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ORIGINAL ARTICLE

Radiochemotherapy-related Lymphopenia in Head-and-Neck Cancer

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OBJECTIVE

This study aimed to determine whether lymphopenia and neutrophil-to-lymphocyte ratio (NLR) could be prognostic factors of overall survival (OS), disease-free survival (DFS), or distant metastasis-free survival (DMFS) in patients with head-and-neck cancer (HNC) undergoing radical radiotherapy or chemoradiotherapy.

METHODS

Eighty-four patients' medical records with HNC who underwent radical radiotherapy/ concurrent chemoradiotherapy were retrospectively included in the study. Blood tests were analyzed at the treatment's beginning, middle, and end. The degree of lymphopenia was categorized according to the Common Terminology Criteria for Adverse Events. The OS, DFS, and DMFS were calculated with the Kaplan–Meier method. In addition, univariate and multivariate Cox regression analyses were used to investigate the relationship between lymphopenia and survival.

RESULTS

The median follow-up time of patients was 20 months (range, 3–103). Forty-five deaths and a median 1-year OS of 76% were found. There was no difference in OS (median 27 months vs. 32 months, p=0.674) and DFS (30 months vs. 31 months, p=0.350) between patients who developed and did not develop lymphopenia during radiotherapy. However, survival was significantly worse in patients with G3 lymphopenia than in G1-2 patients (median 21 months vs. 49 months, p=0.033). When patients with an NLR of ≥4.9 and <4.9 were compared, no difference in OS (p=0.156) and DFS (p=0.830) was observed between these two groups. However, DMFS (43.1 months vs. 66.6 months, respectively, p=0.052) was worse in patients with high NLR (≥4.9).

CONCLUSION

Treatment-related G3 lymphopenia and high NLR rate are poor prognostic factors in patients with HNC.

Keywords: Chemoradiotherapy; head and neck cancer; lymphopenia; neutrophil to lymphocyte ratio; overall survival.

INTRODUCTION

Recent developments in immunotherapy have shown us how important the immune reply is in cancer treatment. Lymphocytes have a critical role in the immune response against cancer.[1] Radiation-induced lymphopenia (RIL) may occur during the passage of circulating immune cells through the radiotherapy field or by irradiation of the bone marrow and other lymphoid organs.[2]

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Effect of radiation on lymphocytes may vary depending on the dose of radiation, the size and number of radiotherapy fields and the simultaneous administration of chemotherapy.[3,4] Multiple fields in radiotherapy and simultaneous chemotherapy were associated with lower lymphocyte counts, while stereotactic schemes were associated with higher lymphocyte counts even at higher total doses.[3–6] Lymphocytes are highly sensitive to radiation, and D50 (the dose required for 50% of cells to be inactive) is as low as 2 Gy.[7] Therefore, even if low doses are given, RIL may develop when long fractionated schemes are used due to greater exposure of the blood volume to radiation.[8]

Compared to the fatal effect of immunosuppression after whole-body radiotherapy, focal radiotherapy's lymphopenia effects are not known for certain.[9] However, many studies have shown that RIL plays a role as a negative prognostic factor in solid tumors that are resistant to treatment.[10–21]

In some studies, it has been shown that low lymphocyte count throughout treatment is associated with poor clinical outcomes, particularly overall survival (OS), disease-specific survival, and progression-free survival (PFS) in head-and-neck, lung, rectal, and pancreatic cancers.[22–24]

In recent years, clinical studies measuring the inflammatory response in cancer patients have been started to determine the poor prognosis. One of the biomarkers showing systemic inflammation is the NLR. In these studies, high NLR was reported as an independent prognostic factor indicating decreased survival in cancer.[25–27]

This study investigated the prognostic effect of lymphopenia, and NLR observed during radiotherapy on OS and disease-free survival (DFS) in patients with head-and-neck cancer (HNC) who underwent radical radiotherapy/chemoradiotherapy.

