

Does the Decrease in Neutrophil-lymphocyte Ratio after BCG Treatment Be a Prognostic Marker for NMIBC?

BCG Tedavisi ile Nötrofil-lenfosit Oranındaki Azalma NMIBC için Prognostik Bir Belirteç Olabilir Mi?

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

The neutrophil-lymphocyte ratio (NLR) has prognostic value for bladder cancer. However, a unique finding of our study is that the decrease in NLR with Bacillus Calmette-Guerin treatment is a good indicator of improved prognosis.

Abstract

Objective: Non-muscle invasive bladder cancer (NMIBC) accounts for 75% of all bladder cancer cases. Several models to predict relapses and progression have been developed. We aimed to determine the predictive value of the neutrophil-lymphocyte ratio (NLR) for recurrence and/or progression of the disease.

Materials and Methods: Seventy patients with high-risk NMIBC according to the European Organization for Research and Treatment of Cancer (EORTC) risk classification who were receiving Bacillus Calmette-Guerin (BCG) treatment and were followed up at our clinic were included in the study.

Results: The average score level and NLR values differed significantly on patient classification according to the EORTC Progression and Recurrence Risk score. The positive correlations among EORTC Recurrence score, EORTC Progression score, Club Urológico Espanol de Tratamiento Oncológico (CUETO) Recurrence score, and CUETO Progression score and NLR values were not statistically significant. The NLR values decreased significantly on follow-ups on BCG treatment.

Conclusion: Patients with bladder cancer have a high NLR, which has predictive utility with regard to prognosis. A decrease in NLR with BCG treatment is indicative of the decreased likelihood of recurrence and progression.

Keywords: Non-muscle invasive bladder cancer, Neutrophil-lymphocyte ratio, BCG treatment, EORTC risk classification, Progression, Recurrence

Öz

Amaç: Kas invazif olmayan mesane kanserleri, tüm mesane kanserlerinin %75'ini oluşturmaktadır. Relaps and progresyonu tahmin etmek için bir çok model geliştirilmiştir. European Organization for Research and Treatment of Cancer (EORTC) risk sınıflandırmasına göre yüksek risk kategorisinde olup Bacillus Calmette-Guerin (BCG) tedavisi başlanmış ve 1 yıllık BCG tedavisinde nüks ve progresyon gözlenmemiş hastalar retrospektif olarak analiz edildi. Bu durumu tahmin edebilecek nötrofil/lenfosit oranları (NLR) araştırıldı.

Gereç ve Yöntem: EORTC risk sınıflandırmasına göre yüksek risk grubunda BCG tedavisi başlatılan ve kliniğimizde takip edilen 70 hasta çalışmaya dahil edildi.

Bulgular: EORTC Progresyon ve Rekürrens Risk Skoru Sınıflamasına göre skor seviyesi ve NLR değerlerinin ortalaması istatistiksel olarak farklı bulundu. EORTC Rekürrens skoru, EORTC İlerleme skoru, Club Urológico Espanol de Tratamiento Oncológico (CUETO) Rekürrens skoru ve CUETO Progresyon skoru artışı ve NLR değerleri arasında yapılan korelasyon analizinde istatistiksel olarak anlamlı bir sonuç saptanmadı. BCG tedavisi ile birlikte takiplerde NLR değerleri önemli ölçüde azaldı.

Sonuç: NLR değeri mesane kanseri ile ilişkili olarak artmakta ve progresyon ve rekürrens tahmini için bir prognoz parametresi olarak kullanılabilir. BCG tedavisi ile birlikte değerinde düşme olması rekürrens ve progresyon olmamasının bir göstergesi olabilir.

Anahtar Kelimeler: Kas invazif olmayan mesane kanseri, Nötrofil-lenfosit oranı, BCG tedavisi, EORTC risk sınıflaması, Progresyon, Nüks

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Introduction

Bladder cancer (BC) is the 9th or 11th most common cancer globally, including in both the sexes (1,2). Among men, it is the 4th-7th most common cancer (1-4). The global incidence rate of BC standardized by age is 9.0 and 2.2 per 100,000 males and females per year, respectively (1). BC is the most common among genitourinary system tumors.

