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Original Article

Prognosis of Nasopharyngeal Carcinoma in the Elderly is Worse than in Younger Individuals—Experience of a Medical Institute☆

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SUMMARY

Purpose: We aimed to evaluate outcomes of the elderly (>65 years) by comparing with younger (<40 years) patients after treatments for nasopharyngeal carcinoma (NPC).

Materials and methods: We retrospectively obtained clinical data from charts for 23 older and 21 younger patients in whom NPC was diagnosed and who underwent curative managements during 2007 and 2011. Occurrence of local recurrence, distant metastasis, and death from any cause were recorded as endpoints. Cox proportional hazards regression was applied to determine age effects on survival risks after adjusting for the potential confounders.

Results: Older patients more commonly received a diagnosis of chronic diseases than the younger patients (56.5% versus 23.8%, $p = 0.036$), whereas they were less likely to have received intensive treatments for NPC. After adjusting for medical history and neoadjuvant chemotherapy, older age was the only significant predictor in the study cohort for overall survival and progression-free survival. The adjusted hazard ratio (HR) for death from all causes in older patients was 6.3 (95% confidence interval [CI] = 1.3–30.2), and the adjusted HR for disease progression in older patients was 10.9 (95% CI = 2.3–50.6).

Conclusion: Aging was the only independent prognostic risk factor in this study cohort. Medical history and treatment variations could not fully explain the difference in prognosis. Our results strengthen the need to ameliorate toxicities and improve supportive care for older patients with a diagnosis of NPC.

1. Introduction

Nasopharyngeal carcinoma (NPC) is common in Chinese descendants in southeast Asia. The prevalence of NPC in Taiwan is 6.17 per 100,000, markedly higher than that (less than 1 per 100,000) in Western countries[1]. The disease has been causally associated with diet (e.g., smoked fish, nitrosamine), infection [e.g., Epstein-Barr virus (EBV)], and genetic factors (e.g. HLA-A2)[2]. When compared with other head and neck cancers, NPC is more radiosensitive and yields better predictions of survival[2]. The mainstay of treatment of NPC is concomitant chemoradiotherapy (CCRT), whereas surgical resection is recommended for local recurrence as a salvage strategy[3,4]. According to the seventh edition of the American Joint Committee on Cancer (AJCC) report, the 5-year rate was 81% for overall survival, 90% for local relapse-free survival, 86% for distant metastasis-free survival, and 77% for disease-free survival[5].

As the population ages and experiences longer life expectancy, diagnosis of NPC at an older age has become more frequent. Treatment and management of the condition in elderly patients is now a pressing task. Several concerns arise when the diagnosis is made at an older age, including tolerance to CCRT versus radiotherapy alone. Management pattern, staging, and comorbidities have been empirically correlated with an increasing age and poor prognosis in patients with NPC[6]. The objective of this retrospective study was to evaluate the effect of age on the outcomes of NPC patients with NPC while taking these factors into account.

☆ Conflicts of interest: The authors have no conflicts of interest to declare.

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2. Materials and methods

The study included patients in whom NPC had been diagnosed at age older than 65 years or younger than 40 years, and who underwent curative therapies between January 2007 and December 2011 in the Mackay Memorial Hospital, Taipei, Taiwan. Twenty-three older patients and 21 younger patients fulfilled the criteria. We retrospectively conducted a detailed chart review to obtain information on medical history, treatment, and clinical outcomes. TNM stage was determined based on the AJCC Staging Manual, sixth edition. Management strategy was discussed within a multidisciplinary team and with the patient soon after the diagnosis. Most of the patients received CCRT. Only 11 older patients received radiotherapy alone for poor condition ($N = 7$) or stage I/II ($N = 4$). During CCRT, a total of 57.6-70 Gy was delivered in 32–35 equal fractions, five daily fractions per week. Weekly cisplatin (30 mg/m^2) or monthly 5-day course of cisplatin (12 mg/m^2) and fluorouracil (600 mg/m^2) were prescribed concurrently with radiotherapy. Neoadjuvant chemotherapy (NACT) prior to radiotherapy was composed of cisplatin (75 mg/m^2) and fluorouracil (2600 mg/m^2) in 2 days (PF2). Two to four courses of PF2 were administered as adjuvant chemotherapy for advanced cases with acceptable performance. This study was approved by the Institutional Review Board of the Mackay Memorial Hospital (No.12MMHIS109).