MATERIALS AND METHODS

Eighty-four patients with HNC who underwent radical radiotherapy/radiochemotherapy between 2010 and 2018 were evaluated retrospectively. Blood tests at the beginning, middle, and end of the treatment were analyzed. The lowest lymphocyte count detected was defined as the nadir lymphocyte count. The degree of lymphopenia was classified according to the common terminology criteria for adverse events (CTCAE) version 4.0.[28] In addition, NLR was found by dividing the neutrophil count during the nadir lymphocyte count by the lymphocyte count. The patients were divided into two separate groups according to the median NLR value (<4.9 vs. ≥4.9). Response to radiotherapy was determined according to (tumor responses were evaluated according to the response evaluation criteria in solid tumors, version 1.1) criteria using MRI and PET-CT examinations.[29]

Statistical Analysis

Statistical analyses were performed using IBM® SPSS® 22 (SPSS Inc., Chicago, IL, USA) software. The conformity of the variables to the normal distribution was examined using analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests). Pearson's Chi-square or Fisher's exact Chi-square test was used to analyze all categorical data. Logistic regression analysis was performed to determine risk factors. Kaplan–Meier survival analysis and log-rank (mantel-cox) test were applied for survival analyses (OS and DFS). For univariate and multivariate survival modeling, Cox regression analyses were performed, and the hazard ratio was calculated. $P<0.05$ was considered statistically significant.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local ethics committee where this research was conducted (date: June 15, 2021; number: 2021/06-19). Patient consent information was taken.

RESULTS

A total of 84 patients were included in this study, and patient characteristics are detailed in Table 1. Twenty-three (27.4%) patients were female, and 61 (72.6%) were male. The median age was 60 (26–86). Cigarette use was present in 60 (71.4%) patients, and alcohol use was present in 23 (27.4%) patients. As comorbidity, 18 patients (21.4%) had diabetes mellitus, hypertension, cardiac disease, or at least one. Of the patients, 42 (50%) had laryngeal cancer, 17 (20.2%) had nasopharyngeal cancer, 10 (11.9%) had hypopharyngeal cancer, and 15 (17.9%) had oropharyngeal cancer. As for the stage, 13 (15.4%) of the patients were Stage I, 10 (11.9%) Stage II, 20 (23.8%) Stage III, 36 (42.9%) Stage IVA, and 5 (6%) Stage IVB. Histologically, 66 (78.6%) of the cases had squamous cell carcinoma. As radiotherapy modality, 3D conformal radiation therapy (3D-CRT) was used in 44 (52.4%) cases and intensity-modulated radiation therapy (IMRT) was used in 40 (47.6%) cases. Concurrent chemotherapy (CT) was applied to 57 of the cases

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Table 1 Patient characteristics

Variables	Subgroups	n	%
Gender	Female	23	27.4
	Male	61	72.6
Smoking	No	24	28.6
	Yes	60	71.4
Alcohol	No	61	72.6
	Yes	23	27.4
Comorbidity	No	66	78.6
	Yes	18	21.4
Diagnosis	Larynx	42	50
	Nasopharynx	17	20.2
	Hypopharynx	10	11.9
	Oropharynx	15	17.9
Staging	I	13	15.4
	II	10	11.9
	III	20	23.8
	IVA	36	42.9
	IVB	5	6
Histology	Squamous cell carcinoma	66	78.6
	Non-keratinized NF carcinoma	17	20.2
	Mucoepidermoid carcinoma	1	1.2
Simultaneous chemotherapy	No	27	32.1
	Yes	57	67.9
Radiother radiotherapy modality	3D-CRT	44	52.4
	IMRT	40	47.6
Response to radiotherapy	Complete response	61	72.6
	Partial response	14	16.7
	Stable disease	3	3.6
	Progressive disease	6	7.1
Lymphopenia	Grade 0	34	40.5
	Grade 1	10	11.9
	Grade 2	17	20.2
	Grade 3	23	27.4
	Grade 4	0	0
Neutrophil/lymphocyte ratio, median (min-max)		4.9 (1.3–22.2)	
Age, median (min-max)		60.5 (26–86)	

3D-CRT: 3D conformal radiation therapy; IMRT: Intensity-modulated radiation therapy

(67.9%). The median number of CTs per week was 5 cycles (2–6). In the evaluation made after radiotherapy; complete response was seen in 61 cases (72.6%), partial response in 14 cases (16.7%), stable disease in 3 cases (3.6%), and progressive disease in 6 cases (7.1%). At the end of the study, 45 deaths and a median 1-year OS was 76%. The median follow-up time of patients was 20 months (range, 3–103 months).

