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Lymphopenia and its association with survival in patients with locally advanced cervical cancer

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Abstract

Objective—To evaluate the association between lymphopenia and survival in women with cervical cancer treated with primary chemoradiation.

Methods—A single institution, retrospective analysis of patients with stage IB2-IVA cervical cancer who received upfront chemoradiation from 1998 to 2013 was performed. Complete blood counts from pre-treatment to 36 months post-treatment were analyzed. Lymphopenia and known prognostic factors were evaluated for an association with progression-free (PFS) and overall survival (OS).

Results—Seventy-one patients met study criteria for whom 47 (66%) had a documented total lymphocyte count (TLC) two months after initiating chemoradiation. FIGO stage distribution was 6% Stage I, 46% Stage II, 45% Stage III and 3% Stage IV. Pre-treatment TLC was abnormal (<1000 cells/mm³) in 15% of patients. The mean reduction in TLC was 70% two months after initiating chemoradiation. Severe post-treatment lymphopenia (TLC <500 cells/mm³) was observed in 53% of patients; they experienced inferior median OS (21.2 vs 45.0 months, $P = 0.03$) and similar 25th percentile PFS (6.3 vs 7.7 months, $P = 0.06$) compared to patients without severe lymphopenia. Multivariate analysis demonstrated pre-treatment TLC >1000 cells/mm³ and post-treatment TLC >500 cells/mm³ had a 77% (HR: 0.23; 95% CI 0.05–1.03; $P = 0.053$) and 58% decrease in hazards of death (HR: 0.42; 95% CI 0.12–1.46; $P = 0.17$) respectively.

Conclusion—More than half of cervical cancer patients treated with chemoradiation experienced severe and prolonged lymphopenia. Although statistical significance was not reached,

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Conflict of interest statement

The authors have no conflicts of interest to report.

the findings suggest that pre- and post-treatment lymphopenia may be associated with decreased survival. Further research is warranted, given that lymphopenia could be a reversible prognostic factor.

Keywords

Lymphopenia; Cervical cancer; Chemoradiation

1. Introduction

Multiple biological studies have demonstrated cancer tissue infiltration by white blood cells, particularly lymphocytes. These findings have led to hypotheses such as the cancer immunosurveillance theory, which proposes that lymphocytes act as safeguards against cancer by identifying and destroying malignant cells [1]. Observational studies have also shown that patients with infiltration of cancer tissue by inflammatory cells, particularly lymphocytic cells, have better survival compared to patients without this finding [2–5].

Severe lymphopenia prior to initiating treatment has been correlated with shorter survival in solid tumors such as breast cancer, soft-tissue sarcoma, renal cell carcinoma, colorectal cancer, lung cancer, and pancreatic ductal adenocarcinoma [6–13]. Lower pre-treatment lymphocyte count has also been shown to be associated with shorter progression-free survival in locally advanced cervical cancer [14–16].

Radiation therapy itself has historically been associated with post-treatment lymphopenia in a wide range of cancers, including in gynecologic neoplasms [17–20]. Recent studies have identified an association between post-treatment lymphopenia and decreased survival in patients with solid tumors who underwent radiation therapy, irrespective of histology, lymphotoxic chemotherapy regimens and/or corticosteroid administration [21–25]. As a result, studies are currently underway to determine whether lymphopenia in patients with high-grade gliomas can be reversed after radiation-related damage, with the hope of identifying promising new therapies.

The impact of lymphopenia on survival after radiation therapy has not been fully addressed in patients with gynecologic malignancies. This study was therefore undertaken to investigate the association between pre- and post-treatment lymphopenia and survival in women with locally advanced cervical cancer treated with primary chemoradiation.

