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The Relationship Between Changes in the Neutrophil-Lymphocyte Ratio (NLR) and Radiological Progression in Cervical Cancer

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ABSTRACT

Introduction: Peripheral counts of neutrophils and lymphocytes and their changes have been associated with disease prognosis in various malignancies. While several studies have investigated the changes and clinical implications of the peripheral blood neutrophil to lymphocyte ratio (NLR) in cervical cancer, the prognostic value of NLR, in locally advanced cervical cancer remains unclear.

Methods: A retrospective analysis of cervical cancer patients who received definitive chemoradiotherapy (CRT) was carried out. NLR values were identified pre-CRT and post-CRT, and changes in these values were calculated. We assessed the relationship between changes in the NLR and clinicopathological features and disease prognosis.

Results: A total of eighty-five patients with locally advanced cervical cancer who received CRT were analyzed in this study. The rate of decrease in NLR in patients with progression was 22.2%, while in patients without progression was 17.2%. The rate of increase in NLR in patients with progression was 77.8%, while in patients without progression it was 82.8%. Higher or lower NLR levels were not found to have a significant relationship with disease progression (p=0.584).

Conclusion: The impact of changes in NLR on the prognosis of cervical cancer patients needs further validation in multicenter studies.

Keywords: Cervical cancer, definitive chemoradiotherapy, neutrophil-to-lymphocyte ratio, prognosis

Introduction

Cervical cancer has the highest mortality rate among gynecological diseases and is one of the most common tumors affecting women globally. Cervical cancer is still a leading cause of death among women, despite modern treatments, mainly due to late diagnosis or insufficient early screening (1). For individuals with locally advanced cervical cancer, the standard treatment is concurrent chemoradiotherapy (CRT) using cisplatin. It is essential to predict the prognosis of patients to improve the standards of care and apply more intensive therapies.

In recent years, changes in peripheral blood indicators, such as variations in neutrophil and lymphocyte numbers, have been linked to tumorigenesis and disease prognosis (2). Although a change in the neutrophil-to-lymphocyte ratio (NLR) is strongly associated with the patient's prognosis, its prognostic significance in locally advanced cervical cancer is yet unknown.

Chemotherapy and radiotherapy (RT) may stimulate tumor-specific cellular immune responses and affect immune suppression in the tumor microenvironment (3). Most clinical investigations have studied the baseline neutrophil and lymphocyte counts as prognostic indicators of treatment outcomes (4,5). Since the immune system is in a dynamic state that can be altered by chemotherapy and radiation, employing dynamic alterations of NLR rather than a single time-point NLR may provide more information.

Research has demonstrated that survival outcomes in different solid tumors are correlated with increasing pre-treatment NLR, post-treatment NLR, and the change in NLR. However, according to some research, pre-treatment NLR has no relationship to prognosis, whereas post-treatment NLR predicts progression-free survival (PFS) (6,7). In this context, the prognostic relevance of the changes in NLR requires additional examination.

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The majority of research on prognostic hematologic markers in cervical cancer has highlighted the critical role of pretreatment NLR, underscoring its significance in patient outcomes. The impact of CRT on hematological parameters during treatment in patients with cervical cancer has not yet been established.

We conducted this study to assess whether the dynamic changes in NLR could serve as a prognostic indicator for patients with locally advanced cervical cancer undergoing definitive CRT. By identifying this relationship, we aim to improve clinical outcomes and provide valuable insights for developing effective treatment strategies.

Methods

Eighty-five patients with locally advanced cervical cancer who had definitive CRT between 2016 and 2023 were included in a retrospective, single-center analysis. The clinical staging criteria of the International Federation of Gynecology and Obstetrics (FIGO) were used to categorize the patients.

This study included patients aged 18 and above who had been diagnosed with cervical cancer through histopathological analysis and had undergone treatment with both RT and chemotherapy. Additionally, patients who had distant metastases, those diagnosed with another tumor within the last three months, or those whose clinical or laboratory data were unavailable, were not included in the study.

In this group, patients received weekly doses of cisplatin along with an efficient pelvic chemoradiation treatment regimen that delivered a total dose of 50 Gy in 25 fractions over 5 weeks. Some patients received brachytherapy.

Clinical and pathological features, comorbidities, and laboratory data were collected from the hospital's information system. Comprehensive blood cell counts, along with differential counts, were conducted at baseline before treatment and again 5 to 6 weeks after the conclusion of CRT. By allowing time between the conclusion of treatment and blood test extraction, we significantly reduce the risk of myelotoxicity, primarily associated with chemotherapy. The ratio of absolute neutrophil to absolute lymphocyte counts in the blood sample was used to compute the NLR before and after therapy. The NLR change percentage was determined as 10% according to ROC analysis. Increased NLR was defined as a ^{3}10% elevation, and decreased NLR was defined as a ^{3}10% reduction.

