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Chronic Inflammation Parameters and Treatment Duration: Implications for Cervical Cancer Survival

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Abstract: Cervical cancer remains a major global health problem requiring precise prognostic markers to improve patient outcomes. This retrospective study investigates the complex relationship between chronic inflammation parameters, treatment duration and survival outcomes in cervical cancer. While traditional markers like C-reactive protein, lactate dehydrogenase, albumin, Platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, lymphocyte-monocyte ratio, CRP-albumin ratio didn't directly impact Disease-Free Survival (DFS) and Overall Survival (OS), an intriguing association emerged with treatment duration. Elevated Neutrophil-to-Lymphocyte Ratio (NLR) correlated with prolonged treatment, revealing a critical threshold of 65 days. Treatment durations ≥65 days led to a significant 2.62-fold (p=0.041) decrease in DFS and 3.74-fold (p=0.04) decrease in OS. These findings underscore the critical need for a comprehensive approach, integrating inflammation markers and treatment duration, to optimize personalized interventions in cervical cancer, potentially reshaping future therapeutic strategies for improved patient outcomes.

Keywords: *Cervical cancer, concurrent chemoradiotherapy, haemato-immunological indicators, total treatment duration*

I. INTRODUCTION

Cervical cancer is the 4th most common cancer among female cancers. Also, it is the 4th most common cause of cancer deaths. Each year, 604,000 new cases and 342,000 deaths are reported worldwide [1]. Surgery alone may be sufficient in early stages (IA-IB2), but the current standard treatment of locally advanced cervical cancer is concurrent chemotherapy and radiotherapy (CCRT) [2,3]. Despite cervical cytological screening for early diagnosis and vaccination against causative viruses for primary prevention, 40-50% of patients are still diagnosed in advanced stages [4] and this is an important health problem especially for underdeveloped or developing countries.

Many prognostic parameters such as tumour size, histological type and grade of the tumour, presence of lyphovascular invasion, lymph node metastasis have been revealed in cervical cancer. However, most of these data are obtained in the postoperative period and are insufficient to predict the results of a radical treatment. Therefore, indicators that can manage before and after treatment are needed. To meet this need, studies have been conducted to examine how patient haematological data, nutritional status and tumour microenvironment govern the initiation, progression, and metastasis of cancer. Chronic inflammation plays an important role in this process [5,6]. Studies have shown that cancer patients with high inflammation-related indicators have worse treatment outcomes and prognosis than those without [7,8]. These indicators are an important topic of current cancer research. Potential prognostic markers such as C-reactive protein (CRP), lactate dehydrogenase (LDH)

level, albumin level, Platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), CRP-albumin ratio (CAR) were studied.

An important treatment-related parameter affecting prognosis in cervical cancer is the total duration of treatment. A total treatment duration of more than 56 days has a negative effect on survival [9-13]. In addition, there is a 1% loss of local control for every 1 day prolonged between 7 and 8 weeks [14,15].

In this study, the relationship between chronic inflammation parameters at the beginning of treatment and the total duration of treatment was analysed and the effect of the results on disease-free (DFS) and overall survival (OS) was reviewed.

II. MATERIALS AND METHODS

This study was conducted as a retrospective investigation of cervical cancer patients that had been referred to Umraniye Training and Research Hospital (Istanbul, Türkiye) between December 2016 and December 2022. Approval for the study was granted by the Medical Ethics Comity of Umraniye Training and Research Hospital.

1.Patients

The study included 65 patients who received postoperative and radical radiotherapy (±chemotherapy) for cervical cancer. Those who had an infection within 2 weeks before radiotherapy, haematological disease, chronic infectious disease or autoimmune disease, organ dysfunction or another concomitant cancer diagnosis were not included in the study. Patients with recurrent disease at presentation, metastatic patients, patients with missing clinical and follow-up data were excluded. Pathological and treatment information were obtained from the archive files of the patients. Staging was performed according to FIGO 2018 [16]. Magnetic resonance imaging (MRI) and A fluorodeoxyglucose-positron emission tomography (PET/CT) were used for staging of all patients.

