Original Research

Survival determinants and treatment patterns in a European multi-center cohort of patients with nasopharyngeal carcinoma

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DOI: 10.15386/mpr-2999

Manuscript received: 07.05.2026
Received in revised form: 01.06.2026
Accepted: 19.06.2026

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Abstract

Background. Nasopharyngeal carcinoma (NPC) is a distinct head and neck malignancy characterized by marked geographic and ethnic variability, with most studies originating from endemic Asian regions. However, the disease also occurs in non-endemic populations, where prognostic factors and treatment outcomes may differ. This study aimed to evaluate overall survival (OS) in a European multi-institutional cohort of patients with NPC and to assess the impact of disease stage and chemotherapy exposure on survival outcomes.

Methods. A retrospective multicenter study was conducted including patients diagnosed with NPC in six oncology centers across Romania, Italy, Spain, and the United Kingdom. Eligible patients had histologically confirmed NPC and a minimum follow-up of five years. Clinical, demographic, staging, and treatment data were collected from medical records. OS was estimated using the Kaplan–Meier method and compared using the log-rank test. Univariable and multivariable Cox proportional hazards regression analyses were performed to identify prognostic factors.

Results. A total of 416 patients were included, with a mean age of 48.2 years and a predominance of males (68%). Most patients presented with advanced-stage disease (83.7%). Concurrent chemotherapy was administered in 73.3% of cases. Median survival was 204 months in patients receiving chemotherapy and 187 months in those without chemotherapy, with no significant difference between groups ($p = 0.85$). Chemotherapy exposure was not independently associated with OS in multivariable analysis. Increasing age was identified as an independent prognostic factor associated with higher mortality risk (HR 1.03 per year, $p < 0.001$).

Conclusions. In this European multicenter cohort, OS in NPC patients was primarily influenced by age, as demonstrated by independent multivariable Cox regression (HR 1.03 per year, $p < 0.001$), while concurrent chemotherapy was not independently associated with improved survival. Disease stage was used as a stratification variable in the multivariable model to account for non-proportional hazards; accordingly, no hazard ratio for stage is estimated. Kaplan–Meier analysis suggested higher survival probabilities in early-stage disease, though this difference did not reach statistical significance (log-rank $p = 0.099$). Further prospective studies are needed to clarify the role of systemic therapy in non-endemic populations.

Keywords: concurrent chemotherapy, chemoradiotherapy, nasopharyngeal carcinoma, multicentric European research, overall survival

Introduction

Nasopharyngeal carcinoma (NPC) is considered nowadays a biologically and epidemiologically particular head and neck malignancy, being characterized by pronounced geographic and ethnic variability. Its highest incidence rates are reported in a few geographic areas, including Southern China, Southeast Asia, and selected regions of Africa and the Arctic [1–3]. Its pathogenesis is complex, being related to factors like Epstein–Barr virus (EBV) exposure and infection, inherited susceptibility, and environmental factors (for instance, consumption of preserved foods and smoking) [4].

Even if NPC cases are rare in Western countries, its clinical relevance in non-endemic regions must not be underestimated, as some recent studies conclude that Caucasian patients might experience inferior survival rates in comparison with Asian cohorts [2,5]. A wide variety of factors might contribute to this fact: the differences regarding the distribution of risk factors, EBV-related tumor biology, but also the access to specialized and high-volume centers on this pathology. All these observations further support the need for tailored diagnostic, and efficient therapeutic strategies, which are adapted to European and other non-Asian populations.

Additionally, global projections estimate a continuous rise in the incidence of NPC by 2040, illustrating its expanding impact in public health beyond the traditionally endemic areas [6]. Despite several improvements in imaging techniques and the development of multimodal treatment strategies, recurrence rates and distant metastasis remain significant challenges. A marked survival heterogeneity persists even in the groups of patients with similar TNM stages [7–10].

For patients with locoregionally advanced NPC, chemotherapy represents a main component of the primary treatment. International guidelines support the use of induction chemotherapy (ICT) followed by chemoradiotherapy (CRT) as a category 1 strategy of treatment in selected cases, particularly those presenting higher tumor burden (like T2 disease with lymph node metastases) [11–13]. Concurrent chemoradiotherapy based on cisplatin raises the risk of severe acute hematological and nonhematological toxicity [14–16]. Additionally, it causes critical weight loss after radiation therapy, which is linked to poor survival in NPC on its own [17,18]. Furthermore, concomitant chemoradiotherapy raises the risk of treatment-related mortality, which may reduce the therapeutic benefit [19].

The aim of the current study is to assess overall survival in a European multi-institutional cohort of patients diagnosed with NPC and to evaluate the impact of disease stage and chemotherapy exposure on survival outcomes. Moreover, this study aims to identify independent prognostic factors in this category of patients.

