TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2019;34(2):92–9
doi: 10.5505/tjo.2019.1845

ORIGINAL ARTICLE

Neutrophil/Lymphocyte Ratio and Prognosis in Patients with Non-Metastatic Nasopharyngeal Cancer: A Single-Center Experience

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OBJECTIVE

Nasopharyngeal cancer's presentation and prognosis are variable. Even patients with the same clinical stage can have very different prognoses. The aim of the present study was to investigate clinical outcomes and prognosis, especially the effects of neutrophil/lymphocyte ratio (NLR), of non-metastatic nasopharyngeal carcinoma (NPC) in patients receiving radiotherapy (RT)±chemotherapy (CT) between March 2006 and August 2017 in the Eskişehir Osmangazi University Medical Faculty of Radiation Oncology Department.

METHODS

Sixty-two patients with non-metastatic NPC treated with RT±CT were retrospectively evaluated. Patient characteristics, such as age, gender, Karnofsky Performance Status (KPS), T phase, N phase, tumor, lymph node, and metastasis phase, histopathologic subgroup, tumor size, NLR, and hemoglobin value, and treatment characteristics, such as concurrent/adjuvant CT status, RT intermission time, and RT total time, were investigated.

RESULTS

Median overall survival (OS) was 55 (10–134) months, whereas median disease-free survival was 44 (6–129) months. The median duration of local control was 48 (6–129) months. Eleven (17.7%) patients developed distant metastases. Distant metastases were detected in 6 (9.7%) patients who had local control. Statistically significant results were obtained between general survival and sex (p=0.015), KPS (p<0.001), and NLR (p<0.001). Distant metastases were found to be significantly higher in male cases, and all 11 metastatic cases were male (Fisher's exact test, p=0.012).

CONCLUSION

Patients with high NLR had lower OS, and pretreatment NLR value may be a guide in determining which patients should receive more aggressive treatment.

Keywords: Nasopharyngeal carcinoma; neutrophil/lymphocyte ratio; prognosis; radiotherapy.

Introduction

The prevalence of nasopharyngeal carcinoma (NPC) varies by race/ethnicity and geographic location.[1] Radiotherapy (RT)±chemotherapy (CT) is the standard treatment for NPC because of its anatomical location and its radiosensitivity.[2] Currently, the prognosis of patients with NPC is primarily evaluated using the tumor, lymph node, and metastasis (TNM) staging system, although in some patients there are inconsis-

Received: February 12, 2019
Accepted: April 14, 2019
Online: May 24, 2019

Accessible online at:
www.onkder.org

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tencies between TNM stages and clinical outcomes.[3] Patients at the same TNM stage show different survival outcomes because the TNM system does not reflect biological heterogeneity.[3,4] To date, plasma cell-free Epstein–Barr virus (EBV) DNA titer remains the only biomarker with clinical utility in NPC.[4-6] Thus, there is a critical need for additional biomarkers for prognostication and precise treatment stratification in patients with this disease. Recently, several studies have reported the association of elevated pretreatment neutrophil/lymphocyte ratio (NLR) with adverse prognoses in multiple tumor types.[7,8] Cancer-associated inflammation has a well-established etiologic link with malignancy.[6] The dynamic crosstalks among immune cells, inflammatory proteins, and cytokines in the tumor microenvironment and systemic circulation are important factors contributing to tumorigenesis and cancer's proliferative and invasive properties. The increased inflammatory response that occurs in response to cancer has been found to correlate with negative clinicopathologic predictors in many operable and inoperable neoplasms.[9] Systemic inflammatory response has been shown to promote cancer progression and metastasis by facilitating angiogenesis, inhibiting apoptosis, and damaging DNA.[5] The NLR is an important biomarker that reflects systemic inflammation.[10]

The aim of the present study was to evaluate the prognostic effect of clinical outcomes and treatment characteristics, especially NLR, in non-metastatic NPC patients receiving RT±CT between March 2006 and August 2017 in our center.

Materials and Methods

Patient Characteristics

A total of 62 patients were included in the study. All patients were diagnosed by a pathologist and were treated with radical treatment between March 2006 and May 2017 in the Eskişehir Osmangazi University Medical Faculty of Radiation Oncology Department. All participants had a detailed history and physical examination records. Patients were evaluated retrospectively.

