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Article

Radiation-Induced Lymphopenia Is Associated with Worse Survival in Patients Treated with Radiation Therapy for Cervical Cancer

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Simple Summary

We retrospectively analyzed 215 patients with histologically confirmed cervical cancer treated with concurrent chemoradiotherapy to evaluate the prognostic role of RT-induced lymphopenia. Lymphopenia was assessed using the ratio of nadir to pretreatment absolute lymphocyte count (ΔALC/preALC), with 0.88 as the optimal cutoff. Patients with severe lymphopenia (ΔALC/preALC > 0.88) had significantly worse disease-free survival and overall survival. The effect was most pronounced among patients receiving extended-field RT, where mean ΔALC/preALC was higher than in whole-pelvis RT (0.85 vs. 0.77, $p<0.001$). These findings suggest RT-induced lymphopenia adversely impacts survival, and mitigation strategies such as minimizing RT fields or adopting marrow-sparing techniques may improve outcomes.

Abstract

To evaluate the prognostic impact of radiation therapy (RT)-induced lymphopenia on survival outcomes in patients with cervical cancer treated with RT, we retrospectively reviewed 215 patients with cervical cancer who received RT with concurrent chemotherapy between January 2001 and December 2017. The severity of lymphopenia was quantified using the ratio of pretreatment absolute lymphocyte count (ALC) to nadir ALC during RT (ΔALC/preALC). The optimal cutoff of ΔALC/preALC for survival analysis was determined to be 0.88. Survival outcomes were assessed using Kaplan-Meier analysis and Cox proportional hazard models. The median follow-up duration was 61.0 months. Patients with severe lymphopenia (ΔALC/preALC > 0.88) had significantly worse disease-free survival (DFS) and overall survival (OS). On multivariable analysis, ΔALC/preALC > 0.88 remained an independent prognostic factor for both DFS (HR 2.18, $p = 0.011$) and OS (HR 2.54, $p = 0.009$). The impact of lymphopenia on survival was most pronounced in patients receiving extended field RT compared to whole pelvis RT (mean ΔALC/preALC: 0.85 vs. 0.77, $p < 0.001$). Subgroup analysis showed lymphopenia was a significant prognostic factor only in the extended field RT group. RT-induced lymphopenia is associated with inferior survival in cervical cancer patients, particularly those receiving extended field RT. Strategies to mitigate lymphopenia, such as minimizing RT fields or using advanced bone marrow-sparing techniques, may improve patient outcomes.

Keywords: cervical cancer; lymphopenia; radiation therapy

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1. Introduction

Cervical cancer is the fourth most common cancer in women [1,2]. Radiation therapy is an important treatment modality in cervical cancer, whether as a definitive or adjuvant treatment [3,4]. Although radiation therapy eliminates clinical and subclinical cancer cells, it can also damage the surrounding normal tissue. Lymphocytes are highly radiosensitive hematopoietic cells and can be depleted with an extremely low dose of 0.5–1 Gy [5]. Depletion of lymphocytes is commonly induced in patients treated with radiation therapy; however, the clinical impact of radiation therapy-induced lymphopenia on cancer survival has recently been recognized in light of the advent of immunotherapy. Lymphocytes play an essential role in cancer immunity by detecting tumor antigens and directly killing tumor cells.

Recently, the unfavorable effect of lymphopenia on survival has been demonstrated in several solid tumors [6,7]. Although several studies have shown that pretreatment lymphopenia is associated with worse survival, the effect of treatment-induced lymphopenia on survival is controversial [8–10]. Because it is a modifiable factor in the era of modern radiation therapy, the influence of radiation therapy-induced lymphopenia on survival outcomes deserves further investigation. It is well known that bone-marrow sparing RT decreases the severe lymphopenia in cervical cancer, and proton therapy is presumed to be able to further reduce the probability and severity of lymphopenia [6,11,12]. The RT field is another selectively modifiable factor in cervical cancer. The RT field in cervical cancer typically extends from the caudal margin of the obturator foramen to the cranial margin of the L5 vertebral spine. In some patients with more advanced disease or paraaortic lymph node involvement, the cranial border of the RT field is extended to T12-L1 level.

In this study, we evaluated the impact of treatment-induced lymphopenia on survival in patients who underwent RT for cervical cancer.

2. Materials and Methods

2.1. Patients

We retrospectively reviewed the medical records of patients with histologically confirmed cervical cancer who received RT between January 2001 and December 2017. This study was approved by the Institutional Review Board of Samsung Medical Center (no. 2022-11-140-002). Patients were excluded if they had the following: 1) RT alone, 2) distant metastases, 3) if patient does not consent to the use of personal data, 4) absence or lack of laboratory test results before or during RT course. Among the searched 400 patients, we identified 215 patients who satisfied the inclusion criteria (Figure 1). Patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) 2018 classification.

