were retrospectively analyzed. Due to pre-operative active follow-up, 11 of the 275 patients treated by RP as the first treatment were excluded from the study. Twelve of the patients were excluded for postoperative early hormone therapy due to metastasis in lymph nodes. In the remaining 256 patients, 18 more were excluded from the study, due to preoperative and postoperative missing data. Finally, 238 patients who underwent RP in our hospital between 2000 and 2012 and who meet these criteria were included in our study group. The age and preoperative prostate specific antigen (PSA) values of all the patients, as well as Gleason score (GS), perineural involvement (PNI), capsule involvement (CI), extracapsular extension (ECE), seminal vesicle involvement (SVI), surgical margin positivity (SMP), which were obtained by pathological examination of RP specimens, in addition to PSA values at postoperative follow-up period were recorded. All the patients were post-operatively controlled in 3-month periods during the first year, 6-month periods in the second and third year and annually thereafter. Biochemical recurrence was defined as a single PSA value measured as more than 0.2 ng/mL, or a postoperative high PSA value (4). For all statistical evaluations, SPSS version 15.0 package software was used. Chi-square test was utilized to categorize the parameters within themselves and to evaluate clinical relevance. Independent risk factors were found for Univariate and multivariate (binary) logistic regression

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analysis and recurrence. P values below < 0.05 were defined as statistically significant.

Results

Average age of the patients was 66,01 ± 6,85 years (48-82), mean PSA value was 11,12 ± 9,32 ng/ml and average follow-up period was 37.2 months. During the follow-up, BCR was determined in 68 (28%) of the patients. When the pathological data of the RP specimen were reviewed, it was determined that SMP was present in 52 (21.8%) of the patients, CI in 89 (37.4%), ECE in 60 (25.2%), SVI in 23(9.7%) and PNI in 84(35.3%). Clinical and pathological features of the patients are summarized in Table 1.

The relationship of BCR with PSA groups following RP can be seen in Table 2. BCR rates of patients with PSA at diagnosis < 10 ng/ml, between 10 and 20 and > 20 were 17.9%, 37.7% and 66.7% respectively. The difference is statistically significant (p = 0,0001). Furthermore, when patients were divided in two groups according to PSA (as PSA < 10 vs PSA ≥ 10), PSA above 10 was proved to be a very powerful risk factor for BCR both in univariate and multivariate analysis (p < 0,001, please see Table 5).

The relationship between Gleason Score distributions and BCR are evaluated in Table 3. It can be observed that the probability of BCR increases with GS. During the 37.2 months of follow-up period, the recurrence rate of the patients with GS 6, GS 7, GS 8, GS 9 were 20,9%, 22%, 82,4% and 81,8% respectively.

The difference between the groups is statistically significant (p = 0,0001). Furthermore, when grouping is implemented according to Gleason Scores (as GS ≤ 7 vs GS > 7), GS above 7 was proved to be a very powerful risk factor for BCR both in univariate and multivariate analysis (p < 0.001, please see Table 5).

The effects of other pathological parameters on BCR can be seen on Table 4. In the univariate analysis, the relationship of surgical margin positivity (p = 0.014), capsule involvement (p = 0.005), extracapsular extension (p = 0.001) and seminal vesicle involvement (p = 0.003) with biochemical recurrence were found to be statistically significant, whereas perineural involvement (p = 0-548) was not found to be related with recurrence. The data of univariate and multivariate analyses of all vari-

Table 1.
Clinical and pathological properties of the patients with RP.

		[mean ± standard deviation, % (n/total n)]
Number of patients		238
Age		66,01 ± 6,85 years
PSA		11,12 ± 9,32 ng/ml
PSA distribution	< 10	%60, 9 (145/238)
	10 < PSA < 20	%29 (69/238)
	> 20	%10,1 (24/238)
Gleason Score (GS)		7 ± 0,79
GS distribution	6	46.2% (110/238)
	7	42% (100/238)
	8	7.1% (17/238)
	9	4.6% (11/238)
PNI		35.3% (84/238)
SVI		9.7% (23/238)
ECE		25.2% (60/238)
CI		37.4% (89/238)
SMP		21.8% (52/238)
BCR		28% (68/238)

Table 2.
BCR relation according to PSA distributions.