Methods

Study population and data curation

This study was approved by the Ethics Committee of Iuliu Hațieganu University of Medicine and Pharmacy (56/10.03.2021) and each center participating in the research obtained Ethics Committee approval before reviewing patient records.

The current study is a multicentric collaboration which included patients diagnosed with NPC from six different European centers, including the Institute of Oncology Cluj-Napoca in Romania, University of Padova and University of Brescia in Italy, Donostia University Hospital in Spain, Cambridge University Hospitals NHS and Guy's and St Thomas' University Hospital in the United Kingdom.

All data, such as demographic characteristics, smoking status, medical history, tumor staging and treatment regimen were retrospectively gathered from the medical records of each center. All included patients underwent radiotherapy treatment, with or without concurrent chemotherapy.

The inclusion criteria were as follows:

(1) confirmation of NPC through biopsy

(2) the selected histology subtypes in patients included keratinizing squamous cell carcinoma (KSCC), differentiated non-keratinizing carcinoma (DNKC), undifferentiated non-keratinizing carcinoma (UNKC), and others

(3) minimum follow-up of 60 months

The exclusion criteria were as follows:

(1) concurrent malignancies

(2) improper cardiac, pulmonary, renal, or hepatic functions

(3) incomplete record of clinical and follow-up data

Patients with a minimum 5 year follow-up were included in the analysis. For each patient, demographic data was gathered (age, sex, race, smoking status), along with a complete pre-treatment blood count, histology and immunohistochemistry, TNM grading, treatment regimen, post-treatment complications, second malignancy during follow-up. Overall survival and 5-year disease free survival were the outcome measures.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 26.0. Continuous variables were summarized using mean and standard deviation (SD) or median and interquartile range (IQR), depending on each case, while categorical variables were represented by frequencies and percentages.

Overall survival (OS) was defined as the interval from diagnosis date to the date of death from any cause (irrespective of its relation to NPC). Patients who were alive at the last follow-up were censored. Survival probabilities at 1, 3, and 5 years were computed and

estimated using the Kaplan–Meier method, and survival curves were compared using the log-rank test.

Survival analyses were performed for the overall cohort and further stratified according to cancer stage (early stage: stages I–II; late stage: stages III–IVB) and by concurrent chemotherapy exposure (chemotherapy vs. no chemotherapy). Median survival times and the corresponding 95% confidence intervals (CI) were computed using the Kaplan–Meier estimator.

The relation between clinical variables and overall survival was assessed using Cox proportional hazards regression models. Initially, univariable Cox regression was performed for each variable of interest. A multivariable Cox regression model was then developed to adjust for potential confounders, including age, sex, treatment center, and chemotherapy exposure. The proportional hazards assumption was evaluated using Schoenfeld residuals for each covariate and globally. Where violations were identified, cancer stage was incorporated as a stratification variable rather than a covariate, allowing separate baseline hazard functions for early- and late-stage disease. Consequently, no hazard ratio is reported for stage in the multivariable model. Hazard ratios (HRs) with 95% confidence intervals were reported. Model performance was evaluated using the concordance index (C-statistic), and overall model significance was assessed using the likelihood ratio test. Statistical significance was defined as a two-sided p-value < 0.05.

Results

Characterization of the cohort

A total of 416 patients were included in the analysis. Age data were available for all patients (n = 416), ranging from 12 to 86 years. The mean age was 48.2 years (SD = 15.8), with a median of 50.0 years. The age distribution peaked in the fifth and sixth decades of life. The cohort showed a male predominance, with 283 male patients (68%) and 133 female patients (32%). The study population was predominantly Caucasian/White, constituting approximately 87% of patients, with smaller representations of Asian and Black ethnic groups.

Patients were treated in six participating oncology centers: Institute of Oncology Cluj-Napoca, Romania (146 cases, 35.1%), University of Padova, Treviso, Italy (89 cases, 21.4%), Guy's and St Thomas' University Hospital, UK (54 cases, 13.0%), Cambridge University Hospitals NHS, UK (48 cases, 11.5%), University of Donostia San Sebastián, Spain (40 cases, 9.6%), and University of Brescia, Italy (39 cases, 9.4%).

Regarding smoking status, 227 patients (54.3%) were non-smokers, 140 (33.5%) were current smokers, 15 (3.6%) were former smokers, while data related to smoking were missing or unspecified for 36 patients (8.6%).

The majority of patients presented with advanced-stage disease, with stage III in 180 patients (43.3%) and stage IV in 168 patients (40.4%). Early-stage disease (stages I and II) was identified in 68 patients (16.3%).

