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ORIGINAL ARTICLE **CME**

Absolute Lymphocyte Count in Cervical Cancer Patients Prior to Definitive Chemoradiotherapy: a Prognostic Indicator?

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ABSTRACT

Objective: *Baseline lymphopenia is associated with poor prognosis in various malignancies. This study aimed to examine the prognostic value of pretreatment lymphocyte count in cervical cancer patients in Hong Kong.*

Methods: *A cohort of 198 cases of cervical cancer patients without evidence of metastatic disease (i.e., International Federation of Gynecology and Obstetrics stage IB to IVA), who completed definitive chemoradiotherapy from January 2009 to December 2014 was analysed. Baseline clinical and pretreatment blood test data were collected. Definitive treatment had included external radiotherapy and brachytherapy with concurrent weekly cisplatin 40 mg/m^2. Log-rank tests and multivariable Cox regression were used to evaluate the association between haematological parameters and survival. Study endpoints were overall survival (OS), recurrence-free survival (RFS), and late radiation-induced grade 3-4 toxicity.*

Results: *Median follow-up period was 6.52 years. A pretreatment absolute lymphocyte count ≤1.7 × 10^9/L was associated with a significantly worse 5-year OS (68.7% vs. 84.4%, p = 0.005). Multivariate analysis confirmed pretreatment lymphocyte count to be an independent predictor of RFS (adjusted hazard ratio = 0.58; 95% confidence interval [CI] = 0.34-0.99, p = 0.046) and OS (adjusted hazard ratio = 0.47; 95% CI = 0.25-0.88, p = 0.018). Absolute lymphocyte count was not associated with late grade 3-4 radiation toxicity.*

Conclusion: *Our data in a local cohort add evidence to findings in other studies that pretreatment absolute lymphocyte count is an independent predictor of both OS and RFS in cervical cancer patients receiving definitive chemoradiotherapy.*

Key Words: *Lymphopenia; Lymphocyte count; Chemoradiotherapy; Cervical cancer; Prognostic factor*

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中文摘要

子宮頸癌病人在接受根治性放化療前的淋巴細胞絕對值：預後指標？

祝菀馨、周重行、張嘉文、謝思華、賀俊義、黃馨誼、楊雅茵、黃錦洪

目的：基線淋巴細胞減少症與多種惡性腫瘤的預後不佳有關。本研究旨在找出香港子宮頸癌病人在接受治療前的淋巴細胞數的預後價值。

方法：本研究分析了198例子宮頸癌病人個案，沒有證據顯示他們有轉移性疾病（即國際婦產科協會分期IB期至IVA期），於2009年1月至2014年12月期間完成根治性放化療。研究收集了基線臨床及治療前的血液檢查數據。根治性治療包括了體外放射治療及腔內治療，同時每星期使用40 mg/m^{2}順鉑。本研究採用了對數等級檢定及多變項Cox迴歸分析來找出血液學參數與存活之間的關係，並以總生存率、無復發生存率及晚期3至4級放射毒性為研究終點。

結果：中位隨訪期為6.52年。治療前的淋巴細胞絕對值≤1.7 × 10^9/L與明顯較差的五年存活率有關（68.7%比84.4%，p = 0.005）。多變項分析確認了治療前的淋巴細胞數能獨立預測無復發生存率（調整風險比 = 0.58；95% 置信區間 = 0.34-0.99，p = 0.046）及總生存率（調整風險比 = 0.47；95% 置信區間 = 0.25-0.88，p = 0.018）。淋巴細胞絕對值與晚期3至4級放射毒性不相關。

結論：本研究利用本港病人的數據，得出與先前研究結果一致的結論，即治療前的淋巴細胞絕對值能獨立預測接受根治性放化療的子宮頸癌病人之總生存率及無復發生存率。

INTRODUCTION

According to the World Health Organization's statistics in 2021, cervical cancer is the fourth most common cancer in the female population. In 2018, it was estimated that 570,000 women were diagnosed with cervical cancer and approximately 311,000 patients died of the disease.[1] Unprecedented progress in oncological management has been seen in the last decade, with the emergence of immunotherapy and adoptive cell transfer therapy.[2,3] However, management of cervical cancer around the world is still performed with chemotherapy and radiotherapy, usually in a combined way (chemoradiotherapy). Given the toxicity of definitive chemoradiotherapy, enhanced knowledge of prognostic factors for better patient selection is warranted.

