



Prognostic Factors and Overall Survival in Nasopharyngeal Carcinoma: A Ten-Year Single-Center Experience

Pelda Zümrüt Sevim¹, Abdurrahman Işıkođan², Ulaş Alabalık³, Savaş Topuk⁴, Zuhat Urakçı²

¹ Diyarbakır Gazi Yaşargil Training and Research Hospital, Department of Internal Medicine. Diyarbakır, Türkiye

² Dicle University Faculty of Medicine, Department of Oncology. Diyarbakır, Türkiye

³ Dicle University Faculty of Medicine, Department of Medical Pathology. Diyarbakır, Türkiye

⁴ Dicle University Faculty of Medicine, Department of Radiation Oncology. Diyarbakır, Türkiye

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Abstract

Objective: Nasopharyngeal carcinoma (NPC) is a malignancy originating from the epithelial layer of the nasopharynx. In our study, we aimed to investigate the factors affecting treatment response and survival in patients diagnosed with NPC.

Methods: A retrospective study was conducted on 76 patients aged ≥ 18 years with a pathological diagnosis of NPC who presented to the Oncology Clinic of Dicle University Faculty of Medicine between January 2010 and May 2020. General characteristics of the patients and their effects on overall survival were evaluated.

Results: The mean age of the patients was 46. There were 39 patients (51.3%) under 50 years and 37 patients (48.7%) ≥ 50 years. 18 were female (23.7%) and 58 were male (76.3%). The mean body mass index (BMI) was 24.1 ± 5.2 . 39 patients (51.3%) were smokers, and 37 patients (48.7%) were not. At the time of diagnosis, 11 patients (14.5%) were TNM Stage 2, 39 patients (51.3%) were Stage 3, and 26 patients (34.2%) were Stage 4. According to the WHO 2005 histological classification, there were 30 patients (39.5%) in Type 2A and 40 patients (52.6%) in Type 2B. There were no patients with Type 1 or Type 3 tumors. Other tumor types were detected in 6 patients (7.9%). In the survival analysis, 25 patients (32.9%) were deceased and 51 (67.1%) were alive. Kaplan-Meier analysis revealed a mean survival time of 108 months (95% CI = 88-128). Multivariate Cox regression analysis showed that advanced stage of TNM at diagnosis, low BMI, and high serum lactate dehydrogenase (LDH) levels negatively impacted survival ($p=0.017$, $p=0.04$, $p=0.04$, respectively).

Conclusion: In NPC, the patient's TNM stage at diagnosis, BMI level, and serum LDH level may be independent prognostic risk factors.

Keywords: Nasopharyngeal carcinoma, prognostic factor, overall survival

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Correspondence / Yazışma Adresi: Zuhat Urakçı, Diyarbakır Gazi Yaşargil Eğitim Araştırma Hastanesi, İç Hastalıkları ABD. Diyarbakır, Türkiye e-mail: dr.zurak@hotmail.com

Nazofaringeal Karsinomda Prognostik Faktörler ve Genel Sağlıkım: Tek Merkezli 10 Yıllık Deneyim

Öz

Amaç: Nazofaringeal karsinom (NFK), nazofarenksin epitel tabakasından kaynaklanan bir malignitedir. Çalışmamızda, NFK tanılı hastalarda tedavi yanıtı ve sağlıkımı etkileyen faktörleri araştırmayı amaçladık.

Yöntemler: Ocak 2010-Mayıs 2020 tarihleri arasında Dicle Üniversitesi Onkoloji polikliniğine başvuran ≥ 18 yaş ve patolojik tanısı NFK olan 76 hasta retrospektif olarak incelendi. Hastaların genel özellikleri ve genel sağlıkım üzerine etkileri değerlendirildi.

