

The Behavior of Nasopharynx Malignancies: a Retrospective Study in a Ten-Year Sample.

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Abstract

OBJECTIVES: Malignant tumors of the nasopharynx make up 3% of malignancies in the ENT area. The most common nasopharyngeal malignancy is nasopharyngeal carcinoma (NPC), followed by lymphomas. Other nasopharyngeal tumors are very rare. In this study, we aimed to assess the age distribution and behavior of the primary nasopharyngeal malignancies, NPC, and lymphoma over a ten-year period in a tertiary hospital patient group.

DESIGN: Retrospective cohort study.

MATERIAL AND METHODS: A total of 48 patients participated in this retrospective monocentric study. The group consisted of 13 females (27.1%) and 35 males (72.9%) diagnosed with nasopharyngeal malignancy and treated between 2012 and 2022. The patients' ages ranged from 14 to 83 years, with a mean age of 57.5 and a median of 55 years. The variables monitored in the study were histology, symptoms (such as nasal obstruction, Eustachian tube function, presence of glue ear, neck mass, weight loss), smoking status, TNM classification, and survival.

RESULTS: In NPC grading and staging, two statistically significant variables were found to be associated with survival: distant metastases ($p < 0.0001$) and stage of the process ($p = 0.0153$). We did not find age and gender to be significant variables for lymphomas ($p = 0.4066$; $p = 0.1797$, respectively) or for NPC ($p = 0.8630$; $p = 0.0573$, respectively). Neither did we find any significant cut-off levels. In our analysis of therapy, we discovered that the use of chemoradiotherapy and palliative care in the NPC group is statistically significantly connected with disease-specific survival ($p = 0.0094$; $p = 0.0004$). This, however, was not the case in the lymphoma group. For the NPC group, we found statistically significant symptoms only in weight loss ($p = 0.0081$) and smoking ($p = 0.0483$).

CONCLUSION: Our research confirmed that nasopharyngeal tumors are rare, with the most common type being nasopharyngeal carcinoma. In our patient group, 76.9% of cases involved nasopharyngeal cancer, which was five times more common in men than in women, and typically occurred in individuals over the age of 50. Lymphomas and other tumors accounted for less than a quarter of the cases. The overall five-year survival rate for nasopharyngeal malignancies in our group was 42.3%. We also observed an interesting gender perspective: 75% of women (6 women) survived for five years, whereas 72.2% of men died within five years of diagnosis.

Abbreviations:

ANOVA	- Wilcoxon Two-Sample test
DSS	- disease-specific survival
WHO	- World Health Organization
HL	- Hodgkin's lymphoma
MC	- myoepithelial carcinoma
NHL	- non-Hodgkin's lymphoma
NPC	- nasopharyngeal carcinoma
PET/CT	- combination of a positron emission tomography (PET) scan and a computed tomography (CT)
PET/MR	- combination of a positron emission tomography (PET) and a magnetic resonance imaging (MRI)
RMS	- rhabdomyosarcoma

INTRODUCTION

Malignant tumors of the nasopharynx make up 3% of malignancies in the ENT area (Chrobok *et al.* 2022). The most common nasopharyngeal malignancy is nasopharyngeal carcinoma (NPC), followed by lymphomas. Other nasopharyngeal tumors are very rare (Slouka, 2018; Stelow & Wenig, 2017).

The occurrence of nasopharyngeal carcinoma (NPC) is well-known to vary widely between regions. The highest occurrence is found in Southern China, ranging from 25 to 50 cases per 100000, while the occurrence in Europe is much lower, at 1 case per 100000 (Chang & Adami, 2006). There are distinct differences in the incidence of tumors between regions. In areas with low incidence, there is a bimodal peak in the age distribution, with the first peak occurring in adolescents and young adults and the second occurring after the age of 65 (Smilek *et al.* 2015). On the other hand, in areas with high incidence, the peak occurs later, between the ages of 40 and 59, and then declines (Tang *et al.* 2016). Furthermore, the incidence of NPC is higher in men than in women, with a ratio of 3:1 (Yu & Yuan, 2002). Environmental factors such as smoking, alcohol consumption, consumption of food containing nitrosamines, demographic and genetic factors, and the Epstein-Barr virus and human papillomavirus infections, are considered to be influential in the development of the disease (Ruuskanen *et al.* 2019; Tsao *et al.* 2014). According to the World Health Organization (WHO), NPC is divided into three subtypes with different clinical attributes: keratinizing squamous cell