2. Methods

2.1. Patient selection

After obtaining approval from the Institutional Review Board, women with advanced cervical cancer treated with definitive platinum-based chemoradiation from 1998 through 2013 were identified. Patients who met the following inclusion criteria were selected: 1) biopsy-confirmed cervical cancer, 2) FIGO stage IB2 to IVA, 3) initial treatment administered at our institution (concurrent platinum-based chemotherapy and external radiation therapy, with or without brachytherapy), and 4) pre-treatment TLC available in the medical record. Patients were excluded if they had a hysterectomy or trachelectomy prior to

chemoradiation. The standard practice at our institution is to administer four to six cycles of platinum chemotherapy during radiation therapy.

2.2. Data collection

Study variables, including demographic, clinicopathologic, and treatment characteristics, were collected from the electronic medical record and our institutional cancer registry. Vital status was extracted from the electronic medical record, the Social Security Death Index, and Accurant® through January 2014. Data from complete blood counts (CBC) were collected from pre-treatment through up to 36 months after initiating treatment. The most recent CBC from within three months prior to treatment was utilized. Pre-treatment lymphopenia was defined as TLC <1000 cm/mm³ based on commonly accepted reference values [26]. The total lymphocyte count two months after starting chemoradiation was used to analyze post-treatment lymphopenia. The time interval was based on studies in other solid tumors that found lymphocyte counts at two months to be a prognostic factor for survival [21–25]. If a TLC was not available at two months, the closest value within two weeks was used. The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 threshold for grade III–IV lymphopenia was used to define post-treatment lymphopenia as TLC <500 cm/mm³. The Charlson Comorbidity Index was calculated for each patient as a proxy for state of health [27,28].

2.3. Statistical analysis

Demographic, clinicopathologic, and treatment characteristics were summarized using descriptive statistics. The Wilcoxon rank-sum and Fisher exact tests were used to compare medians and the proportions between the groups respectively. The primary outcomes of interest were progression free survival (PFS) and overall survival (OS). OS was calculated from the start date of chemoradiation to the date of death and PFS was calculated from the start date of chemoradiation to the date of first radiographic progression or recurrence. Women determined to be progression or recurrence free or alive at the end of this period of observation were administratively censored. If median PFS was not attained, and therefore not measurable, we calculated the 25th percentile PFS in our analysis. Given that clinicians use the absolute change in lymphocyte counts as well as specific thresholds, TLC was evaluated as both continuous and categorical variables. When categorized, the cutoff for the pre-treatment TLC was <1000 cells/mm³ and for post-treatment TLC was <500 cells/mm³ [26].

The log-rank tests were used to compare Kaplan–Meier estimates of event rates (time to progression/recurrence and death) between the groups. All demographic and baseline clinical variables in Table 1 were evaluated as covariates. Factors included in the final multivariate stratified Cox regression model were those with a significant unadjusted association with PFS and OS ($p < 0.05$) or those known from the literature as independent prognostic factors for PFS and OS (age, race, FIGO stage, histology, tobacco use, Charlson Comorbidity Index, platelet count). The multivariate Cox model was stratified by grade. HIV status was not analyzed separately, as it was accounted for in the Charlson Comorbidity index where patients with HIV received significantly more points than other patients. However, a sensitivity analysis was performed excluding HIV positive patients.

To account for potential bias and confounding introduced by participants with missing clinicopathologic data, multiple imputation analyses were also performed. Missing-at-random (MAR) assumptions were made and the Markov Chain Monte Carlo approach (chained equations) was used to generate 10 imputed data sets based on age, race, FIGO stage, Charleston score, and the outcome variable. Data were imputed and analyzed using the STATA MI command with STATA version 12. Multivariate analysis results using multiple imputation were similar to those from the complete case series. Thus, only the results from the multivariate analysis using multiple imputation are shown. For all analyses, we used the two-sided level of 0.05 for significance and STATA version 12 (StataCorp) statistical software.

