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Efficacy of the neutrophil-lymphocyte ratio on biochemical recurrence in patients treated with radical prostatectomy

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Summary. *Objective:* Radical prostatectomy (RP) is considered as the gold standard method in the treatment of localized prostate cancer in patients with more than 10 years' life expectancy. Biochemical recurrence (BCR) is seen in patients followed up after surgery and additional treatment is required for these patients. In our study, we aimed to evaluate those who were clinically diagnosed with localized prostate cancer, had an RP operation and then developed biochemical recurrence; we also aimed to determine the efficacy of the neutrophil-lymphocyte ratio (NLR) to predict BCR. *Materials and Methods:* The data of 996 patients diagnosed with prostate cancer in our clinic were analyzed retrospectively. Age, PSA value before transrectal ultrasonography guided prostate biopsy, digital rectal examination, Gleason score on biopsy, neutrophil and lymphocyte values detected by preoperative routine hemogram analysis, date of RP, pathological examination data of RP specimen, PSA values at follow-up after surgery, date of BCR and follow-up period of all patients were recorded. *Results:* We found that PSA, RP Gleason score and extracapsular spread were significant in predicting BCR in multivariate analysis while other parameters and the NLR were not. *Conclusion:* NLR did not prove statistically significant in univariate analysis although it was high in the patients with BCR that we evaluated in this study.

Key words: prostate cancer, biochemical recurrence, neutrophil, lymphocyte

«Efficacia del rapporto neutrofili-linfociti sulla recidiva biochimica in pazienti trattati tramite prostatectomia radicale»

Riassunto. *Oggetto:* Nel trattamento del cancro prostatico localizzato, in pazienti con più di 10 anni di aspettativa di vita, la prostatectomia radicale è considerata il metodo standard ottimale. Durante il follow-up postoperatorio dei pazienti che hanno subito prostatectomia radicale, in caso di recidiva biochimica, è necessario un trattamento addizionale. In tale studio sono stati valutati i pazienti con diagnosi clinica di cancro prostatico localizzato, che hanno subito un intervento chirurgico di prostatectomia radicale, e che hanno in seguito sviluppato la recidiva biochimica. Si è inoltre valutato se il rapporto neutrofili-linfociti potesse esser un efficace indice predittivo di recidiva biochimica. *Materiali e metodi:* Nella nostra clinica sono stati valutati retrospettivamente 996 pazienti con diagnosi di cancro prostatico. Sono stati considerati i seguenti parametri: età, valore del PSA prima della biopsia prostatica guidata da ultrasonografia transrettale, esaminazione manuale rettale, indice Gleason sulla biopsia, valori di neutrofili e linfociti individuati mediante emocromo analisi di routine preoperatorio, data della prostatectomia radicale, analisi patologica della biopsia prostatica, valori di PSA durante il follow-up post operatorio, data della recidiva biochimica, periodo di follow-up di tutti i pazienti. *Risultati:* Dalla analisi multivariata è emerso che il PSA, l'indice di Gleason della prostatesctomia radicale e la diffusione extracapsulare sono significativi nella predizione della recidiva biochimica, mentre tutti

gli altri parametri, tra cui il rapporto neutrofili-linfociti, non si sono dimostrati predittivi. *Conclusioni:* mediante analisi univariata, il rapporto neutrofili-linfociti non si è dimostrato statisticamente significativo, sebbene fosse più alto nei pazienti con recidiva biochimica.

Parole chiave: Cancro prostatico, recidiva biochimica, neutrofili, linfociti

Introduction

Prostate cancer is the second leading cause of cancer death in men (1). The risk of developing clinical prostate cancer in a man's lifetime was found to be 16% in a study conducted in the United States, while the death rate from this disease was 3% (1). Radical prostatectomy (RP) is accepted as the gold standard method for the treatment of localized prostate cancer in patients with a life expectancy of 10 years. However, biochemical recurrence (BCR) is observed in 35% of patients after RP operations (2). It is important for treatment and follow-up to predict such recurrence. Genetic and environmental factors play a role in cancer development and progression as well as the patient's inflammatory response (3, 4). Considerable improvements have been made in recent years regarding survival in urologic cancers, especially sipuleucel-T immunotherapy and targeted drug therapies (5-7). However, mortality rates remain high in some cancer types due to rapid progression. Thus, there is a need for better prognostic factors in this group of diseases. In our study, we aimed to evaluate those who were clinically diagnosed with localized prostate cancer, had and RP operation and then developed biochemical recurrence; we also aimed to determine the effectiveness of the neutrophil-lymphocyte ratio (NLR) in predicting BCR.