Lymphopenia has been suggested to reflect low host immune reactivity.[4] The tumour microenvironment has been of interest in tumour immunology. Although not directly reflecting tumour microenvironment, peripheral lymphocytes, especially cytotoxic T lymphocytes,[5] are critical to anti-tumour immunity. The neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lymphocyte-to–white blood cell count percentage[6-8] have been shown to be of prognostic value in cancer outcomes. Pretreatment lymphopenia in cancer outcomes has been found to be associated with poor prognosis in colorectal cancer, breast cancer, renal carcinoma, bladder cancer, sarcomas and gynaecological cancers.[9-13] This study aimed to add evidence on the prognostic value of pretreatment lymphopenia in cervical cancers in a local cohort.

METHODS

This was a retrospective cohort study conducted in a tertiary clinical oncology centre in Hong Kong. A total of 218 consecutive patients with primary cervical cancer who completed definitive chemoradiotherapy from January 2009 to December 2014 were analysed. Definitive chemoradiotherapy consisted of concurrent weekly cisplatin 40 mg/m^2, external beam radiotherapy comprising 40 Gy in 20 fractions with high-dose-rate intracavitary brachytherapy twice weekly for four fractions up to 7 Gy per fraction at point A (2 cm lateral to the central uterine canal and 2 cm from the mucous membrane of the lateral fornix in the axis of the uterus) and additional pelvic irradiation and parametrial boost up to a total of 64 to 68 Gy at point B (which was designated as 5 cm from midline at the level of point A) according to the recommendations of

the International Commission on Radiation Units and Measurements[13,14]; aiming for a total biologically EQD2 (equivalent dose delivered in 2 Gy fractions) of 80 Gy to the tumour and limiting the dose to bladder and rectum to EQD2 of 75 Gy. Pretreatment investigations included physical examination, comprehensive baseline blood investigations, magnetic resonance imaging of the pelvis, computed tomography of thorax, abdomen and pelvis or positron emission tomography/computed tomography, and endoscopic examination including sigmoidoscopy/cystoscopy in cases of suspected mucosal invasion. Patients were staged according to the 2018 FIGO (International Federation of Gynecology and Obstetrics) criteria. The study inclusion criteria consisted of: (1) histologically confirmed cervical cancer; (2) FIGO stage IB to IVA; (3) completion of treatment; and (4) pretreatment blood counts available in our records. Patients were excluded if they had (1) synchronous malignancy at baseline; (2) pre-existing autoimmune diseases; or (3) defaulted or failed to complete treatment. Patients were followed up by physical examination and interval imaging at 3- to 6-month intervals in the first 2 years after treatment and every 6 to 12 months subsequently.

Data Collection

Clinical variables, including patients' baseline demographics and clinicopathologic and treatment details, were collected from the electronic patient record system in our institution. Pretreatment blood values, including absolute neutrophil counts, absolute lymphocyte counts (ALCs), haemoglobin levels, and absolute platelet counts were collected. A Charlson Comorbidity Index[15] was calculated for each patient as a reference for baseline comorbidity. Grade 3-4 toxicities were classified according to The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 of the United States.

Statistical Analysis

The abovementioned clinical variables were summarised with descriptive statistics. A low pretreatment ALC was defined as lower than the median of the pretreatment ALC in the patient sample, i.e., $\leq 1.7 \times 10^9$/L. This pretreatment lymphocyte cut-off was based on previous pilot studies that attempted to find the optimal cut-off in baseline haematological parameters.[11] The primary outcomes of the study were recurrence-free survival (RFS) and overall survival (OS). RFS was calculated from the start of treatment to the date of first evidence of recurrence or death. OS was defined as the time period from the date of start of treatment to the date of last follow-up or death. RFS and OS were estimated using the Kaplan–Meier method and were compared using the log-rank test. Clinically known prognostic factors were also evaluated using multivariate Cox regression. The association between low and high pretreatment lymphocyte counts with grade 3-4 toxicity was evaluated with the Chi squared test. All statistical analyses were performed with commercial software SPSS (Windows version 24.0; IBM Corp, Armonk [NY], United States). All p values were two-sided and a p value <0.05 was considered statistically significant. The STROBE checklist for observational studies was used.