carcinoma, differentiated nonkeratinizing carcinoma, and undifferentiated carcinoma (Sinha & Gajra, 2023). In recent decades, both the incidence and mortality of NPC have been decreasing steadily. This shift is likely due to changes in lifestyle and environment, a better understanding of risk factors and disease pathogenesis, increased access to medical care, advances in diagnostic tools—especially in imaging methods—and personalized, comprehensive therapy strategies (Smilek *et al.* 2015, Chen *et al.* 2019).

Lymphoma is the most common type of non-epithelial malignant tumor in the nasopharynx. It is divided into two main groups: Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). Lymphomas account for approximately 5% of head and neck malignancies (Vega *et al.* 2005; Sorrentino *et al.* 2022). Non-Hodgkin's lymphomas are more common (90%) in this area, while Hodgkin's lymphoma accounts for 10% of cases, making up less than 1% of all head and neck lymphomas (Shankland *et al.* 2012; Völker *et al.* 2020). These lymphomas can affect the lymph nodes (nodal) and other areas outside of the lymphatic system (extranodal). Most lymphomas in this area are B-cell non-Hodgkin's lymphomas, with diffuse large B-cell lymphoma being the most common type. However, other types of lymphomas, such as extranodal marginal zone lymphoma (MALT), follicular lymphoma, mantle cell lymphoma, and T-cell lymphoma, can also occur here (Han *et al.* 2017; Hsueh *et al.* 2019; Vega *et al.* 2005). Patients with nasopharyngeal lymphomas are typically over 50 years old, and men are more commonly affected. The five-year survival rate is around 65% (Thompson, 2012). Hodgkin's lymphoma in the nasopharynx is extremely rare, accounting for about 0.32% of all cases of Hodgkin's lymphomas. When it does occur, it is usually diagnosed at stage I or stage II, and, given that most patients are young men, the prognosis with proper diagnosis and treatment is generally good. However, due to its rarity, there is a risk of misdiagnosis with other more common types of tumors (Johnson *et al.* 2014).

The symptoms of nasopharyngeal tumors include obstruction of the upper airways, particularly nasal obstruction, nasal and nasopharynx secretions, nosebleeds, Eustachian tube blockage, neck mass, headaches, and neurological symptoms resulting from pressure on cranial nerves, particularly when the base of the skull is affected. The diagnosis is made through endoscopic and biopsy procedures, along with imaging tests such as ultrasound, CT, or MRI to determine the tumor extent and any potential metastasis. The treatment for nasopharyngeal cancers differs from other ENT area cancers, typically involving radiation therapy (photon or proton) and chemotherapy. Complete surgical removal is usually not feasible; surgery may be considered if lymph node metastases persist after oncological treatment. In cases of persistent or recurrent tumors, surgical resection using an endoscopic approach has