Lymphopenia was detected during radiotherapy in 50 (59.5%) of the patients. Grade 1 lymphopenia developed in 10 (11.9%) patients, Grade 2 in 17 (20.2%), and Grade 3 in 23 (27.4%) patients, whereas G4 was not observed in any patient. When we grouped the cases with lymphopenia, 27 (32.1%) had Grade 1–2, and 23 (27.4%) had Grade 3 (Table 2). The median neutrophil-to-lymphocyte ratio was 4.9 (1.3–22.2).

Considering the risk factors related to the development of lymphopenia, in the male gender (p=0.008, OR: 4.6), in Stage III–IV cases (p<0.0001, OR: 7.4), in those who received concomitant chemotherapy (p=0.016, OR: 3.2), in patients without comorbidity (p=0.044, OR: 0.34). Moreover, those with NLR value

Table 2 CTCAE and distribution of our patients' grade groups

Lymphopenia scales	Lymphocyte count	n	%
Grade 0	≥1000 cell/μL	0	0
Grade 1	≥800 cell/μL & <1000 cell/μL	27	32.1
Grade 2	≥500 cell/μL & <800 cell/μL		
Grade 3	≥200 cell/μL & <500 cell/μL	23	27.4
Grade 4	<200 cell/μL	0	0

CTCAE; version 4.0; CTCAE: Common terminology criteria for adverse events

≥4.9 (p<0.0001, OR: 9) were found to develop more lymphopenia (Table 3).

There was no difference in OS (median 27 months vs. 32 months, p=0.674) and DFS (30 months vs. 31 months, p=0.350) between patients who developed and did not develop lymphopenia during radiotherapy. However, survival was significantly worse in patients with Grade 3 lymphopenia than in Grade 1–2 patients (median 21 months vs. 49 months, p=0.033). In addition, there was no difference in DFS between these two groups (p=0.115) (Fig. 1).

Univariate survival analyses for patients with and without lymphopenia are detailed in Table 4. In patients with lymphopenia; While age (<70 vs. ≥70), gender, smoking, alcohol status, comorbidity, histopathology, diagnosis, stage, radiotherapy modality, simultaneous chemotherapy, and NLR value were found to be unrelated for OS, choosing IMRT as the radiother-

Table 3 Factors associated with lymphopenia and risk factors

Variables	Subgroups	Lymphopenia				p	χ^2	Odds ratio
		No		Yes				
		n	%	n	%			
Gender	Female	4	11.8	19	38	**0.008**	**7.0**	**0.22**
	Male	30	88.2	31	62			
Age	<70	23	67.6	42	84.0	0.079	3.1	0.4
	≥70	11	32.4	8	16.0			
Smoking	No	7	20.6	17	34	0.182	1.8	0.5
	Yes	27	79.4	33	66			
Alcohol	No	24	70.6	37	74	0.731	0.12	0.8
	Yes	10	29.4	13	26			
Comorbidity	No	23	67.6	43	86	**0.044**	**4.1**	**0.34**
	Yes	11	32.4	7	14			
Diagnosis	Larynx	19	55.9	23	46	0.791	1.04	0.6
	Nasopharynx	6	17.6	11	22			
	Hypopharynx	3	8.8	7	14			
	Oropharynx	6	17.6	9	18			
Stages	1 and 2	17	50	6	12	**<0.0001**	**14.7**	**7.4**
	3 and 4	17	50	44	88			
Radiotherapy modality	3D-CRT	14	41.2	30	60	0.090	2.88	1.5
	IMRT	20	58.8	20	40			
Simultaneous treatment	Radiotherapy	16	47.1	11	22	**0.016**	**5.83**	**3.2**
	Radiochemotherapy	18	52.9	39	78			
Neutrophil/lymphocyte ratio (median)	<4.9	27	79.4	15	30	**<0.0001**	**19.8**	**9.0**
	≥4.9	7	20.6	5	70			