Bulgular: Hastaların ortalama yaşı 46 idi. < 50 yaş 39 (%51,3), ≥ 50 yaş 37 hasta (%48,7) vardı. 18'i kadın (%23,7), 58'i erkekti (%76,3). Ortalama beden kitle indeksi (BMI) 24.1 ± 5.2 idi. 39 hastada (%51,3) sigara içimi vardı, 37 hastada (%48,7) yoktu. Tanı anında 11 hasta (%14,5) TNM Evre 2, 39 hasta (%51,3) Evre 3 ve 26 hasta (%34,2) Evre 4 idi. WHO 2005 histolojik sınıflamasına göre Tip 2A'da 30 (%39,5) ve Tip 2B'de 40 (%52,6) hasta vardı. Tip 1 ve Tip 3 hasta yoktu. 6 hastada (%7,9) diğer tümör tipleri tespit edildi. Sağlıkım analizinde, hastaların 25'i (%32,9) ölü, 51'i (%67,1) hayattaydı. Kaplan-Meier analizi sonucu ortalama sağlıkım süresi 108 ay (%95 CI= 88-128) olarak bulundu. Multivariate Cox regression analizinde tanı anındaki TNM ileri evrenin, BMI düşüklüğünün ve serum laktat dehidrogenaz (LDH) düzeyi yüksekliğinin sağlıkımı olumsuz etkilediği bulundu (sırasıyla, $p=0.017$, $p=0.04$, $p=0.04$).

Sonuç: NFK'de hastanın tanı anındaki TNM evresi, BMI düzeyi ve serum LDH düzeyi bağımsız prognostik risk faktörü olabilir.

Anahtar kelimeler: Nazofaringeal karsinom, prognostik faktör, overall survival.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a rare malignancy originating from the epithelium of the nasopharynx, accounting for approximately 0.6% of newly diagnosed cancers¹. It differs from other head and neck tumors due to its epidemiology, histological features, and biological behavior. It is more common in Southeast Asia, South China, the southern coast of Hong Kong, and Taiwan, and this geographical difference is thought to be related to dietary and genetic factors². The incidence of NPC increases with age, peaks between the ages of 50–59, and then decreases³.

Treatment success and survival are higher in patients diagnosed at an early stage, and chemotherapy (CT) toxicity and additional costs can be avoided. However, due to the anatomical location of the nasopharynx, NPC is usually diagnosed at a late stage, and the risk of metastasis is high at the time of diagnosis⁴. These anatomical features also complicate treatment planning. A multidisciplinary

approach is essential in the treatment of NPC; Surgery has a limited role in NPC, whereas radiotherapy (RT) remains the primary treatment modality in early-stage disease. However, since most patients present in the advanced stages, it has been shown that adding chemotherapy to RT increases disease-free survival in this group^{5–8}.

Prognostic factors affecting survival in NPC are classified as patient-related, disease-related, and treatment-related factors. In this study, we aimed to evaluate the treatment response and factors affecting survival in patients diagnosed with NPC in our own patient population.

METHODS

The study included 76 patients aged ≥ 18 years with a pathological diagnosis of NPC who were followed up and treated at the Oncology Clinic of Dicle University Faculty of Medicine between January 2010 and May 2020. The primary endpoint was the examination of factors

affecting overall survival (OS) during the follow-up period. OS was defined as the time from the date of diagnosis to death from any cause or last follow-up. Patients under 18 years of age, those without a pathological diagnosis, and those who went to another center for follow-up after diagnosis were excluded from the study. Epidemiological factors, tumor characteristics, laboratory and radiological findings, treatment plan, and application methods of the patients were examined. The WHO 2005 classification and the AJCC UICC 8TH (2017) TNM staging classification were used at the time of diagnosis. During the follow-up of the patients, whether recurrence (local-distant disease) occurred, the patient's final status (alive-dead), and mean survival time were examined. Patients with missing recurrence data were excluded from recurrence-related analyses, but were included in survival analyses where outcome data were available.

