Nasopharyngeal carcinoma: an ENT's department 14-year experience

Original Article

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Abstract

Objectives: To analyse the population diagnosed with nasopharyngeal carcinoma over a 14-year period and evaluate the impact of clinical characteristics on overall survival.
Study Design: Retrospective.
Materials and Methods: Review of medical records and analysis of clinical variables, including sex, age, staging, histological subtype, presenting symptoms and their duration, presence of alcohol or tobacco use, EBV status, treatment administered, and overall survival.
Results: A total of 36 patients were included. The most common histological subtype was keratinizing squamous cell carcinoma (61.1%) with a median overall survival of 8,0 ± 6,1 months.
Conclusion: Age, sex, referral, presenting symptoms, symptom duration, staging, EBV status, treatment, and risk factors (smoking and alcohol use) did not have a statistically significant impact on overall survival. In our study, keratinizing carcinoma was associated with a significantly poorer prognosis (HR=7.3; p=0.026).

Keywords: nasopharyngeal cancer, head and neck cancer, risk factors, epidemiology.

Introduction

Nasopharyngeal carcinoma is the most common malignant neoplasm (70–95%) in the nasopharynx, and originates from the respiratory epithelium.[1,2] Globally, its incidence peaks at 40–60 years of age, with a higher prevalence in men.[1,3-7] The disease often presents in the advanced stages, with the most common initial symptom being the onset of cervical swelling.[6] According to the latest World Health Organization classification (2022), nasopharyngeal carcinoma is categorized into three histological types: keratinizing squamous cell carcinoma, non-keratinizing squamous cell carcinoma (subclassified into differentiated and undifferentiated), and basaloid squamous cell carcinoma.[5]

The etiology of nasopharyngeal carcinoma is multifactorial, involving a combination of genetic susceptibility, environmental factors (such as tobacco and alcohol consumption), dietary influence (high intake of nitrosamines and smoked products), and occupational exposure (prolonged contact with formaldehyde and wood dust).[1,4]

Epstein-Barr virus (EBV) infection is a well-known risk factor for nasopharyngeal carcinoma, particularly in endemic (high-risk) regions, where the non-keratinizing histological type predominates, accounting for approximately 90% of the cases.[1,4,5]

These high-risk regions include Southeast Asia, North Africa, Greenland, and Alaska, where the incidence can reach up to 30 cases per 100,000 population.[1,5,8] Mediterranean regions are considered intermediate-risk zones, with an incidence of 3–7 cases per 100,000 population annually.

In Western populations, the incidence of nasopharyngeal carcinoma is estimated at 0.9 per 100,000 population annually, with the keratinizing type being more prevalent than the non-keratinizing variant.

This difference may be attributed to factors such as tobacco and alcohol consumption, as well as human papillomavirus (HPV) infection.[1,4,8-10]

However, studies conducted in Portugal have shown that non-keratinizing squamous cell carcinoma is the predominant histological type (88.0–95.8%),[1,4] with EBV infection consistently associated with this variant. Exogenous risk factors have been identified in the Portuguese population, including the consumption of dried and salted fish and occupational exposure to wood dust among certain professional groups.[1,4,10]

This study aimed to characterize patients diagnosed with nasopharyngeal carcinoma and referred to the otorhinolaryngology service of the Gaia and Espinho Local Health Unit between January 2010 and December 2023, and to evaluate the impact of clinical and epidemiological factors on overall survival.

Materials and methods

This retrospective cohort study analyzed the medical records of patients referred to the otorhinolaryngology service of the Gaia and Espinho Local Health Unit from January 2010 to December 2023. A total of 36 patients diagnosed with nasopharyngeal carcinoma were included in this study. Tumor staging was performed in accordance with the guidelines of the eighth edition of the TNM Cancer Staging System of the American Joint Committee on Cancer.[11]

The evaluated clinical and epidemiological parameters were patient sex, age, tumor stage, histological type, presenting symptoms, duration of symptom progression, referral source, alcohol or tobacco consumption, EBV infection, treatment used, and overall survival. Data were statistically analyzed using the SPSS® version 27.0 .

Overall survival was analyzed using the Kaplan-Meier method complemented with the log-rank test. The relationship between overall survival and clinical characteristics was assessed using Cox regression analysis, with results deemed statistically significant at $p < 0.05$.