Patients aged between 18 and 80 years with a Karnofsky Performance Status (KPS) score ≥60 and without distant metastasis were included in the study. Pre-existing cases with NPC with RT, multiple cancer diagnosis, and infection at the beginning of treatment were excluded from the study.

Diagnosis and staging of all patients were completed before treatment. NPC was diagnosed by biopsy in endoscopy guide. All patients underwent head and neck magnetic resonance imaging and/or computed tomography, fluorodeoxyglucose–positron emission tomography computed tomography (FDG-PET CT) imaging and, if necessary, magnetic resonance imaging of the brain. Staging was based on the Union for International Cancer Control/American Joint Committee on Cancer (7th Edition) TNM staging system.

Treatment Characteristics

Ten early-stage cases (T1–T2N0) received RT alone. Two advanced stage cases received RT alone due to age and/or comorbidities. Fifty cases with local advanced disease received both RT and concomitant CT. In consideration of the patient's age, KPS, and comorbid diseases, 43 patients were treated with cisplatin 80–100 mg/m^2 every three weeks, and seven patients were treated with weekly 40 mg/m^2 cisplatin CT regimen. Patients were seen at the clinic at least twice a week. Weekly full blood and blood biochemical controls were performed, and side effects were recorded in our patient tracking system. Forty (64.5%) patients were treated with amifostine. The oral intake and weight of the patient were monitored weekly, and oral nutrition solution or intravenous nutritional support was given according to the needs of the patients. Patients were divided into two groups according to their RT modalities as non-intensity-modulated radiotherapy (IMRT) and IMRT groups. Non-IMRT techniques were applied between 2006 and 2013, and IMRT technique was applied to all patients from 2014 to 2017.

Statistical Analysis

Data were analyzed using SPSS 22.0 (released 2013, IBM SPSS Statistics for Windows, version 22.0; IBM Corp., Armonk, NY, USA). Data are expressed as mean±standard error and number and percentage. Shapiro–Wilk test was used to evaluate the normality of the distribution. Variance analysis (ANOVA) was used to determine the differences between group averages, and Tukey's test was used for post hoc tests to determine the differences. Chi-square test was used in the analysis of the generated cross tables. Kaplan–Meier test was used to compare the mean life span, and the log-rank test was used to identify different groups. Significant variables in the univariate analyses were included in a multivariate Cox regression model to identify the most important prognostic factors. A p value <0.05 was considered statistically significant.

Patient Monitoring

Patients were called for control the first month after treatment, every 3 months for the first 2 years, every

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doi: 10.5505/tjo.2019.1845

6 months until 5 years, and then annually. Detailed head and neck examination and endoscopic evaluation were performed at each control visit. Response evaluation was performed with BT/MR at 1 month after RT and FDG-PET CT at 3 months after RT. If there was a history of cigarette use and clinical indications, thorax CT was required. When local/locoregional relapse or metastasis was detected, treatment decisions were made in multidisciplinary oncology councils.

Results

The median age of the patients was 50 (20–76) years. The study included 42 (67.7%) male patients. The most common histopathologic subtype was undifferentiated nonkeratinized squamous cell carcinoma (SCC) (87.1%). Others were differentiated nonkeratinized SCC (8.1%) and keratinized SCC (4.8%), respectively.

According to the T stage, 6 (9.7%) were T1, 37 (59.7%) were T2, 11 (17.7%) were T3, and 8 (12.9%) were T4. Thirteen (21.0%) cases were N0, 11 (17.7%) cases were N1, 27 (43.5%) cases were N2, and 11 (17.7%) cases were N3. According to the TNM stage, 4 (6.5%) patients had stage I, 10 (16.1%) had stage II, 29 (46.8%) had stage III, 8 (12.9%) had stage IVa, and 11 (17.7%) had stage IVb. Patient characteristics are summarized in Table 1.

The median duration of RT was 52 (42–69) days, and the median time interval between RT was 3 (0–15) days. Adjuvant CT was administered to 49 (79%) cases. Treatment characteristics are summarized in Table 2.

Median overall survival (OS) was 55 (10–134) months, whereas median disease-free survival was 44 (6–129) months. The median duration of local control was 48 (6–129) months. Eleven (17.7%) patients developed distant metastases. Distant metastases were detected in 6 (9.7%) patients who had local control. The median weight loss on follow-up during RT was 3 (0–27) kg. During the follow-up period, 9 (14.2%) cases were diagnosed with hypothyroidism, and 14 (22.5%) cases died due to disease.