RESULTS

A total of 198 patients undergoing definitive chemoradiotherapy in our institution from January 2009 to December 2014 met our inclusion criteria. The median follow-up period for our cohort was 6.52 years. Demographics, clinicopathological and treatment details for the study cohort are summarised in Table 1.

Table 1. Patient demographics (n = 198).*

Age, median (range), y	50 (25-72)
Smoker	20 (10.1%)
Drinker	8 (4.0%)
Charlson Comorbidity Index score	
0	157 (79.3%)
1	11 (5.6%)
2	30 (15.2%)
ECOG performance status	
0-1	194 (98.0%)
2	4 (2.0%)
BMI, median (range), kg/m^2	23.2 (19.0-27.2)
Histology	
Squamous cell carcinoma	164 (82.8%)
Adenocarcinoma	22 (11.1%)
Adenosquamous carcinoma	2 (1.0%)
Others	10 (5.1%)
FIGO stage	
IB	8 (4.0%)
IIA	6 (3.0%)
IIB	90 (45.5%)
IIIA	2 (1.0%)
IIIB	40 (20.2%)
IIIC1	37 (18.7%)
IIIC2	12 (6.1%)
IVA	3 (1.5%)
Absolute lymphocyte count, median (IQR), $\times 10^9$/L	1.7 (1.4-2.2)
Cumulative cisplatin dose, median (IQR), mg/m^2	200 (160-240)
Total treatment time, median (IQR), d	43 (43-46)

Abbreviations: BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynecology and Obstetrics; IQR = interquartile range.
* Data are shown as No. (%), unless otherwise specified.

The median age of the population was 50 years (range, 25-72). The majority of our study patients were non-smokers, non-drinkers, had good baseline comorbidities with a Charlson Comorbidity Index of 0 and an Eastern Cooperative Oncology Group performance score of 0 to 1. The histology of the cohort consisted of squamous cell carcinoma (82.8%), adenocarcinoma (11.1%), adenosquamous carcinoma (1.0%), and others (5.1%). Out of the 198 patients, eight patients (4.0%) had stage IB disease, 96 (48.5%) had stage II disease, 42 (21.2%) had stage IIIA-B disease, 49 (24.7%) had stage IIIC disease and three (1.5%) had stage IVA disease (i.e., invasion of adjacent organs). The cohort had a median cumulative cisplatin dose of 200 mg/m^2 (interquartile range, 160-240) and a median total treatment time of 43 days (interquartile range, 43-46).

The median pretreatment ALC was 1.7 × 10^9/L. Patients with pretreatment ALC ≤1.7 × 10^9/L were classified as the 'low pretreatment ALC group' whereas patients with pretreatment ALC >1.7 × 10^9/L were classified as the 'high pretreatment' ALC group.

At the median follow-up period of 6.52 years, the 5-year RFS was 63.4% in the low pretreatment ALC group compared to 79.0% for those in the high pretreatment ALC group (p = 0.004; Figure 1). The 5-year OS was 68.7% in the low pretreatment ALC group compared to 84.4% in the high pretreatment ALC group (p = 0.005; Figure 2).

On multivariate analysis (Table 2), a high pretreatment ALC remained an independent prognostic factor for longer RFS with an adjusted hazard ratio (HR) of 0.58 (95% confidence interval [CI] = 0.34-0.99; p = 0.046). Squamous cell carcinoma was also associated with longer RFS (p < 0.001). As shown in Table 3, high pretreatment ALC remained an independent predictor of longer OS in multivariate analysis (adjusted HR = 0.47; 95% CI = 0.25-0.88, p = 0.018). Negative prognostic factors for OS included old age (adjusted HR = 1.04; 95% CI = 1.00-1.09; p = 0.041) and non-squamous histology (adjusted HR = 4.56; 95% CI = 2.24-9.36; p < 0.001).