3. Results

Seventy-one patients diagnosed with cervical cancer from 1998 through 2013 met the inclusion criteria and were included in the analysis. A documented total lymphocyte count (TLC) two months after initiating chemoradiation was available for 47 of these patients. Among the patients with a pre-treatment TLC documented ($n = 71$), the median follow-up was 25 months [interquartile range (IQR), 9.2–50.7]. Table 1 shows the demographic, clinicopathologic, and treatment characteristics for the study population. The median age was 49 years (IQR 40–56). Fifty-three patients (75%) had a Charlson Comorbidity Index of 0. Four patients (6%) had stage I disease, 33 (46%) stage II disease, 32 (45%) stage III disease, and two (3%) stage IV disease. On histology, 59 patients (83%) had squamous cell carcinoma. The remaining patients had adenocarcinoma (1%), adenosquamous carcinoma (9%), or other histology (7%). Two patients (3%) had well-differentiated histology, 22 (31%) moderately differentiated histology, 19 (27%) poorly differentiated histology, and 28 (39%) unknown histology. Four patient (6%) were HIV positive.

Prior to initiating treatment, eleven of the patients (15%) had lymphopenia (based on $\text{TLC} < 1000 \text{ cells/mm}^3$ defined in methods above). The median pre-treatment TLC in our study population decreased from 1640 cells/mm^3 to 480 cells/mm^3 two months after initiating chemoradiation ($P < 0.01$). Fig. 1 shows the distributions of lymphocyte count at pre-treatment and through 12 months after initiating treatment. The lymphocyte count nadir occurred two months after initiating chemoradiation, and then slowly increased over time. However, 12 months after treatment initiation, some patients' counts had not returned to pre-treatment values. The median hematocrit was slightly higher in patients with pre-treatment TLC counts $\geq 1000 \text{ cells/mm}^3$ compared to patients with lymphocyte counts $< 1000 \text{ cells/mm}^3$ (35% vs. 32%; $P = 0.04$). Otherwise there were no significant differences between the two groups including race, stage, grade, histology, smoking status, Charlson Comorbidity Index and time from diagnosis to treatment initiation. One out of 11 patients (9%) with pre-treatment lymphopenia and three out of 60 patients (5%) without pre-treatment lymphopenia were HIV positive.

Of the 71 patients in this study, TLC two months after initiating chemoradiation (post-treatment TLC) was available for 47 patients. There was no statistically significant difference in OS and PFS when comparing patients with and without two-month post-treatment TLC measurements (data not shown). Among the 47 patients with post-treatment

TLC, those with TLC ≥ 500 cells/mm³ were slightly older than those with post-treatment TLC < 500 cells/mm³ (52 vs. 46; $P = 0.04$; data not shown). There were otherwise no significant differences between the two groups including race, stage, grade, histology, smoking status, Charlson Comorbidity Index and time from diagnosis to treatment initiation. Two out of 25 patients (8%) with post-treatment lymphopenia and one out of 22 (5%) patients without post-treatment lymphopenia were HIV positive.

3.1. Overall-survival

The median OS was 30.8 months (95% CI, 21.2–50.7) for the entire cohort. When subdivided into exposure groups, the median OS was 10.6 months (95% CI, 4.0–23.9) in patients with pre-treatment lymphopenia (TLC of < 1000 cells/mm³) compared to 45.0 months for patients with TLC group ≥ 1000 cells/mm³ ($P < 0.01$, log-rank test). As seen in Fig. 2, patients with TLC ≥ 1000 cells/mm³ prior to initiating treatment had longer unadjusted overall survival compared to patients with pre-treatment lymphopenia. Patients with post-treatment TLC ≥ 500 cells/mm³ two months after initiating treatment had a longer unadjusted OS compared to patients with TLC < 500 cells/mm³ (21.2 vs 45.0 months, $P = 0.03$, log-rank test; Fig. 3).