OS was 93±8 months for male patients and 126±5 months for female patients (univariate analysis p=0.042 and multivariate analysis p=0.018) (Fig. 1).

Table 1 Patient characteristics

Patient characteristics	Criteria	No. of patients	%
Sex	Male	42	67.7
	Female	20	32.3
Age	≤50	24	38.7
	>50	38	61.3
KPS	≤70	16	25.8
	>70	46	74.2
WHO histologic type	Keratinizing squamous cell carcinomas	3	4.8
	Differentiated nonkeratinizing carcinomas	5	8.1
	Undifferentiated nonkeratinizing carcinomas	54	87.1
T-status	T1	6	9.7
	T2	37	59.7
	T3	11	17.7
	T4	8	12.9
N-status	N0	13	21.0
	N1	11	17.7
	N2	27	43.5
	N3	11	17.7
TNM stage	I	4	6.5
	II	10	16.1
	III	29	46.8
	IVa	8	12.9
	IVb	11	17.7
Tumor diameter	≤3 cm	40	64.5
	>3 cm	22	35.5

RT: Radiotherapy; WHO: World Health Organization.

Table 2 Treatment characteristics

Treatment characteristics	
RT dose	Median 70 (66.6-70) Gy
Duration of RT	Median 52 (42-69) days
RT break time	Median 3 (0-15) days
Amifostine	
+	40 (64.5%) (no. of patients)
-	22 (35.5%) (no. of patients)
Concomitant chemotherapy	
+	50 (80.6%) (no. of patients)
-	12 (19.4%) (no. of patients)
Concomitant chemotherapy protocol	
Weekly cisplatin (40 mg/m^2)	7 (11.3%)
Cisplatin every 3 weeks (80-100 mg/m^2)	43 (69.4%)
Adjuvant chemotherapy	
+	49 (79.0%)
-	13 (21.0%)

RT: Radiotherapy.

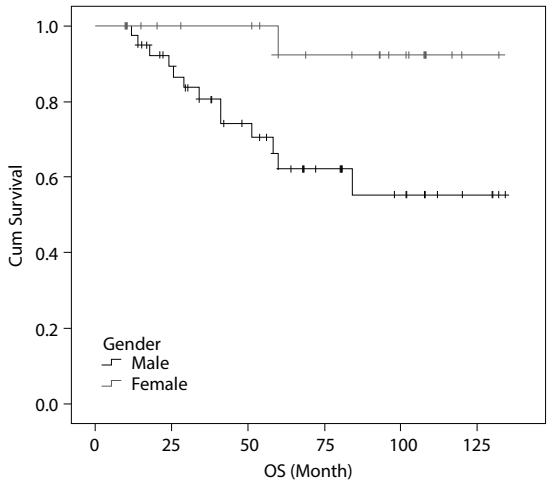

Fig. 1. OS, female versus male patients.

OS was 62±9 months in patients with a KPS ≤70 and 119±6 months in patients with a KPS >70 (univariate analysis p=0.002 and multivariate analysis p=0.067) (Fig. 2).

A significant correlation was found between OS and NLR. In our study, a cut-off value of 3 for NLR was accepted because the mean was 3.3±0.3 and the median was 2.5.

Mean OS was 124±5 months in an NLR <3 cases and 69±9 months in an NLR ≥3 cases (univariate analysis p=0.008 and multivariate analysis p=0.002) (Fig. 3).

The mean OS was 101±9 months in cases with an initial hemoglobin level of ≤13 g/dl and 107±8 months in patients with a hemoglobin level >13 g/dl (univariate analysis p=0.498 and multivariate analysis p=0.234).

The mean OS was 108±7 months in patients with a baseline platelet value ≤250,000/mm^3 and 99±10 months with a platelet count >250,000/mm^3 (univariate analysis p=0.562 and multivariate analysis p=0.206).