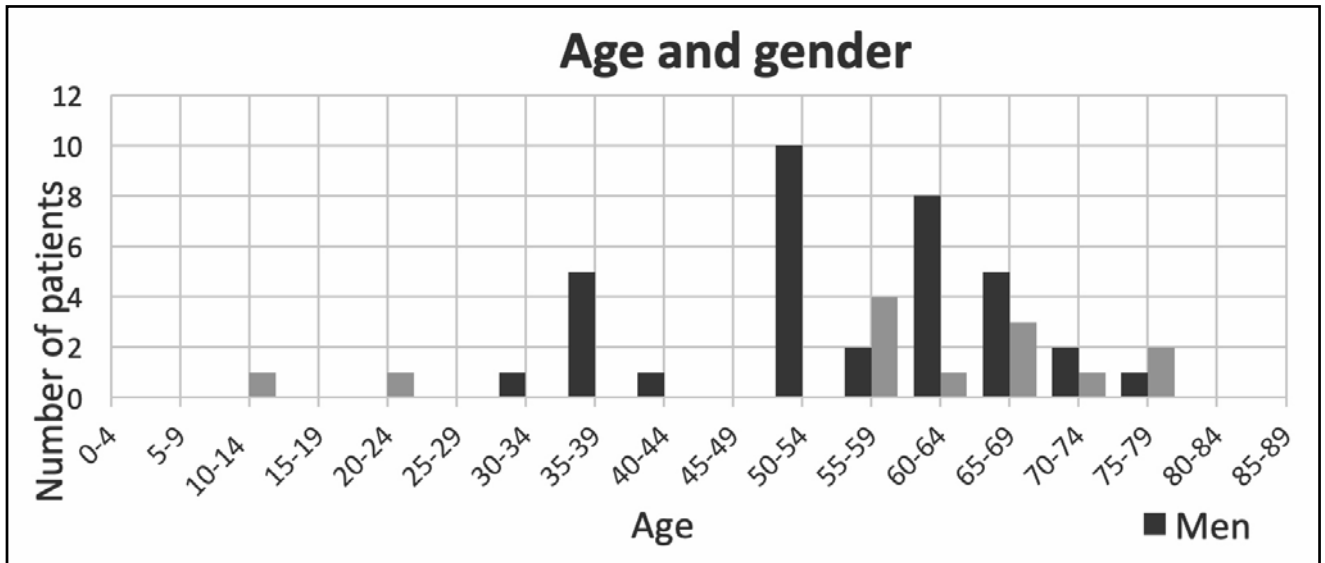


Fig. 1. Age and gender

seen favorable results in recent years (Klozar *et al.* 2021; Tang *et al.* 2021). Nasopharyngeal lymphomas may also present non-specific symptoms like night sweats, fevers, swollen nodes, or weight loss. The diagnosis and non-surgical treatment are similar to those for nasopharyngeal tumors, guided by a hematologist-oncologist (Shankland *et al.* 2012).

In this study, we aimed to assess the age distribution and behavior of the primary nasopharyngeal malignancies, NPC, and lymphoma over a ten-year period in a tertiary hospital patient group.

MATERIAL AND METHODS

Material

Age and gender distribution

A total of 48 patients participated in this retrospective monocentric study. The group consisted of 13 females (27.1%) and 35 males (72.9%) diagnosed with nasopharyngeal malignancy and treated between 2012 and 2022. The patients' ages ranged from 14 to 83 years, with a mean age of 57.5 and a median of 55 years. The mean age for the female group was 62.1 years, while for the male group, it was 55.8 years. The distribution of patients by gender and age can be seen in Figure 1.

Histology and gender distribution

NPC occurred in 37 cases (77,1%), lymphomas in nine cases (18,8 %), rhabdomyosarcoma, and myoepithelial carcinoma in one case. We excluded 13 patients based on the exclusion criteria. (Details in flowchart, figure 2)

Methods

Patients diagnosed with nasopharyngeal tumors were included in the study. All participants underwent an ENT examination and various imaging methods. At the beginning of the ten-year study, CT and sonography were used, but from 2017 onwards, sonography and hybrid versions of CT and MR imaging methods (PET/MR, PET/CT) were employed. Biopsies with histological and immunohistochemical examinations were also carried out. Immunohistochemical examination became a routine practice only during the latter half of the observation period, and not all patients underwent this procedure.

The exclusion criteria for this study included the following: age under 18, incomplete data, prior cancer treatment, previous nasopharyngeal surgery (except adenoid removal), patient non-cooperation with treatment, receiving care from a different ENT department, and alcohol abuse (Fig. 1). The variables monitored

Tab. 1. Histology and gender

	NPC (N=37; 77.1%) Definition						Lymphomas (N=9; 18.8%)				Others (N=2; 4.2%)			
	I.		II.		III.		HL		NHL		RMS		MC	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Men	2	5.4	15	40.5	14	37.8	1	11.1	3	33.3	0	0	0	0
Women	0	0	2	5.4	4	10.8	0	0	5	55.5	1	50	1	50
Total	2	5.4	17	45.9	18	48.6	1	11.1	8	88.8	1	50	1	50

Legend: NPC – nasopharyngeal carcinoma (stage I., II., III.), HL – Hodgkin lymphoma, NHL – non-Hodgkin lymphoma, RMS – rhabdomyosarcoma, MC – myoepithelial carcinoma