2.Treatment

2.1. Radiotherapy (RT): The initial external RT field includes the primary tumour and pelvic lymph nodes and, if indicated, paraaortic lymph nodes. For external treatment, 3-D conformal, intensity modulated RT (IMRT) or volumetric modulated arc therapy (VMAT) techniques were used. Standard treatment was 45-50.4 Gy in 25-28 fractions with fraction doses of 1.8-2 Gy. In the presence of involved lymph node, an additional dose (boost) equivalent to 60 Gy was given. According to the response to external treatment, external or intracavitary boost (or both) was applied to the primary disease. Iridium 192 high-dose-rate afterloading device was used for intracavitary RT (ICRT).

Radiotherapy interval was calculated as the sum of the first and the last day of the patient's break. If more than one break was taken, their cumulative duration was taken into consideration. Weekends corresponding to the break period were included; weekends in standard fractionation were not considered as treatment breaks.

Total treatment time was calculated as the time from the start of external RT to the end of ICRT.

2.2. Chemotherapy (CT): Cisplatin 40 mg/m2 weekly for at least 3 weeks.

3. Laboratory data:

Laboratory data were obtained from the electronic records of the patients. Platelet, CRP, LDH, albumin, neutrophil, lymphocyte, and monocyte absolute values within 1 week before radiotherapy were used in the evaluation.

4. Evaluation and Follow-up

Patients were followed up every 3 months for the first 2 years, every 6 months for 2-5 years and then annually. Recurrence and distant metastasis were evaluated by MRI and PET/CT. The last follow-up is September 2023. Disease-free survival (DFS) is defined as the time from the date of diagnosis to the last follow-up or the occurrence of relapse or death, and overall survival (OS) is defined as the time from the date of diagnosis to the last follow-up or death.

5. Statistics

SPSS (Statistical Package for the Social Sciences) version 26 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. Whether the scores obtained from each continuous variable were normally distributed was analysed by descriptive, graphical, and statistical methods. Shapiro-Wilk test was used to test the normality of the scores obtained from a continuous variable by statistical method. Categorical variables are presented as frequency (n, %), continuous variables as mean±standard deviation, median and inter quartile range (P_{25}-P_{75}). The level of relationship between two continuous variables was analysed by Pearson correlation test. Survival calculations were performed by Kaplan-Meier analysis method. The effects of various prognostic factors related to tumour and patient characteristics on progression-free and overall survival were investigated by Cox regression analysis. The results were evaluated within 95% confidence interval and significance was evaluated under $p<0.05$.

III. RESULTS

The median age of the patients included in the study was 49 years (24-85). Squamous histology constituted the major group (87.7%). Surgery was performed in 15 patients. Thirty-eight point five per cent of the patients were in Stage IIIC1. One patient could not receive concurrent chemotherapy because of high creatinine values and 2 patients could not receive concurrent chemotherapy because of their advanced age. The other 4 patients who did not receive chemotherapy underwent surgery and there was no indication in terms of stage.

Paraaortic irradiation was performed in 11 patients. External RT doses were 46 Gy (45-50.4 Gy) in 23-28 fractions. External boost was applied in 28 (25-39) fractions with a mean of 53.99 Gy (50.4-70.2 Gy). External boost was given to the primary tumour, parametrium and involved lymph nodes. ICRT was 24.8 Gy (11.5-30 Gy) in 2-5 fractions.

The mean total treatment duration was 69.60 (35-135) days. During RT, 46 patients had to break treatment. The mean inter-treatment interval given was 11.46 (2-53 days). The most common reason for discontinuation was development of acute cystitis (31%). The need for an adaptive plan due to weight loss and tumour regression was second (26%). These were followed by diarrhoea, nausea, and neutropenia. One patient had interrupted treatment for 14 days due to Covid infection.