	Recurrence +	Recurrence -	Total	P value
PSA < 10	26 (17.9%)	119 (82.1%)	145 (100%)	P = 0,0001
10 ≥ PSA < 20	26 (37.7%)	43 (62.3%)	69 (100%)	
PSA ≥ 20	16 (66.7%)	8 (33.3%)	24 (100%)	

Table 3.
BCR relation according to Gleason Score distributions.

	Recurrence +	Recurrence -	Total	P value
GS 6	23 (20.9%)	87 (79.1%)	110 (100%)	P = 0,0001
GS 7	22 (22%)	78 (78%)	100 (100%)	
GS 8	14 (82.4%)	3 (17.6%)	17 (100%)	
GS 9	9 (81.8%)	2 (18.2%)	11 (100%)	

Table 4.
The effect of pathological parameters on BCR.

Parameters		Recurrence + (%)	Recurrence - (%)	P value
SMP	Yes	22 (42.3%)	30 (57.7%)	0,014
	No	46 (24.7%)	140 (75.3%)	
CI	Yes	35 (39.3%)	54 (60.7%)	0,005
	No	33 (22.1%)	116 (77.9%)	
PNI	Yes	26 (31%)	58 (69%)	0,548
	No	42 (27.3%)	112 (72.7%)	
ECE	Yes	30 (50%)	30 (50%)	0,001
	No	38 (21.3%)	140 (78.7%)	
SVI	Yes	13 (56.5%)	10 (43.5%)	0,003
	No	55 (25.6%)	160 (74.4%)	

Table 5.
Univariate and multivariate analyses of all variables in predicting BCR.

Variables	Univariate analysis	P value	Multivariate analysis	P value
GS	2,597	0,0001	_	_
GS Groups (GS ≤ 7 vs GS > 7)	16,867	< 0,0001	10,187	< 0,0001
PSA	1,090	0,001	_	_
PSA groups (PSA < 10 vs PSA ≥ 10)	3,877	0,0001	2,416	0,01
SVI	3,782	0,003	1,738	0,312
ECE	3,684	0,001	1,668	0,310
PNI	1,195	0,548	_	_
CI	2,278	0,005	1,041	0,930
SMP	2,232	0,014	1,081	0,859

ables are summarized in Table 5. When the variables that proved significant in the univariate analysis were again evaluated using multivariate analysis, only GS and PSA were found to be related with BCR (p values 0.003 and 0.002, respectively). Furthermore, when we group the patients according to PSA values as less than 10 ng/ml and more than 10 ng/ml, statistically significant difference (p = 0.01) was determined between BCR groups both in univariate and multivariate analysis.

Discussion

Prostate cancer is a disease which requires a long-term treatment and has to be properly followed up. Following the initial curative treatment, 16-35% of the patients require a secondary treatment, regardless of the treatment method received before (5-9).Radical prostatectomy (RP) is one of the most commonly used treatments for prostate cancer and provides a very good cancer control. In radical prostatectomy, the main aim is totally removing the cancer while it is still confined within the prostate. However due to clinical staging deficiency, it is known that extraprostatic disease occurs in RP specimens in about 30-40% of the patients with localized prostate cancer (10-11). In addition, BCR develops in 35% of the patients within 10 years of the surgery (12-14). Thanks to the excellent sensitivity of PSA, recurrence of the disease can be detected early. Again due to the very same reason, there is a long time interval between BCR and local recurrence or development of distant metastasis. Within these time intervals, the patient may require secondary treatments. Which patients and/or in which stage should receive these treatments is disputable. For this reason, it has become important to know the factors predicting BCR, even if they are postoperative. Several factors are found to be effective on the postoperative result after radical prostatectomy.