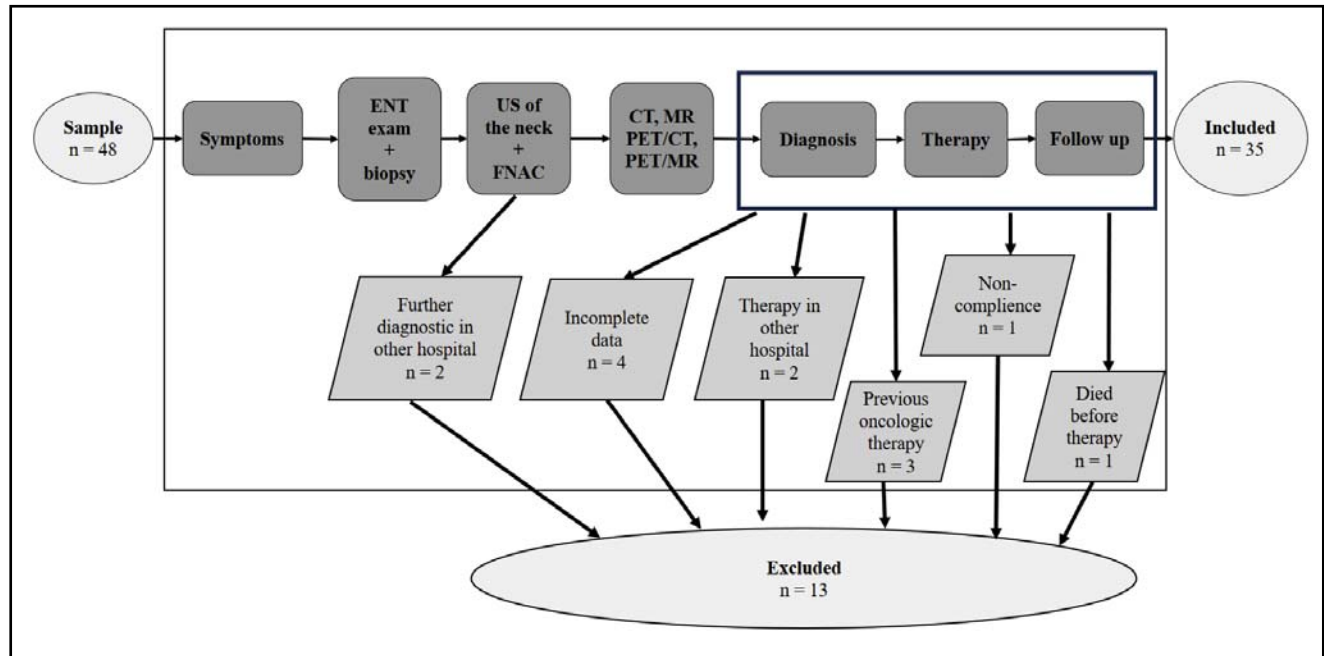


Fig. 2. Flowchart of study

in the study were histology, symptoms (such as nasal obstruction, Eustachian tube function, presence of glue ear, neck mass, weight loss), smoking status, TNM classification, and survival.

The WHO classifies NPC into three distinct histological subtypes: NPC-I. – keratinizing squamous cell carcinoma, NPC-II. – differentiated nonkeratinizing carcinoma, NPC-III. – undifferentiated carcinoma.

RESULTS

Histology in the analyzed sample

There were 35 patients in the final sample. Histological examination revealed only two diagnoses: NPC group with 28 patients (NPC I: 2, NPC II: 13, NPC III: 13) and lymphomas with seven patients (1 HL, 6 NHL patients). Please refer to Table 2 for details. There was no statistically significant connection between disease-specific survival and the type of disease; not for the NPC group ($p = 0.1822$), nor for lymphomas.