Approximately 75% of the patients receive the diagnosis of non-muscle invasive, submucosa (stage T1) or mucosal [stage Ta or carcinoma *in situ* (CIS)] neoplasia (1,5-7). Because non-muscle invasive bladder cancer (NMIBC) constitutes a heterogeneous group, its recurrence and progression also differ by stages and grades. The European Organization for Research and Treatment of Cancer (EORTC) and Club Urológico Español de Tratamiento Oncológico (CUETO) risk tables were devised to predict recurrence and progression. Furthermore, NMIBCs have been divided into low-, medium-, and high-risk groups for the EORTC treatment protocol. The European Urology Guide (EAU) guidelines recommend the treatment protocol according to these risk groups. However, reliable prognostic factors that can help in patient-specific estimation rather than group-specific estimation of recurrence and progression risk are lacking (8). Tumor-induced host inflammatory responses play an important role in tumor development and progression. According to the literature, hematologic markers have been used in predicting prognosis in various cancers and urothelial carcinoma. The neutrophil-to-lymphocyte ratio (NLR) has been used as a marker in various types of cancer, and it has been shown to be of predictive value for prognosis (9,10). In patients with NMIBC, increase in NLR has been shown to be associated with progression and recurrence (11). NLR is a hematologic parameter that can be determined easily and quickly. The inclusion of NLR along with parameters such as number of tumors, tumor size, tumor stage, tumor grade, presence of concomitant CIS, and previous recurrence in progression and recurrence prediction models could be useful. Consensus on a threshold NLR value is lacking (12).

We aimed to investigate the predictive value of changes in NLR with regard to progression and recurrence after 1 year maintenance BCG treatment in patients with high-risk NMIBC and to determine the association between NLR and EORTC progression and recurrence risk classifications.

Materials and Methods

This study complied with the Helsinki Declaration and was conducted with the approval of the local ethics committee (Hitit University Faculty of Medicine Ethics Committee; decision no: 87). Patients undergoing transurethral bladder tumor resection

(TURB) due to bladder tumor between September 2015 and September 2018 at a single center were retrospectively screened. The pathology reports followed the 2009 TNM classification and 2004 WHO grading system. We included 70 patients classified as high-risk according to the EORTC risk classification (2019 EAU NMIBC guideline recommendations; T1, grade 3, presence of CIS, multiple, recurrent, or tumor diameter >3 cm) who were receiving BCG treatment and were being followed up at our clinic.

The medical records, laboratory results, and pathology reports of the patients included in the study were evaluated. The number of tumors, tumor size, and previous recurrence rate before TURB, and tumor stage, tumor grade, and the presence of accompanying CIS in line with the pathology report after TURB were obtained from the medical records. Recurrence and progression scores were calculated according to the EORTC risk tables. Similarly, CUETO recurrence and progression scores were calculated.

Neutrophil and lymphocyte counts of the patients were calculated by dividing the absolute neutrophil values by the absolute lymphocyte values at different time points: NLR 1, pre-TURB; NLR 2, before control cystoscopy performed after 6 courses of BCG treatment; NLR 3, hemogram values before control cystoscopy performed after 1 year of BCG induction.

We excluded patients with non-transitional BC, transitional cell BC without muscle invasion, cancer other than BC, hematological and bleeding disorders, BCG intolerance, and BCG failures.

Statistical Analysis

IBM SPSS for Windows, version 22.0, was used for statistical analyses. Means, standard deviations, and percentages were calculated for descriptive statistics. The Student t-test and 1-way analysis of variance (ANOVA) were used for parametric data, and the Mann-Whitney U and Kruskal-Wallis tests were used for non-parametric data. Repeated-measures ANOVA and Friedman tests were used for the analysis of repeating measurements, and the chi-square or Fischer Exact test was used to evaluate categorical data. The results were expressed at a 95% confidence interval, and $p < 0.05$ was considered statistically significant.

Results

From among the patients in the EORTC high-risk group undergoing BCG treatment between January 2015 and September 2018, 70 patients who did not have recurrence and progression in the first year of maintenance treatment were included in the study. The associations between the clinical features of EORTC and CUETO scoring in the high-risk group and NLR were examined.

The mean age of the study population (59 males and 11 females) was 68.06±9.70 years. The values of tumor-related features, EORTC and CUETO recurrence and progression scores, and NLRs of the patients at 1-year follow-up are summarized in Table 1.