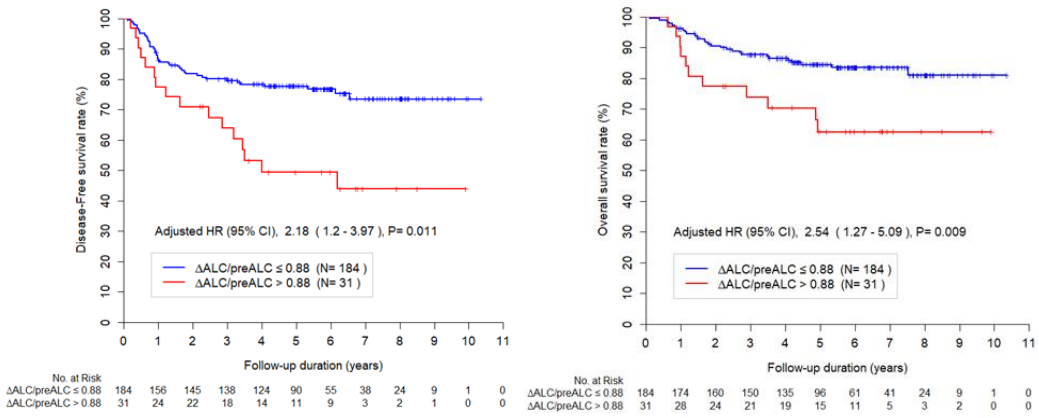

Figure 1. Kaplan-Meier Curves According to ΔALC/preALC for (A) Disease-free Survival and (B) Overall Survival in Total Dataset (n = 215).

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2.2. Treatment

All Patients received external beam radiation therapy with concurrent chemotherapy. A total of 50.4 Gy with daily fraction size of 1.8 Gy was administered five times per week to the whole pelvis or extended field. Four-field box technique using anteroposterior/posteroanterior and two lateral fields was used in 99.5% of the patients and only one patient received intensity modulated radiation therapy (IMRT). The upper margin of whole pelvic RT was L4-5 junction or L5-S1 junction and that of extended field RT was T12-L1. Extended field RT was performed in case of suspected or positive para-aortic lymph node and the additional lymph node boost was delivered if necessary. High dose-rate intracavitary brachytherapy was started 4–5 weeks after the initiation of external beam radiation therapy in case of definitive treatment or close or positive vaginal resection margin after hysterectomy. The concurrent chemotherapy regimen was weekly cisplatin for six cycles or 5-fluorouracil and cisplatin every three weeks for two to three cycles.

2.3. Endpoints and Statistical Analysis

Patients underwent regular follow-up examinations, including physical examination, hematologic studies, and CT. The endpoints included disease free survival (DFS) and overall survival (OS). DFS is calculated from the start date of initial treatment to the date of recurrence, death, or last follow up. OS is calculated from the start date of initial treatment to the date of death or last follow-up.

To evaluate RT-induced lymphopenia, we used 'ΔALC/preALC' for analysis. 'ΔALC/preALC' was defined as (pre-treatment absolute lymphocyte count (ALC) – nadir ALC during CCRT/pre-treatment ALC) and converted to categorical variable. The optimal cut point of ΔALC/preALC was determined using a Contal and O'Quigley method [13].

A T-test was used to compare the mean values between the groups. The Kaplan-Meier method and log-rank test were used for survival curves. The Cox proportional hazard regression model was used to calculate hazard ratios (HR) and confidence intervals (CI) in univariable and multivariable survival analysis. A p-value of less than .05 was considered statistically significant. Multivariable analysis was performed on variables that showed a probability value of <0.2 or on those that were thought to be relevant with backward selection method. Path analysis was performed using logistic model to examine the relationships between RT-field, lymphopenia, and survival outcome. Statistical analyses were performed using SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patient Characteristics

Patients' characteristics are summarized in Table 1. The median age was 53 years (range, 27–81). Seventy-seven patients (35.8%) had stage I disease, 43 (20.0%) had stage II disease, 91 (42.3%) had stage III disease, and 4 (1.9%) had stage IVa disease. Squamous cell carcinoma was the most frequent histology (n = 180, 83.7%), followed by adenocarcinoma in 30 patients (14.0%), adenosquamous cell carcinoma in 4 patients (1.9%), and mixed cell carcinoma in 1 patient (0.5%). Ninety-eight patients (45.6%) received adjuvant concurrent chemoradiotherapy. In terms of RT field, 179 (83.3%) patients received whole pelvis RT and 36 (16.7%) patients received extended field RT. The median pre-treatment ALC was 1.731 × 103/μL (0.862-3.940) and the median nadir ALC was 0.35 x 103/μL (0.03-0.93).