Results

A total of 36 patients were included in this study, comprising 26 men (72.2%) and 10 women (27.8%) (Table 1). The median age at diagnosis was 55.5 ± 11.0 years, (range: 28–81 years). Among men, the median age was 56.0 ± 11.6 years (range: 28– 81 years), while it was 54.0 ± 9.9 years (range: 43– 75 years) among women (Table 1). Patients were referred to the otorhinolaryngology service through the emergency room (n = 17, 47.2%), attending physician (n = 7, 19.4%), and internal referral (n = 12, 33.3%) (Table 1).

Histologically, the most frequent type of primary tumor was keratinizing squamous cell carcinoma (n = 22, 61.1%), followed by non-keratinizing squamous cell carcinoma (n = 13, 36.1%) and basaloid carcinoma (n = 1, 2.8%). Among patients with non-keratinizing squamous cell carcinoma, the differentiated

Table 1
Clinical characteristics

Parameter	Frequency	Percentage	p-value
Sex			0,662
Male	26	72,2%	
Female	10	27,8%	
Source of referral			0,992
Emergency service	17	47,2%	
Attending physician	7	19,4%	
Internal referral request	12	33,3%	
Histology of the primary tumor			0,026
Keratinizing squamous cell	22	61,1%	
Non-keratinizing squamous cell	13	36,1%	
Differentiated subtype	9	25,0%	
Undifferentiated subtype	4	11,1%	
Basaloid squamous cell	1	2,8%	
Presenting symptom			0,412
Asymptomatic	1	2,8%	
Cervical mass	12	33,3%	
Otitis media with effusion	10	27,8%	
Nasal obstruction	8	22,2%	
Pain	3	8,3%	
Odynophagia	1	2,8%	
Blood loss	1	2,8%	
Duration of symptom progression			0,412
Asymptomatic	1	2,8%	
< 1 month	4	11,1%	
[1–3] months	15	41,7%	
[3–6] months	13	36,1%	
> 6 months	3	8,3%	
EBV			0,252
Positive	18	50,0%	
Negative	6	16,7%	
Unknown	11	30,6%	
Inconclusive	1	2,8%	
Treatment			0,040
RT[1]	3	8,3%	
QT[2]	2	5,6%	
CRT[3]	29	80,6%	
CRT3 + salvage surgery	1	2,8%	
Palliative care	1	2,8%	
Death			
Yes	11	30,6%	
No	25	69,4%	
Habits			0,281
None	18	50,0%	
Alcohol consumption	1	2,8%	
Tobacco consumption	12	33,3%	
Alcohol consumption and smoking	5	13,9%	

[1]RT - Radiotherapy; [2]CT - Chemotherapy; [3]CRT – Chemoradiotherapy; EBV - Epstein-Barr virus

subtype (n = 9, 25.0%) was more frequent than the undifferentiated subtype (n = 4, 11.1%) (Table 1). The most common presenting symptoms were cervical swelling (n = 12, 33.3%), otitis media with effusion (n = 10, 27.8%), nasal obstruction (n = 8, 22.2%), and pain (n = 3, 8.3%). Less frequent symptoms included odynophagia (n = 1, 2.8%) and blood loss (n = 1, 2.8%). Only one patient was asymptomatic (n = 1, 2.8%) (Table 1).

Regarding the duration of symptom progression, four patients (11.1%) reported symptoms that lasted for less than one month, 15 patients (41.7%) had symptoms for 1–3 months, 13 patients (36.1%) for 3–6 months, three patients (8.3%) for over six months, and one patient was asymptomatic (2.8%) (Table 1).

Regarding testing of histological samples for EBV, 50.0% of patients were EBV-positive and 16.7% were EBV-negative. Among the remaining cases, one patient had an inconclusive result, while EBV testing was not performed in the other cases (Table 1).

Regarding the treatment modalities, the majority of patients (n = 29, 80.6%) underwent chemoradiotherapy (CRT), three patients (8.3%) received only radiotherapy (RT), and two patients (5.6%) received only chemotherapy (CT). Only one patient (2.8%) underwent salvage surgery for cervical metastasis following CRT, while one patient (2.8%) received palliative care alone (Table 1).

At the time of diagnosis, tumor staging revealed that 58.4% of patients had T stage 3 or 4 tumors, reflecting the tumor size. Regarding N staging (regional lymph node involvement), 61.1% of patients were classified as N stage 2 or 3. The majority of patients (83.3%) did not present with metastasis (M staging). Overall, 83.3% of the patients were diagnosed with stage III or IV disease (Table 2).

