



# Demographic and clinicopathological characteristics of nasopharyngeal carcinoma and survival outcomes according to age at diagnosis: A population-based analysis

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## ARTICLE INFO

### Keywords:

Nasopharyngeal carcinoma  
Cancer epidemiology  
Age  
Radiotherapy  
Survival  
SEER

## ABSTRACT

**Objective:** To investigate the demographic features, clinicopathological characteristics and treatment outcomes of patients with nasopharyngeal carcinoma (NPC) according to age at diagnosis.

**Methods:** We assessed demographic and clinicopathological variables extracted from the Surveillance, Epidemiology, and End Results database (2004–2014). The Cox proportional hazards regression model was used to perform univariate and multivariate analyses of NPC-related mortality (cause-specific survival).

**Results:** A total of 3880 patients were analyzed. Median age was 55-years-old; 108 (2.8%), 508 (13.1%), 1876 (48.4%), 1240 (32.0%), and 148 (3.8%) patients were aged 1–19, 20–39, 40–59, 60–79, and 80–99-years-old, respectively. Younger patients tended to be black and present with poorly/undifferentiated disease and advanced tumor and nodal category compared to older patients. Younger patients were more likely to receive chemotherapy than older patients. In multivariate analyses, age at diagnosis was an independent prognostic factor for cause-specific survival. Increasing age at diagnosis was associated with a significantly higher risk of NPC-related mortality. Compared to patients aged 1–19-years-old, the hazard ratios for patients aged 20–39, 40–59, 60–79, and 80–99-years-old were 2.030 (95% confidence interval 1.004–4.104), 2.871 (1.474–5.590), 4.443 (2.273–8.683), and 12.024 (5.855–24.695), respectively. With the exception of black patients ( $P = 0.100$ ), older age was associated with poor survival in all demographic and clinical subgroups.

**Conclusion:** Although younger patients tended to have advanced disease at diagnosis, older age at diagnosis was associated with a higher risk of NPC-related mortality.

## Background

Though rare in Japan and western countries, nasopharyngeal carcinoma (NPC) is endemic in southern China, Southeast Asia and Southern Africa. In general, the incidence of NPC in endemic and non-endemic areas has stabilised in recent decades [1,2]; however, the age distribution varies between endemic and non-endemic areas. The age distribution of NPC is unimodal in endemic areas, peaking in individuals aged 45–59-years-old [1,2]. However, in low risk populations, the age distribution is bimodal, with a first peak in young adolescents (aged 15–19) and a second peak in individuals aged 65–79 [1].

Whether different age groups of patients with NPC have different survival outcomes remains controversial. Studies have reported children and adolescents (< 20-years-old) achieve better survival outcomes than adult patients [3,4]. However, the effect of age on survival in adult patients was not further analyzed. A study that included 4630 adult patients with NPC found that being aged  $\geq 60$  was associated with poorer survival compared to being aged 18–29, with no significant survival differences among patients aged 30–39, 40–49 and 50–59 and those aged 18–29 [5]. In contrast, another study found younger patients (aged < 45) were more likely to have a higher risk of distant metastasis and poorer survival outcomes than older patients [6]. The

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heterogeneity of the cohorts and different treatment strategies may be the main reasons for these conflicting results. Therefore, the current study aimed to investigate the demographic and clinicopathological characteristics and treatment outcomes of patients with NPC according to age at diagnosis using data from a population-based cancer registry.

## Materials and methods

### Patients

Patients from the Surveillance, Epidemiology, and End Results (SEER) cancer registry diagnosed with non-metastatic NPC between 2004 and 2014 were included [7]. Patients received primary radiotherapy (RT); tumor (T) and nodal (N) category data were available. The SEER program is a publicly accessible database; Institutional Review Board approval was not required for this study. We obtained permission from the SEER registry to access the database (authorization number 11025-Nov2016).

### Demographical and clinicopathological variables

The distributions of categorical demographic and clinicopathological variables, including gender (male, female), ethnicity (white, black, other, unknown), tumor grade (well-differentiated, moderately differentiated, poorly/undifferentiated, unknown), T category (T1, T2, T3, T4), N category (N0, N1, N2, N3), and chemotherapy status (no/unknown, yes) were determined for different age groups (1–19, 20–39, 40–59, 60–79, 80–99-years-old). T and N category were determined according to the sixth edition of Union for International Cancer Control/American Joint Committee on Cancer staging system. The primary outcome was cause-specific survival (CSS), defined as time from initial treatment to death due to NPC.

### Statistical analysis

The Chi-square test and Fisher's exact probability test were used to compare demographic and clinicopathological variables between age groups. Kaplan-Meier curves for CSS were estimated and compared using the log-rank test. The Cox proportional hazards regression model was used to perform univariate and multivariate analyses for CSS. Multivariate Cox regression analysis was performed using variables significantly associated with CSS in univariate analysis. Statistical analysis was performed using SPSS 21 (IBM Corporation, Armonk, NY, USA). Statistical significance was defined as  $P < 0.05$ .