Pearson's and Fisher Exact Chi-Square tests were used, and p<0.05 was considered significant. Odds Ratio was found with logistic regression analysis. 3D-CRT: 3D conformal radiation therapy; IMRT: Intensity-modulated radiation therapy

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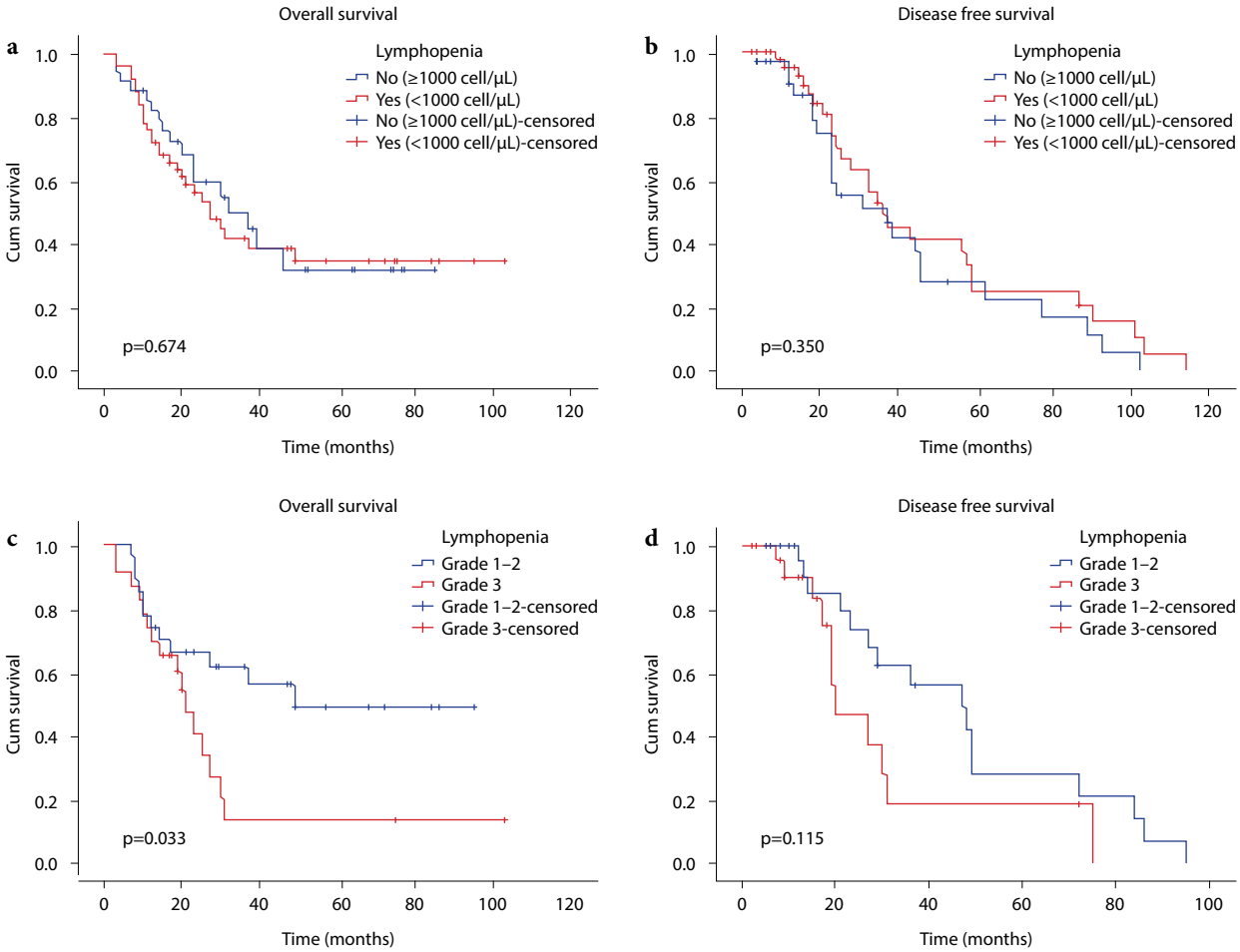