Statistical analyses of the data obtained in the study were performed using the SPSS (Statistical Package for the Social Sciences) 25.0 statistical software package. Normality of continuous variables was assessed using the Shapiro-Wilk test and visual methods (histograms and Q-Q plots). Variables with normal distribution were expressed as mean \pm standard deviation, while non-normally distributed variables were presented as median (interquartile range). Pearson Chi-square test and Fisher's exact test were used in the analysis of categorical data. Survival analyses were performed using Kaplan-Meier and Cox Regression tests. In these tests, a p-value less than 0.05 was considered statistically significant. Since the survival data were right-skewed, median survival time could not be reached; therefore, mean survival time was reported. This study was approved by the Dicle University Non-Interventional Clinical Research Ethics Committee with decision number 244 dated 16.07.2020.

RESULTS

Demographic characteristics

Data of 76 patients diagnosed with NPC were analyzed. The average age of the patients was 46 years. It was observed to be more frequent in males (76.3%). Most patients had no history of cancer in their personal or family history (96.1% and 75.0%, respectively). The proportion of smokers and non-smokers was similar. Demographic and laboratory parameters of the patients are shown in Table I.

Table I: Demographic and laboratory characteristics of patients

Variable	n=76 (%)	Min	Max
Gender			
Female	18 (23.7)		
Male	58 (76.3)		
Age			
<50	39 (51.3)		
\geq 50	37 (48.7)		
BMI	24.1 \pm 5.2	15.0	43.0
Family history of cancer			
Yes	19 (25)		
No	57 (75)		
History of cancer			
Yes	3 (3.9)		
No	73 (96.1)		
Cigarette			
Yes	39 (51.3)		
No	37 (48.7)		
Cigarettes (packs/year)	26.7 \pm 32	1	100
Alcohol			
Yes	3 (3.9)		
No	73 (96.1)		
Neutrophil ($10^3/uL$)	5.88 \pm 2.33	1.20	12.00
Lymphocyte ($10^3/uL$)	2.04 \pm 1.49	0.38	11.00
Neutrophil/Lymphocyte	3.8 \pm 2.9	0.1	18.1
Platelets ($10^3/uL$)	292 \pm 105	96	690
Hemoglobin (gr/dL)	13.3 \pm 1.9	8.8	17.0
Albumin (gr/dL)	3.6 \pm 0.4	2.4	4.6
LDH (U/L)	251 \pm 160	114	1406
ALP (U/L)	91 \pm 61	23	465

ALP, alkaline phosphatase; BMI, body mass index; LDH, lactate dehydrogenase.

Regarding the occupational groups of the patients, it was found that 12 patients (15.8%) were farmers, 14 (18.4%) were housewives, 11 (14.5%) were laborers, and 10 (13.2%) were unemployed. 29 patients (38.2%) were in various occupations (retired, accountant, teacher, self-employed, engineer, etc.).

Clinical Features

The most frequent symptom at presentation was cervical lymphadenopathy (LAP) (50.0%). Ear pain, tinnitus, and hearing problems were presenting symptoms in 15 patients (19.7%). When the histological types of tumors in our patients were analyzed according to the WHO classification, no patients with Type 1 (keratinized squamous cell carcinoma) and Type 3 (basaloid squamous cell carcinoma) tumors were found. Type 2A (non-keratinized differentiated squamous cell) was detected in 30 patients (39.5%), Type 2B (non-keratinized undifferentiated squamous cell) carcinoma in 40 patients (52.6%), and other tumors were detected in 6 patients (7.9%). Parameters related to the disease and its involvement are summarized in Table II.