Concurrent platinum-based chemotherapy was administered to 305 patients (73.3%), while the remaining 111 patients (26.7%) did not receive systemic chemotherapy. Radiotherapy was part of the treatment strategy in all of the cases. Surgical treatment consisted of neck dissection for lymph node metastasis and was performed in 48 patients (11.5%), whereas 368 patients (88.5%) were managed without surgical intervention. Lymph node excision was carried out in 46 patients (11.0%), while 370 patients (89.0%) did not undergo lymphadenectomy.

A second primary tumour (SPT) was found in 62 patients (14.8%) during the follow-up period.

Survival analysis

Survival analysis was conducted in a cohort of 416 patients, of whom 161 experienced the event of interest during follow-up. Patients were stratified by stage of cancer (Table I and Figure 1), respectively by chemotherapy exposure (CHT vs. no chemotherapy), as represented in figure 2.

Table I. Survival at 1, 3 and 5 years, by cancer stage.

Levels	Time	Number at Risk	Number of Events	Survival	95% Confidence Interval	
					Lower	Upper
Early	12	66	1	98.5%	95.6%	100.0%
Early	36	56	11	82.0%	73.3%	91.8%
Early	60	51	2	78.9%	69.7%	89.4%
Late	12	326	22	93.7%	91.1%	96.3%
Late	36	269	45	80.4%	76.3%	84.7%
Late	60	241	20	74.3%	69.8%	79.1%

For each group, the number at risk, number of events (deaths), survival percentage, and 95% confidence interval are reported.

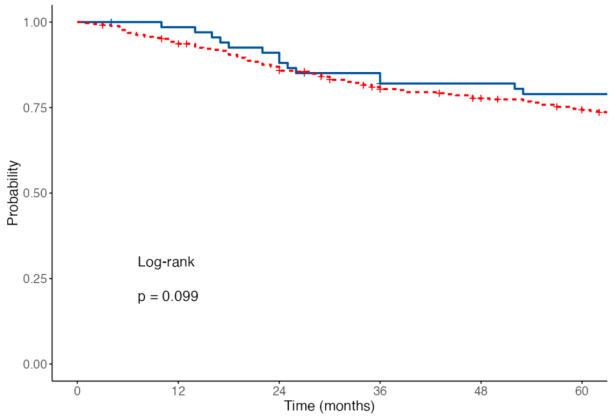

Figure 1. Kaplan–Meier OS curves according to cancer stage (early vs. late).
The Kaplan–Meier analysis demonstrates higher survival probabilities in patients with early-stage cancer compared to those with late-stage disease throughout the follow-up period, although the difference did not reach statistical significance (log-rank p = 0.099).

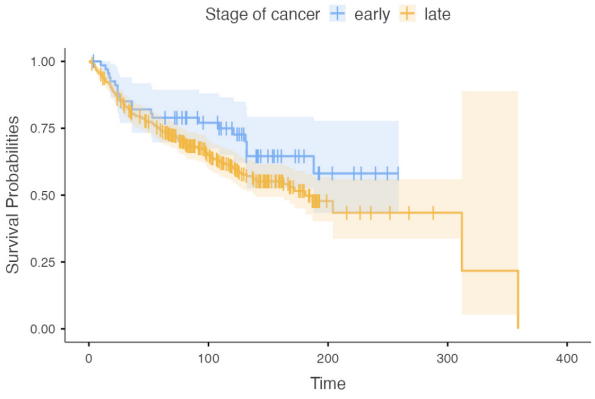

Figure 2. Kaplan–Meier survival curves for the overall cohort.
The curve shows the probability of overall survival for all patients, stratified by chemotherapy status (CHT vs. no chemotherapy).

In patients who did not receive chemotherapy (n = 111, 26.7%), the median survival was equal to 187 months (95% CI: 132–not reached), while patients receiving chemotherapy (n = 305, 73.3%) had a median survival of 204 months (95% CI: 168–not reached). The upper bound of these confidence intervals could not be estimated as the Kaplan–Meier survival curve had not yet crossed the 50% survival threshold by end of follow-up. The log-rank test which compared survival between chemotherapy groups showed no statistically significant difference (p = 0.85). One-year survival probabilities were high in both groups, with 95.5% (95% CI: 91.7–99.4%) in the no-chemotherapy group and 94.1% (95% CI: 91.5–96.8%) in the chemotherapy group. Furthermore, three-year survival was 82.5% versus 80.0%, and five-year survival was 74.8% versus 75.2% for the no-chemotherapy and chemotherapy groups, respectively.