The final follow-up occurred in October 2024. For the first two years following therapy, all patients were assessed every three months; after that, they were reviewed every six months. The follow-up examination included, among other things, a blood test, pelvic magnetic resonance imaging, chest radiography, and a gynecological physical examination. When cancer returns to the primary tumor site or to the regional lymph nodes in the pelvic or para-aortic regions, it is referred to as locoregional recurrence. A disease recurrence outside the pelvic or para-aortic areas that is verified by pathological or radiological evidence is referred to as distant metastasis. Disease-free survival (DFS) measures the time from a patient's definitive diagnosis to the recurrence or metastasis of the disease.

The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2024-05-17, date: 18.03.2024). Because the study was carried out retrospectively and participant confidentiality was guaranteed, informed consent was not required.

Statistical Analysis

The descriptive statistics of the data include mean, standard deviation, median, minimum, maximum, frequency, and ratio values. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the distribution of variables. The independent sample t-test was used to analyze quantitative independent data with a normal distribution. The Mann-Whitney U test was utilized to analyze independent quantitative data with a non-normal distribution. The chi-square test was employed to analyze independent qualitative data. Kaplan-Meier was used in the survival analysis. The SPSS 28.0 program was used in the analyses.

Results

Following a thorough screening, 85 patients were included in this study, with ages ranging from 33 to 77 years. The average patient age was 53.3±11.4 years. The median follow-up period was 37.1 months. According to the FIGO Criteria for cervical cancer, five patients were identified as having clinical stage I, 35 as clinical stage II, and 45 as clinical stage III. Eastern Cooperative Oncology Group, performance score (ECOG) was 0 in 68 patients and 1 in 17 patients. In terms of pathological types, there were 78 patients diagnosed with squamous carcinoma and seven patients diagnosed with adenocarcinoma. The tumor size ranged from 2 to 11 cm, with a median of 4.6 cm. There were 24 and 64 patients with and without involvement of parametrial tissue, respectively. Lymph node metastasis was detected in 37 patients. 82.4% of patients received pelvic RT, and 17.6% received pelvic and paraaortic RT. Additionally, brachytherapy was performed in 85.9% of the patients. All patients received concurrent chemotherapy. Cisplatin was the only chemotherapeutic agent used during RT. 89.4% of the patients received 40 mg/m^2 cisplatin, while 10.6% received 25 mg/m^2 (Table 1).

The mean pretreatment NLR was 3.4±2.5, while the mean posttreatment NLR was 6.3±5.6. There was an increase in NLR in 81.2% of patients and a decrease in NLR in 18.8% (Table 1). The median DFS was 54.1 months.

There was local/locoregional or distant metastasis in 27 patients (31.8%). We classified the patients into two groups according to their progression status. The patients' ages did not differ significantly (p=0.035) between the groups with and without progression. ECOG score, histology, tumor size, parametrium involvement, lymph node metastasis, and FIGO stage did not differ significantly (p=0.351, p=0.132, p=1.00, p=0.175, p=0.127, respectively) between the groups with and without progression. There was no statistical difference in these groups in terms of RT area, whether they received brachytherapy, or platinum doses (p=0.886, p=0.900, p=0.516). The median follow-up was similar (p=0.278) (Table 2).

We analyzed the impact of pretreatment, and post-treatment NLR levels and their change on progression. The pretreatment NLR was 3.8±3.4 in patients with progression and 3.2±1.9 in those without progression.

There was no statistically significant difference (p=0.543). Post-treatment NLR was 6.5±4.5 in the patients with progression and 6.3±6.1 in those without progression. There was no statistically significant difference (p=0.637). The rate of decrease in NLR in patients with progression was 22.2%, while in patients without progression it was 17.2%. There was no statistically significant difference between them. The rate of increase in NLR in patients with progression was 77.8%, while in patients without progression it was 82.8%. There was no statistical significance between them (p=0.584) (Table 2).

DFS was 49.9 months in patients with decreased NLR and 54.8 months in those with increased NLR. No statistically significant difference was found between the two groups (p=0.510) (Figure 1).