One of the best known of these factors is the PSA value at the time of diagnosis. Many authors studying on biochemical recurrence predictors after radical prostatectomy have found that PSA value at the time of diagnosis was a very powerful preoperative indicator both in univariate and multivariate analysis (15-19). Supporting these findings, it has been also determined in our study that PSA was an independent predictor for biochemical recurrence. Besides, *Kupelian et al.* in their study in 1996, have determined the rates of biochemical recurrence at 5 years of follow-up, with respect to PSA distributions (PSA < 10 ng/ml, 10 < PSA < 20 ng/ml, PSA > 20 ng/ml) were 31,2%, 44% and 74% respectively (20). These rates seem to be higher than the values obtained in our study but this difference might be due to our comparatively shorter follow-up period.

Radical prostatectomy specimen GS is also an independent and a powerful predictor for biochemical recurrence in both univariate and multivariate analyses in many studies (15-18). This relationship is much more apparent for the patients with Gleason score total value 7 or more. This observation is also confirmed in our study as the most powerful variable in multivariate analysis (p < 0.0001). When we have a look over the studies in general from recurrence point of view, there is no statistical difference in values of Gleason score total up to 6. In their study in 2002, *Hull GW. et al.* have determined that the biochemical recurrence rates of the patients with Gleason score total value of 6, 7 and 8-10 in 5 years of follow-up period were as 26.6%, 40.1% and 52%, respectively (13). Besides, in another study conducted in our country with a mean follow-up period of 43 months, recurrence rates for the same Gleason groups were found as 12%, 29% and 90%, respectively (21). In our study, these rates were 20.9%, 22% and 82.1%. The reason that these values do not coincide might be due to the differences in definitions of recurrence as well as the differences in number of patients or follow-up periods.

Following radical prostatectomy, SMP occurs at the rate of 6-41% (22). The difference within these rates may be related to surgical experience. These rates decrease as the surgical experience increases (23-24). In our study, this rate was determined as 21.8%. As it is in many branches of oncological surgery, SMP occurrence is an undesired situation that surgeons are concerned in radical prostatectomy as well. Although this term means that there are still alive cancer cells remaining in the patient's body, prognostic significance of occurrence of SMP is still disputable for prostate cancer. While SMP is shown to be related with high rate of BCR in various studies (25-27), such a relationship could not be shown in many others (28-29). On the contrary, *Stephenson et al.* have determined that number of SMP (≥ 1) and extended SMP were significant in predicting biochemical recurrence in multivariate analysis (30). Again, in their study that investigated 932 patients treated by radical prostatectomy, *Ahyai et al.* have reported that biochemical recurrence developed only in 20% of the patients with SMP and remarked that implementation of adjuvant treatment to only selected patients would decrease the risk of overtreatment (31). Biochemical recurrence risk of SMP in average 5 years of follow-up period varies between 20% and 47% (32-33). Moreover, in their study conducted in 2011, *Psutka et al.* have concluded that positivity of surgical margins was an independent predictor for recurrence in pT2 patients, while it was insignificant for pT3 patients (34). In our study within the follow-up period this value was found as 42.3%; as for the patients with surgical margin negativity however, biochemical recurrence rate was found to be 24.7%. Although this difference appears to be statistically significant (p: 0,014) in univariate analysis, it is observed that SMP is not an independent predictor for BCR in multivariate analysis (p: 0,859).

The relationship of tumor with prostate capsule is another factor effecting prognosis. In their study in 1993, *Epstein et al.* have reported that capsular involvement and its degree had prognostic significance (35). Yet again, in a relevant serial study with 688 patients, *Wheeler et al.* have evaluated the CI degree of cancer prognosis and its level in multivariate analysis. According to this study, while the rate of recurrence of the patients with only CI in 5 years was 13 %, meanwhile the patients with local ECE this rate was found as 27% (36). In the same study, the rate of recurrence of the patients with extended ECE in 5 years was found as 58% and extended ECE was reported as an independent predictor for biochemical recurrence. In another study by *Theiss et al.* however,