Table 2 shows the univariate regression analysis of potential prognostic factors of OS. Pretreatment TLC ≥ 1000 cells/mm³ (HR: 0.26; 95% CI 0.12–0.55; $P < 0.01$), post-treatment TLC ≥ 500 cells/mm³ (HR: 0.44; 95% CI 0.21–0.95; $P = 0.04$) and never smokers (HR: 0.37; 95% CI 0.17–0.81; $P = 0.01$) were statistically significantly associated with longer OS. On multivariate analysis (Table 3), pre-treatment TLC ≥ 1000 cells/mm³ (HR: 0.23; 95% CI: 0.05–1.03; $P = 0.053$) and post-treatment TLC ≥ 500 cells/mm³ (HR: 0.42; 95% CI: 0.12–1.46; $P = 0.17$) had a decreased hazard of death compared to patients with pre and post-treatment lymphopenia respectively. However, this was not statistically significant. Patients with FIGO stage III (HR: 9.65; 95% CI 1.20–156.60; $P = 0.04$) had higher hazard of death compared to patients with Stage I disease. Smoking status was no longer statistically associated with OS (HR: 0.32; 95% CI: 0.08–1.26; $P = 0.13$) on multivariate analysis.

3.2. Progression-free survival

PFS was known for 60 (85%) out of the 71 patients. In this subset of patients, the median PFS was 44.3 months (95% CI, 17.8—not estimable). When subdivided into the exposure groups, the 25th percentile unadjusted PFS was 4.8 months (95% CI 1.9–9.8) in patients with pre-treatment lymphopenia (TLC of < 1000 cells/mm³) compared to 10.6 months (95% CI 4.6–22.3) for patients with TLC ≥ 1000 cells/mm³ ($P < 0.01$, log-rank test).

Table 2 shows the univariate analysis of potential prognostic factors and PFS. On univariate analysis, pretreatment TLC ≥ 1000 cells/mm³ (HR: 0.29; 95% CI 0.11–0.72; $P = 0.01$) and older age (HR: 0.97; 95% CI 0.94–0.996; $P = 0.03$) were associated with prolonged PFS. Higher pre-treatment platelet count (HR: 1.01; 95% CI 1.00–1.01; $P < 0.01$) was associated with shorter PFS. On multivariate analysis (Table 3), pre-treatment (HR: 0.65; 95% CI: 0.11–3.75; $P = 0.63$) and post-treatment (HR: 0.40; 95% CI: 0.12–1.35; $P = 0.14$) lymphopenia were not statistically significantly associated with shorter PFS. Other factors

included in the multivariate analysis were age, Charlson Comorbidity Index, race, stage, tobacco use, pre-treatment platelet count and histology.

A sensitivity analysis was conducted by excluding patients with HIV from the analysis, and the results were similar as described above (data not shown). Lastly, to account for the time-varying nature of all hematologic markers (platelet, leukocyte, hematocrit, and lymphocyte counts), a separate multivariate analysis was performed by using the post-treatment time-varying hematologic markers with similar finds as described above (data not shown).

4. Discussion

While multiple studies have found pre-treatment lymphopenia to be predictive of survival, post-treatment lymphopenia after radiation therapy has only more recently been quantitatively studied. Our study examined the lymphocyte trend after initiating treatment and the impact of pre-treatment and post-treatment lymphopenia on survival in women with locally advanced cervical cancer treated with primary chemoradiation. Our results showed that the TLC nadir occurred two months after treatment initiation. The median reduction in TLC was 70%, and 53% of patients had a TLC <500 cells/mm³. Some patients had persistent lymphopenia even 12 months post-treatment. The timing, frequency, severity and persistence of lymphopenia in our study is consistent with studies in other solid tumors, which represent a diverse set of tumor sites, stages, and chemotherapy regimens. These studies showed a 51–73% decrease in TLC and 45–61% frequency of lymphopenia (TLC <500 cells/mm³) two months after treatment initiation [22–25]. Based on prior studies [19,20,29–32] and the above results, radiation therapy may be a driving factor in the lymphopenia patterns observed. In cervical cancer, substantial immune suppression has been observed in patients who received primary radiation therapy, regardless of whether they received concurrent chemotherapy [32].