LDH, NLR, LMR, PLR and CAR were evaluated as chronic inflammation parameters. None of these parameters had a statistically significant relationship with DFS and OS. However, as the NLR increased, the total treatment duration increased statistically significantly ($p<0.01$). The cut-off value for the number of days in which total treatment duration was effective on survival was found to be 65 days. A 2.62-fold ($p=0.041$) and 3.74-fold ($p=0.04$) worsening in DFS and OS, respectively, was found when the total treatment duration was ≥65 days. This was statistically significant.

Table 1. Means, Standard Deviations, and Correlations

No.	Variables	Mean(SD)	1	2	3	4	5
1	TTD, day	69.60(20.35)	N/A				
2	NLR	4.06(3.12)	**0.333****				
3	LMR	4.19(2.06)	-0.169	**-0.554****			
4	PLR	0.24(0.24)	0.213	**0.560****	-0.228		
5	CAR	0.82(1.74)	0.110	**0.574****	**-0.250***	**0.379****	
6	LDH	209.42(60.94)	-0.056	-0.051	-0.015	-0.082	-0.023

**p<0.01, *p<0.05, Pearson correlation test, SD=Standard deviation, N/A: Not available
TTD: total treatment duration

Table 2. Survival correlations

	Disease-free survival				Overall survival			
Variables	**HR(95% CI)**			**P-value**	**HR(95% CI)**			**P-value**
TTD(≥65-day vs <65-day**)	2.62	1.04	6.60	**0.041***	3.74	1.06	13.12	**0.040***
NLR	1.05	0.93	1.19	0.418	1.08	0.96	1.20	0.193
LMR	1.20	0.99	1.46	0.071	1.18	0.92	1.52	0.189
PLR	0.72	0.10	4.96	0.738	1.01	0.16	6.46	0.989
CAR	1.08	0.84	1.38	0.538	1.16	0.95	1.40	0.143
LDH	1.00	0.99	1.01	0.831	1.00	0.99	1.01	0.374

*p<0.05; Univariate Cox Regression Analysis, HR: Hazard Ratio, CI: Confidence Interval, **1, Reference value
TTD: total treatment duration

Figure 1. DFS according to total treatment duration

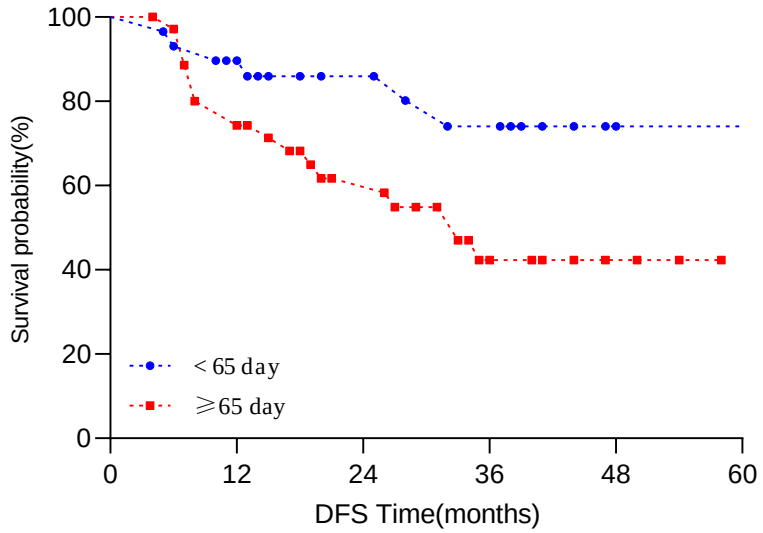
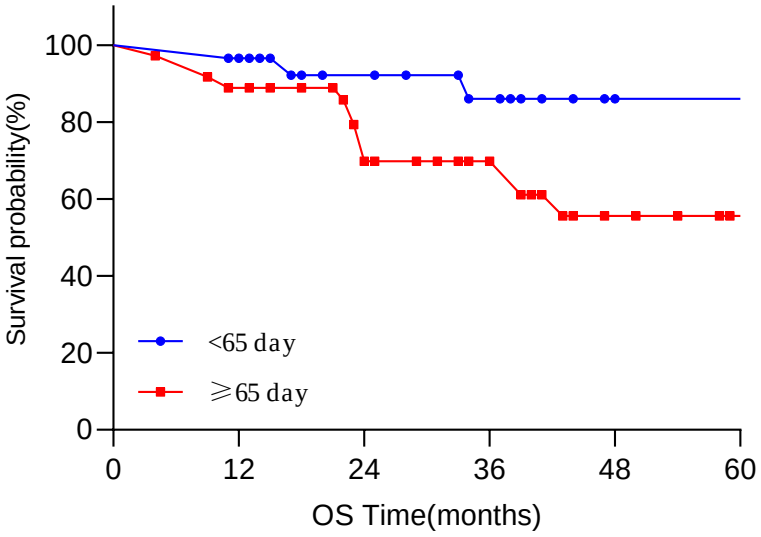