Table 1. Tumor-related characteristics of patients, EORTC and CUETO recurrence and progression scores, and 1-year follow-up values of NLR

		n	%
Age (years)		68.06±9.70	
Male		59	84.3
Female		11	15.7
Number of tumors	Single	38	54.3
	2-7	24	34.3
	≥8	8	11.4
Tumor diameter	<3 cm	27	38.6
	≥3 cm	43	61.4
Category	Ta	12	17.1
	T1	58	82.9
Concurrent CIS	Yes	7	10
	No	63	90
Grade	G1	12	17.1
	G3	58	82.9
Prior recurrence rate	Primer	56	80
	≤1/year	14	20
	>1/year	0	0
EORTC Recurrence score		6.43±3.36	
EORTC Recurrence score classification	1-4	25	35.7
	5-9	32	45.7
	10-17	13	18.6
EORTC Progression score		11.57±3.95	
EORTC Progression score classification	2-6	7	10
	7-13	37	52.9
	14-23	26	37.1
CUETO Recurrence score		5.50±3.17	
CUETO Progression score		7.97±3.19	
NLR 1		2.31±1.03	
NLR 2		2.24±1.17	
NLR 3		2.13±1.10	
Total		70	100.0

EORTC: European organization for research and treatment of cancer, CUETO: Club Urológico Español de Tratamiento Oncológico, NLR: Neutrophil-lymphocyte ratio, CIS: Carcinoma *in situ*

We investigated the threshold values of NLR1 measurement according to the EORTC Progression and Recurrence Risk score classification in predicting non-progression and non-recurrence in high-risk NMIBCs at the first 1-year maintenance BCG treatment. Upon dividing the patients into 3 groups according to the EORTC Recurrence score and Progression score classifications, the mean NLR1 values differed significantly only in the high-score group per the EORTC recurrence score classification (p=0.023; Table 2).

According to repeated-measures ANOVA, NLR1 differed significantly from NLR2 and NLR3 on induction BCG treatment (p=0.002; Table 3).

Among patients with high-risk NMIBC, the threshold NLR1 values for non-recurrence after 1 year of BCG treatment were 1.88 with a score of 1-4, 2.47 for a score of 5-9, and 2.75 for a score of 10-17, according to the EORTC Recurrence score classification.

Discussion

The prediction of recurrence and progression is critical in cases of NMIBC. Patients with NMIBC are divided into risk groups according to prognostic factors, which allows for appropriate treatment to be administered. The EORTC risk table lists probabilities of recurrence and importantly, risk of progression. The risk scoring model was created by CUETO for patients treated with BCG. Although the EORTC and CUETO risk classifications are currently used to predict recurrence and progression, effort to find novel parameters has been ongoing. NLR is an indicator of systemic inflammation. Neutrophils and lymphocytes have immunomodulatory activities. Several studies investigating the prognostic role of NLR in many solid tumors have yielded significant results. Paramanathan et al. (13) found that high NLR values in solid tumors were associated with poorer overall survival rates and cancer-specific survival rates and noted that NLR was preferred for its easy availability and easy evaluation.

Studies have reported a positive correlation between the NLR and recurrence and progression in patients with NMIBC

Table 3. Change in NLR value after 1-year BCG treatment

	NLR1	NLR2	NLR3	p
Neutrophil-lymphocyte ratio	2.31±1.03	2.24±1.17	2.13±1.10	0.002

NLR: Neutrophil-lymphocyte ratio, BCG: Bacillus Calmette-Guerin

Table 2. NLR1 value according to EORTC progression and recurrence risk score classification

	EORTC Recurrence score classification			p	EORTC Progression score classification			p
	1-4	5-9	10-14		2-6	7-13	14-23	
NLR1	1.88±0.54	2.47±1.05	2.75±1.43	0.023	1.78±0.64	2.18±0.85	2.63±1.26	0.087

NLR: Neutrophil-lymphocyte ratio, EORTC: European organization for research and treatment of cancer

