

Comparison of Prognosis Between Juvenile and Adult Nasopharyngeal Carcinoma: A Propensity Score-Matched Analysis

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Purpose: To investigate whether juvenile patients with nasopharyngeal carcinoma (NPC) in China have better prognosis than their adult counterparts in the intensity-modulated radiation therapy (IMRT) era, after controlling for potential confounding variables.

Methods: Data pertaining to 1139 patients with newly diagnosed NPC without metastasis, who were treated with IMRT at our hospital, were retrospectively analyzed. Of these, 60 patients were juvenile (age ≤ 18 years) diagnosed between January 2003 and December 2018, while 1079 patients were adults (≤ 65 years) diagnosed between January 2013 and December 2014. To minimize the influence of selection and confounding bias, 1:2 propensity score matching (PSM) was used. Overall survival (OS), disease-free survival (DFS), locoregional relapse-free survival (LRFS), and distant metastasis-free survival (DMFS) were estimated using the Kaplan–Meier method and between-group differences assessed using the Log rank test. The long-term toxicity of the juvenile patients was evaluated according to the criteria of the Radiation Therapy Oncology Group (RTOG) and the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Results: Five-year OS of juvenile and adult patients were 88.07% and 85.08%, respectively. Before PSM, OS, PFS, DMFS, or LRFS were comparable in the two groups (all $P > 0.05$). After PSM, OS, DFS, and LRFS in the juvenile group were markedly longer than that in adults ($P = 0.005$, $P = 0.027$, and $P = 0.024$, respectively). With respect to long-term toxicity, the most common adverse effects in juvenile patients were cervix fibrosis, ototoxicity, and xerostomia. However, except for two patients who developed grade 3 ototoxicity, all adverse effects were within grade 2.

Conclusion: In the IMRT era, juvenile Chinese patients with NPC had better 5-year OS, DFS, and LRFS than their adult counterparts. The adverse events in the juvenile cohort were relatively mild; however, the risk of severe ototoxicity should not be neglected.

Keywords: juvenile nasopharyngeal carcinoma, intensity-modulated radiotherapy, prognosis

Introduction

Nasopharyngeal carcinoma (NPC) is an epithelial-derived malignant tumor. The incidence of NPC varies across regions, races, and ages.¹ Juvenile NPC (jNPC) is a rare disease that reportedly accounts for $<1\%$ of malignant tumors in children in Europe and America.² In China, where NPC has a relatively high incidence, the incidence rate of jNPC is 0.1–2.3%, accounting for 1–2% of all patients with NPC.^{3,4} With much lower incidence and more advanced staging,⁵ NPC in the juvenile population may have distinctive biological characteristics from those in

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adults. Consequently, the majority of prospective studies about NPC excluded patients aged <18 years; therefore, there had been limited knowledge pertaining to this disease in the juvenile population for a long time.

In recent decades, the attention paid to jNPC has been on the rise, and several studies have reported the survival rates of patients with jNPC.⁶ In general, the prognosis of jNPC is believed to be better than that of adult NPC (aNPC). Nevertheless, the previous studies showed considerable variability with respect to ethnicity of study population, geographic region, and therapeutic regimes used. In addition, there were vast differences in the sample size in the two groups, thus limiting the comparability. Some researchers have sought to address this issue in the era of two-dimensional conventional radiotherapy (2D-CRT); however, the results have not been consistent. Studies conducted in America have found significant differences between the two cohorts.^{7–9} However, in studies conducted in China and Tunisia, juvenile patients with NPC showed similar survival as adults, with a greater tendency for distant failure and more severe late toxicity.^{10–12}

Studies conducted in the era of intensity-modulated radiotherapy (IMRT) have documented reduced incidence of toxicity and improved survival in patients with jNPC.^{13,14} However, only two recent studies have compared the outcomes and prognosis between adult and juvenile patients.^{15,16} Analysis of data from Surveillance, Epidemiology, and End Results (SEER) database demonstrated better prognosis of jNPC as compared to that of aNPC, which is consistent with previous studies conducted in America in the 2D-CRT era. A recent study in Guangdong, China also found significant differences with respect to disease-free survival (DFS) and locoregional relapse-free survival (LRFS), but not with respect to overall survival (OS) or distant metastasis-free survival (DMFS). Overall, there is a paucity of comparative studies, especially in China. In particular, there is no compelling evidence to support the assumption that jNPC has better prognosis than aNPC in endemic areas.

In this study, we used propensity score matching (PSM) to investigate whether the juvenile patients with NPC treated at our institution have better prognosis than their adult counterparts, after controlling for multiple confounding variables. Our findings may provide a reference for clinical treatment and help characterize jNPC in high-prevalence areas.

Patients and Methods

Patients

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the institutional review board at Fujian Cancer Hospital (Ref no. SQ2019-018-01). For the retrospective nature of the study, the requirement for informed consent of patients was waived off by the institutional review board. The confidentiality of patient data was completely respected. We defined juvenile patients as those aged ≤18 years, while the adult patients were aged 19–65 years. Based on the information of 11,790 patients diagnosed with NPC in our hospital from January 2003 to December 2018, two databases were set up. One database included 100 juvenile patients who were aged <19 years at the time of diagnosis between January 2003 and December 2018; the other database included 1696 adult patients treated from January 2013 to December 2014. Eventually, a total of 60 juveniles and 1079 adults with NPC were included based on the following inclusion criteria: (1) patients with pathologically confirmed NPC; (2) newly diagnosed NPC with no distant metastasis; (3) IMRT was the definitive treatment for NPC.