Although, the impact of radiation therapy on lymphopenia is well-documented, there are few studies correlating post-treatment lymphopenia with survival, particularly in gynecological cancers. TLC two months after treatment initiation has been shown to be a prognostic factor for survival in patients with pancreatic adenocarcinoma, non-small cell lung cancer, head and neck squamous cancer, and high-grade glioma who received radiation therapy [21–25].

In our study, we found that the unadjusted OS was inferior for patients with pre-treatment (10.6 vs 45.0 months, $P < 0.01$) and post-treatment (12.2 vs 45.0 months, $p = 0.03$) lymphopenia compared to those without. On multivariate analysis patients without pre-treatment and post-treatment lymphopenia appeared to have a 77% (HR: 0.23; 95% CI 0.05–1.03; $P = 0.053$) and 58% (HR: 0.42; 95% CI 0.12–1.46; $P = 0.17$) decreased hazards of death respectively, but this was not statistically significant. Closer examination of the unadjusted (Table 2) and adjusted (Table 3) hazard ratios showed similarities that led us to suspect that the results did not reach statistical significance because of our small sample size.

The mechanism by which lymphopenia contributes to a worse prognosis in individuals with advanced cancer undergoing radiation with or without chemotherapy is unclear. The

association between pre-treatment lymphopenia and shorter progression free and/or overall survival has previously been theorized to be due to poor overall health status; however, in studies that have analyzed this hypothesis, lymphopenia remains an independent predictor after controlling/adjusting for functional status [9,12]. Moreover, those with lymphopenia do not appear to have shorter survival related to infections [21,22]. There is ongoing research and debate regarding the role the immune system plays in cancer biology, and whether it serves as a defense mechanism or if immune activation stimulates tumor cells [33,34]. This is likely just a small aspect of the multi-dimensional and complex interaction between the immune system and carcinogenesis. Post-treatment lymphopenia has been postulated to be secondary to inadvertent radiation to circulating lymphocytes as they pass through the radiation beam [35]. In the case of lymphopenia and survival in cervical cancer, we theorize that patients who can maintain lymphocyte counts may have a more robust immune reaction, which may in itself convey an improved prognosis in cancer. As we better understand how lymphopenia contributes to survival, we will also need to better understand whether lymphopenia is a direct contributor to shorter survival, or simply another prognostic marker.

In addition to understanding how lymphopenia contributes to a worse prognosis, additional studies are needed to determine whether lymphopenia can be reversed and if this will improve survival. A recent study at Johns Hopkins University investigated the utility of reinfusing harvested pre-treatment circulating lymphocytes after radiation [36]. The use of exogenous Interleukin-7 is being studied in high grade gliomas by the Adult Brain Tumor Consortium and the Cancer Therapy Evaluation Program because a recent study showed that patients with high-grade gliomas did not have the expected IL-7 physiologic elevation in response to radiation-induced lymphopenia [37]. Should future studies further establish a correlation between post-treatment lymphopenia and survival in women with cervical cancer, these women may potentially be considered for these studies.

The current study is limited by its retrospective nature and relatively small sample size. In addition, the availability of detailed clinical treatment, post-treatment CBCs and follow-up data varied across the cohort, and progression-free survival was available for only 85% of the study population. Multiple imputations were performed to analyze the impact of the missing data and results were similar to the complete case series analysis. Treatment techniques may have also changed over the course of our study period, which was not taken into account in our model. Despite these limitations, this study investigates both the trend and impact of pre- and post-treatment lymphopenia on survival outcome in women with locally advanced cervical cancer. Although the association between survival and lymphopenia (pre- and post-treatment) was not statistically significant (likely due to our small sample size) there appeared to be a trend toward decreased survival in patients with pre-treatment and post-treatment lymphopenia. Our findings regarding total lymphocyte count over time were similar in timing, severity, and duration as patterns seen in other solid tumors.

This study is hypothesis-generating and should be validated in a larger, cooperative group study cohort. Given that lymphopenia may be a reversible prognostic risk factor, further research to clarify the association between lymphopenia, treatment response, and survival should be explored. If lymphopenia is established as a mechanism for decreased survival,

rather than just a prognostic indicator, this may better steer future developments in treatment. Possible novel therapeutic strategies could include pre- or post-treatment immune preservation or modulation to improve response rates and overall survival in women with locally advanced cervical cancer.