In patients with early-stage disease, survival analysis included 68 cases, with 47 censored and 21 events observed (Figure 3). Median survival for the non-chemotherapy group was equal to 188 months (95% CI: 132–not reached); The log-rank test which compared survival between chemotherapy and non-chemotherapy groups showed no significant difference (p = 0.533).

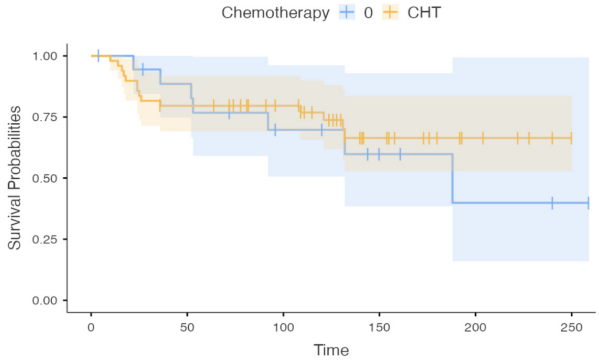

Figure 3. Kaplan–Meier survival curves for the early-stage patients.
The curve shows the probability of overall survival for all patients, stratified by chemotherapy status (CHT vs. no chemotherapy).

In patients with late-stage disease, 348 cases were included, with 208 censored and 140 events observed. Median survival was equal to 181 months (95% CI: 140–not reached) for the non-chemotherapy group and 204 months (95% CI: 132–not reached) for the chemotherapy group. The log-rank test again demonstrated no significant difference between groups (p = 0.931) (Figure 4).

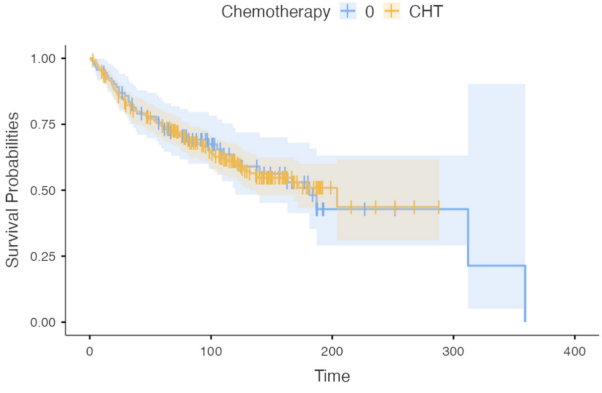

Figure 4. Kaplan–Meier survival curves for the late-stage patients.
The curve shows the probability of overall survival for all patients, stratified by chemotherapy status (CHT vs. no chemotherapy).

Table II. Univariable and multivariable Cox proportional hazards analysis with death as the event of interest.

Variable	Category	N (%) / Mean (SD)	HR (Univariable)	HR (Multivariable)
Chemotherapy	0	111 (26.7)	-	-
	CHT	305 (73.3)	0.97 (0.68–1.37), p=0.852	1.31 (0.87–1.96), p=0.198
Sex	F	133 (32.0)	-	-
	M	283 (68.0)	1.18 (0.84–1.65), p=0.343	1.12 (0.79–1.57), p=0.530
Group	Cambridge University Hospitals, UK	48 (11.5)	0.83 (0.41–1.68), p=0.599	0.65 (0.32–1.34), p=0.243
	University of Donostia San Sebastián, Spain	40 (9.6)	0.83 (0.41–1.68), p=0.599	0.65 (0.32–1.34), p=0.243
	Guy's and St Thomas' Hospital, UK	54 (13.0)	1.19 (0.62–2.29), p=0.610	1.22 (0.63–2.35), p=0.558
	The Oncological Institute of Cluj-Napoca, Romania	146 (35.1)	0.71 (0.40–1.26), p=0.240	0.80 (0.44–1.44), p=0.450
	University of Padova, Treviso, Italy	89 (21.4)	1.20 (0.67–2.14), p=0.547	1.08 (0.59–1.97), p=0.803
	University of Brescia, Italy	39 (9.4)	0.40 (0.17–0.91), p=0.029	0.41 (0.18–0.95), p=0.038
Age	Mean (SD)	48.2 (15.8)	1.03 (1.02–1.04), p<0.001	1.03 (1.02–1.04), p<0.001

HR > 1 indicates increased risk of death. Ref = reference category.