Discussion

In addition to its role in tumoral surveillance, the immune system plays a crucial part in cancer development, as it can create an inflammatory environment and facilitate tumor proliferation (8). Since inflammation linked to cancer is one of its distinguishing features, comprehending the host's immunological and inflammatory states is crucial, as inflammation is essential for the development and progression of tumors (9). Extensive research has demonstrated that inflammatory responses are fundamental to the processes of cancer development, invasion, metastasis, and tumorigenesis across various cancer types (10).

These characteristics can be assessed using cost-effective and easily repeatable indicators from peripheral blood samples. The NLR is one of the most extensively researched inflammation-based indices. Tumor growth is thought to be significantly influenced by neutrophils and lymphocytes. While lymphocytes serve as the primary antitumor cells, neutrophils produce pro-inflammatory mediators that suppress other immune cells' cytolytic function and facilitate cancer onset and advancement (11).

Peripheral blood NLR has emerged as a research focus in recent years due to its superior prognostic and predictive value in various tumors, including renal cell carcinoma (12), intrahepatic cholangiocarcinoma (13), esophageal cancer (14), and colorectal cancer (15).

Numerous studies exclusively examined the pretreatment values of inflammatory markers.

One study indicated that increased pretreatment NLR levels were substantially correlated with worse survival (16). On the other hand, DFS and overall survival (OS) did not significantly differ between patients

Table 1. Patient characteristics

		Min.-Max.			Median	Mean ± SD/n=%		
Age (years)		33.3	-	77.3	52.0	53.3	±	11.4
ECOG-PS	0					68		80.0%
	I					17		20.0%
Histology	SCC					78		91.8%
	Adenocarcinoma					7		8.2%
Tumor size (cm)		2.0	-	11.0	4.6	4.6	±	1.4
Parametrium involvement	(-)					24		28.2%
	(+)					61		71.8%
Lymph node metastasis	(-)					48		56.5%
	(+)					37		43.5%
FIGO stage	I					5		5.9%
	II					35		41.2%
	III					45		52.9%
RT field	Pelvic Pelvic + paraaortic					70 15		82.4% 17.6%
Brachytherapy	(-) (+)					12 73		14.1% 85.9%
CRT platine dose	25 mg/m^2 40 mg/m^2					9 76		10.6% 89.4%
Progresyon	(-) (+)					58 27		68.2% 31.8%
NLR								
Pretreatment		1.1	-	18.5	2.8	3.4	±	2.5
Posttreatment		0.7	-	43.0	4.7	6.3	±	5.6
Decresed NLR Incresed NLR						16 69		18.8% 81.2%

ECOG-PS: Eastern Cooperative Oncology Group, performance score, NLR: Neutrophil-lymphocyte ratio, CRT: Chemoradiotherapy, RT: Radiotherapy, FIGO: International Federation of Gynecology and Obstetric, Min.: Minimum, Max.: Maximum, SD: Standard deviation, SCC: Squamous cell carcinoma

with high and low NLR, in another trial (17). This finding underscores the complexity of patient outcomes and highlights the need to understand these factors more thoroughly. We also found no significant relationship between patients' pretreatment or post-treatment NLR and survival outcomes. One reason for the difference in these findings may be the variety of the NLR cutoff value.

Many studies have explored the dynamic changes in various markers that could reveal the delicate balance between the host's immune response and inflammation. The clinical and cutoff values of the change in NLR in relation to cervical cancer are still a topic of controversy, even though a limited number of studies have reported on its clinical prognostic value. In one trial, it was observed that a change in NLR, particularly after the third week of treatment, may be indicative of the treatment outcomes, of definitive CRT for cervical cancer patients (18).

Trinh et al. (19) revealed an association between elevated NLR levels post-treatment and significantly poorer outcomes in both PFS and OS. This finding highlights the importance of monitoring NLR as a potential prognostic marker for patients. While LMR pre- and post-treatment were positively correlated with PFS, an increase in LMR during CRT was negatively correlated with PFS and OS. In various studies, it has been demonstrated that patients with cervical cancer who present a high preoperative NLR face markedly poorer OS and PFS compared to their counterparts. This highlights the critical importance of monitoring NLR levels in preoperative assessments to better predict patient outcomes and tailor treatment strategies effectively. However, no prognostic difference was noted between the groups with elevated and reduced NLR (20). In our study, we found no clinical difference between patients with increased and decreased NLR in terms of prognosis. This outcome is expected, as NLR is a dynamic indicator that is susceptible to the host's condition, and inflammation, the administered treatment, and the resultant response. In addition, the small sample size may have influenced these results. In this context, we believe blood biomarkers, including NLR, need a prospective investigation in randomized clinical trials.