2.1. Statistical analysis

Differences in diagnostic and treatment characteristics between the old and young groups of patients were evaluated by Fisher exact test and Mann-Whitney *U* test. Information on medical history of other cancers, benign tumors, cardiovascular diseases, hypertension, diabetes, tuberculosis, and chronic hepatitis was extracted from charts as the comorbidities. Among these conditions, only other history of cancers, diabetes, cardiovascular diseases, and hypertension showed a mild to significant association with age at diagnosis, and were included in the following analyses. Occurrence of local recurrence, distant metastasis, and death from any cause were recorded as the endpoints in the present study. Cumulative survival rates from the day of diagnosis to the endpoints were computerized using the Kaplan-Meier survival analysis. Cox proportional hazards regression was also applied to evaluate the effect of age on survival risks after adjusting for the potential confounders. Hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated with significance level set at 0.05 for all the two-sided tests.

3. Results

The median duration of follow-up was 25.8 months for older patients (range, 2.8–66.2 months) and 32.7 months for younger patients (range 8.6–68.3 months, $p = 0.307$, data not shown). Medical history, including cancers, diabetes, cardiovascular diseases, and hypertension, was significantly more prevalent in the older group than in the younger group (56.5% in older patients vs. 23.8% in younger patients, $p = 0.036$, Table 1). There was no difference in clinical stage and baseline EBV titers between the age groups.

Treatment history and clinical response are summarized in Table 2. Fewer older patients received NACT (52.2%), CCRT (52.2%), and adjuvant chemotherapy (26.1%) than their younger counterparts (80.9% for NACT, 100% for CCRT, and 76.2% for adjuvant chemotherapy, Table 2). All of the older patients initially responded to treatment, achieving complete response (CR) in 78.3% and partial response (PR) in 21.7%, but more than a third of the older patients developed second primary malignancy, locoregional recurrence, or distant metastasis later during follow-up (Table 2). Three younger patients (14.3%) had distant metastasis, and 85.7% of the younger patients remained CR or PR during follow up.

Five-year overall survival (OS) was 45.3% in older patients (median 41.4 months), relative to 88.8% in younger patients (median not reached, $p = 0.015$). We also observed significantly higher risk of disease progression or death for older patients (5-year progression-free survival, PFS, 18.7%, median 32.2 months) when

Table 1
Demographic and diagnostic characteristics of nasopharyngeal cancer patients by age group.

	Age <40 y $N = 21$	Age >65 y $N = 23$	p[a]
Age	33 (26–39)	70 (66–81)	
Sex			
Female	4 (19.0)	9 (39.1)	0.194
Male	17 (81.0)	14 (60.9)	
Comorbidity[b]			
None	16 (76.2)	10 (43.5)	0.036
Any	5 (23.8)	13 (56.5)	
Clinical T			
1–2	14 (66.7)	12 (52.2)	0.373
3–4	7 (33.3)	11 (47.8)	
Clinical N			
0–1	7 (33.3)	11 (47.8)	0.373
2–3	14 (66.7)	12 (52.2)	
Stage			
I–II	7 (33.3)	7 (30.4)	0.351
III–IVB	12 (57.2)	16 (69.6)	
IV C	2 (9.5)	0	
Baseline EBV VCA-IgA	3.1 (0.6–9.7)	2.3 (0.6–7.0)	0.239[c]
Baseline EBV EA + NA1 IgA	34.4 (2.2–242)	49.9 (2.4–137.3)	0.735[c]

Data are presented as *n* (%) or median (range).
EA = early antigen; EBV = Epstein-Barr virus; IgA = immunoglobulin A; NA = nuclear antigen; VCA = viral capsid antigen.
[a] Fisher's exact test.
[b] Medical history of cancers, diabetes, cardiovascular diseases, or hypertension.
[c] Mann-Whitney *U* test.

Table 2
Treatment courses and clinical outcomes by age group.