Materials and methods

Data from 996 patients diagnosed with prostate cancer in our clinic were analyzed retrospectively. Twenty-five out of 439 patients who had RP as the primary tretment were excluded because they were under active follow-up prior to the operation. Again, 19 patients were excluded because they had early hormonotherapy postoperatively due to metastasis being detected in the lymph nodes removed. Thirty-one of the remaining 395 were also excluded because of missing data. Twelve more patients were excluded due to accompanying hematologic disorders (polycythemia, leukemia, etc). A total of 352 patients who underwent RP in our clinic in the period between 2004 and 2014 and met the criteria, were enrolled in our study group.

We recorded all the patients' age, PSA value before transrectal ultrasonography guided prostate biopsy (TRUSPB), digital rectal examination, Gleason score (GS) on TRUS biopsy, neutrophil and lymphocyte values measured by preoperative routine hemogram analysis, pathological examination data of RP specimen, PSA values at follow-up after surgery, and follow-up periods.The TNM 2009 classification was used for staging. In the pathology reports, zonal origin, placement, perineural invasion (PNI), prostate capsule invasion (PCI), seminal vesicle invasion (SVI), extracapsular spread (ECS), presence of high-grade PIN, continuity at the surgical margins (CSM), integrity of prostatic capsule and the status of the nodes were investigated, regarding the tumor. After the operation, a general check-up on all patients were performed every 3 months in the first year, every 6 months in the 2nd and 3rd years, and in the following years once a year. Biochemical recurrence was defined as a single PSA value >0.2 ng/mL or a postoperatively high PSA value (8).

NLR was calculated by the following formula: "NLR=neutrophil/lymphocyte". When the mean NLR of all patients was determined as the threshold value, the effect on BCR was examined for patients below or above the threshold. In addition, the effect on BCR was examined with respect to the threshold NLR value of 1,2,3, and 4, respectively. Windows Statistical Package for Social Sciences (SPSS) version 22.0 software package was used for all statistical evaluations. Data were evaluated using logistic regression analysis and

Chi-square tests. P values <0.05 were considered to be statistically significant.

Results

The mean age of the patients was 67±6.36 years (50-81), and the mean PSA value was 11.34 ng/mL. The mean follow-up period was 39.7 months. In the follow-up, BCR was detected in 83 patients (23%). The mean time for development of biochemical recurrence was found to be 6.56 (1-41) months.

PSA was ≤10 ng/mL in 29 (34.9%), between 10 ng/mL to 20 ng/mL in 29 (34.9%), and ≥20 ng/mL in 25 (30.1%) patients who developed BCR. A statistically significant difference was observed between PSA and recurrence in univariate analysis (Table 1) (p<0.0001). Regarding the distribution of Gleason scores (GS), the sum of GS was determined as 6 in 148 (42%), 7 in 158 (44.9%), 8 in 26 (7.4%), and 9 in 20 (5.7%) of the patients. It was determined to be statistically significant that as GS increased, so did the probability of BCR (p<0.0001).

BCR was detected in 34 (34.3%) of the patients with CSM+, and in 49 (19.3%) of those with CSM-, the difference between them being statistically significant (p=0.003). Again, BCR was detected in 55 (32.9%) of the patients with PCI+, and the difference between

Table 1. Univariate and multivariate analysis results of all parameters affecting biochemical recurrence

	BCR(+) (n)	BCR(+) (%)	BKR(-) (n)	BCR(-) (%)	Total	Univariate Analysis	Multivariate Analysis
Age (year)	69.1		65.3		67	**0.014**	0.93
PSA (ng/mL)						**<0.0001**	**0.001**
<10	29	12.9	195	87.1	224		
10-20	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		
CSM						**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		

Table 2. The effect of neutrophil-lymphocyte ratio on biochemical recurrence (threshold value: 2.58)

	BCR(+) (*1000/μL)	BCR(-) (*1000/μL)	Univariate analysis (p)
Neutrophil (*1000/ μL)	5.15	5	0.994
Lymphocyte (*1000/ μL)	1.92	2.27	0.348
NLR	2.77	2.52	0.107

those with and without PCI was statistically significant (p<0.0001). Forty-three (30.9%) of the patients with PNI showed BCR, which was statistically significant (p=0.009). BCR was observed in 51 (44.7%) of the patients with ECS, which was found to be statistically significant (p <0.0001). Of the patients with SVI, BCR was observed in 50% and this was statistically significant (p<0.0001). The univariate analysis indicated an increase in BCR with age (p=0.014) but this was not statistically significant when considered together with other factors (p=0.93).