In the NPC sample, 10 patients died of NPC, seven died of another disease and 11 patients survived. In

the lymphoma sample, four patients survived, whereas 3 patients died of lymphoma. (Details in Fig. 3)

TNM classification in the NPC group and stage of lymphomas at the time of diagnosis

In the NPC group, there were seven patients graded as T1, ten as T2, four as T3, two as T4, and five as Tx. As for "N-grading," N0 was recorded in two cases, N1 in seven cases, N2 in 14 cases, N3 in three cases, and NX in two cases. (Details in Table 2.) Lymphomas were staged as II., III. and IV. in two cases, and as I. in one case.

In NPC grading and staging, two statistically significant variables were found to be associated with survival: distant metastases ($p < 0.0001$) and stage of the process ($p = 0.0153$). More details can be found in Table 4. In the case of lymphomas, staging was found to be statistically insignificant ($p = 0.1116$).

In the NPC group, the Cox regression hazard model revealed that the hazard ratio for distant metastases was 30.5 with a confidence interval of 3.282-283.111 ($p = 0.0027$), and for stage IV in NPC, the hazard ratio

Tab. 2. Histology and gender

	NPC (N=28; 80 %)						Lymphomas (N=7; 20 %)			
	I.		II.		III.		HL		NHL	
	N	%	N	%	N	%	N	%	N	%
Men	2	7.1	11	39.3	11	39.3	1	12.5	2	25
Women	0	0	2	7.1	2	7.1	0	0	4	50
Total	2	7.2	13	46.4	13	46.4	1	12.5	6	75

Legend: NPC – nasopharyngeal carcinoma (stage I., II., III.), HL – Hodgkin lymphoma, NHL – non-Hodgkin lymphoma