	Age <40 y $N = 21$	Age >65 y $N = 23$	p[a]
NACT			
No	4 (19.1)	11 (47.8)	0.060
Yes	17 (80.9)	12 (52.2)	
Definitive treatment[b]			
Radiotherapy only	0	11 (47.8)	<0.001
CCRT	19	12 (52.2)	
Adjuvant			
No	5 (23.8)	17 (73.9)	0.002
Yes	16 (76.2)	6 (26.1)	
Response to treatment			
CR	18 (85.7)	18 (78.3)	0.416
PR	2 (9.5)	5 (21.7)	
No response	1 (4.8)	0	
EBV VCA-IgA 1 y after treatment	4.2 (1.0–6.5)	4.7 (0.9–8.5)	0.659[c]
EBV EA + NA1 IgA 1 y after treatment	22.0 (2.6–128.0)	62.3 (0.2–128.0)	0.631[c]
Disease status during follow-up			
Remained CR or PR	18 (85.7)	14 (60.9)	0.135
Second primary malignancy	0	1 (4.4)	
Recurrence	0	4 (17.4)	
Metastasis	3 (14.3)	4 (17.4)	

Data are presented as *n* (%) or median (range).
CCRT = concurrent chemoradiotherapy; CR = complete response; EBV = Epstein-Barr virus; IgA = immunoglobulin A; NACT = neoadjuvant chemotherapy; PR = partial response; VCA = viral capsid antigen.
[a] Fisher's exact test.
[b] Two younger and one older patient receiving target therapy concurrent with radiotherapy were excluded from the analysis.
[c] Mann-Whitney *U* test.

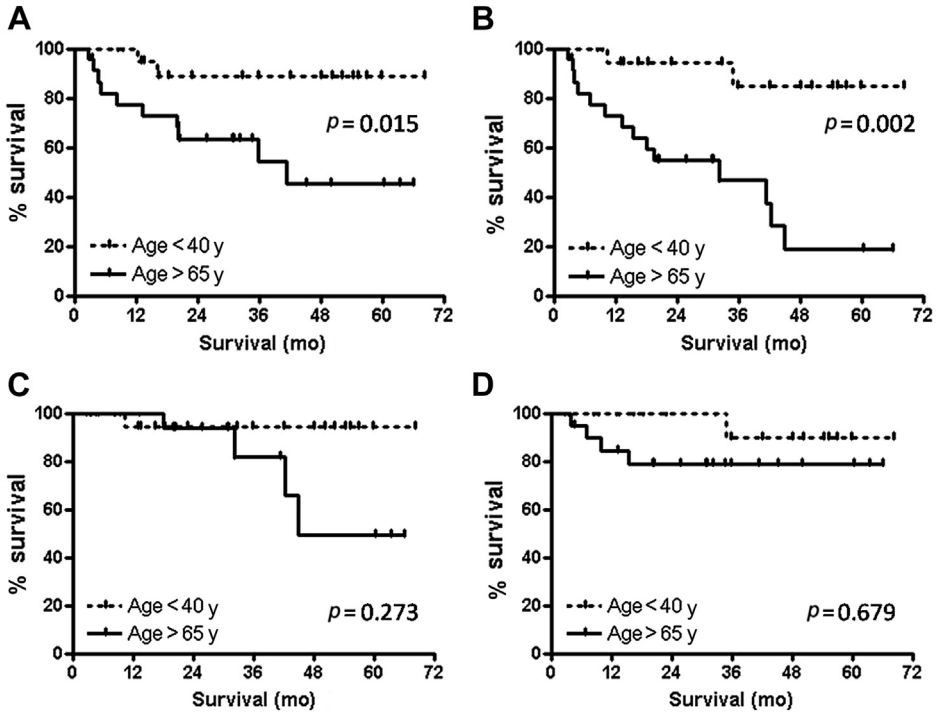

Fig. 1. Kaplan-Meier survival analysis for patients with nasopharyngeal cancer by age group. (A) Overall survival. (B) Progression-free survival. (C) Local recurrence-free survival. (D) Distant metastasis-free survival.

compared to younger patients (5-year PFS 81.0%, median not reached, $p = 0.002$). The 5-year local recurrence free survival (LRFS) and distant metastasis free survival (DMFS) were 49.2% and 78.8% in the older patients, respectively. The estimates tended to favor younger patients (5-year LRFS 90.0% and DMFS 81.4%), but the difference was not statistically significant (Fig. 1C and D).

After adjusting for medical history and neoadjuvant chemotherapy, age older than 65 years was the only significant predictor in the study cohort for OS and PFS. The adjusted HR for death from all causes in older patients was 6.3 (95% CI = 1.3–30.2), and the adjusted HR for disease progression in elder patients was 10.9 (95% CI = 2.3–50.6, Table 3). Adding CCRT and adjuvant chemotherapy to the multivariate model did not significantly change the results. Adjusted HR was 31.0 (95% CI 3.2–302.1) for disease progression in older patients.

Table 3
Cox proportional hazard models for prognostic factors in patients with nasopharyngeal cancer by age group.