(11,14-19). Furthermore, association between NLR and tumor aggressiveness has also been reported (14,20-22). The threshold values for prediction of non-progression and non-recurrence vary in the literature. In the study by Mano et al. (14) that included 122 patients with newly diagnosed NMIBC, the threshold NLR value was 2.41; they reported that T1 tumor incidence was higher and 3-year progression-free survival was lower in the NLR >2.41 group, which was associated with the EORTC high-risk group. Racioppi et al. (15) in their study of 100 patients considered the NLR threshold as 3; they reported that the incidence of CIS, tumors of diameter >3 cm, and multiple tumors was significantly higher in the NLR >3 patient group. Yuk et al. (16) included 385 patients with NMIBC who received BCG treatment; they reported that NLR \geq 1.5 was associated with poor prognosis, with regard to overall survival and cancer-specific survival. Favilla et al. (17) conducted a prospective study including 178 patients to evaluate the role of NLR as a biomarker of NMIBC; they found that a higher NLR (NLR threshold \geq 3) predicted disease recurrence in patients with NMIBC but did not predict disease progression. In their retrospective study, D'Andrea et al. (18) included 918 patients under BCG treatment and considered an NLR threshold of 3; they reported that NLR \geq 3 was significantly associated with recurrence-free and progression-free survival. Çelen et al. (19) reported high recurrence rates with NLR >2.5. Aydın et al. (20) reported that NLR >2.41 was associated with higher incidence of T1 tumor, G3 tumor, tumor diameter >3 cm, and multiple tumors and that the high-risk group (according to EORTC risk classification) had higher NLR values. Varying NLR thresholds have been considered in various studies, and a consensus in this regard is lacking. Most studies grouped patients on the basis of occurrence or non-occurrence of recurrence and progression. Although an agreed-upon NLR threshold, such as the international normalized ratio is required, recurrence and progression of BC are affected by several factors, which make arriving at a common NLR value challenging. An increase in NLR is reportedly associated with tumor aggressiveness and prognosis. We did not compare patients with and without recurrence and progression; hence, we could not suggest a threshold NLR. However, our study evaluated recurrence and progression after 1-year of BCG treatment. Racioppi et al. (15) reported a linear relationship between the NLR value and EORTC Recurrence Risk score and EORTC Progression score. Similarly, Aydın et al. (20) observed that recurrence and progression scores increased significantly as the NLR value increased. Consistent with the published findings, NLR values increased as the EORTC Recurrence and Progression scores increased in our study, with the correlation achieving statistical significance only with the EORTC Recurrence score. We recommend using the following NLR1 values to predict non-recurrence after 1 year of BCG treatment among patients with high-risk NMIBC: 1.88 for those with a score of 1-4, 2.47 for

those with a score of 5-9, and 2.75 for those with a score of 10-17, according to the EORTC recurrence score classification. Aydın et al. (20) recommended these values to be 1.9, 2.16, and 3.8, respectively. Getzler et al. (8) reported NLR >2.5 as an important marker of disease recurrence, particularly in NMIBC patients treated with BCG. Similarly to our study, the study by Favilla et al. (17) indicated NLR predicted disease recurrence but not progression; however, they used the NLR threshold of \geq 3.

Getzler et al. (8) reported that the efficacy of BCG was higher among patients with low NLR. Contrasting with the results of this study, our study indicates that NLR could be used to predict non-recurrence and non-progression at 1-year follow-up. In our study, NLR1, NLR2, and NLR3 measurements under BCG treatment showed significant differences, making NLR for an effective marker for prognosis and BCG response.

Study Limitations

This study has some limitations. The follow-up period was limited to 1 year, which may lead to selection bias owing to the retrospective design. We only included patients without progression and recurrence. This study aimed to establish the difference in NLR1 threshold according to EORTC progression and recurrence risk classification in patients with NMIBC after 1 year of BCG treatment who did not develop recurrence or progression. However, the NLR1 threshold may differ in patient groups without progression and recurrence at 3- and 5-year follow-ups. Furthermore, the magnitude of decrease in NLR values may predict non-recurrence and non-progression. Further well-designed prospective studies with longer follow-up periods (5 years) are required to validate these results.

Conclusion

The NLR value and the decrease in NLR at follow-up evaluations can be used as markers of prognosis in patients with NMIBC. NLR is an easily calculated, low-cost prognostic marker, and the thresholds could be determined basis the NMIBC risk classifications. Large prospective studies with longer follow-up periods are required to determine the normalized NLR thresholds.

Ethics

Ethics Committee Approval: This study complied with the Helsinki Declaration and was conducted with the approval of the local ethics committee (Hitit University Faculty of Medicine Ethics Committee; decision no: 87).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the author.

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