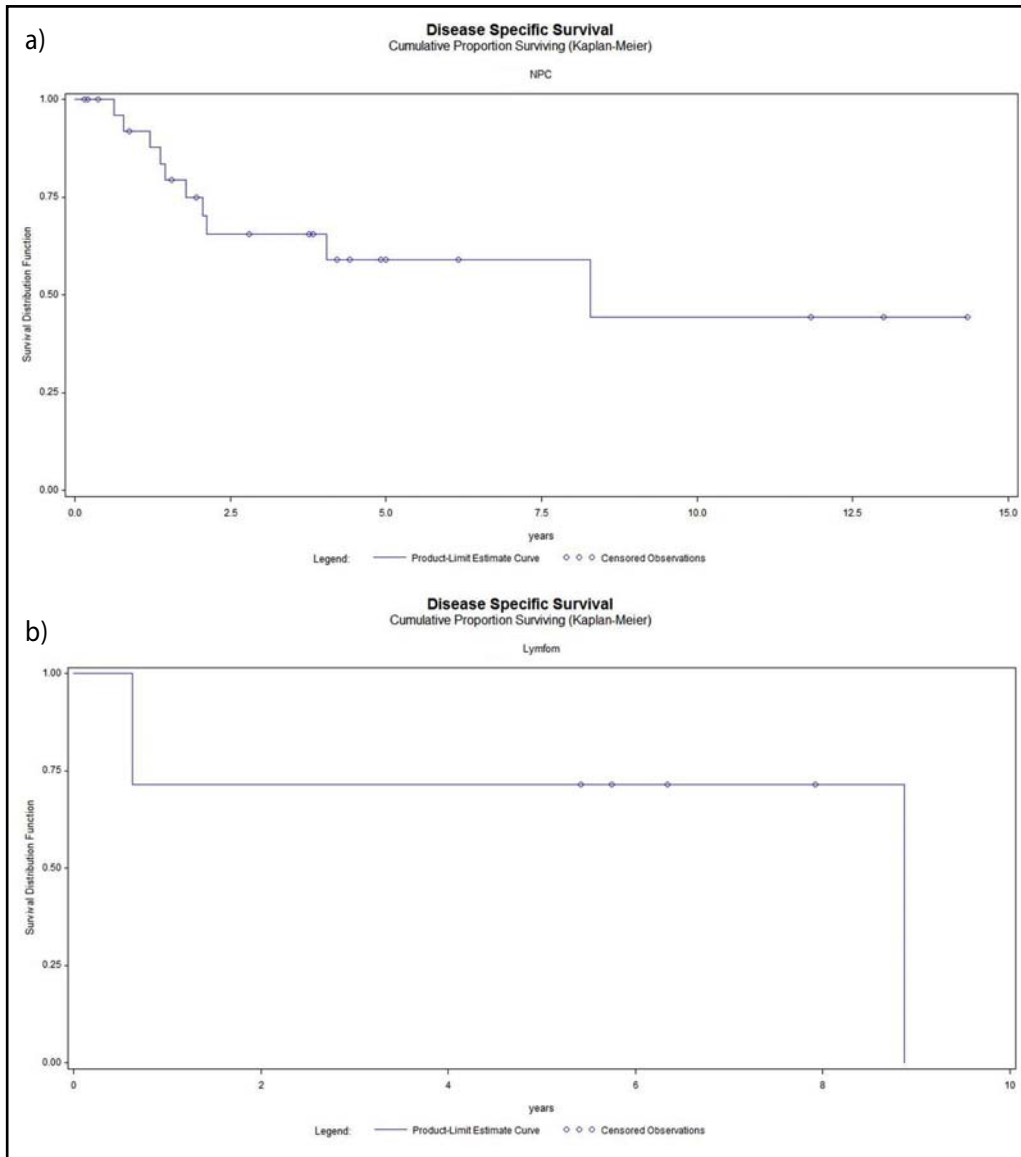


Fig. 3. Disease-specific survival in the NPC group (a) and in the lymphoma group (b)

was 7.718 with a confidence interval of 1.727-29.831 ($p = 0.0067$). Additional details are presented in Table 4.

Symptoms, gender, age and therapy analysis

In our analysis, we did not find age and gender to be significant variables for lymphomas ($p = 0.4066$; $p = 0.1797$, respectively) or for NPC ($p = 0.8630$; $p = 0.0573$, respectively). Neither did we find any significant cut-off levels. In our analysis of therapy, we discovered that the use of chemoradiotherapy and palliative care in the NPC group is statistically significantly connected with disease-specific survival ($p = 0.0094$; $p = 0.0004$). This, however, was not the case in the lymphoma group. For the NPC group, we found statistically significant symptoms only in weight loss ($p = 0.0081$) and smoking ($p = 0.0483$). Further details are provided in Table 5. According to the Cox regression hazard model, in the NPC group, weight loss showed a hazard ratio of 6.9 with a confidence interval

of 1.328-35.317 ($p = 0.0215$), and smoking showed a hazard ratio of 4.4 with a confidence interval of 0.899-21.437 (although $p = 0.0674$). The group of patients with lymphoma showed no statistically significant relationship to the monitored variables.

DISCUSSION

This study is a retrospective analysis of nasopharyngeal tumors sample collected over ten years at the ENT Department in a tertiary hospital. Initially, there were 49 patients in the original group, with 48 patients who had been diagnosed with a malignant tumor and one who had been diagnosed with a benign one (oncocytic cystadenoma). This ratio is consistent with the reported incidence of neoplasia in this location (Mohanty *et al.* 2013; Chrobok *et al.* 2022). After applying the exclusion criteria, 14 patients were excluded, including one with a benign tumor who received further treatment at

Tab. 3. TNM of the NPC sample (a) and stage in lymphomas (b)

a)

	T1		T2		T3		T4		TX	
	N	%	N	%	N	%	N	%	N	%
Men	4	14.3	8	28.6	4	14.3	2	7.1	5	17.9
Women	3	10.7	2	7.1	0	0	0	0	0	0
Total	7	25	10	35.7	4	14.3	2	7.1	5	17.9
	N0		N1		N2		N3		NX	
	N	%	N	%	N	%	N	%	N	%
Men	1	3.6	6	21.4	12	42.9	3	10.7	1	3.6
Women	1	3.6	1	3.6	2	7.1	0	0	1	3.6
Total	2	7.1	7	25	14	50	3	10.7	2	7.1
	M0		M1		MX					
	N	%	N	%	N	%				
Men	14	50	4	14.3	5	17.9				
Women	5	17.9	0	0	0	0				
Total	19	67.9	4	14.3	5	17.9				

b)

		I	%	II	%	III	%	IV	%
		Lymphoma 7	Men	0	0	2	28.6	1	14.3
Women	1		14.3	0	0	1	14.3	2	28.6
Total	1		14.3	2	28.6	2	28.6	2	28.6

a different facility. As a result, the final dataset consisted of 35 patients with malignancies.