	Death	Disease progression	Local recurrence	Distant metastasis
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Crude				
age (y)				
<40	1.0	1.0	1.0	1.0
>65	5.4 (1.2–24.7)	8.8 (2.0–39.1)	2.5 (0.5–14.0)	1.4 (0.3–6.1)
Adjusted				
age (y)				
<40	1.0	1.0	1.0	1.0
>65	6.3 (1.3–30.2)	10.9 (2.3–50.6)	3.2 (0.5–20.1)	1.6 (0.3–8.4)
Comorbidity				
None	1.0	1.0	1.0	1.0
Any	0.6 (0.3–1.2)	0.8 (0.4–1.3)	0.6 (0.2–1.9)	0.7 (0.2–2.0)
Neoadjuvant				
No	1.0	1.0	1.0	1.0
Yes	0.5 (0.1–1.5)	1.1 (0.4–3.2)	0.7 (0.1–3.8)	0.7 (0.1–3.3)

CI = confidence interval; HR = hazard ratio.

4. Discussion

Despite a decrease in overall cancer death rates, the increase in the elderly population is expected to increase the burden of cancer in the United States[7]. Therefore, it is important to recognize age-specific differences in common cancer[8]. The purpose of this study was to compare the outcomes between elderly and younger patients with NPC, after controlling for comorbidity and treatment. Our data suggested age is an independent prognostic factor.

Many older patients refuse intensive treatments because they fear the adverse effects might not be bearable in addition to the existing comorbidities. More often than not, there are also concerns about family and financial supports during the process of medical care. Results of this study confirmed that older patients are less likely to receive NACT (52.2% in older patients vs. 81.0% in younger patients), CCRT (52.2% in older patients vs. 100.0% in younger patients), and adjuvant chemotherapy (26.1% in older patients vs. 76.2% in younger patients) regardless of clinical stage. Although aging may induce poor performance and aggressive treatment-related toxicities, all of the older patients initially achieved CR or PR to the treatments with curative intent. Long-term survival may be influenced by the compromised treatments in the elderly. Prolonged benefit in OS and DFS might be plausible for older patients if they are encouraged to complete the treatments with carefully adjusted drug doses.

Nonetheless, effectiveness and tolerability of chemotherapy and radiotherapy remain critical controversy for older patients with malignancy. Several retrospective oncologic studies reported no increased toxicity in the elderly, during treatments against breast cancer[9], colon cancer[10], or cervical cancer[11], whereas other studies[12–15] observed older patients suffered more from treatment-related complications. Intensity of the treatments may help to

explain the difference in tolerance for elderly, and consequently alter the outcome. Vercelli et al[12] found worse prognosis following the increased toxicities for elder cancer patients in a European trial. However, older age at diagnosis was a predictor of worse survival in patients with head and neck cancer[13] but also a favorable factor in survivals for breast cancer[14] and esophageal cancer[15].

In addition to the concerns of tolerance, older age has been associated with metabolic changes, higher incidence of comorbidities, and polypharmacia[16]. These conditions potentially increase treatment-related complications[17]. Acute treatment-related toxicities, such as neutropenia and gastrointestinal symptoms, commonly occur with chemotherapy and radiotherapy, but the symptoms are transient and patients spontaneously recover with proper nutrition support. In the current study, we observed more comorbidities in older patients than younger patients. History of malignancies, hypertension, diabetes, and cardiovascular diseases were significantly more prevalent in older patients, taking on possible competing causes of death. These conditions may also compromise the administration of treatments for NPC. Therefore, it is important to closely monitor the condition of older patients during treatment.

We observed a significantly higher risk of death from all causes and disease progression in older patients when compared to younger ones after controlling for medical history and treatment-related factors. Aging is the only prognostic factor significantly associated with the outcomes in the study cohort, and the difference in survival could not be simply explained away by diagnosis of comorbidities or treatment intensity. We believe the results underline both risks and benefits for older patients when compared to younger patients diagnosed with NPC. Such information is essential for physicians and patients during the decision-making process.

Because of the relatively low incidence of NPC in the elderly, we conducted a retrospective case−case comparison with information on medical history, treatment responses, and survival outcomes extracted from charts. The study design may introduce bias unknown to the authors, and brought limitations such as missing data on laboratory examinations. However, the study highlights the need to carefully adjust the treatment strategies, and to ameliorate the treatment-related toxicities for elder patients with NPC. Prognosis may be improved with CCRT and other intensive medical care for elderly as it is for younger patients.

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