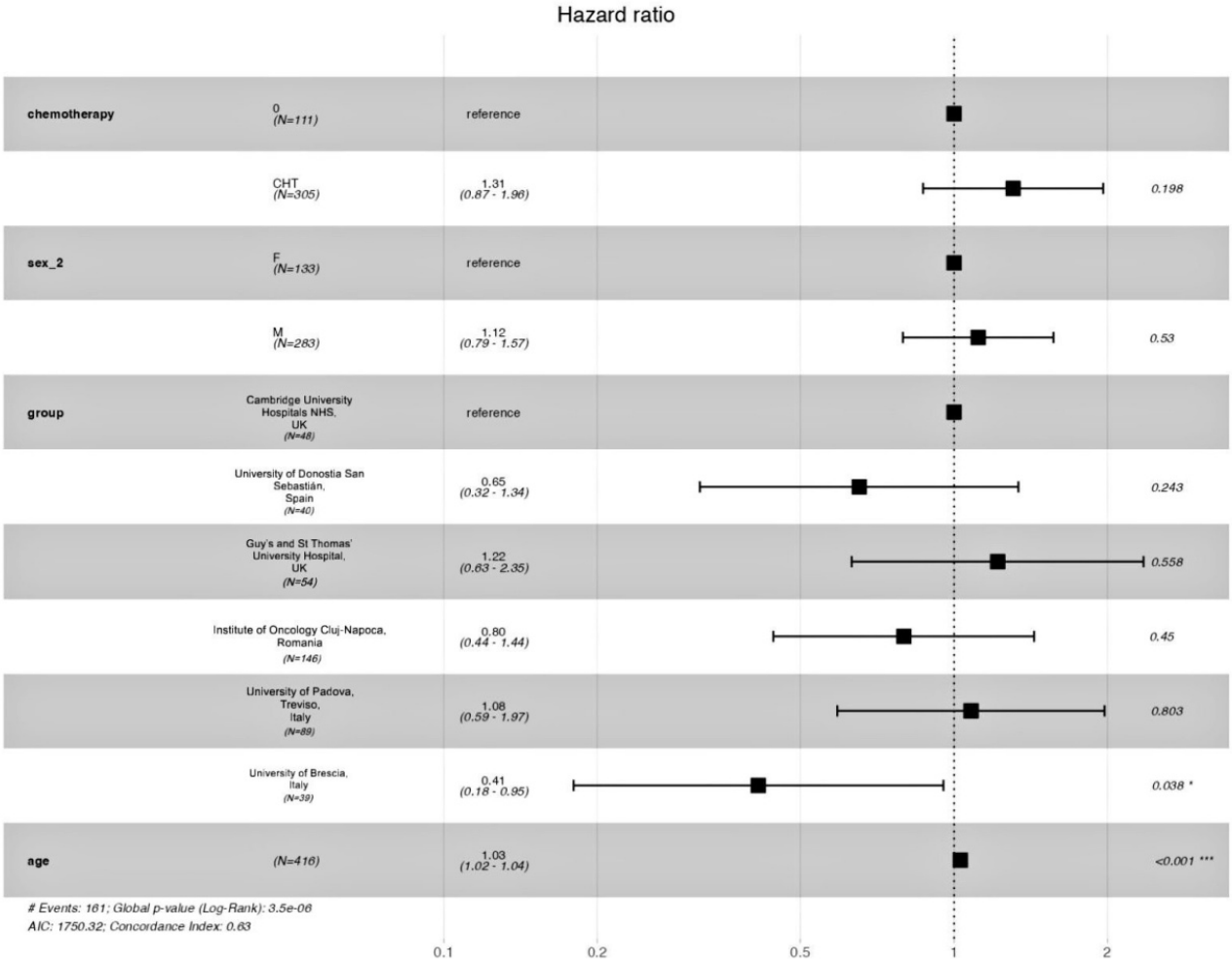

Figure 5. Hazard Regression Plot for OS.
The hazard regression plot illustrates the hazard ratios with 95% confidence intervals derived from the multivariable Cox proportional hazards model.

Univariable Cox proportional hazards regression was performed (stratified by cancer stage) and yielded a hazard ratio (HR) equal to 0.97 (95% CI: 0.68–1.37, p = 0.852) for chemotherapy versus no chemotherapy, confirming the absence of significant difference in risk of event. Multivariable Cox regression adjusting for age, sex, and treatment center returned consistent results (HR 1.31, 95% CI: 0.87–1.96, p = 0.198 for chemotherapy), while sex did not reach statistical significance; however, age was independently and significantly associated with OS (HR 1.03 per year, 95% CI: 1.02–1.04, p < 0.001) — see table II. Treatment center was linked to variable hazard ratios, with one center showing a lower risk (HR 0.41, 95% CI: 0.18–0.95, p = 0.038).

The proportional hazards assumption was evaluated using Schoenfeld residuals (Figure 5). The model demonstrated moderate predictive performance with a concordance index (C-statistic) of 0.634 (SE = 0.022) and an R^2 of 0.091. Likelihood ratio testing for the full multivariable model indicated overall statistical significance ($\chi^2 = 39.801$, df = 8, p < 0.001).