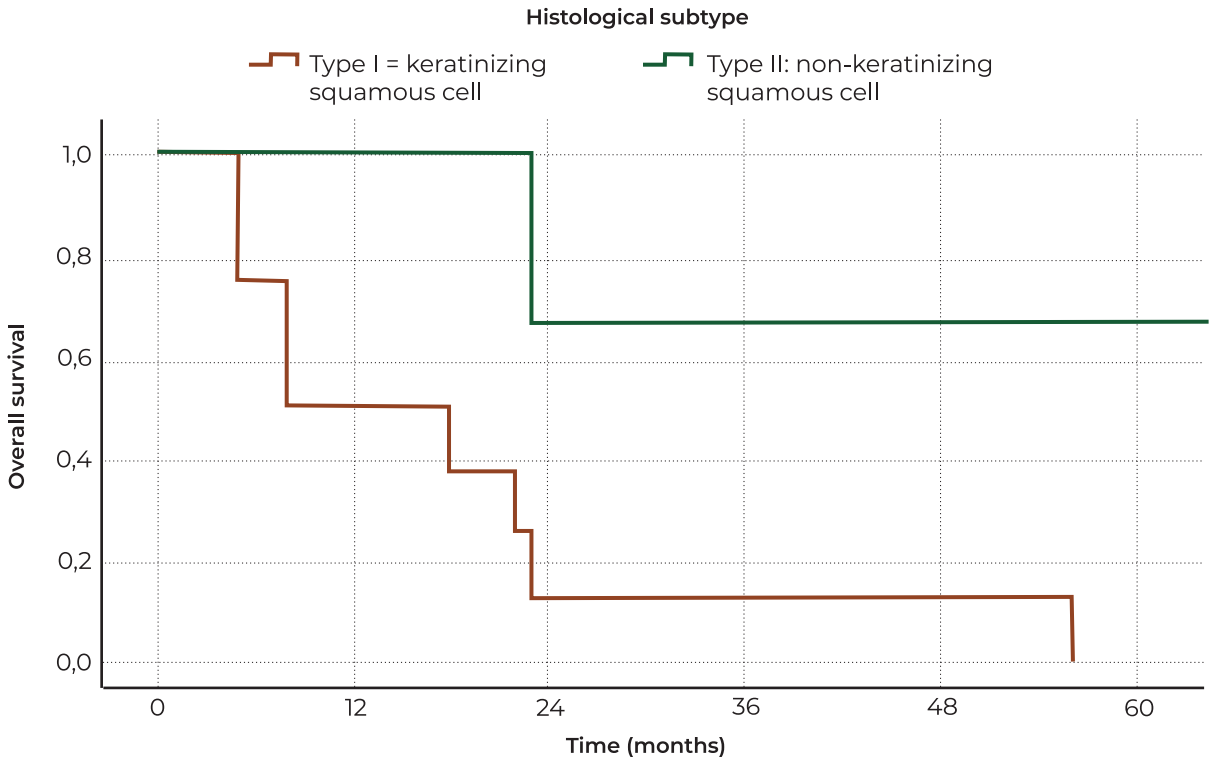
The log-rank test revealed a statistically significant relationship between the histological subtype and overall survival (p=0.026), with keratinizing squamous cell carcinoma being associated with a poorer prognosis. In our cohort, patients with keratinizing squamous cell carcinoma had a median survival of 8.0 ± 6.1 months (95% confidence interval [CI]: 0.0–20.0 months), whereas those with non-keratinizing squamous cell carcinoma had a median survival of 96.0 ± 59.6 months (95% CI: 0.0–212.9 months) (Figure 1). Cox regression analysis revealed a hazard ratio (HR) of 7.3 between the different histological subtypes, with a p-value of 0.035.