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Table 1. Patients' characteristics.

Characteristics		*N* (%)
Median age (range, years)		53 (27-81)
FIGO 2018 stage		
	I	77 (35.8%)
	II	43 (20.0%)
	III	91 (42.3%)
	IVa	4 (1.9%)
Pathology		
	Squamous cell carcinoma	180 (83.7%)
	Adenocarcinoma	30 (14.0%)
	Adenosquamous	4 (1.9%)
	Mixed cell carcinoma	1 (0.5%)
RT aim		
	Definitive	117 (54.4%)
	Adjuvant	98 (45.6%)
RT technique		
	2D	48 (22.3%)
	3D	166 (77.2%)
	IMRT	1 (0.5%)
RT field		
	Whole pelvis	179 (83.3%)
	Extended	36 (16.7%)
CTV(Clinical Target Volume) (median, range)		352.75 (120-1122)
Pre-treatment ALC (median, range)		1.731 (0.862-3.940)
Nadir ALC (median, range)		0.35 (0.03-0.93)
ΔALC/pre ALC (%, median, range)		0.804 (0.425-0.981)
Pre-treatment SCC(median, range)		3.45(0.10-78.50)

FIGO = International Federation of Gynecology and obstetrics, RT = radiotherapy, IMRT = Intensity Modulated Radiation Therapy, CTV = clinical target volume, ALC = absolute lymphocyte count, SCC = squamous cell cancer antigen. ΔALC/pre ALC is defined as (pre-treatment ALC - nadir ALC during RT course/pre-treatment ALC). Stage according to the FIGO 2018 classification.

3.2. Cutoff Value of ΔALC/pre ALC

The median ΔALC/pre ALC was 0.804 (0.425-0.981). The optimal cutoff value of ΔALC/pre ALC for prediction of OS and DFS was analyzed and determined to be 0.88.

3.3. Survival Outcomes and Prognostic Factors

The median follow-up time was 61.04 months (range, 1.34-124.02). The DFS at 3-year and 5-year were 85.0% and 73.6%, and OS at 3-year and 5-year were % and 81.0%, respectively. Multivariable analysis for DFS revealed that pre-treatment SCC (HR, 1.02; 95% CI, 1.00–1.03; p = 0.037), pathology (others *vs.* squamous cell carcinomas, HR, 2.58; 95% CI, 1.37-4.83; p = 0.003) and ΔALC/preALC level (>.88 *vs.* ≤0.88, HR, 2.18; 95% CI, 1.20-3.97; p = 0.011) were independent prognostic factors (Table 2).

Multivariable analysis for OS revealed that pathology (others *vs.* squamous cell carcinomas, HR, 2.41; 95% CI, 1.22-4.75; p = 0.011) and ΔALC/preALC level (>.88 *vs.* ≤0.88, HR, 2.54; 95% CI, 1.27–5.09; p = 0.009) were independent prognostic factors (Table 3).

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Table 2. Univariable and multivariable Cox proportional hazard model for disease-free survival (DFS) (n = 215).

Variables	Univariable		Multivariable	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	0.99 (0.97-1.01)	0.314		
Pre SCC (*n* = 208)	1.02 (1.00-1.03)	0.031	1.02 (1.00-1.03)	0.037
FIGO 2018 stage				
I-II	Reference			
III-IV	1.75 (1.04-2.92)	0.034		
Pathology				
SQ	Reference		Reference	
Others	2.03 (1.14-3.61)	0.016	2.58 (1.37-4.83)	0.003
RT field				
Whole pelvis	Reference			
Extended	1.83 (1.01-3.34)	0.048		
ΔALC/preALC				
≤ 0.88	Reference		Reference	
> 0.88	2.47 (1.39-4.39)	0.002	2.18 (1.20-3.97)	0.011

FIGO = International Federation of Gynecology and obstetrics, RT = radiotherapy, ALC = absolute lymphocyte count, SCC = squamous cell cancer antigen. Stage according to the FIGO 2018 classification.

Table 3. Univariable and multivariable Cox proportional hazard model for overall survival (OS) (n = 215).s.