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HIGHLIGHTS

- Patients with cervical cancer treated with chemoradiation experience severe and sustained lymphopenia.
- Pre- and post-treatment lymphopenia appear to be associated with shorter overall survival in women with advanced cervical cancer.
- Further research is warranted, given that lymphopenia could be a reversible prognostic factor.

Fig. 1.
Total lymphocyte count prior to treatment and in the first 12 months after initiating chemoradiation.

Fig. 2.
Kaplan–Meier plot of survival stratified by pre-treatment total lymphocyte count (TLC).

Fig. 3.

Kaplan–Meier plot of survival stratified by post-treatment total lymphocyte count (TLC).

Table 1

Demographic and pre-treatment clinical characteristics of patients with locally advanced cervical cancer.

		Pre-treatment lymphocyte count			
	All patients N=71	TLC <1000 cells/mm ³ N = 11	TLC 1000 cells/mm ³ N = 60	P	
Demographic data					
Age, years, [median (IQR)]	49 (40–56)	46 (39–57)	49 (42–56)	0.81	
Race, [N (%)]					
White	25 (35)	6 (55)	19 (32)	0.41	
Black	43 (61)	5 (45)	38 (63)		
Other	3 (4)	0 (0)	3 (5)		
Tobacco use, [N (%)] ^a					
Never smokers	23 (32)	3 (27)	20 (33)	0.73	
Former smokers	9 (13)	2 (18)	7 (12)		
Current smokers	29 (41)	6 (55)	23 (38)		
Charlson Comorbidity Index, (cont.), [N (%)]	0 (0–1)	0 (0–0)	0(0–1)	0.59	
0 points	53 (75)	9 (82)	44 (73)	0.56	
1–2 points	13 (18)	1 (9)	12 (20)		
3–4 points	1 (1)	0 (0)	1 (2)		
5 points	4 (6)	1 (9)	3 (5)		
Baseline tumor data					
Histologic grade, [N (%)] ^a					
Well differentiated	2 (3)	0 (0)	2 (3)	0.91	
Moderately differentiated	22 (31)	4 (36)	18 (82)		
Poorly differentiated	19 (27)	3 (27)	16 (27)		
Histology, [N (%)]					
Squamous carcinoma	59 (83)	9 (82)	50 (83)	0.28	
Adenocarcinoma	1 (1)	0 (0)	1 (2)		
Adenosquamous	6 (9)	0 (0)	6 (10)		
Other	5 (7)	2 (18)	3 (5)		
FIGO stage, [N (%)]					
Stage I	4 (6)	0(0)	4 (6)	0.17	
Stage II	33 (46)	3 (27)	30 (50)		
Stage III	32 (45)	7 (64)	25 (42)		
Stage IV	2 (3)	1 (9)	1 (2)		
Treatment data					
Time from diagnosis to chemoradiation initiation, days [median (IQR)]	43 (29–69)	59 (23–91)	43 (29–69)	0.66	
Pretreatment laboratory data					
Hematocrit, % [median (IQR)]	34 (29–38)	32 (26–34)	35 (30–38)	0.04	
Platelet count, ×10 ⁹ /L [median (IQR)]	318 (247–385)	363 (306–420)	318 (245–372)	0.12	
Leukocyte count, cells/μL [median (IQR)]	9170 (6570–12,550)	12,980 (6460–16,560)	9060 (6815–11,010)	0.31	

^a Percentages don't sum up to 100 due to missing data.

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Table 2

Univariate analysis of potential factors associated with the overall survival and progression-free survival of patients with advanced stage cervical cancer.