Figure 2. OS according to total treatment duration



IV. DISCUSSION

Cervical cancer remains a significant global health concern, necessitating a constant search for prognostic markers to enhance the management and outcomes of affected patients. Some immune response indicators obtained from routine blood tests have been widely studied in terms of indicating the course of the disease in terms of being easily accessible in daily practice and being cost-effective. Systemic immune response is widely involved in the initiation and progression of solid tumours, including cervical cancer, including malignant proliferation, survival, invasion, angiogenesis, and metastasis [17,18]. CRP and albumin which are proteins synthesised in the liver as acute phase reactants, neutrophils which constitute acute immune response, lymphocytes which are immune response mediators and responsible for antibody production, LDH which is a general indicator of acute or chronic tissue damage are the elements of the systemic immune response.

High CAR has been associated with poor prognosis and tumour progression [19]. Survival is lower in patients with high CRP and LDH values before treatment [20]. In a study by Kumar et al. analysing the data of 1000 patients receiving radical chemoradiotherapy, platelet-to-lymphocyte ratio (PLR) was found to be a determinant indicator for both DFS and OS [21].

In a meta-analysis investigating haemato-immunological indicators in cervical cancer, the relationship between neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), thrombocyte-to-lymphocyte ratio (TLR), C-reactive protein/albumin ratio (CAR) and prognosis was examined in the light of data obtained from approximately 10000 patients. All these parameters were found to be associated with prognosis. High NLR is most significant [22]. There are other studies suggesting that high NLR is an indicator of poor prognosis [23].

The relationship between prolongation of the total treatment time in cervical cancer treatment and tumour progression and its negative effect on treatment outcomes has been known for many years, and the optimal treatment duration not exceeding 8 weeks has been included in current guidelines [24]. However, this classic 56-day information is a legacy of the years before concurrent chemotherapy was added to radiotherapy. Studies have reported that only 58% of patients were able to complete treatment within this period [25]. Song et al. reported that exceeding this period decreased pelvic control but made no difference

in distant failure (DF) or disease-specific mortality (DSM) in patients undergoing concurrent chemoradiotherapy [26].

In our study, 65 days was found to be the cut-off value in relation with total treatment duration and DFS and OS. In addition, it was determined that patients with high NLR values before treatment completed the treatment in 65 days or more. Therefore, these results were also reflected in survival. Nevertheless, other immune markers may not have been significant in our study due to the small number of patients.

V. CONCLUSION

In conclusion, our study sheds light on the intricate relationship between inflammation, treatment duration, and survival outcomes in cervical cancer. While traditional inflammation markers did not directly correlate with DFS and OS, the impact of prolonged treatment duration on patient outcomes, especially in the context of elevated NLR, underscores the need for further research. By embracing a multidimensional approach and exploring emerging biomarkers and therapeutic targets, the medical community can pave the way for more effective, personalized, and timely interventions, ultimately improving the lives of cervical cancer patients.

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