Fig. 1. Kaplan–Meier curves show overall survival (a, c), disease-free survival (b, d) of head-and-neck patients grouped by lymphopenia.

apy modality decreased DFS (HR: 5.13 [1.94–13.53], p=0.001). While only the advanced stage reduced OS in patients without lymphopenia (HR: 4.13 [1.34–12.70], p=0.013), choosing IMRT as a radiotherapy modality decreased DFS (HR: 2.88 [1.01–8.22], p=0.048).

In multivariate survival analyses, these factors were found to be unrelated for survival in patients who developed lymphopenia while smoking (HR: 0.14 [0.02–0.78], p=0.026) and using IMRT as a radiotherapy modality (HR: 15.01 [2.66–84.64], p=0.002) decreased DFS. In patients without lymphopenia, advanced stage (HR: 26.30 [2.67–258.83, p=0.005) and oropharyngeal tumors were associated with worse survival compared to non-oropharyngeal tumors (HR: 15.21 [1.44–160,67], p=0.024), whereas advanced stage (HR: 14.35 [1.02–202.92], p=0.049), use of IMRT (HR: 0.03 [0.00–072], p=0.031) and concurrent chemotherapy (HR: 11.69 [2.05–66.54], p=0.006) were associated with worse DFS.

According to the neutrophil-to-lymphocyte ratio, when patients with ≥4.9 and <4.9 were compared, there was no difference in OS (p=0.156) and DFS (p=0.830). However, patients with high NLR (≥4.9) had worse distant metastasis-free survival (DMFS) (43.1 months vs. 66.6 months, p=0.052, respectively) (Fig. 2), whereas no significance was found for local recurrence (p=0.084). Furthermore, considering the risk factors related to NLR, early-stage (p=0.028), radiochemotherapy (p=0.035), and presence of lymphopenia (p<0.001) were associated with higher NLR.

DISCUSSION

In our study, the effect of lymphopenia and high neutrophil-to-lymphocyte ratio developed during the treatment on OS and DFS was investigated in 84 patients with HNC who underwent RT/CRT. Grade 3 lympho-

Table 4 Univariate and multivariable analysis of OS and DFS in lymphopenia and non-lymphopenia patients