The distribution of cisplatin dose was similar across the two groups (p = 0.139). Cumulative cisplatin dose was not an independent prognostic factor for either RFS or OS. In all, 52 out of 94 patients (55.3%) in the high pretreatment ALC group needed chemotherapy dose reduction, compared to 63 out of 104 patients (60.6%) in the low pretreatment ALC group (p = 0.32). In total,

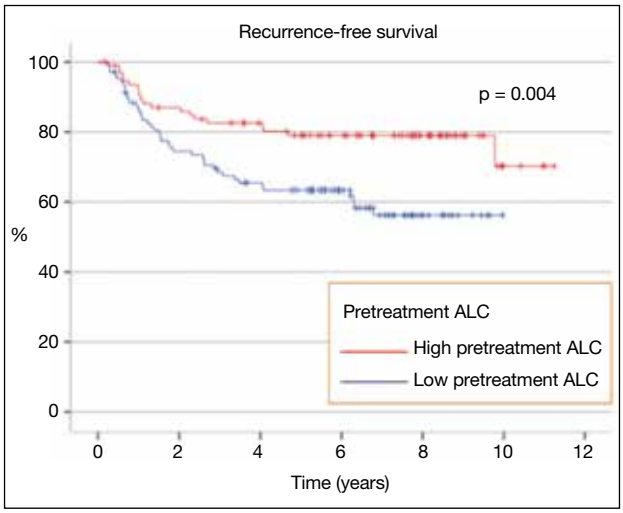

Figure 1. Kaplan–Meier survival curves for recurrence free survival for patients with a high pretreatment absolute lymphocyte count (ALC) and those with a low pretreatment ALC.

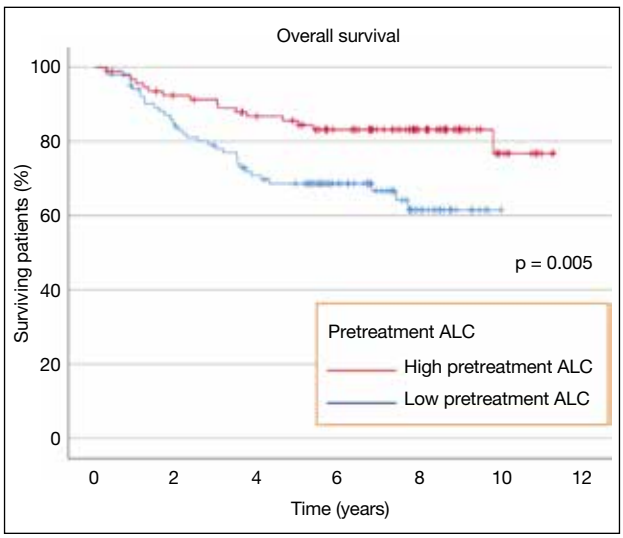

Figure 2. Kaplan–Meier survival curves for overall survival for patients with a high pretreatment absolute lymphocyte count (ALC) and those with a low pretreatment ALC.

18 out of 94 patients (19.1%) in the high pretreatment ALC group experienced grade 3-4 toxicity, compared to 13 out of 104 patients (12.5%) in the low pretreatment ALC group (p = 0.199).

We explored the relationship of local RFS and distant recurrence-free survival (DRFS) in the two groups. The 5-year DRFS was 72.4% in the low pretreatment ALC group compared to 83.1% in the high pretreatment ALC

Table 2. Multivariate analysis of recurrence-free survival.

Variable	Adjusted hazard ratio	95% confidence interval	p Value
Age	1.03	0.99-1.07	0.084
Smoker vs. non-smoker	0.63	0.17-2.29	0.49
CCI ≥ 1 vs. 0	1.32	0.65-2.67	0.43
BMI	1.09	0.99-1.20	0.081
Non-SCC vs. SCC	3.38	2.02-7.33	< 0.001
FIGO stage			0.15
IB	-	-	-
II	0.81	0.10-6.70	0.84
IIIAB	1.00	0.10-9.70	1.00
IIIC1	1.52	0.16-14.1	0.71
IIIC2 + IVA	3.18	0.29-35.2	0.35
Cisplatin cumulative dose	0.99	0.99-1.00	0.07
Treatment time	1.00	0.97-1.04	0.94
Absolute neutrophil count	0.98	0.84-1.15	0.84
Absolute lymphocyte count	0.58	0.34-0.99	0.046
Haemoglobin level	0.92	0.73-1.16	0.48
Absolute platelet count	1.00	0.99-1.00	0.46
Radiotherapy technique 3D vs. 2D	1.18	0.34-4.08	0.79

Abbreviations: BMI = body mass index; CCI = Charlson Comorbidity Index; FIGO = International Federation of Gynecology and Obstetrics; SCC = squamous cell carcinoma.

Table 3. Multivariate analysis of overall survival.