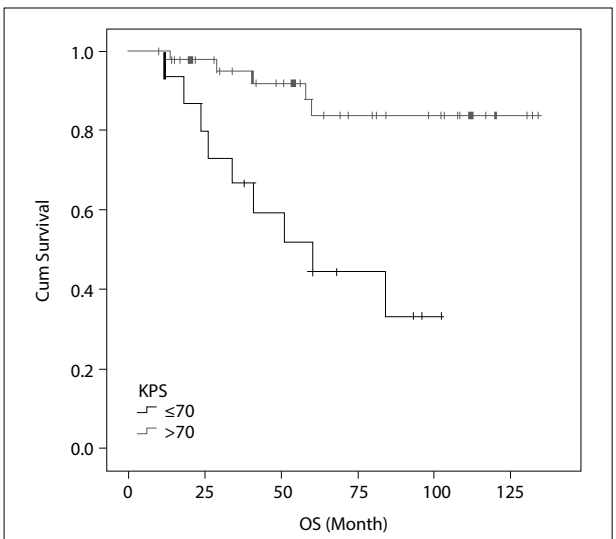

Fig. 2. OS, KPS>70 versus KPS≤70.

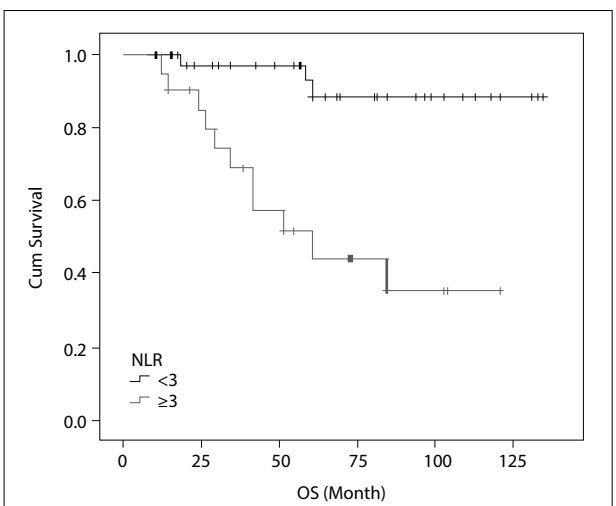

Fig. 3. OS, NLR<3 versus NLR≥3.

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doi: 10.5505/tjo.2019.1845

Table 3 The relationship between hematological blood values and overall survival

Blood value characteristics	Median overall survival (months)	p (univariate/ multivariate)
NLR		p=0.008/p=0.002
NLR <3	124±5	
NLR ≥3	69±9	
Hemoglobin		p=0.498/p=0.234
Hemoglobin ≤13	101±9	
Hemoglobin >13	107±8	
Platelets		p=0.562/p=0.206
Platelets ≤250.000/mm^3	108±7	
Platelets >250.000/mm^3	99±10	

Table 3 summarizes the relationship between hematological blood values and OS.

Weight loss in the 14 patients who died due to cancer progression was 6.0±8.5, whereas it was 3.9±4.0 in the living cases (univariate analysis p=0.025 and multivariate analysis p=0.006). The mean lactate dehydrogenase (LDH) value was found to be 420.2±131.2 in 14 cases who died due to cancer progression, whereas it was 318.7±117.4 in living cases (univariate analysis p=0.011 and multivariate analysis p=0.063).

The results of the univariate and multivariate analyses of OS are summarized in Table 4.

Patients without distant metastasis were found to have statistically significantly longer survivals, as expected. The mean OS was 42±6 months in patients with distant metastases and 121±5 months in patients without distant metastases (p<0.001).

When the relationship between distant metastases and NLR was examined, of the 11 metastatic patients, 7 (63.6%) were in the NLR ≥3 group, and 4 (36.4%) were in the NLR <3 group (p=0.082).

The six cases with distant metastasis while locoregional control was present were also distributed evenly between the NLR groups (three cases in the NLR ≥3 groups and three cases in the NLR <3 group, p=0.661).

NLR status according to some clinical characteristics is shown in Table 5. Mean NLR values according to the TNM stage are shown in Table 6.

Table 5 NLR status according to some clinical characteristics.

Clinical characteristics	Low NLR	High NLR	p
Gender			0.575
Female	14 (70%)	6 (30%)	
Male	25 (59.5%)	17 (40.5%)	
T status			0.605
T1-T2	27 (62.7%)	16 (37.3%)	
T3-T4	12 (63.1%)	7 (36.9%)	
N status			0.338
N0	10 (76.9%)	3 (23.1%)	
N+	29 (59.1%)	20 (40.9 %)	
Distant metastasis			0.082
Yes	4 (36.4%)	7 (63.6%)	
No	35 (68.6%)	16 (31.4%)	

NLR: Neutrophil/lymphocyte ratio.