Regarding treatment, the log-rank test identified a statistically significant correlation between treatment and overall survival (p=0.040). However, Cox regression analysis did not show a statistically significant difference between the different treatment modalities (p = 0.365). Tumor stage did not significantly affect overall survival (p = 0.739). Separate analyses of T, N, and M staging

Table 2
Staging

Parameter	Frequency	Percentage	p-value
T			0,096
is (in situ)	1	2,8%	
1	8	22,2%	
2	6	16,7%	
3	11	30,6%	
4	10	27,8%	
N			0,897
0	3	8,3%	
1	11	30,6%	
2	17	47,2%	
3	5	13,9%	
M			0,114
0	30	83,3%	
1	4	11,1%	
x	2	5,6%	
Stage			0,739
0	1	2,8%	
I	0	0,0%	
II	5	13,9%	
III	14	38,9%	
IVa	13	36,1%	
IVb	3	8,3%	

Figure 1
Overall survival by histological type



showed no significant differences between the groups (p = 0.096, p = 0.897, and p = 0.114, respectively). Additionally, no statistically significant associations were found between overall survival and factors such as sex (p = 0.662), referral source (p = 0.992), presenting symptoms (p = 0.412), duration of symptom progression (p = 0.412), alcohol or tobacco consumption (p = 0.281), and EBV infection (p = 0.252).

Discussion

The findings of this study align with previously reported data that show the predominance of nasopharyngeal carcinoma in men across all analyzed populations.[1,3-6] Regarding the age distribution, nasopharyngeal carcinoma in non-endemic (low-risk) regions typically has a bimodal distribution, with the first peak at 15–24 years of age and the second peak at 65–79 years. Conversely, in endemic (high-risk) regions, incidence increases with age, peaking between 45–55 years.[7] Although Portugal is considered a low-risk region, national studies have indicated that the median age at diagnosis corresponds to the peak typically observed in high-risk regions.[1,4] In our study, the median age of the patients was at the upper limit of the peak in high-risk regions.

In terms of histology, the most frequent subtype was keratinizing squamous cell carcinoma (61.1%, n = 22) (Table 1). This finding is concurrent with the results of studies on Western populations but differs from the findings of other Portuguese research groups, who reported a significantly higher incidence of non-keratinizing squamous cell carcinoma (95.8%). Potential predisposing factors for nasopharyngeal carcinoma, such as exposure to environmental agents (e.g., wood dust) or dietary habits (e.g., consumption of dried salted fish and smoked products, common in Portugal), as well as the affected ethnic groups, were not evaluated in this study. Future analyses of these factors could help to explain the observed differences in histological distribution of the primary tumor.[1,4,12]

The most common presenting symptom in

our study was cervical swelling (33.3%, n = 12). Although the percentage is lower, this finding is consistent with those of studies from non-endemic countries, where this symptom was described in approximately 60% of the cases. Other frequent symptoms in our study were otitis media with effusion (27.8%, n = 10) and nasal obstruction (22.2%, n = 8), in line with the findings of other national and international studies.[1,6,13]

Most patients reported symptom progression for 1–3 months (41.7%), followed by 3–6 months (36.1%), with only three patients reporting symptoms persisting for more than six months (8.3%). The diagnosis of nasopharyngeal carcinoma tends to be delayed in approximately 50–80% of cases due to a lack of symptoms in the early stages. This is reflected in the high percentage of patients referred in the advanced stages (III and IV) in our study (83.3%) and in the national and international studies.[1,6,13]

The source of referral did not correlate with either the duration of symptom progression (p = 0.128) or overall survival (p = 0.992), indicating that this factor does not influence prognosis.

Previous studies have revealed that nasopharyngeal carcinoma generally has a better prognosis regardless of the histological subtype in an endemic population (often EBV-positive).[1,4,14] Serum EBV levels are a well-studied biomarker for the early diagnosis and prognosis of nasopharyngeal carcinoma, particularly the non-keratinizing type.[14] This biomarker has considerable prognostic value for evaluating the treatment response and detecting disease recurrence,[15] and is also useful in patients with occult primary tumors.[11] However, there are no guidelines regarding the use of EBV plasma assays for staging nasopharyngeal carcinoma, and EBV testing is not routinely performed at our center. In our study, no statistically significant association was found between EBV infection and overall survival (p = 0.252), although not all patients underwent EBV testing.

Regarding the risk factors, *Ji* et al. and *Chang* et al. reported that tobacco use has a prognostic association with nasopharyngeal carcinoma, but alcohol consumption does not.[12,16] *Guo* et al. also identified an association between tobacco use and increased recurrence risk.[17] In our study, no statistically significant association was observed between overall survival and tobacco and/or alcohol consumption (p = 0.281).

The survival rates of patients treated with curative-intent RT are reportedly 80–90% at three years, similar to those of patients treated with CRT, whereas CT alone is associated with lower survival rates.[14] At our center, cT1N0M0 nasopharyngeal carcinoma cases are treated with curative-intent RT, while cT1 N1-3 and cT2-4 tumors are treated with CRT.[9] In our study, most patients underwent CRT (n = 29, 80.6%), with RT alone administered in three cases (8.3%) and palliative CT in two cases (5.6%). Cases with treatment non-compliance or incomplete CRT are detailed in Table 3.