Table 2. The relationship between clinical parameters and NLR change with progression

		Progression (-) (n=58)				Progression (+) (n=27)				p	
		Mean ± SD/n-%			Median	Mean ± SD/n-%			Median		
Age (years)		51.6	±	11.7	48.8	56.7	±	9.8	57.3	0.035	m
ECOG-PS	0	48		82.8%		20		74.1%	68	0.351	X^2
	I	10		17.2%		7		25.9%	17		
Histology	SCC	55		94.8%		23		85.2%	78	0.132	X^2
	Adenocarcinoma	3		5.2%		4		14.8%	7		
Tumor size (cm)		4.7	±	1.5	4.6	4.6	±	1.2	4.5	1.000	m
Parametrium involvement	(-)	19		32.8%		5		18.5%	24	0.175	X^2
	(+)	39		67.2%		22		81.5%	61		
Lymph node metastasis	(-)	36		62.1%		12		44.4%	48	0.127	X^2
	(+)	22		37.9%		15		55.6%	37		
FIGO stage	IB	3		5.2%		2		7.4%	5	0.426	X^2
	IIB	26		45.0%		9		33.3%	23		
	IVA	29		50.0%		16		59.2%	30		
RT field											
Pelvic		48		82.8%		22		81.5%	70	0.886	X^2
Pelvic + paraaortic		10		17.2%		5		18.5%	15		
Brachytherapy	(-)	8		13.8%		4		14.8%	12	0.900	X^2
	(+)	50		86.2%		23		85.2%	73		
CRT platine dose (mg/m^2)	25 40	7 51		12.1% 87.9%		2 25		7.4% 92.6%	9 76	0.516	X^2
NLR											
Pretreatment		3.2	±	1.9	2.7	3.8	±	3.4	3.1	0.543	m
Posttreatment		6.3	±	6.1	4.3	6.5	±	4.5	5.2	0.637	m
Decresed NLR		10		17.2%		6		22.2%	16	0.584	X^2
Incresed NLR		48		82.8%		21		77.8%	69		

ECOG-PS: Eastern Cooperative Oncology Group, performance score, NLR: Neutrophil-lymphocyte ratio, CRT: Chemoradiotherapy, RT: Radiotherapy, FIGO: International Federation of Gynecology and Obstetric, SD: Standard deviation, SCC: Squamous cell carcinoma

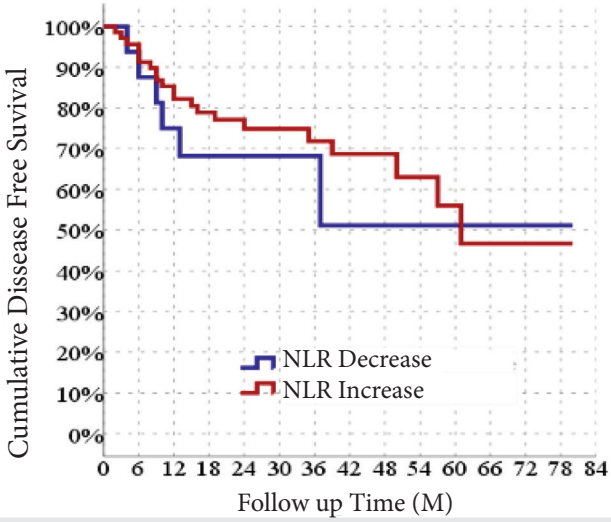

Figure 1. The relationship between NLR change with disease free survival
NLR: Neutrophil-lymphocyte ratio

Study Limitations

First, this study is a retrospective investigation of a single institution, which is one of its limitations. Second, NLR may be affected by potential confounding variables. Third, our study's small sample size and demographic differences can limit how broadly our results can be applied; therefore further confirmation through a multicenter, extensive investigation is required.

Conclusion

We did not observe a change in NLR values in the prognosis of patients treated with CRT. Enhancing comprehension of prognostic biomarkers like NLR, and the molecular mechanisms influencing their changes in cervical cancer patients receiving CRT may offer further clinical value to treatment decisions. However, it is crucial to understand their time dependency with regard to definitive therapy, as we continue to explore the usefulness of these markers.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2024-05-17, date: 18.03.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions: Concept - E.D., M.Y.; Design - E.U.; Data Collection or Processing - R.Ç., İ.G., C.K.; Analysis or Interpretation - R.Ç., C.K.; Literature Search - R.Ç., E.D., S.Y.T.; Writing - R.Ç., İ.G.

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

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