Table 4 Cox regression analysis: overall survival

Variables	Univariate			Multivariate		
	HR	%95 CI	p	HR	%95 CI	p
Male	8.26	1.07-63.50	0.042	31.45	1.80-547.83	0.018
KPS ≤70	5.63	1.88-16.84	0.002	3.89	0.91-16.65	0.067
T stage	0.82	0.22-2.46	0.733	---		
N stage	0.03	0.00-18.36	0.299	---		
Tumor diamater	0.87	0.29-2.61	0.806	2.32	0.50-10.74	0.281
Concomitant chemotherapy	1.56	0.43-5.62	0.492	0.72	0.06-8.68	0.800
Adjuvant chemotherapy	1.04	0.23-4.67	0.959	126.80	1.89-8471.12	0.024
Hemoglobin	1.44	0.49-4.19	0.498	3.59	0.43-29.43	0.234
Platelets	0.73	0.25-2.11	0.562	0.20	0.03-1.38	0.206
Duration of RT	1.00	0.92-1.09	0.881	---		
RT break time	1.02	0.89-1.17	0.762	---		
LDH	1.00	1.00-1.00	0.011	1.00	1.00-1.01	0.063
NLR ≥3	1.19	1.04-1.35	0.008	0.02	0.00-0.25	0.002
Weight loss	1.11	1.01-1.23	0.025	1.19	1.05-1.34	0.006

KPS: Karnofsky performance status; RT: Radiotherapy; LDH: Lactate dehydrogenase; NLR: Neutrophil/lymphocyte ratio.

Table 6 NLR values according to the TNM stage

TNM stage	Mean NLR	Standard deviation
1	3.13	2.343
2	2.655	1.041
3	2.903	1.611
4	4.446	3.417

NLR: Neutrophil/lymphocyte ratio.

Distant metastases were found to be significantly higher in male cases, and all 11 metastatic cases were male patients (Fisher's exact test p=0.012).

At diagnosis, distant metastases were more frequent in the KPS ≤70 group (Fisher's exact test p=0.026). Additional chronic diseases in patients decrease the KPS values of patients. Patients cannot receive synchronous/adjuvant CT because of comorbidities and secondary low KPS values. It is thought that the increase in the frequency of distant metastases in low KPS patients is due to the lack of CT in their treatment.

The initial hemoglobin level was statistically higher in male patients than in female patients (Fisher's exact test p=0.007); 65% of the female patients had a hemoglobin level ≤13, whereas only 28.6% of male patients were below this level.

Discussion

Nasopharyngeal cancer (NPC) is rather radiosensitive, and RT is the main treatment for NPC. NPC's presentation and prognosis are variable. Even patients with the same clinical stage can have very different prognoses. The aim of the present study was to investigate prognostic factors, especially NLR.

Inflammation is considered to play an important role in the development of cancer, and inflammation may be a negative factor affecting OS of patients with cancer.[11] A statistically significant correlation was found between NLR and OS in the present study. In our study, survival rates were found to be lower in patients with an NLR ≥3.

Different cut-off values are available from different studies. Using an NLR limit of 2.7, Sun et al. found that higher NLR values are associated with shorter progression-free survival.[12] In another study of NPC, an NLR value of ≥3.6 was associated with shorter progression-free survival, disease-specific survival, and OS. Compared with early-stage disease, the statistical relationship between high NLR and poor prognosis was found to be stronger in advanced stage disease.[13] In another study of 229 patients with NPC, the NLR threshold value was accepted as 3.6, and the median survival in the high NLR group was 15.3 months, whereas it was 23.5 months in the low NLR group (p<0.001).[14] In the study conducted by Chen et al. of 211 patients with metastatic NPC, OS was lower in the NLR 5 group (univariate analysis p=0.025 and multivariate analysis p=0.019).[15] In a study of 140 patients with non-metastatic NPC, the NLR threshold was accepted as 2.28, with a lower progression-free survival and OS rates in the high NLR group (p<0.05).[16] In a study of 98 patients with non-metastatic NPC, the NLR limit value was 2.995, and the treatment failure and recurrence rates were higher in patients in the high NLR group (p=0.001).[17] A summary of the literature is shown in Table 7. Similarly, NLR is associated with poor prognosis when we examine the literature examples.