biochemical recurrence rate in a 10 year follow-up period was reported as 21% for patients with no CI while it was 35.3% for patients with CI, and 61.5% for patients with ECE (37). The reporters have suggested that CI and ECE should be differentiated. In our study BCR was found in the patients with no CI as 22.1%, in patients with CI as 39.3% and in patients with ECE as 50%. While CI and ECE were significant for recurrence in univariate analysis, it was determined that it was not an independent variable in multivariate analysis for recurrence. Clinical relevance of PNI in the radical prostatectomy specimen is controversial. *D'Amico et al.* have shown that PNI was an independent prognostic factor for biochemical recurrence (38). However the studies showing that PNI was not correlated with BCR have the majority (39-41). *Jeon et al.* also have reported that the patients with PNI were related with high Gleason scores, extracapsular extension, seminal vesicle involvement and surgical margin positivity (42). In their study in 2010, *Jun Taik Lee et al.* have determined that PNI occurrence was related with lymph node involvement, high Gleason score, surgical margin positivity, high volume of tumor and advanced stage prostate cancer. Nonetheless, they have determined that PNI was not an independent factor for BCR in multivariate analysis (43). In our study, in line with the literature, the patients with PNI were not related with BCR in univariate analysis.

Seminal vesicle involvement is a bad prognostic parameter with biochemical rates of no progression varying between 5-60% (44-45). *Bloom et al.* have published that SVI was correlated with high BCR following RP and distant metastasis afterwards (46). *Freedland et al.* have shown the occurrence of significantly high PSA values, advanced pathological stage, high grade tumors, accompanying extracapsular extension and/or surgical margin positivity for patients with SVI. However in the same study, they stated that prognosis was better in elder patients with SVI, low Gleason score and surgical margin negativity. This study has concluded that SVI was not always an indicator of negative prognosis (47). The reason for different series will result in different outcomes might be due to hidden micro metastases and/or frequently occurring concomitant prognostic pathological data (Gleason score > 7, SMP, ECE). Another explanation may be due to the differences in definitions/descriptions of SVI. While some authors visualize real seminal vesicle as an intraprostatic part, others accept the part outside the capsule as seminal vesicle involvement (48). What for certain is that SVI is a significant prognostic factor. *Debras et al.* have determined that prognostic significance of SVI was not stable and the limited involvement in proximal section would progress better than the involvement extending up to distal parts (49). In our study, the probability of biochemical recurrence in patients with SVI is a rather high rate of 56.5%, in line with the literature. It did not come out as significant for BCR in multivariate analysis although it did in univariate analysis. The reason for that might be, as mentioned above, the difference in SVI definition or the high level of concomitant bad prognostic factors.

As previously mentioned, one should keep in mind while evaluating these studies that prostate cancer varies quite a lot with racial and geographical differences.. As much as differences in nutritional habits, black race with more aggressively progressing prostate cancer risk might explain this situation. It is clearly observed in a study conducted in Turkey that the patients treated by radical prostatectomy were at a more advanced stage (50).

As for our study, the fact that it was retrospective, a shorter follow up period compared to the literature and limited number of patients can be mentioned among the weaknesses. Besides, more detailed information could have been obtained from pathological data. For example, if the parameters such as the extension of surgical margins and its number, extracapsular extension being focal or extended, depth of seminal vesicle invasion/involvement and its bilateral character, etc. were also included in the variables, more significant/important information could have been obtained. This is another weakness of our study.

Conclusions

In our study, 28% of the patients treated by radical prostatectomy due to localized prostate cancer developed BCR within an average follow-up period of 37.2 months. In the univariate analysis, PSA value, RP specimen Gleason score, surgical margin positivity, capsule invasion, extracapsular extension and seminal vesicle involvement/invasion were found to be significant for BCR. Perineural invasion however did not turn out to be statistically significant. In the multivariate analysis PSA and GS came out as independent factors predicting biochemical recurrence in our study. In particular, PSA values over 10 ng/ml and Gleason scores above 7 considerably increase the probability of recurrence. We can state that it is still controversial which treatment should be given within the time interval between BCR following RP and metastatic disease Main variables that would guide us in treatment should be PSA and Gleason score. Even though SVI, ECE and SMP do not turn out to be independent predictors, in studies with larger series, with longer follow-up period, and with more extensive pathological data, such dilemmas about these topics may disappear.

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