The most common tumor found in the nasopharynx is carcinoma, which is typically prevalent in Southeast Asia (Tang *et al.* 2016). There is a low incidence of NPC in the Czech Republic. This fact that was reflected in our group of patients. In countries where the tumor is not common, there are usually two peaks in its occurrence: the first peak is seen in young adults and the second peak around the age of 65 (Bossi *et al.* 2021). Our study shows a similar pattern, but with the peaks of occurrence shifted to the age range of 35-39 years and 50-65 years. According to the literature, the incidence of NPC in men is approximately three times higher than in women (Yu & Yuan, 2002), similar to what we observed in our study.

The five-year disease-specific survival rate for adults with nasopharyngeal cancer was 49% in Europe during

the period 2000-2007 and has continued to increase since. However, in Eastern Europe, the trend is that of decreasing incidence (Gatta *et al.* 2015). In the USA, the average five-year survival rate for 2009-2015 was 60%, with variations mainly observed among different ethnic groups (ACS, 2021). According to the work of Zhou *et al.* (2019) the survival rate among Asians is somewhat independent of gender or age at the time of first detection, grading, staging, and treatment. For other ethnicities, age is a variable that impacts the survival rate. In younger individuals (15-45 years), the five-year survival rate is 72%, while in the oldest patients (65-74 years) it is 36% (Bossi *et al.* 2021). In our study, only 30% of patients diagnosed with NPC survive for longer than five years, and there is no established age dependence ($p = 0.0573$), which differs from the aforementioned study. According to the work of Yang *et al.* (2015), the survival rate is influenced

Tab. 4. Analysis of grading and staging in NPC survival

	<i>p</i>	For	<i>p</i>	Hazard ratio	Confidence Limits
N	0.2782	N2,3 versus N0,1	0.1052	5.545	0.698.- 44.020
M	<0.0001	M1 versus M0	0.0027	30.484	3.282-283.111
Stage	0.0153	Stage IV. versus I.,II.,III.	0.0067	7.178	1.727-29.831

Tab. 5. Gender and symptoms

	Gender		Cephalea		Nasal obstruction		ET dysfunction		OMS		Weight loss		Neck mass		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
NPC	Men	23	82.1	6	21.4	5	17.9	8	28.6	4	14.3	4	14.3	17	60.7
	Women	5	17.9	1	3.6	2	7.1	5	17.9	1	3.6	1	3.6	4	14.3
	Total	28	100	7	25	7	25	13	46.4	5	17.9	5	17.9	21	75
	p	0.0573		0.2562		0.4932		0.8825		0.6140		0.0081		0.3360	
Lymphoma	Men	3	42.9	0	0	0	0	1	14.3	0	0	1	14.3	1	14.3
	Women	4	57.1	1	14.3	1	14.3	0	0	1	14.3	0	0	2	28.6
	Total	7	100	1	14.3	1	14.3	1	14.3	1	14.3	1	14.3	3	42.9
	p	0.1797		0.1138		0.3272		0.5271		0.5271		0.1138		0.8231	

by the histological type of tumor and gender, with women having a better prognosis than men. In our work, we did not find an association of disease-specific survival with gender or NPC subtype ($p = 0.8630$ and $p = 0.1822$, respectively). Our results on grading and staging partially differ from the 2019 results of Zhou *et al.* We found a statistically significant connection of disease-specific survival only for the presence of distant metastases in NPC ($p < 0.0001$) and the presence of stage IV disease ($p = 0.0153$).

Hsueh *et al.* (2019) stated in their paper that nasopharyngeal lymphomas are a rare form of primary malignancy, and there is limited data available regarding their epidemiology and treatment outcomes. In our study, we found that the staging of lymphoma was not statistically significant ($p = 0.1116$). Due to the small number of respondents and the extremely rare occurrence of Hodgkin's lymphoma in the nasopharynx, analyzing the connection between survival and lymphoma types was not beneficial. Patients are typically over 50 years old when diagnosed with lymphoma (Skálová, 2007). Tumors are often diagnosed at early stages, leading to a higher five-year survival rate of around 65% (Thompson, 2012). Within our study group, more women (4) than men (3) were diagnosed with lymphomas, but we found no significant connection between survival and age ($p = 0.4066$) or gender ($p = 0.1797$). Our overall survival results align with the global average, with four patients surviving longer than five years post diagnosis, amounting to 80%.