Discussion

Interpretation of the main results

Several clinically relevant observations (regarding survival outcomes and prognostic factors) appeared in this large European multicentric cohort, consisting of 416 patients diagnosed with NPC.

Predominantly, the cohort was characterized by cases of advanced-stage disease, with more than 80% of patients with stage III and stage IV tumors. This distribution further emphasizes the diagnostic challenge of NPC, because early symptoms are frequently nonspecific. Even if Kaplan–Meier curves illustrated consistently higher survival probabilities in early-stage disease cases compared with late-stage disease cases, the difference did not reach statistical significance threshold (log-rank p = 0.099). The absence of statistical significance is most likely caused by a relatively small number of early-stage disease cases (n = 68), which may have contributed to a limitation in statistical power.

Moreover, chemotherapy exposure was not linked to a statistically significant improvement in OS, in both the univariable (HR 0.97, p = 0.852) and multivariable analysis (HR 1.31, p = 0.198). Median times of survival were equivalent between the group of patients who received chemotherapy and those who did not. The 1, 3, and 5-year survival probabilities were almost the same. Similar findings were noticed when analyses were stratified by stage (early stage compared to late stage disease). These results imply that, within this heterogeneous real-world cohort, chemotherapy was not independently associated with improved long-term survival.

In addition, age turned out to be a significant and independent prognostic factor. Not only in the univariable Cox regression model, but also in the multivariable one, increased age was linked to a higher risk of death (HR 1.03 per year, p < 0.001). This indicates a 3% increase in mortality risk for every additional year of age, highlighting the importance of patient-related factors in survival outcomes.

Inter-center variability was observed, with one treatment center showing a significantly lower hazard ratio in the multivariable model (HR 0.41, p = 0.038). This finding might reflect some differences regarding institutional protocols, techniques of radiotherapy, multidisciplinary expertise or patient selection. Even though this observation is acknowledged, it should be interpreted cautiously due to the relatively small sample size within some centers of treatment and the potential influence of a few unmeasured confounders.

Globally, the main findings of this study emphasize that, in a European multicentric real-world cohort of NPC patients, age was independently associated with survival outcomes in multivariable Cox regression. Disease stage was incorporated as a stratification variable to address non-proportional hazards, and thus no independent hazard ratio for stage is available from this model; descriptive Kaplan–Meier analysis suggested a trend toward better survival in early-stage disease (log-rank p = 0.099), though not statistically significant. Chemotherapy exposure status was not independently associated with an improved OS after adjustment for confounders. These results suggest the need for standardized treatment protocols and more granular analysis of therapeutic regimens across homogeneous patient subgroups.

Comparison with the existing literature

There are conflicting literature findings regarding the necessity of concurrent chemotherapy. Similar to our findings, certain research papers show similar survival for radiotherapy alone compared with chemoradiotherapy, while other publications state the opposite. The most relevant studies on the matter are summarized in table III.

In their retrospective study, Li et al. compared radiotherapy (RT) alone and chemoradiotherapy (RT-chemo) in a group of 343 patients who were diagnosed with T1–2N1M0 NPC treated between 2008 and 2016 in the IMRT era. Every patient received either RT alone or a combination of therapeutic strategies: concurrent chemoradiotherapy (CCRT), induction chemotherapy and CCRT, or CCRT and adjuvant chemotherapy. After a median follow-up period of 93 months, no significant difference was found between the RT-chemo and the RT group in 5-year overall survival, progression-free survival, locoregional failure-free survival, or distant metastasis-free survival. Subgroup analyses for T1N1M0 and T2N1M0 disease also demonstrated comparable outcomes. Multivariable analysis confirmed that treatment strategy was not an independent prognostic factor. The authors concluded that IMRT alone achieved survival outcomes equivalent to chemoradiotherapy, supporting the omission or postponement of chemotherapy in this patient population [20].

Table III. Recent studies investigating differences in clinical outcomes in NPC patients with the addition of chemotherapy to the treatment regimen.