The mean NLR of all the patients was determined as 2.58*1000/μL. NLR was 2.77*1000/μL in patients with BCR, as against 2.52*1000/μL in patients without BCR, and univariate analysis showed there was no statistically significant difference when the mean value was taken as the threshold (Table 2) (p=0.107). Again, no statistically significant difference was determined when the NLR threshold was taken as 1, 2, 3 and 4 (*1000/μL) (p=0.101, p=0.157, p=0.205, p=0.407).

As a result, PSA, GS, SVI, CSM, ECS, PCI, the PNI and age were found to be statistically significant in predicting postoperative BCR, in univariate analysis, while the NLR was not statistically significant (p=0.107). Multiple logistic regression analysis of these variables revealed GS, PSA and ECS variables as statistically significant in terms of BCR. P values were calculated as 0.006, 0.001 and 0.004, respectively.

Discussion

Prostate cancer is a common type of cancer requiring long-term treatment, close monitoring, and support with adjuvant therapy when needed. Regardless of the initial curative treatment, 16-35% of patients require a secondary treatment within the first 5 years (9-13). RP is one of the most commonly used treatments for prostate cancer. Nevertheless, BCR develops in 35% of patients over 10 years after surgery (14, 15). Due to the sensitivity of PSA, disease recurrence may be identified before clinical signs appear. Thus, there is rather a long period between BCR and local recurrence or distant metastasis, which is the appearance of clinical signs. During this time period, secondary treatment should be administered. It is controversial which patients and/or in which period they should be given, because there are also side effects from these additional treatments. For this very reason, recognizing factors that can predict BCR, even though postoperatively, has come into prominence and many factors have been found to be capable of influencing the outcome after radical prostatectomy. Despite all these data, BCR can be seen even in patients without any predicted BCR risk and this suggests that there are different factors influencing the development of BCR.

One of the best known factors is PSA at the time of diagnosis. The PSA value at the time of diagnosis has been found to be a strong preoperative indicator both in univariate and in multivariate analysis by many authors who have studied the predictors of biochemical recurrence after radical prostatectomy (16-20). In our study too, PSA at the time of diagnosis was found to be statistically significant for biochemical recurrence, supporting these data.

The total GS of RP specimen has been found statistically significant for BCR in many studies (16-19). This result was confirmed in our study, by multivariate analysis.

In our study, the biochemical recurrence rate proved to be 28.1% during the follow-up time of patients with CSM positivity. The CSM positivity rate in the literature varies between 20% and 47% (20, 21) In patients with negative CSM, however, the biochemical recurrence rate was found to be 19.3%. This difference was statistically significant by univariate analysis, whereas CSM positivity showed no significance for BCR by multivariate analysis.

In the study by Epstein *et al.*, the 5-year BCR rate was 13% in patients who had only PCI, whereas it was 27% in patients with ECS (22, 23). In our study, the BCR rate was 32.9% in patients with PCI, 15.1%

in patients without PCI, and 44.7% in patients with ECS. Univariate analysis showed that PCI and ECS were significant for recurrence, though multivariate analysis revealed that PCI was not statistically significant for recurrence but ECS was.

The clinical significance of the presence of PNI in radical prostatectomy specimen is controversial. D'Amico *et al.* have shown that PNI is an independent prognostic factor for BCR (24). However, the majority of studies have demonstrated that perineural invasion and BCR were not correlated (25-27). In accordance with the literature, our study too found a significant difference for patients with PNI by univariate analysis, whereas this difference lost its significance by multivariate analysis.

SVI has been reported as a poor prognostic parameter with biochemical progression-free rates ranging between 5-60% (28, 29). Similarly, in our study the likelihood of BCR was 52.1% in patients with SVI. This was statistically significant in univarite analysis but not in multivariate analysis.

Age of the patient at diagnosis is another variable that can affect the biochemical recurrence. Kunz *et al.* have evaluated the effects of age of the patient at RP for prostate cancer upon tumor characteristics and oncologic and functional outcomes (30). According to the result of that study, there was no significant correlation between advanced age and total survival, disease-specific survival and BCR free survival. In our study, no difference was determined by multivariate analysis while a significant difference was observed by univariate analysis.