Variable	Adjusted hazard ratio	95% confidence interval	p Value
Age	1.04	1.00-1.09	0.041
Smoker vs. non-smoker	0.23	0.27-1.91	0.17
CCI ≥ 1 vs. 0	1.27	0.55-2.92	0.58
BMI	1.31	1.02-1.25	0.21
Non-SCC vs. SCC	4.56	2.24-9.36	<0.001
FIGO stage			0.067
IB	-	-	-
II	0.61	0.07-5.36	0.66
IIIAB	0.99	0.094-10.38	0.99
IIIC1	1.06	0.10-11.21	0.96
IIIC2 + IVA	3.72	0.31-44.56	0.30
Cisplatin cumulative dose	1.00	0.98-1.00	0.47
Treatment time	1.00	0.96-1.03	0.78
Absolute neutrophil count	0.97	0.81-1.15	0.71
Absolute lymphocyte count	0.47	0.25-0.88	0.018
Haemoglobin level	0.82	0.63-1.08	0.16
Absolute platelet count	1.00	0.99-1.00	0.71
Radiotherapy technique, 3D vs. 2D	0.86	0.23-3.30	0.83

Abbreviations: 2D = two-dimensional; 3D = three-dimensional; BMI = body mass index; CCI = Charlson Comorbidity Index; FIGO = International Federation of Gynecology and Obstetrics; SCC = squamous cell carcinoma.

group (p = 0.047). The 5-year local RFS was 85.0% in the group with low pretreatment ALC, compared to 92.0% for those with high pretreatment ALC (p = 0.065).

DISCUSSION

In our study, we found that low pretreatment ALC was associated with inferior RFS of borderline significance in cervical cancer patients who underwent definitive chemoradiotherapy. OS was significantly improved in the high pretreatment ALC group. The prognostic value of pretreatment ALC in cervical cancer was independent of other major prognostic factors across cancer stages and regardless of chemotherapy intensity. This finding is consistent with multiple studies, which established the relationship between pretreatment ALC with survival outcome of multiple solid tumours, including tumours of the cervix[16-18] and haematological malignancies.[19]

The cut-off for the pretreatment ALC was defined as a median of 1.7 × 10^9/L in our patient population. To our knowledge, there is no consensus as to the cut-off between high or low pretreatment ALC.[20] Previous studies on prognostic impact of ALC had found the median ALC of the study population to be an independent prognostic factor of survival.[18] According to a cohort study by den Ouden et al[21] comparing haematological abnormalities of metastatic and benign ovarian tumours, the authors found that the median lymphocyte counts of the malignant group (1.2 g/L) were significantly lower than those in the benign tumour (1.8 g/L) and age-matched control groups (2 g/L) with p values of 0.02 and 0.00005, respectively. Although the study was not done in cervical cancer patients, it reflects that cancer patients often have intrinsically lower pretreatment ALC. In 2016, Cho et al[17] studied the prognostic value of lymphopenia according to the CTCAE grade during chemoradiotherapy in cervical cancer. Grade 4 lymphopenia during chemoradiotherapy predicted a significantly shorter disease-specific survival and progression-free survival (PFS). The authors also found that patients with Grade 4 lymphopenia had relatively lower baseline ALC despite not statistically significant (p = 0.07) and a more rapid decrease during treatment.[17] It is known that concurrent chemoradiotherapy might have both a positive effect on sustaining peripheral lymphocytes by tumour control and a deleterious effect from lymphocyte depletion in the radiation portal.[22] This suggests that ALC before, during, and after treatment is probably reflective of baseline disease extent, treatment toxicity, and treatment response.

A systematic review and meta-analysis based on 42 studies by Zhao et al[16] evaluated the pretreatment ALC cut-off; the largest effect size was observed with a cut-off of ≤1.0 × 10^9/L, followed by a cut-off between

>1.0 and 2.0 × 10^9/L. Their high ALC cut-off (>2.0 × 10^9/L) subgroup was not associated with poorer OS.[16] They found similar results on subgroup analysis of PFS.[16] This shows a trend for a lower pretreatment ALC cut-off for a larger effect on the prognostic value of pretreatment ALC. The pretreatment ALC cut-off used in our patient population falls into the range reported. Some authors had arbitrarily chosen to use CTCAE as cut-off for pretreatment ALC but this was less applicable to this study, as pretreatment ALC was the study interest instead of treatment-related lymphopenia. This reflects the complexity of finding a definitive cut-off for clinical utility; however, this does not diminish the importance of pretreatment ALC as a prognostic factor of survival outcomes.