Table II: Clinical characteristics of the patients

Variable	n=76 (%)	Min	Max
Presenting symptom			
<i>Cervical LAP</i>	38 (50.0)		
<i>Otological</i>	15 (19.7)		
<i>Rhinitis</i>	12 (15.8)		
<i>Headache</i>	8 (10.5)		
<i>Sore throat</i>	3 (3.9)		
Histological type			
<i>Type 1</i>	0		
<i>Type 2A</i>	30 (39.5)		
<i>Type 2B</i>	40 (52.6)		
<i>Type 3</i>	0		
<i>Other</i>	6 (7.9)		
TNM stage			
<i>Stage 1</i>	0		
<i>Stage 2</i>	11 (14.5)		
<i>Stage 3</i>	39 (51.3)		
<i>Stage 4</i>	26 (34.2)		
Presence of cervical LAP	67 (88.2)		
Cranial nerve involvement	2 (2.6)		
PET-CT (SUVmax)	13.0±6.4	4.6	34.0

LAP, lymphadenopathy; PET-CT, positron emission tomography-computed tomography; SUVmax, maximum standardized uptake value

The TNM stages of the patients at the time of diagnosis were examined. In the T staging, 5 patients (6.6%) were found to be T1, 38 patients (50.0%) T2, 20 patients (26.3%) T3, and 13 patients (17.1%) T4. In the classification based on regional lymph nodes, 8 patients (10.5%) had N0, 11 (14.5%) had N1, 50 (65.8%) had N2, and 7 (9.2%) had N3 disease. In the classification based on M status, 61 patients (80.3%) were found to have M0 disease, while 15 patients (19.7%) were found to have M1 disease.

When the treatment modalities of the patients were examined, it was determined that none of them underwent primary surgery after diagnosis. A total of 34 patients (44.7%) received induction CT (6 (7.9%) received only neoadjuvant CT, 28 (36.8%) received CT and RT after neoadjuvant CT). Of these, 16 (21.1%) received DCF, 8 (10.5%) received cisplatin+docetaxel, 3 (3.9%) received cisplatin+gemcitabine, and 7 (9.2%) received cisplatin+5FU. Apart from induction therapy, 22 (28.9%) patients received primary CT and RT, 11 (14.5%) received consolidation CT after primary CT and RT, 7 (9.2%) received only RT, and 2 (2.6%) patients received RT after primary CT. When the patients' treatment completion status was examined, it was determined that 47 patients (61.8%) completed the treatment and 29 patients (38.2%) did not.

When the response status after induction CT was examined, partial response was observed in 20 patients (26.3%), complete response in 9 patients (11.8%), stable disease in 3 patients (3.9%), and progression in 2 patients (2.6%). Recurrence status in 76 patients was examined; recurrence occurred in 21 (27.6%), while 33 (43.4%) did not. Recurrence status could not be determined in 22 patients (28.9%). Of the 21 patients who experienced recurrence, 4 (5.3%) had local disease and 17 (22.4%) had distant disease.

Survival analysis

The mean follow-up period for patients was 44 months, with a median follow-up period of 28 months. 25 patients (32.9%) died, while 51 (67.1%) were alive. Kaplan-Meier analysis revealed a mean survival time of 108 months (95% CI: 88-128). The median survival time could not be determined.

When the factors affecting OS were examined using univariate Cox regression analysis, it was observed that advanced age, BMI \geq 25, non-

alcohol consumption, TNM stage 2 and 3, completion of treatment, increase in hemoglobin and albumin, and decrease in serum lactate dehydrogenase (LDH) levels increased survival. Significant data from the univariate analysis were examined using multivariate analysis. The results showed that in our study, BMI, TNM stage, and LDH level were independent factors affecting OS ($p=0.04$, $p=0.017$, $p=0.04$, respectively). The results are shown in detail in Table III.