## Results

A total of 3880 patients were included in this study. Median age was 55 (range, 7–92-years-old); 108 (2.8%) patients were aged 1–19, 508 (13.1%) were aged 20–39, 1876 (48.4%) were aged 40–59, 1240 (32.0%) were aged 60–79, and 148 (3.8%) were aged 80–99. The demographic and clinicopathological variables of the cohort are listed in Table 1. Patients aged 20–39 and 80–99 were more likely to be female; patients aged 60–79 and 80–99 were more likely to be white, and patients aged 1–19 were more likely to be black. Younger patients (< 60-years-old) more frequently presented with poorly/undifferentiated disease, advanced T category and advanced N category, and were more likely to receive chemotherapy compared to older patients.

Median follow-up was 37 months (range, 1–131 months). A total of 612 patients died due to NPC. The 3- and 5-year CSS rates were 85.4% and 79.6%, respectively.

The results of the univariate and multivariate analyses are summarized in Table 2. In multivariate analysis, age was an independent prognostic factor for NPC-related mortality. Increasing age at diagnosis of NPC was associated with a significantly higher risk of NPC-related mortality. Compared to patients aged 1–19, the hazard ratios for

patients aged 20–39, 40–59, 60–79, and 80–99 were 2.030 (95% confidence interval [CI] 1.004–4.104), 2.871 (95% CI 1.474–5.590), 4.443 (95% CI 2.273–8.683), 12.024 (95% CI 5.855–24.695), respectively. The survival curves are shown in Fig. 1. T category and N category were also independent prognostic factors for CSS; gender, ethnicity, grade, and chemotherapy status were not associated with CSS in univariate analyses.

Finally, we performed subgroup analysis to assess the effect of age on CSS for patients stratified by demographic and clinicopathological status. Increased age was associated with poor CSS in all demographic and clinicopathological subgroups (all  $P < 0.05$ ), except for patients who were black ( $P = 0.100$ ).

## Discussion

The effect of age on survival in NPC remains unclear. In this population-based study, we found different age groups of patients have distinct demographical and clinicopathological characteristics, and age was an independent prognostic factor for NPC-related death.

The incidence of childhood and adolescent NPC in this study (2.8%) was similar to previous studies (0.1–4.2%) in endemic and non-endemic areas [4,8–10]. Consistent with previous studies [4,8,11–13], childhood and adolescent patients were more likely to be black and present with poorly/undifferentiated disease, advanced T category and advanced N category than adult patients. In a study of Chinese patients with locoregionally advanced NPC, older age was associated with more advanced stage disease (stage IV), but not with T or N category [14]. Overall, these findings suggest childhood and adolescent NPC exhibits distinct biological behavior. The development of NPC in childhood and adolescence may be due to Epstein-Barr virus infection or an inherited genetic predisposition in the black population [4].

Several studies have reported older age is associated with poor survival in NPC. However, a variety of cut-off points have been employed, including 40, 47, 50 or 60-years-old, and the effect of younger age (< 20) on prognosis was not further analyzed [5,15–17]. Age had different effects on survival in two clinical trials of adult patients [17,18]. Fountzilias et al. showed patients aged < 50 had better survival outcomes than patients aged ≥ 50 [17]. However, Chen et al. found age had no effect on survival outcomes [18]. In contrast, Xiao et al. found younger patients (< 45) were more likely to have a higher risk of distant metastasis and inferior survival rates than older patients [6].

One study in an area where NPC is endemic in China found patients aged ≥ 60 had increased risk of mortality, while survival outcomes did not differ for patients aged 18–59 [5]. Another study in the endemic area of China found patients aged 50–59 and ≥ 60 had a significantly higher risk of death than patients aged 20–49 [14], though this study only included patients aged ≥ 18. In an analyses of the United States National Cancer Database, Richards et al. showed childhood and adolescent patients were more likely to receive RT and chemotherapy (81.3% vs. 64.2%,  $P < 0.001$ ), especially multiple-agent chemotherapy (80.9% vs. 62.4%,  $P < 0.001$ ), and had a lower risk of mortality than adult patients [4]. However, the authors did not further analyze the impact of age stratification among adult patients. Our study further clarifies the clinical relevance of age to prognosis in NPC. We classified all patients using five age groups for prognostic analysis. Although younger age was associated with poorly/undifferentiated and advanced disease, younger patients had better survival outcomes than adult patients. The inconsistent effects of age on survival in other studies may be related to variations in population distribution, sample sizes and definition of cut-off points.

The effect of age on survival may be related to a number of factors. Although more younger patients had adverse clinicopathological factors, more younger patients received chemotherapy, generally tolerated high-dose RT and chemotherapy, and were less likely to have serious comorbidities, resulting a higher rate of standard treatment completion and better treatment response [19]. The 5-year overall survival rate for

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