In 2016, Wu et al[18] conducted a cohort study of lymphopenia in 71 patients and its association with locally advanced cervical cancer. They found that subjects with low pretreatment ALC <1 × 10^3/L and persistent lymphopenia <500 cells/mm^3 2 months after initiating treatment tended towards shorter OS, though not to a statistically significant degree on multivariate analysis, contrary to our finding of pretreatment ALC being an independent prognostic factor of OS. This might be explained by their smaller study population of 71 patients and of which only 47 had ALC documented 2 months after initiating treatment.[18] Another cohort study by Jeong et al[23] found pretreatment lymphocyte percentage (calculated as the proportion of the ALCs in the total white blood cell count) predictive of PFS and OS; however it also did not remain significant in multivariate analysis for OS.

The mechanisms that govern the relationship between pretreatment ALC and poorer treatment outcomes are likely multifactorial. In our study, we found no significant association among pretreatment ALC, chemotherapy tolerance, and treatment-related toxicities. Therefore, the negative survival outcomes in patients with low pretreatment ALC were not mediated by suboptimal therapy nor by treatment complications. Lower pretreatment ALC was associated with poorer DRFS in solid cancers,[8,10] although it was only of borderline significance in our cohort.

Lymphopenia and decrease in T and B lymphocyte subpopulations leads to a lower ability to activate an effective antitumour cellular immune response.[24] T lymphocytes drive cancer cell apoptosis,[25] and induce cancer cell death in response to chemotherapy by presenting tumour-associated antigens to immune cells.[26] Current concepts of tumour immunoediting explain the interplay between tumour growth and the cellular immune system.[27] Tumour growth is suppressed by a host of immune cells including natural killer T cells and $CD8^+$ T cells. It is followed by an equilibrium phase, where tumour cells withstand the selection pressure of immune cells. Tumour cells then escape from the immune system by inhibition of immune cells or inducing tolerance.[28] The authors postulated that a low pretreatment absolute lymphocyte cell count would reflect a lower ability of the host's immune response to react to the tumour. Another possible mechanism is a reduction in cytokine production. Circulating lymphocytes produce cytokines to inhibit tumour growth.[29] The balance between immunostimulatory cytokines and blocking of immunosuppressive cytokines facilitates antitumoural immune responses.[30] Failure to maintain the cytokine response tips the equilibrium towards tumour proliferation. A low pretreatment ALC could represent a depleted host immune state that leads to a poorer ability to respond to the subsequent treatment. Pre-clinical studies have shown that a depletion of $CD8^+$ T cells significantly reduced treatment efficacy of radiotherapy.[31] Failure to stimulate the innate and adaptive immunity negatively impacts treatment responses to radiotherapy.[32] Given that the exact levels of $CD8^+$ T cells and $CD4^+$ T cells are not easily measurable in clinical practice, peripheral pretreatment ALC may act as a surrogate to reflect the robustness of the host immune system.

Peripheral pretreatment ALC may act as a surrogate to reflect the robustness of the host immune system. This study contributes to the evidence of utilising pretreatment ALC as a prognostic factor clinically.

There are several limitations of our study. First, this was a retrospective cohort study with limited cohort size which made it an exploratory analysis. Second, the choice of median as the cut-off for high and low pretreatment ALC was based on observation and further external validation is warranted to confirm our findings. Third, the choice of brachytherapy practised in our institution during the study period adopted the conventional Manchester system instead of image-guided brachytherapy, which is now the standard of care that improves pelvic control and reduces treatment toxicities.[33] However, this should not diminish the importance of this study as the prognostic relationship of pretreatment ALC focuses on the immune mechanism towards tumourigenesis and antitumour responses. The choice of brachytherapy

would be unlikely to affect the prognostic implication of pretreatment ALC.