Table III: Univariate and multivariate Cox regression analysis of factors affecting OS

Variable	Group *	n †	Univariate			Multivariate		
			HR	95% CI	p	HR	95% CI	p
Gender	Male	22/58	2.73	0.81-9.15	0.103			
	Female, r.	3/18						
Age		76	1.04	1.01-1.06	0.002	1.03	0.98-1.07	0.18
BMI	\geq 25	7/38	0.86	0.78-0.95	0.005	0.87	0.77-0.99	0.04
	<25, r.	18/38						
Cigarette	Yes	15/39	n.s.	n.s.	0.239			
	No, r.	10/37						
Alcohol	Yes	2/3	5.20	0.04-23.93	0.040	5.08	0.05-25.58	0.32
	No, r.	23/73						
Histological type	Type 2A	9/30	n.s.	n.s.	0.584			
	Type 2B	13/40						
	Other, r.	3/6						
TNM stage ‡	Stage 2	2/11	0.21	0.04-0.94		0.24	0.04-0.96	0.017
	Stage 3	9/39	0.30	0.13-0.72	0.010	0.31	0.13-0.73	
	Stage 4, r.	14/26	-	-	-	-	-	
Presence of cervical LAP	Yes	22/67	n.s.	n.s.	0.904			
	No, r.	3/9						
Treatment completion status	No	15/29	2.65	1.19-5.92	0.017	2.37	0.71-7.83	0.15
	Yes, r.	10/47						
RT type	Conventional	9/21	n.s.	n.s.	0.81			
	IMRT, r.	11/47						
Neutrophil		76	n.s.	n.s.	0.97			
Lymphocyte		76	n.s.	n.s.	0.38			
Neutrophil/Lymphocyte		76	n.s.	n.s.	0.19			
Platelets		76	n.s.	n.s.	0.44			
Hemoglobin		76	0.77	0.63-0.95	0.014	0.82	0.61-1.11	0.21
Albumin		76	0.18	0.08-0.40	<0.001	0.67	0.16-2.71	0.58
LDH		76	1.002	1.000-1.004	0.015	1.00	1.000-1.006	0.04
ALP		76	n.s.	n.s.	0.11			

ALP, alkaline phosphatase; BMI, body mass index; CI, confidence interval; HR, hazard ratio; IMRT, intensity modulated radiation therapy; LAP, lymphadenopathy; LDH, lactate dehydrogenase; n.s., not significant; OS, overall survival; r., reference category; RT, radiotherapy.

* The effects between groups are indicated based on the group in the first row, and the group specified in the second row is referenced. † The ratios show the number of deaths/total number of patients. ‡ Calculations were made in the TNM phase using the Stage 4 group as a reference.

The stages were compared among themselves. A statistically significant difference was found between Stage 2 and Stage 4, favoring Stage 2 (HR=0.24; 95% CI=0.04-0.96; $p=0.043$). When comparing Stage 3 and Stage 4, a statistically

significant difference was found in favor of Stage 3 (HR=0.31; 95% CI=0.13-0.73; $p=0.007$). However, no significant difference was found between Stage 2 and Stage 3 ($p=0.63$). This is shown in Figure 1.

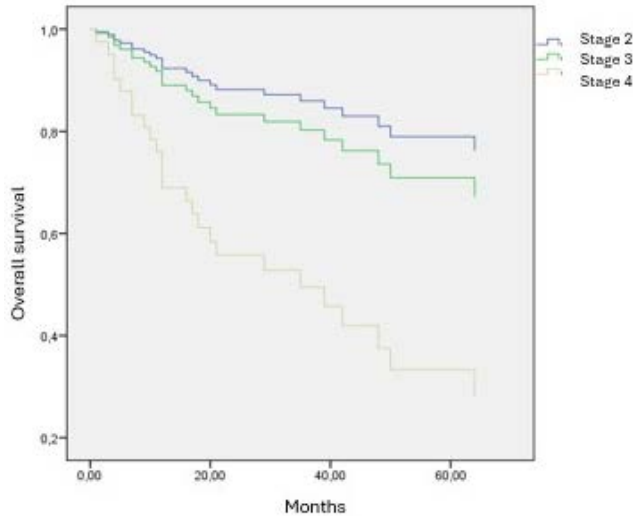


Figure 1. OS graph according to TNM stage

DISCUSSION

Although rare worldwide, NPC is a malignancy with a high incidence in regions such as Southeast Asia, China, and Taiwan, exhibiting a distinct geographical distribution. This epidemiological difference is reported to be related to genetic predisposition and dietary habits^{2,9,10}. The male/female ratio is reported to be approximately 2–3/1 in the literature, with two peaks identified in the age distribution at 15–25 and 50–59 years. In our study, consistent with the literature, male predominance was detected, and the mean age was found to be 46.