Variables	Univariable		Multivariable	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	0.99 (0.97-1.02)	0.488		
Pre SCC (*n* = 208)	1.01 (0.99-1.02)	0.572		
FIGO 2018 stage				
I-II	Reference			
III-IV	1.81 (0.97-3.40)	0.063		
Pathology				
SQ	Reference		Reference	
Others	2.34 (1.19-4.60)	0.014	2.41 (1.22-4.75)	0.011
RT field				
Whole pelvis	Reference			
Extended	2.17 (1.08-4.35)	0.029		
ΔALC/preALC				
≤ 0.88	Reference		Reference	
> 0.88	2.46 (1.23-4.93)	0.011	2.54 (1.27-5.09)	0.009

FIGO = International Federation of Gynecology and obstetrics, RT = radiotherapy, ALC = absolute lymphocyte count, SCC = squamous cell cancer antigen. Stage according to the FIGO 2018 classification.

3.4. Lymphopenia and RT Field

The mean values of ΔALC/pre ALC according to the RT field were 0.77 and 0.85 in whole pelvis and extended RT group, respectively ($p < 0.001$). The effect of lymphopenia was evaluated in each subset of RT field and Figure 2 shows the Kaplan-Meier curves according to ΔALC/preALC for survival in whole pelvis and extended RT group. In whole pelvis RT subgroup, ΔALC/preALC level was not a significant factor for DFS or OS. In extended RT subgroup, ΔALC/preALC level was a significant factor for DFS or OS.

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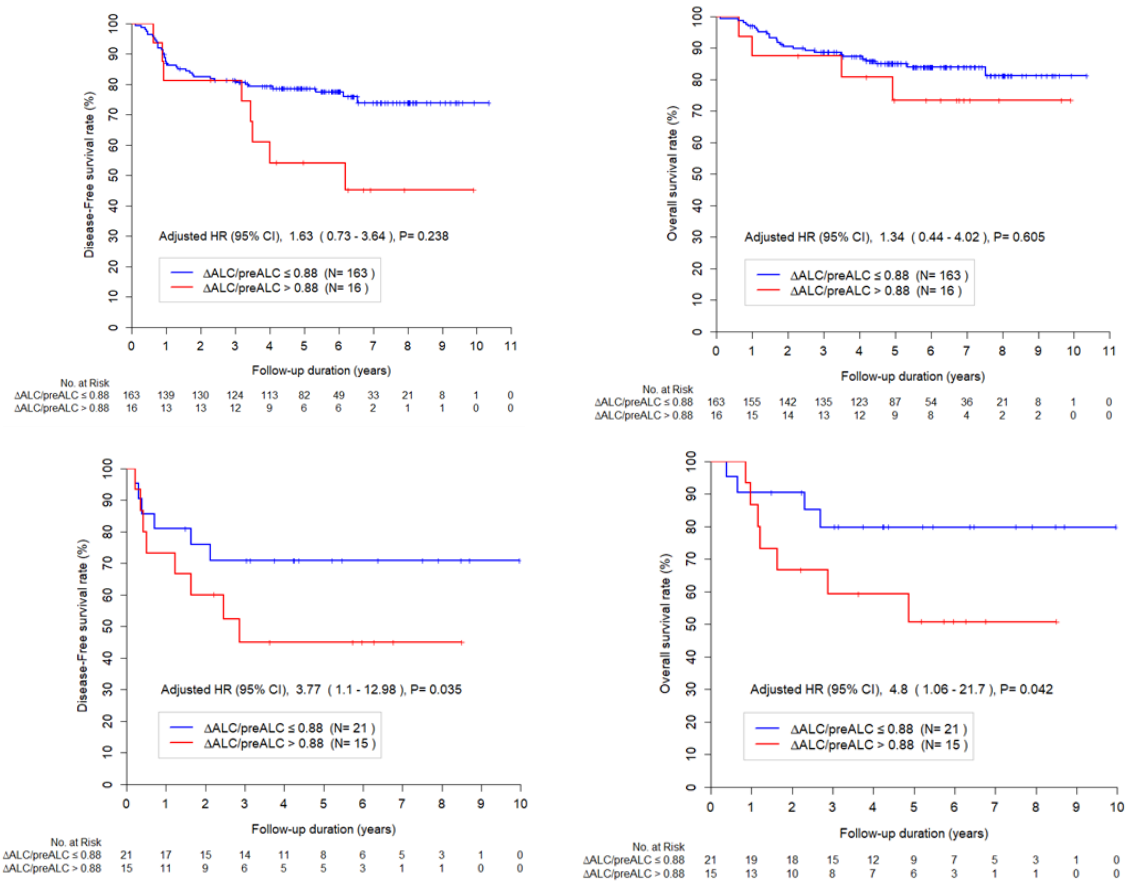

Figure 2. Kaplan-Meier Curves According to ΔALC/preALC for (A) Disease-free Survival, (B) Overall Survival in Whole Pelvis Subset (n = 179), and (C) Disease-free Survival, (D) Overall Survival in Extended Subset (n = 36).