In the analysis of the symptoms conducted on the NPC group, we did not find a significant relationship for most of the individual symptoms (headache, nasal obstruction, Eustachian tube dysfunction, secretory otitis media, or neck mass), nor for their combination ($p = 0.3367$). Furthermore, we found no evidence of a relationship in the literature (Siti-Azrin *et al.* 2017; Suresh & Chandrashekar, 2012). In NPC, only the presence of weight loss showed a hazard ratio of 6.9, with a confidence interval of 1.328-35.317

($p = 0.0215$). In the lymphoma group, there were no statistically significant symptoms from the perspective of disease-specific survival.

Tumors in the nasopharynx, like other tumors, can recur. Based on several studies, recurrence happens in 15-58% of patients (Xu *et al.* 2013). In line with the literature, we found that six of our patients (15.4%) experienced recurrence. Five of these cases were nasopharynx cancer (16.7% of patients), and all of the affected individuals were men who passed away within five years of their diagnosis. Additionally, one woman who was diagnosed with non-Hodgkin's lymphoma in 2014 had repeated recurrences, but is still alive.

The results of our study are limited by its monocentric nature and because of the small number of patients. A change in the TNM classification occurred while the study was taking place in 2017; the change was finalized in the Czech Republic in 2018 (Brierley *et al.* 2017). We only started monitoring immunohistochemical markers (p16 positivity, antibodies against LMP-1, p40 antigen, OSCAR positivity) in the middle of the study, so we were unable to include them in a statistical evaluation.

The findings of our research, along with the work of Chua *et al.* (2019) and Jiromaru *et al.* (2022), confirm that despite significant medical advancements, treating nasopharyngeal tumors remains a formidable challenge. While disease diagnosis is generally advanced and prompt in countries with well-developed healthcare systems, we continue to encounter limitations in local screening options, early and late therapy complications, patient quality of life, and suboptimal survival outcomes. We believe that research on transoral robotic resection, immunotherapy, biological treatment, and third-generation chemotherapy regimens shows promise as potential avenues for progress. However, conclusive clinical evidence is currently lacking (Castelnuovo *et al.* 2013; Chua *et al.* 2016; Xu *et al.* 2013).

CONCLUSION

Our research confirmed that nasopharyngeal tumors are rare, with the most common type being nasopharyngeal carcinoma. Our findings generally align with prior publications, particularly regarding the geographical occurrence and the influence of ethnic and genetic factors, as well as patient lifestyles. In our patient group, 76.9% of cases involved nasopharyngeal cancer, which was five times more common in men than in women, and typically occurred in individuals over the age of 50. Lymphomas and other tumors accounted for less than a quarter of the cases. The overall five-year survival rate for nasopharyngeal malignancies in our group was 42.3%. We also observed an interesting gender perspective: 75% of women (6 women) survived for five years, whereas 72.2% of men died within five years of diagnosis.

Statistics

Statistical analysis was performed using SW SAS (SAS Institute Inc., Cary, NC, USA). The investigated groups and subgroups were analyzed using descriptive statistics such as mean, standard deviation, variance, median, interquartile range, minimum, and maximum. Categorical variables were described using absolute and relative frequencies.

The differences in observed distributions were tested using nonparametric ANOVA (Wilcoxon Two-Sample test and Median test). Additionally, the differences in proportions were tested using a χ^2 test and Fisher's exact test.

We calculated the probabilities of disease-specific survival (DSS) using the Kaplan-Meier method. Univariate analyses were conducted using the log-rank test to evaluate survival differences between groups of patients. The Cox proportional hazard model was used to determine the role of individual prognostic factors in assessing DSS. The clinical impact of the investigated factors was evaluated by calculating the hazard ratio. The remission of the disease was analyzed using logistic regression, and the clinical impact of the investigated factors was assessed by calculating the odds ratio.

Statistical significance was determined at the 5% level.

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CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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