Variables	Overall survival				PFS			
	Univariate, HR (95 % CI)	p	Multivariable, HR (95 % CI)	p	Univariate, HR (95 % CI)	p	Multivariable, HR (95 % CI)	p
Lymphopenia (n=48)								
Age (<70 vs ≥70)	2.07 (0.88–4.88)	0.097	0.81(0.12–5.36)	0.826	1.62 (0.59–4.40)	0.347	0.82 (0.05–12.59)	0.888
Gender (males vs females)	0.84 (0.39–1.83)	0.657	0.86(0.24–3.11)	0.815	0.65 (0.30–1.42)	0.281	2.84 (0.67–12.05)	0.156
Smoking status (yes vs no)	1.31 (0.56–3.09)	0.539	0.55(0.13–2.35)	0.423	0.65 (0.30–1.42)	0.280	0.14 (0.02–0.78)	0.026
Alcohol status (yes vs no)	1.31 (0.58–2.95)	0.523	1.81(0.65–5.03)	0.258	1.51 (0.54–4.25)	0.430	1.76 (0.28–11.04)	0.544
Comorbidity (yes vs no)	2.48 (0.59–10.42)	0.216	0.62(0.10–3.65)	0.596	1.75 (0.68–4.50)	0.244	0.22 (0.04–1.13)	0.069
Histopatology (squamous vs non-squamous)	0.36 (0.11–1.20)	0.097	0.47(0.12–1.80)	0.569	0.72 (0.29–1.81)	0.487	1.13 (0.31–4.11)	0.855
Diagnosis (oropharyngeal vs non-oropharyngeal)	0.78 (0.27–2.27)	0.650	0.82(0.25–2.63)	0.734	0.83 (0.28–2.45)	0.729	0.77 (0.15–3.91)	0.756
Stages (I-II vs III-IV)	2.27 (0.54–9.52)	0.266	0.32(0.06–1.56)	0.156	0.69 (0.27–1.77)	0.446	0.45 (0.12–1.68)	0.232
Radiotherapy (3DCRT vs IMRT)	0.45 (0.18–1.09)	0.075	0.53(0.18–1.55)	0.250	5.13 (1.94–13.53)	0.001	15.01 (2.66–84.64)	0.002
Simultaneous treatment (RT vs CRT)	0.55 (0.25–1.22)	0.142	0.66(0.15–3.01)	0.594	0.46 (0.19–1.12)	0.087	0.07 (0.00–1.31)	0.075
NLR (<4.9 vs ≥4.9)	1.54 (0.65–3.62)	0.326	1.98(0.63–6.24)	0.244	1.35 (0.58–3.18)	0.487	2.49 (0.68–9.08)	0.167
Non–lymphopenia (n=34)								
Age (<70 vs ≥70)	2.48 (0.95–6.5)	0.064	2.12 (0.23–19.57)	0.509	1.22 (0.50–3.02)	0.662	0.78 (0.10–6.19)	0.814
Gender (males vs females)	0.40 (0.13–1.25)	0.117	0.10 (0.00–2.79)	0.173	22.78 (0.00–35.98)	0.498	0.00	0.981
Smoking status (yes vs no)	0.69 (0.24–1.97)	0.489	0.89 (0.02–35.87)	0.952	1.35 (0.39–4.62)	0.634	0.42 (0.02–7.97)	0.560
Alcohol status (yes vs no)	1.02 (0.37–2.77)	0.970	2.78 (0.36–21.32)	0.324	0.63 (0.23–1.72)	0.366	0.79 (0.23–2.80)	0.721
Comorbidity (yes vs no)	1.32 (0.46–3.78)	0.609	2.58 (0.28–23.84)	0.403	2.33 (0.95–5.75)	0.065	2.32 (0.63–8.52)	0.203
Histopatology (squamous vs non-squamous)	0.78 (0.25–2.44)	0.675	1.63 (0.27–9.67)	0.591	0.96 (0.33–2.79)	0.835	1.11 (0.12–10.66)	0.928
Diagnosis (oropharyngeal vs non-oropharyngeal)	2.63 (0.92–7.54)	0.072	15.21 (1.44–160.67)	0.024	1.55 (0.51–4.70)	0.436	14.73 (0.32–669.03)	0.167
Stages (I-II vs III-IV)	4.13 (1.34–12.70)	0.013	26.30 (2.67–258.83)	0.005	0.89 (0.35–2.29)	0.813	14.35 (1.02–202.92)	0.049
Radiotherapy (3DCRT vs IMRT)	0.71 (0.26–1.94)	0.506	0.08 (0.00–1.62)	0.101	2.88 (1.01–8.22)	0.048	0.03 (0.00–0.72)	0.031
Simultaneous treatment (RT vs CRT)	2.17 (0.76–6.21)	0.149	1.76 (0.35–8.89)	0.496	0.83 (0.34–2.03)	0.682	11.69 (2.05–66.54)	0.006
NLR (<4.9 vs ≥4.9)	1.53 (0.53–4.37)	0.431	1.18 (0.21–6.69)	0.851	1.68 (0.20–2.36)	0.547	0.77 (0.14–4.12)	0.758

P-value from Cox regression log likelihood-ratio test and p<0.05 was considered significant. OS: Overall survial; DFS: Disease-free survival; PFS: Progression-free survival; HR: Hazard ratio; CI: Confidence interval; 3D-CRT: 3D conformal radiation therapy; IMRT: Intensity-modulated radiation therapy; RT: Radiotherapy; CRT: Chemoradiotherapy; NLR: Neutrophil-to-lymphocyte ratio