Cytokine boost has been a subject of interest given the plethora of evidence supporting better treatment responses with a strong innate and adaptive immune system. Cervical cancer is one of the best-known cancers related to chronic viral infection, specifically with the human papillomavirus (HPV) types 16 and 18, making them an attractive target for immunotherapy.[34-36] Studies have shown that enhanced $CD4^+$ and $CD8^+$ T cell expression in response to HPV type 16 E7 peptides was associated with better treatment prognosis in HPV-positive oropharyngeal cancer.[36]

CONCLUSION

In conclusion, our study shows the independent prognostic value of pretreatment ALC in OS and RFS in cervical cancer patients. Further tumour immunology investigations are warranted to explore the mechanism underlying pretreatment ALC and treatment outcomes. Raising pretreatment ALC by cytokine boost may be a valuable direction in improving cervical cancer treatment outcomes.

REFERENCES

1. World Health Organization. Cervical cancer. Available from: https://www.who.int/health-topics/cervical-cancer#tab=tab_1. Accessed 20 Jun 2021.
2. Caldwell KJ, Gottschalk S, Talleur AC. Allogeneic CAR cell therapy—more than a pipe dream. Front Immunol. 2021;11:618427.
3. June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T cell immunotherapy for human cancer. Science. 2018;359:1361-5.
4. Patel S, Chiplunkar S. Host immune responses to cervical cancer. Curr Opin Obstet Gynecol. 2009;21:54-9.
5. Tindle RW. Immune evasion in human papillomavirus-associated cervical cancer. Nat Rev Cancer. 2002;2:59-65.
6. Howard R, Kanetsky PA, Egan KM. Exploring the prognostic value of the neutrophil-to-lymphocyte ratio in cancer. Sci Rep. 2019;9:19673.
7. Bardash Y, Olson C, Herman W, Khaymovich J, Costantino P, Tham T. Platelet-lymphocyte ratio as a predictor of prognosis in head and neck cancer: a systematic review and meta-analysis. Oncol Res Treat. 2019;42:665-77.
8. Kim GM, Koh HD, Kim JH, Park BW, Cho YU, Kim SI, et al. Baseline lymphocyte counts predict distant recurrence in early breast cancer. Ann Oncol. 2018;29(Suppl 8):viii62-3.
9. Joseph N, Dovedi SJ, Thompson C, Lyons J, Kennedy J, Elliott T, et al. Pre-treatment lymphocytopaenia is an adverse prognostic biomarker in muscle-invasive and advanced bladder cancer. Ann Oncol. 2016;27:294-9.
10. Vicente Conesa MA, Garcia-Martinez E, Gonzalez Billalabeitia E, Chaves Benito A, Garcia Garcia T, Vicente Garcia V, et al. Predictive value of peripheral blood lymphocyte count in breast cancer patients treated with primary chemotherapy. Breast. 2012;21:468-74.
11. Cho O, Noh OK, Oh YT, Chang SJ, Ryu HS, Lee EJ, et al. Hematological parameters during concurrent chemoradiotherapy as potential prognosticators in patients with stage IIB cervical cancer. Tumour Biol. 2017;39:1010428317694306.
12. Ray-Coquard I, Cropet C, Van Glabbeke M, Sebban C, Le Cesne A, Judson I, et al. Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas. Cancer Res. 2009;69:5383-91.
13. Lee LJ, Sadow CA, Russell A, Viswanathan AN. Correlation of point B and lymph node dose in 3D-planned high-dose-rate cervical cancer brachytherapy. Int J Radiat Oncol Biol Phys. 2009;75:803-9.
14. Nag S, Erickson B, Thomadsen B, Orton C, Demanes JD, Petereit D. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. Int J of Radiation Oncol Biol Phys. 2000;48:201-11.
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373-83.
16. Zhao J, Huang W, Wu Y, Luo Y, Wu B, Cheng J, et al. Prognostic role of pretreatment blood lymphocyte count in patients with solid tumors: a systematic review and meta-analysis. Cancer Cell Int. 2020;20:15.
17. Cho O, Chun M, Chang SJ, Oh YT, Noh OK. Prognostic value of severe lymphopenia during pelvic concurrent chemoradiotherapy in cervical cancer. Anticancer Res. 2016;36:3541-7.
18. Wu ES, Oduyebo T, Cobb LP, Cholakian D, Kong X, Fader AN, et al. Lymphopenia and its association with survival in patients with locally advanced cervical cancer. Gynecol Oncol. 2016;140:76-82.
19. Kusano Y, Yokoyama M, Terui Y, Nishimura N, Mishima Y, Ueda K, et al. Low absolute peripheral blood $CD4^+$ T-cell count predicts poor prognosis in R-CHOP-treated patients with diffuse large B-cell lymphoma. Blood Cancer J. 2017;7:e558.
20. Prochazka V, Trneny M, Salek D, Belada D, Kozak T, Papajik T, et al. Median absolute lymphocyte count independently predicts survival of elderly patients with diffuse large B-cell lymphoma treated with R-chemotherapy: analysis of 651 patients included in the Czech lymphoma project. Blood. 2010;116:2882.
21. den Ouden M, Ubachs JM, Stoot JE, van Wersch JW. Whole blood cell counts and leucocyte differentials in patients with benign or malignant ovarian tumours. Eur J Obstet Gynecol Reprod Biol. 1997;72:73-7.
22. Yovino S, Grossman SA. Severity, etiology and possible consequences of treatment-related lymphopenia in patients with newly diagnosed high-grade gliomas. CNS Oncol. 2012;1:149-54.
23. Jeong MH, Kim H, Kim TH, Kim MH, Kim BJ, Ryu SY. Prognostic significance of pretreatment lymphocyte percentage and age at diagnosis in patients with locally advanced cervical cancer treated with definite radiotherapy. Obstet Gynecol Sci. 2019;62:35-45.
24. Ménétrier-Caux C, Ray-Coquard I, Blay JY, Caux C. Lymphopenia in cancer patients and its effects on response to immunotherapy: an opportunity for combination with cytokines? J Immunother Cancer. 2019;7:85.
25. Dworacki G, Meidenbauer N, Kuss I, Hoffmann TK, Gooding W, Lotze M, et al. Decreased zeta chain expression and apoptosis in $CD3^+$ peripheral blood T lymphocytes of patients with melanoma. Clin Cancer Res. 2001;7(3 Suppl):947s-57s.
26. Apetoh L, Ghiringhelli F, Tesniere A, Obeid M, Ortiz C, Criollo A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med. 2007;13:1050-9.
27. Vesely MD, Schreiber RD. Cancer immunoediting: antigens, mechanisms, and implications to cancer immunotherapy. Ann N Y Acad Sci. 2013;1284:1-5.