Study	Sample size	Race	Disease stage	Treatment modality	Mean follow-up	Outcome measures	Findings
Li et al. [20]	343 adults	Asian	$T_{1,2}N_1M_0$	IMRT vs. IMRT+ChT (Induction/ concurrent/ adjuvant)	93 months	5 years OS, PFS, LRFS, DMFS	IMRT alone comparable to IMRT+ChT
Liang et al. [21]	810 (age ≤ 21 years)	Asian	I-IVA	Comparison of advances vs older technology and treatments in three time frames (1989-2002, 2003-2011, and 2012-2020)	56 months	PFS, OS, DMFS, LRFS	Increase in survival rates: PFS 65.9 vs 88.1%; OS 69.9 vs. 95%
Tang et al. [22]	341 adults	Asian	$T_3N_0M_0$	IMRT vs. IMRT with concurrent cisplatin ChT	46 months	FFS, OS, LRFS, DMFS	3 years FFS 90.5% IMRT alone vs. 91.9% IMRT+concurrent ChT; no other significant differences
Goshtasbi et al. [23]	8260 adults	Mixed, 58.3% Caucasian	I-IVA	RT alone, CRT, surgery	40 months	OS	CRT improves OS compared to RT alone in stage II and III. Surgery+CRT improves OS compared to CRT alone in keratinizing or stage IVA NPC. CRT provided benefits over RT alone only in keratinizing NPC.
Huang et al. [24]	821 adults	Asian	Metastatic NPC	ChT alone vs. RT alone vs. CRT	22.4 months	3 year OS, PFS	Increased 3 year OS for CRT vs. ChT or RT alone (35.7% vs. 11.7% or 22.9%)

IMRT- intensity modilated radiotherapy; ChT- chemotherapy; CRT- chemoradiotherapy; OS- overall survival; PFS- progression-free survival; LRFS- locoregional recurrence-free rate; DMFS- distant metastasis-free survival; FFS- failure-free survival.

A large retrospective cohort study from China, conducted by Liang et al., enrolled 810 pediatric and adolescent patients (aged ≤21 years) who were diagnosed with nonmetastatic NPC and treated between 1989 and 2020. The study assessed if advances in imaging, radiotherapy and systemic therapy were linked to improved survival outcomes. Recently, the use of MRI (either with or without PET-CT), IMRT or TomoTherapy, and combined-modality methods like concurrent chemoradiotherapy (CCRT), induction chemotherapy plus CCRT, and adjuvant chemotherapy were associated with significant improvements in progression-free survival (PFS) and OS. Five-year survival parameters increased as follows: PFS from 65.9% (1989–2002) to 88.1% (2012–2020), while OS varied from 69.9% to 95.0% (across the same periods). Due to better imaging and radiotherapy techniques, locoregional recurrence rates significantly declined. Despite this, the incidence of distant metastasis was relatively stable, emphasizing distant failure as the principal remaining therapeutic challenge in pediatric cases of NPC [21].

Tang et al. conducted a multicenter, open-label, phase 3 noninferiority randomized clinical trial in 5 Chinese hospitals. The study evaluated whether concurrent chemotherapy could be safely omitted in 341 adults with low-risk stage II/T3N0M0 NPC treated with IMRT. Patients were randomized to IMRT alone or IMRT with concurrent cisplatin. After a median follow-up of 46 months, 3-year failure-free survival was 90.5% in the IMRT-alone group versus 91.9% in the chemoradiotherapy group. No significant difference was observed in OS, locoregional relapse-free survival, or distant metastasis-free survival. IMRT alone was associated with better quality-of-life scores and significantly fewer grade 3–4 adverse events (17% vs. 46%) [22]. These findings suggest that in carefully selected low-risk NPC patients, IMRT alone achieves equivalent oncologic outcomes with lower toxicity compared with concurrent chemoradiotherapy.

Using the National Cancer Database (2004–2015), Goshtasbi et al. conducted a large retrospective study that analyzed 8,260 patients with NPC to evaluate patterns of treatment, OS, respectively the impact of clinical and sociodemographic factors. The cohort included predominantly male patients (71.4%), with a substantial proportion of keratinizing histology (42.5%). The 5-year OS was equal to 63.4%. On multivariate analysis, worse survival outcomes were independently linked to age ≥65 years, increased comorbidity burden (assessed by Charlson/Deyo score ≥1), advanced stages (III–IV), respectively the lack of private insurance. Improved survival was linked to a few parameters: female sex patients, Asian/Pacific Islander race, undifferentiated and nonkeratinizing histology, and therapy performed in academic centers. From a therapeutic point of view,

chemoradiotherapy (CRT) was associated with better OS in comparison with radiotherapy (RT) alone in stage II–III disease, respectively compared with RT or chemotherapy alone in stage IVA disease. Surgery combined with CRT registered additional benefits in keratinizing tumors and stage IVA disease. Suboptimal radiation dosing (<60 Gy or <30 fractions) were associated with inferior survival outcomes. Globally, survival in NPC was in strong relation with both tumor-related and sociodemographic factors. Stage-adapted CRT is considered the optimal strategy for most stage III–IV patients [23].