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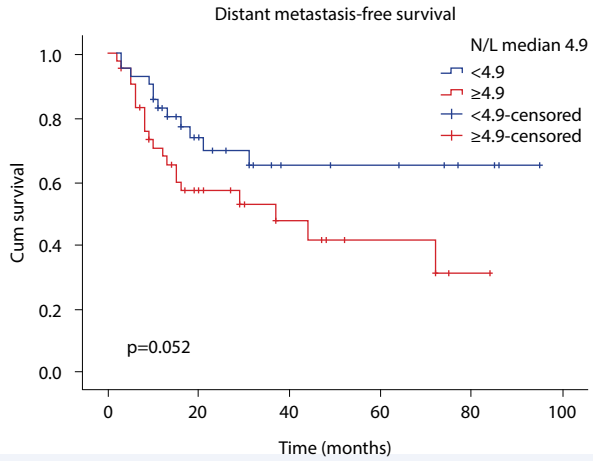

Fig. 2. Kaplan–Meier distant disease-free survival curves for patients with head-and-neck cancer in different N/L groups.
N/L: Neutrophil-to-lymphocyte ratio

penia was found to be associated with poor survival (p=0.033). Considering the risk factors for the development of lymphopenia, it was found that male gender, advanced stage, concomitant chemotherapy, the absence of comorbidity, and high NLR value were associated with lymphopenia development. In the univariate and multivariate analyses, the use of IMRT as a radiotherapy modality in patients with lymphopenia seemed to reduce DFS due to the use of multiple sites (Table 5).

Xie et al.[30] retrospectively evaluated 374 patients with stage I-IVA HNC who underwent definitive RT. Their study reported that low baseline lymphocyte count and IMRT as an RT technique are two independent factors for developing radiation-induced G3-4 lymphopenia. Furthermore, in multivariate analysis, they found longer local recurrence-free survival (p=0.005) and PFS (p=0.022) in patients with G3-4 lymphopenia compared to those with G0-2 lymphopenia, and shorter DMFS in patients who developed only G4 lymphopenia (p=0.037).

In the study of Byun et al.,[31] it was found that in 336 cases with GBM who were treated with RT (3D-CRT/IMRT) and concomitant temozolomide, acute severe lymphopenia (<500/μL) that developed during the treatment and within 3 months of the start of radiotherapy was associated with worse survival (median 18.2 months vs. 22 months, p=0.028). In multivariate analyses, larger PTV increased lymphopenia (p=0.042), and less lymphopenia (p=0.015) developed with the IMRT technique.

In the study of Davuluri et al.,[18] 504 patients with stage I-III esophageal cancer who underwent radiochemotherapy were retrospectively analyzed, and it was observed that G4 lymphopenia developed in 27% of the patients during the treatment. The development of G4 lymphopenia was associated with distal localization, definitive chemoradiotherapy, chemotherapy containing taxan/5-fluorouracil, and photon-based radiation instead of protons. In cases with G4 lymphopenia, worse survival (median 2.8 years vs. 5 years, HR: 1.58, p=0.027) and DFS (median 1.1 vs. 5.1 years, HR: 1.70, p<0.001) were found compared to G0 cases.

In the study of Suzuki et al.,[32] the relationship between pre-treatment lymphocyte count, neutrophil-to-lymphocyte ratio, and platelet-lymphocyte ratio with OS and DFS was evaluated in 122 limited-stage small cell lung cancer patients who underwent chemoradiotherapy. Cutoff values were taken as $1.86.10^3$/mL for lymphocyte count, 3.44 for neutrophil-to-lymphocyte ratio, and 170.53 for platelet-lymphocyte ratio. They showed that high baseline lymphocyte counts were associated with better median survival (17.4 months vs. 15.7 months p=0.029), whereas high neutrophil-lymphocyte and platelet-lymphocyte ratios were associated with worse median survival (14.9 months vs. 17.8 months, p=0.026 and 14.8 months vs. 18.9 months, p=0.009, respectively).