Kaplan-Meier analysis, complemented with log-rank testing, revealed a correlation between the treatment modality and overall survival (p = 0.040). However, Cox regression analysis did not identify statistically significant differences between the effects of different treatment modalities on overall survival (p = 0.365). These results suggest that while all treatment modalities improve overall survival, no statistically significant differences were observed between them.

The histological subtype demonstrated a statistically significant impact on overall survival, with keratinizing carcinoma associated with the worst prognosis (p = 0.026) (Figure 1). Cox regression analysis revealed an HR of 7.3 (p = 0.035), indicating that patients with keratinizing squamous cell carcinoma have a 7.3-fold higher risk of death compared to those with non-keratinizing carcinoma. The median overall survival was significantly lower for keratinizing carcinoma (8.0 ± 6.1 months) compared to that for non-keratinizing carcinoma (96.0 ± 59.6 months). These findings differ from those reported in national and international studies, which showed similar survival rates for the two histological

Table 3
Clinical characteristics of the patients who did not complete CRT [3]

Staging	Proposed treatment	Treatment given	Observations
T3N2M0	CRT[3]	RT[1]	Due to nephrotoxicity induced by the first cycle of CT2, patient underwent radical-intent RT[1].
TisN0M0	RT[1]	RT[1]	History of sinonasal inverted papilloma; patient underwent Caldwell-Luc procedure. Diagnosis of nasopharyngeal carcinoma was made on routine endoscopic examination.
T3N2M0	CRT[3]	RT[1]	Hematologic toxicity after administration of the first cycle of CT[2].
T1N2M1	Palliative CT[2]	Palliative CT[2]	Liver and bone marrow/bone metastases
T3N1M1	Palliative CT[2]	Palliative CT[2]	Lung metastasis
T3N2M0	CRT[3]	CRT[3] + surgery	Imaging suspicion of persistent disease after CRT[3]. Patient underwent bilateral selective CLND[4] of levels II–IV. Histological analysis identified no signs of malignancy.
T4N2M0	Palliative care	Palliative care	Synchronous lung carcinoma

[1]RT - Radiotherapy; [2]CT - Chemotherapy; [3]CRT - Chemoradiotherapy; [4]CLND - Cervical lymph node dissection

types (64.5–65.1% and 80–90% at five years, respectively), but worse outcomes in the advanced stage IV.[1,2,4,14,18] In our study, tumor staging did not demonstrate a statistically significant influence on prognosis (p = 0.364).

Conclusion

This study analyzed 36 patients diagnosed with nasopharyngeal carcinoma at a central hospital in Portugal. It was found that age, sex, referral source, presenting symptoms, duration of symptom progression, staging, EBV infection, treatment modality, and risk factors (tobacco and alcohol consumption) did not significantly affect overall survival. The most frequent histological subtype was keratinizing squamous cell carcinoma, consistent with the findings of previous studies in low-risk regions, but contrasting with the results of other Portuguese studies. This subtype was associated with worse overall survival in our study, a finding that was not significant in previous larger Portuguese studies. These differences in overall survival from those reported in national and international studies may be explained by the high prevalence of keratinizing histology, older median age of patients, presence of risk factors, and advanced disease stage at diagnosis in our sample.

In the future, globalization and migration may contribute to greater genetic and ethnic diversity, potentially impacting the outcomes of nasopharyngeal carcinoma. Given the rarity of this tumor and this study's inherent limitations, further research is warranted. Multicenter and prospective studies focusing on the identification of genetic factors, prevalence of EBV infection, and region-specific environmental parameters are crucial to better understand the observed discrepancies in overall survival.

Conflict of Interests

The authors declare that they have no conflict of interest regarding this article.

Data Confidentiality

The authors declare that they followed the protocols of their work in publishing patient data.

Human and animal protection

The authors declare that the procedures followed are in accordance with the regulations established by the directors of the Commission for Clinical Research and Ethics and in accordance with the Declaration of Helsinki of the World Medical Association.

Privacy policy, informed consent and Ethics committee authorization

The authors declare that they have obtained signed consent from the participants and that they have local ethical approval to carry out this work.

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Scientific data availability

There are no publicly available datasets related to this work.

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