Smoking is known to increase the risk of developing NPC. A meta-analysis by Possenti et al. reported that the risk of NPC was 2.37 times higher in smokers¹¹. Although the survival rate was higher in non-smoking patients in our study, this difference was not statistically significant. This may be related to the limited number of patients and the dominant influence of other prognostic factors. Malnutrition and cachexia have significant effects on cancer progression and treatment response.

Cancer-cachexia syndrome has been shown to be associated with increased morbidity and decreased treatment response^{12,13}. A retrospective analysis by Huang et al. reported

that high BMI was associated with better survival¹⁴. In our study, overall survival was found to be significantly higher in patients with BMI ≥ 25 and was confirmed as an independent prognostic factor in multivariate analysis. This finding supports the importance of nutritional status in the prognosis of NPC.

Serum albumin level is an important prognostic marker reflecting inflammation and nutritional status. Low albumin levels have been shown to suppress the immune response, increase systemic inflammation, and accelerate tumor progression¹⁵. A meta-analysis by Yang et al. revealed that low albumin levels are associated with poor prognosis in NPC¹⁶. Although low albumin levels negatively affected survival in our study, they were not identified as an independent factor in the multivariate analysis. This can be attributed to the interaction of albumin with other nutritional and inflammatory parameters.

Hypoxia is one of the fundamental mechanisms of treatment resistance in solid tumors. Hemoglobin level is directly related to tumor oxygenation, and low levels have been associated with decreased tumor control and survival^{17,18}. In the literature, anemia is reported as a poor prognostic factor in NPC patients and is included in prognostic scoring systems¹⁹. In our study, the degree of anemia negatively affected overall survival, but it was not confirmed as an independent factor in multivariate analysis.

LDH is an important biomarker associated with tumor metabolism and hypoxia. High LDH levels are known to reflect tumor burden and aggressive biological behavior²⁰. Previous studies have shown that high LDH is a poor prognostic factor in NPC^{21–23}. In our study, high LDH levels were also identified as an independent prognostic factor negatively affecting overall survival in both univariate and multivariate analyses.

Although the prognostic value of histological subtypes is debatable, non-keratinized types are reported to be more radiosensitive^{24,25}. However, no significant relationship has been shown between histological type and survival in large series¹¹. In our study, no significant difference in survival was found between Type 2A and Type 2B subgroups.

TNM stage is one of the strongest prognostic factors in NPC²⁶. It has been shown that survival decreases significantly as the stage progresses²⁷. In our study, it was also shown that OS decreased significantly as the stage increased and that TNM stage as an independent prognostic factor.

The main limitations of this study are its single-center, retrospective design, the limited number of patients, and the relatively short follow-up period. Furthermore, heterogeneity in treatment protocols and the inability to assess certain prognostic parameters such as EBV viral load limit the generalizability of the results. Nevertheless, the findings are largely consistent with the literature and highlight the prognostic importance of nutritional status, LDH level, and TNM stage in NPC. These results need to be confirmed by larger, prospective studies.

CONCLUSION

In NPC, the patient's TNM stage at diagnosis, BMI level, and serum LDH level can be independent prognostic risk factors. Evaluating these parameters in clinical practice can guide the identification of high-risk patients and the planning of treatment strategies.

Ethics Committee Approval: This study was approved by the Dicle University Non-Interventional Clinical Research Ethics Committee with decision number 244 dated 16.07.2020.

Conflict of Interest: The author(s) declare that there is no financial conflict of interest related to this article.

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