Variable	Overall survival (N = 71)		Progression-free survival (N = 60)	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age	0.98 [0.96–1.00]	0.10	0.97 [0.94–0.996]	0.03
Tobacco use				
Current/former	Reference		Reference	
Never	0.37 [0.17–0.81]	0.01	0.58 [0.24–1.42]	0.23
Charlson Comorbidity Index				
0 points	Reference		Reference	
1–2 points	0.58 [0.25–1.30]	0.19	0.38 [0.11–1.26]	0.11
3–4 points	1.07 [0.14–7.91]	0.95	1.29e-15 [0–NM]	1.00
5 points	1.63 [0.57–4.62]	0.36	0.74 [0.10–5.49]	0.77
Pre-treatment lymphocyte count				
<1000 cells/mm ³	Reference		Reference	
1000 cells/mm ³	0.26 [0.12–0.55]	<0.01	0.29 [0.11–0.72]	0.01
Post-treatment lymphocyte count ^{*+}				
<500 cells/mm ³	Reference		Reference	
500 cells/mm ³	0.44 [0.21–0.95]	0.04	0.43 [0.18–1.06]	0.07
Pre-treatment platelet count	1.00 [0.99–1.01]	0.06	1.01 [1.00–1.01]	<0.01
FIGO stage				
Stage I	Reference		Reference	
Stage II	2.52[0.33–19.05]	0.37	1.26 [0.16–9.70]	0.83
Stage III	5.64[0.75–42.30]	0.09	2.41 [0.31–18.48]	0.40
Stage IV	5.57[0.49–62.77]	0.17	2.95 [0.18–47.54]	0.45
Tumor histology				
Other	Reference		Reference	
Squamous carcinoma	1.49 [0.63–3.53]	0.36	1.22 [0.42–3.54]	0.71
Race				
Others	Reference		Reference	
Caucasian	0.90 [0.50–1.65]	0.74	1.29 [0.61–2.74]	0.51
Tumor histology grade				
Well/moderately differentiated	Reference		Reference	
Poorly/undifferentiated	0.89 [0.41–1.94]	0.77	1.13 [0.44–2.86]	0.80
Duration from diagnosis to chemoradiation initiation	1.00 [0.99–1.01]	0.33	1.0 [1.00–1.01]	0.71
Pre-treatment hematocrit	0.98 [0.93–1.03]	0.37	0.97 [0.91–1.04]	0.44

* N = 47; of the 71 patients, post-treatment TLC was known for 47 patients.

⁺ N = 43; of the 60 patients, post-treatment TLC was known for 43 patients.

Table 3

Multivariate analysis of potential factors associated with overall survival and progression-free survival of patients with advanced stage cervical cancer.

Variable [^]	Overall Survival N = 47 ^a		Progression-free survival N = 43 ^b	
	Adjusted hazard ratio ^c (95% CI)	P	Adjusted hazard ratio ^c (95% CI)	P
Age	–	NS	0.95 [0.90–1.01]	0.13
Tobacco use				
Current/former				
Never	0.32 [0.08–1.26]	0.13	–	NS
FIGO stage				
Stage I				
Stage II	3.14 [0.26–50.10]	0.34		
Stage III	9.65 [1.20–156.60]	0.04	–	NS
Stage IV	6.47 [0.24–179.89]	0.50		
Pre-treatment lymphocyte count				
<1000 cells/mm ³	Reference		Reference	
1000 cells/mm ³	0.23 [0.05–1.03]	0.053	0.65 [0.11–3.75]	0.63
Post-treatment lymphocyte count				
<500 cells/mm ³	Reference		Reference	
500 cells/mm ³	0.42 [0.12–1.46]	0.17	0.40 [0.12–1.35]	0.14

[^] Showing only the exposures of interest and variables that achieved statistical significance.

^a Of the 71 patients, post-treatment TLC was known for 47 patients.

^b Of the 60 patients, post-treatment TLC was known for 43 patients.

^c Adjusted for age, pre-treatment platelet count, Charlson Comorbidity Index, FIGO stage, race, tumor histology, pre-treatment lymphocyte count, post-treatment lymphocyte count, and tobacco use.