Despite all these parameters, no reliable parameter that can exactly predict BCR has yet been found. Current data indicate the role of inflammation in the development and progression of many cancer types, including prostate cancer. Inflammatory mediators play a role in the proliferation of cancer cells, angiogenesis and metastasis by initiating molecular signals (31-33). A high neutrophil lymphocyte ratio (NLR) indicates that the neutrophil-dependent inflammatory process is increased and the lymphocyte-dependent anti-tumor response is reduced. Thus, high NLR has been shown to reflect aggressive tumor biology, cancer progression and poor prognosis (34, 35). And neutrophils in the circulation, as one of the mechanisms explaining the relationship between NLR and tumor, have been shown to secrete cytokines which affect the development of cancer, such as tumor necrosis factor, interleukin (IL)-1, IL-6 as well as vascular endothelial growth factor (35). It has been shown that a low lymphocyte ratio decreased CD4-T helper cells and accordingly the lymphocyte dependent immune response against malignancies declined (35).

Hematological components in the systemic inflammatory response also play a role in cancer development and progression. In particular, the effectiveness of the NLR in cancer prognosis has been shown in many studies (36-41). Peripheral blood tests performed at diagnosis or before treatment reflect the inflammatory process within the tumor (31, 42, 43). The easily calculated NLR may thus provide useful information about the prognosis of cancer (44). Previous studies have indicated that high NLR is a poor prognostic factor for many malignancies such as stomach (45), liver (46), kidney (47), small cell lung cancer (38) and ovarian cancer (37). Proctor *et al.* have shown high NLR to indicate a poor prognosis in a large cohort study including all cancer types (48). Gondo *et al.* have shown that C-reactive protein (CRP), lymphocyte and neutrophil counts, hemoglobin levels and NLR were associated with survival in patients with hydronephrosis and bladder tumor accompanied by carcinoma in situ (49).

In a meta-analysis of 17 studies involving 3159 patients with urological cancer, high NLR was shown to be associated with poor clinical outcome (44). In another study concerning patients with metastatic prostate cancer, progression-free survival was shown to be lower in patients with NLR>3 (50). Again, Heng *et al.* have indicated NLR as an independent prognostic factor in metastatic renal tumors (51, 52). In urinary tract cancer too, it has been shown by some studies that high NLR is a poor prognostic factor (52, 55) - though there are also some studies suggesting just the opposite (54).

This NLR effect has been proven not only in cancer but also in other systemic diseases. High NLR has been shown to adversely affect the prognosis of cardiovascular diseases. One of these studies was conducted by Tsai *et al.* in 1872 patients with metabolic syndrome and high NLR was associated with increased ischemic cardiovascular events (56). Imtiaz *et al.* have reported

high NRL in patients with hypertension and diabetes mellitus as well (57).

In our present study, however, NLR was examined in addition to the factors known to affect postoperative biochemical recurrence in patients who underwent radical prostatectomy for benign prostatic adenocarcinoma. In our univariate analysis, the mean NLR value (2.58) of the patients was observed to have no effect on BCR. There being no absolute limit value of NLR, the mean NLR of the patients investigated or some different values have been taken as the limit value. Accordingly, we used NLR threshold values of 1, 2, 3, 4 (*1000/mL) but still observed no statistical significance in the univariate analysis. We concluded in our study that NLR has no effect in predicting BCR.

A literature review on this topic would reveal that the NLR value has not been examined for BCR previously. Hence, we cannot make any comparisons for our results regarding BCR. However, given the studies relating to recurrence, progression, and survival, NLR has been considered as a predictor value for many cancer types.The fact that we did not obtain similar results may be attributed to (i) the limited number of patients, (ii) the relatively slower progression of prostate cancer compared with other cancer types, (iii) the presence of other much stronger factors affecting BCR and (iv) the ineffectiveness of BCR to prompt the systemic inflammatory response due to much earlier detection of BCR than clinical recurrence.

As previously mentioned, it should be borne in mind while evaluating all these studies that prostate cancer exhibits great geographic and racial differences. Different dietary habits and belonging to the black race carry a risk of more aggressive prostate cancer, and this may explain such different results. One study conducted in our country clearly showed that Turkish patients who underwent RP were in rather advanced stages (58). The weak points of our study may be listed as being a retrospective study, having a short follow-up period compared to the literature and a limited number of patients.

Conclusion

We can claim that the main variables leading us to optimal treatment should be PSA, the GS and ECS, particularly now that the treatment to be administered after RP, namely in the period between BCR and local recurrence is still controversial. The NLR rate that we evaluated in our study was not found to be statistically significant although it was high in the patients with BCR. All in all, larger scale further studies are called for on this subject.

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