4. Discussion

This study evaluated the impact of lymphopenia during RT on survival in cervical cancer patients. We found that the severe lymphopenia (ΔALC/preALC level > 0.88) was associated with worse DFS and OS in all patients. The definition of RT-induced lymphopenia is heterogeneous in relevant studies [6,8,14]. Several studies use CTCAE criteria and define severe lymphopenia as more than grade 3 or 4 lymphocytopenia while other authors used the cutoff value of 1000cm/L [15]. In this study, we defined RT-induced lymphopenia as the ratio of an individual's pre-treatment ALC to their nadir ALC, in order to reflect the individual's baseline values. In this study, lymphocyte counts decreased by 80% on average from the baseline values during RT, and this is similar to the results from other studies [14].

Furthermore, we found that the severity of lymphopenia and the impact of lymphopenia on survival differ according to the RT field. The degree of lymphopenia was more prominent in the extended RT field group compared to the whole pelvis RT group (mean 0.77 vs. 0.85, $p < 0.001$). The effect of lymphopenia on survival in cervical cancer is not yet established. Several studies showed that lymphopenia is related to worse survival, while others reported that the effect of lymphopenia was not significant after adjustment of other factors [14]. We found that lymphopenia (ΔALC/pre ALC > 0.88) after RT was associated with worse OS in all patients. Because RT field and tumor burden are the most critical confounders for identifying the independent impact of lymphopenia, we examined the effect of lymphopenia in different RT fields. After controlling for all relevant parameters, the effect of lymphopenia (ΔALC/preALC level > 0.88) on survival was most pronounced in the extended field RT group (HR = 5.58) compared to the whole pelvis RT group (HR = 1.20). This finding suggests that we should pay greater attention to the RT-related lymphopenia in individuals who require extended field RT.

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It is essential to determine the influence of treatment-induced lymphopenia on survival because it is a modifiable factor. There are several methods to prevent lymphopenia. Reducing the RT field as much as possible may be the simplest strategy to prevent lymphopenia. Although most guidelines do not recommend irradiating the para-aortic area in patients with just pelvic lymph node metastases, the role of prophylactic extended field RT remains controversial [16–18]. When paraaortic area irradiation is inevitable, the upper margin of the extended RT field may be adjustable factor [18,19]. In this study, T12-L1 was the upper margin in all patients who received extended field RT; however, subrenal vein level (L2-3) could be an option for those with common iliac lymph node metastases or paraaortic lymph node metastases at low level [20]. Bone-marrow sparing planning employing advanced RT techniques such as IMRT or proton therapy is another way to prevent lymphopenia. Recent systematic reviews reported that pelvic bone marrow-sparing radiotherapy significantly decreased severe lymphopenia in cancer patients [21,22]. Proton therapy is remarkably superior in sparing the irradiated volume of the spine and pelvic bone [23]. Hypofractionation is an additional approach that may be utilized to prevent lymphopenia. Sun et al. showed that nadir-ALC was significantly higher in patients who received hypofractionated RT compared to conventional RT [24]. However, whether avoiding lymphopenia with these methods could improve survival is another question that requires further investigation.

This study has several limitations. First, it is a retrospective study with a small number of patients, and potential bias might exist, although we did our best to adjust for confounders with multivariate analysis. In addition, a dosimetric study of irradiated bone marrow in relation to lymphopenia is lacking. Recent studies indicate that certain dosimetric factor of bone marrow are associated with lymphopenia [25,26]. In light of our finding that the RT field is associated with OS, particularly in extended field RT, we will analyze specific dosimetric parameters in a subsequent study. Despite several limitations, this study suggests that radiation oncologists should consider RT-related lymphopenia and try to prevent lymphopenia in cervical cancer patients as much as possible. More research is needed to determine the benefit of bone-marrow sparing IMRT/proton therapy, hypofractionation, or minimizing the RT field in reducing lymphopenia and improving prognosis.

In conclusion, lymphopenia (ΔALC/pre ALC > 0.88) was associated with worse PFS and OS in patients who received RT for cervical cancer; and it was prominent in those who received para-aortic radiation.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Samsung Medical Center (approval number:2022-11-140).

Informed Consent Statement: Patient consent was waived due to its retrospective nature.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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