Huang et al. conducted a retrospective study including 821 patients with initially metastatic NPC (between 2008–2017) and evaluated the optimal therapeutic strategies and prognostic factors. Systemic chemotherapy, when followed by sequential locoregional radiotherapy of the primary tumor, achieved a significantly improved OS at three years (40.3%), in comparison with chemotherapy alone (11.7%) or radiotherapy alone (22.9%) ($P < 0.001$). Among first-line regimens, the triplet therapy TPF (paclitaxel, platinum, fluorouracil) was associated with a higher response rate compared the TP doublet (78.2% vs 70.0%), respectively an increased 3-year OS (35.7% vs 25.3%, $P < .001$) [24]. Their findings emphasize that combined systemic chemotherapy and sequential locoregional radiotherapy might improve survival outcomes in selected cases diagnosed with de novo metastatic NPC.

Strengths of this study

- First, it describes a large multicentric European cohort, including 416 patients who were diagnosed with NPC, selected from six tertiary oncology centers across a variety of countries: Romania, Italy, Spain, and the United Kingdom. Importantly, the inclusion of multiple institutions increases the generalizability of the findings, as it resembles real-world clinical practice settings, across different healthcare systems.
- Second, the current study benefits from a long-term follow-up period, of at least 5 years for all included patients. This ensured proper evaluation of OS and provided clinically meaningful outcome data.
- Third, extensive clinicopathological data were extracted, including demographic variables, smoking status, TNM staging, treatment options and second primary tumors. The availability of these variables enabled thorough survival analyses.
- Fourth, survival was evaluated using well-known statistical methods, including Kaplan–Meier curves, log-rank tests, and Cox proportional hazards regression models. The use of both univariable and multivariable Cox regression allowed for the adjustment for potential confounders like age, sex, treatment center, and chemotherapy exposure status. Thus, it increased the methodological rigor of the analysis.
- Fifth, a key strength of the current study is that the cohort was predominantly composed of Caucasian/White patients. Given that most of the existing literature on NPC is based on East Asian populations (where features like the disease epidemiology, tumor biology, and outcomes can differ significantly), this study presents valuable data from a less frequently represented demographic group. Even more, the inclusion of a representative number of cases collected from this population strengthens the robustness of the analysis and extends the applicability of findings to non-Asian NPC populations, addressing an important gap in the current literature.
- Finally, the assessment of outcomes depending on cancer stage (early vs. late) and chemotherapy exposure provides clinically relevant subgroup analyses, leading to a better understanding of therapeutic impact in different disease settings.

Limitations of this study

Despite its strengths, this study has several limitations that need to be mentioned.

- First, the design of the study introduces an inherent risk of selection bias. The variability of cases across centers may have affected data completeness and consistency.
- Second, heterogeneity regarding treatment regimens was observed, which reflected real-world practice, but limited the ability to standardize comparisons. Differences across radiotherapy, chemotherapy protocols, and even surgical approaches might have introduced confounding factors that were not fully taken into account in the analysis.
- Third, even if multivariable Cox regression was performed, residual confounding factors cannot be excluded. Important biological factors like molecular markers, performance status, and other comorbidities were not uniformly available and therefore were not included in the final models.
- Fourth, some of the collected parameters (e.g., smoking status) registered missing data, and no imputation strategy was described in that case. In addition, the unbalanced proportion between early-stage and late-stage patients (with the majority of them presenting in advanced stages) may have influenced survival comparisons and also limited statistical power in subgroup analyses.
- Last but not least, even though chemotherapy exposure was documented, the current study did not differentiate between induction, concurrent, or adjuvant chemotherapy regimens. Furthermore, the study did not assess compliance to treatment and dose intensity, which might influence survival outcomes.

Conclusions

In this European multi-institutional real-world cohort of patients with NPC, increasing age was independently associated with higher mortality risk (HR

1.03 per year, $p < 0.001$) in multivariable Cox regression. Disease stage was incorporated as a stratification variable to account for non-proportional hazards; accordingly, its independent effect on survival cannot be directly quantified from this model, though Kaplan–Meier analysis demonstrated a trend toward better survival in early-stage patients (log-rank $p = 0.099$). After adjustment for confounding factors, chemotherapy exposure was not independently associated with improved OS. Further prospective studies are required to clarify the role of systemic therapy in diverse NPC populations, ideally distinguishing between induction, concurrent, and adjuvant chemotherapy regimens.

Notably, this study contributes valuable data from a predominantly Caucasian population, addressing a relative gap in the current literature, which is largely focused on endemic Asian cohorts. The multi-institutional European cohort optimizes the methodological rigor of the study and reinforces its relevance for the process of clinical decision-making outside endemic regions.

Funding

Research was funded by Iuliu Haţieganu University of Medicine and Pharmacy Cluj-Napoca, grant number 1032/56/13 January 2021.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Iuliu Haţieganu University of Medicine and Pharmacy Cluj-Napoca, Romania (56/10.03.2021).

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