28. Galon J, Bruni D. Tumor immunology and tumor evolution: intertwined histories. Immunity. 2020;52:55-81.
29. Berraondo P, Sanmamed MF, Ochoa MC, Etxeberria I, Aznar MA, Pérez-Gracia JL, et al. Cytokines in clinical cancer immunotherapy. Br J Cancer. 2019;120:6-15.
30. Shimizu K, Iyoda T, Okada M, Yamasaki S, Fujii SI. Immune suppression and reversal of the suppressive tumor microenvironment. Int Immunol. 2018;30:445-54.
31. Chen HY, Xu L, Li LF, Liu XX, Gao JX, Bai YR. Inhibiting the $CD8^+$ T cell infiltration in the tumor microenvironment after radiotherapy is an important mechanism of radioresistance. Sci Rep. 2018;8:11934.
32. Burnette BC, Liang H, Lee Y, Chlewicki L, Khodarev NN, Weichselbaum RR, et al. The efficacy of radiotherapy relies upon induction of type I interferon-dependent innate and adaptive immunity. Cancer Res. 2011;71:2488-96.
33. Sturdza A, Pötter R, Fokdal LU, Haie-Meder C, Tan LT, Mazeron R, et al. Image guided brachytherapy in locally advanced cervical cancer: improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. Radiother Oncol. 2016;120:428-33.
34. Atherton MJ, Stephenson KB, Pol J, Wang F, Lefebvre C, Stojdl DF, et al. Customized viral immunotherapy for HPV-associated cancer. Cancer Immunol Res. 2017;5:847-59.
35. Stevanović S, Draper LM, Langhan MM, Campbell TE, Kwong ML, Wunderlich JR, et al. Complete regression of metastatic cervical cancer after treatment with human papillomavirus-targeted tumor-infiltrating T cells. J Clin Oncol. 2015;33:1543-50.
36. Masterson L, Lechner M, Loewenbein S, Mohammed H, Davies-Husband C, Fenton T, et al. $CD8^+$ T cell response to human papillomavirus 16 E7 is able to predict survival outcome in oropharyngeal cancer. Eur J Cancer. 2016;67:141-51.