Neutrophils, an inflammatory cell type, are thought to be involved in different stages of tumor development through the production of various cytokines, such as oncostatin M, hepatocyte growth factor, and transforming growth factor-beta.[18] In addition, neutrophils support tumor angiogenesis and also support the release of angiogenic factors, such as vascular en-

Table 7 Literature summary

First author/year	Study year	Number of patients	The reference value of NLR	Outcomes
SUN W, 2015[12]	2008-2011	251	2.70	Short PFS (p=0.001)
LIAO L.J, 2017[13]	2007-2013	180	3.6	Short PFS (p=0.28), OS (p=0.022) and DSS (p=0.011)
JIN Y, 2015[14]	2006-2011	229	3.6	Short OS (p<0.001)
CHEN C, 2014[15]	2005-2011	211	5	Short OS (p=0.025 univariate analysis, p=0.019 multivariate analysis)
LU A, 2017[16]	2009-2010	140	2.28	Short OS (p<0.05) and PFS (p<0.05)
LIEW Y.L, 2017[17]	2005-2009	98	2.995	Short DFS (p=0.000077).

PFS: Progression-free survival; OS: Overall survival; DSS: Disease-specific survival; DFS: Disease-free survival; NLR: Neutrophil/lymphocyte ratio.

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doi: 10.5505/tjo.2019.1845

dothelial growth factor, angiopoietin-1, and fibroblast growth factor-2.[19,20] On the other hand, lymphocytes are also responsible for removing tumor cells.[21] NPC is usually infiltrated by lymphocytes, such as T helper 17 (Th17) cells. Th17 cells are partially regulated by macrophage migration inhibitory factor, produce high levels of cytokines, including tumor necrosis factor and interferon-γ, and mediate the antitumor effects.[22]

For this reason, NLR can affect the survival of patients with NPC by affecting the tumor microenvironment and the immune system. Almost all NLR-related studies in cancer have shown a worsening of the prognosis with higher NLR.[14,23-25] Given the results of various investigations, neutrophil and lymphocyte values appear to provide a balance between inflammation and angiogenesis (neutrophils) and protective immunity (lymphocytes). Disruption of this balance in favor of neutrophils can lead to tumor progression by stimulating angiogenesis.

In the present study, deaths due to disease progression were found to be higher in patients with higher weight loss and those with high pretreatment serum LDH. Weight loss is common in the treatment of NPC. In a study evaluating 2399 patients with NPC, ≥4.6% weight loss was evaluated as critical weight loss. Compared with patients without critical weight loss, patients with critical weight loss had significantly lower 5-year OS (72.4% vs. 79.3%, $p<0.001$), failure-free survival (71.1% vs. 78.4%, $p<0.001$), and locoregional failure-free survival (78.1% vs. 84.8%, $p<0.001$), respectively. In the present study, critical weight loss was accepted as a prognostic factor.[26] There are many studies investigating pretreatment serum LDH levels in NPC. Turen et al. reported the relationship between LDH and OS in 61 patients with stage III–IV NPCs. Serum LDH level was found to be higher (>460 IU/l) in 24.6% of the patients. LDH level was found to correlate with poor 4-year OS (28.5% vs. 68.7%, $p=0.01$).[27]

Limitations of the Study

Our study has limitations. The limitations of the present study include its retrospective and single-centered design and having a small number of patients.

Conclusion

In the present study, pretreatment NLR was found to be a prognostic factor for nasopharyngeal cancer. More patient-specific, multicenter and prospective studies are needed to use NLR as a marker for nasopharyngeal cancer, similar to EBV DNA.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

Ethics Committee Approval: This study was conducted in accordance with local ethical rules.

Financial Support: No support.

Authorship contributions: Concept – M.A., D.E., A.Ö., S.Ş.; Design – M.A., D.E.; Supervision – M.A., D.E.; Materials – M.A., D.E., A.Ö., S.Ş.; Data collection &/or processing – M.A., D.E., A.Ö., S.Ş.; Analysis and/or interpretation – M.A., D.E., A.Ö., S.Ş.; Literature search – M.A., D.E., S.Ş.; Writing – M.A., D.E., A.Ö., S.Ş.; Critical review – M.A., D.E., A.Ö., S.Ş.

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