In the study of Liu et al.,[14] it was reported that in 413 Stage II-IVB nasopharyngeal cancer patients who underwent chemoradiotherapy, a minimum lymphocyte count of <390 cells/μL or <705 cells/μL 3 months after treatment was associated with poor prognosis. In multivariate analyses performed, 3rd-month lymphopenia was reported to be an independent prognostic factor for OS (p=0.015), DFS (p=0.003), and distant metastasis-free survival (p=0.014), and they also reported that lymphopenia was associated with a high risk of death (p=0.001), disease progression (p=0.001) and an increased risk of distant metastasis (p=0.002).

Abravan et al.[33] found that OS was associated with high mean thoracic radiotherapy dose, high CRP/albumin ratio, large tumor volume, and corticosteroid use in 62 patients with advanced-stage non-small cell lung cancer who received palliative thoracic radiotherapy. However, they could not detect a relationship between G3 lymphopenia.

Recent studies emphasize that inflammatory markers in peripheral blood (neutrophils, white blood cells, lymphocytes, and monocytes counts, neutrophil-to-lymphocyte ratio, platelet-lymphocyte ratio, and lymphocyte-monocyte ratio) may play a key role in predicting survival.[34–36]

Charles et al.[35] reported that a high NLR (>5) value was predictive for short survival and recurrence-free survival in 145 patients with HNC who received radiotherapy.

Table 5 Differences in clinical characteristics for high and low NLR groups

Characteristic	Subgroups	All patients (n=84)				p
		NLR				
		<4.9		≥4.9		
		n	%	n	%	
Gender	Male	33	78.6	28	66.7	0.221
	Female	9	21.4	14	33.3	
Age	<70	29	69.0	36	85.7	0.068
	≥70	13	31.0	6	14.3	
Smoking	No	12	28.6	12	28.6	1.000
	Yes	30	71.4	30	71.4	
Alcohol	No	30	71.4	31	73.8	0.807
	Yes	12	8.6	11	26.2	
Comorbidity	No	32	76.2	34	81.0	0.595
	Yes	10	23.8	8	19.0	
Diagnosis	Non-oropharynx	34	81.0	35	83.3	0.776
	Oropharynx	8	19.0	7	16.7	
Histopathology	Squamous	33	78.6	33	78.6	1.000
	Non-squamous	9	21.4	9	21.4	
Stages	1 and 2	26	61.9	35	83.3	0.028
	3 and 4	16	38.1	7	16.7	
Radiotherapy method	3DCRT	20	47.6	24	57.1	0.382
	IMRT	22	52.4	18	42.9	
Simultaneous treatment	Radiotherapy	18	42.9	9	21.4	0.035
	Radiochemotherapy	24	57.1	33	78.6	
Metastasis	No	30	71.4	21	50.0	0.044
	Yes	12	28.6	21	50.0	
Grade lenphopenia	Grade 0	27	64.3	7	16.7	<0.001
	Grade 1-2	9	21.4	18	42.9	
	Grade 3-4	6	14.3	17	40.5	
During lenphopenia	No	27	64.3	7	16.7	<0.001
	Yes	15	35.7	35	83.3	

Pearson's and Fisher Exact Chi Square test were used and p<0.05 was considered significant. NLR: Neutrophil-to-lymphocyte ratio; 3D-CRT: 3D conformal radiation therapy; IMRT: Intensity-modulated radiation therapy

In their study, Li et al.[37] investigated the relationship between pre-treatment blood inflammatory markers and survival in 204 advanced-stage esophageal cancer patients who received concurrent chemoradiotherapy. They reported that survival was worse in the high NLR group (mean survival 10.3 months vs. 19.8 months, p<0.05).

In our study, the presence of early-stage disease, administration of radiochemotherapy, and the presence of lymphopenia were found to be risk factors for high NLR. While no correlation was found between NLR and survival and DFS, a borderline increased risk of distant metastases (p=0.053) was found in the high NLR group.

CONCLUSION

Treatment-related lymphopenia and high NLR values are associated with poor prognosis in patients with head-and-neck tumors.

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