Pretherapeutic evaluation was based on a thorough historical and physical examination, complete blood count, biochemistry tests, Epstein-Barr Virus (EBV) serology tests, nasopharyngoscopy with pathological biopsy, magnetic resonance imaging (MRI) of nasopharynx and neck, abdominal ultrasonography, computed tomography (CT) of chest, and bone scanning. To enhance the comparability of data, all patients were re-staged according to the 8th edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system.¹⁷

Treatment

Definitive IMRT was administered to all patients. Details about the planning and implementation of IMRT at our hospital are described elsewhere.¹⁸ For both juvenile and adult patients with NPC, the median dose of the primary tumor was 69.75 Gy (60.2–74.25 Gy and 42.4–80 Gy, respectively), and those of the regional lymph node were 69.3 Gy (50–70.95Gy) and 68.2 Gy (49.6–80Gy), respectively. One fraction of 2 Gy (1.8–2.2 Gy) was delivered daily for 5 days per week. After the definitive radiotherapy, 250 patients were found to have residual disease, of which 93 had residual disease at the primary site, 103 in

the cervical lymph node region, and 54 in both. All of these patients accepted 2.1–16 Gy additional radiation, except for 8 adult patients who refused the salvage treatment.

Platinum-based chemotherapy was delivered to 1103 (96.8%, 1103/1139) patients according to the national comprehensive cancer network (NCCN) guidelines and based on the patients' condition and the attending physician's judgement. Among the aNPC patients, 97 (8.99%) were treated with induction chemotherapy alone, while 74 (6.86%) were treated with concurrent chemotherapy, 370 (34.29%) with induction-concurrent chemotherapy, 132 (12.23%) with induction-adjuvant chemotherapy, 23 (2.13%) with concurrent-adjuvant chemotherapy, and 348 (32.25%) with induction-concurrent-adjuvant chemotherapy. With regard to the jNPC patients, 12 (20.00%) were treated with induction chemotherapy alone, while 1 (1.67%) were treated with concurrent chemotherapy, 16 (26.67%) with induction-concurrent chemotherapy, 8 (13.33%) with induction-adjuvant chemotherapy, and 22 (36.67%) with induction-concurrent-adjuvant chemotherapy.

Follow-Up

Follow-up investigations were conducted trimonthly for the first two years, semi-annually for the next three years, and annually thereafter. During follow-up, routine examinations were performed such as complete blood count, blood chemistry, EBV DNA load, chest CT, MRI of nasopharynx and neck, and abdominal sonography.

Data pertaining to long-term toxicity in the juvenile group were obtained at the clinic or telephonically, and evaluated according to the criteria of the Radiation Therapy Oncology Group (RTOG)¹⁹ and the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.²⁰

Statistical Analysis

Statistical Product and Service Solutions (SPSS) version 26.0 was used for data processing and analysis. Patient characteristics were compared using the Chi-squared test and independent-sample *t*-test. To reduce selection and confounding bias, 1:2 propensity score matching (PSM) was used based on sex (male or female), cervical lymph node biopsy (yes or no), histopathological classification, T stage, N stage, overall stage, chemotherapy cycles (≤ 3 or > 3) and radiation dose for gross tumor volume of the primary site (GTVp).

Survival outcomes (OS, LRFS, DMFS, and DFS) were calculated from the time of diagnosis. The endpoints were

death or most recent follow-up, local or regional relapse, distant failure and any form of progression or onset of second primary tumor, respectively. The survival rates were estimated using the Kaplan–Meier method and compared using the Log rank test. Two-sided *P* values less than 0.05 were considered indicative of statistical significance.

Results

Incidence of jNPC and Treatment Failure Patterns

From January 2003 to December 2018, patients with jNPC accounted for approximately 0.85% (100/11,790) of all patients with NPC in our hospital database. With regard to the patients treated between January 2013 and December 2014, patients with jNPC accounted for 0.53% (9/1705) of all patients with NPC.

A total of 60 juvenile patients qualified the inclusion criteria for this study. The 5-, 10-, and 15-year OS of juvenile patients was 88.07%, 88.07%, and 84.20%, respectively. None of the patients experienced local relapse. However, eight patients (13.3%, 8/60) had distant failure and two of them had concurrent regional relapse (3.33%, 2/60). Seven patients died (11.7%, 7/60), of which six patients died of the progression of NPC (10%, 6/60), and one died of other diseases.

Comparisons of Patient Characteristics

The median age of the juvenile patients was 16 (range: 10–18) years, while that of the adult patients was 47 (range: 19–65) years. Prior to PSM, a significant between-group difference was observed with respect to T stage ($P < 0.001$), overall stage ($P = 0.006$), induction chemotherapy ($P = 0.037$), and average radiation dose for GTVp ($P = 0.009$). No significant between-group differences were observed with respect to sex, lymph node biopsy, pathological classification, N stage, chemotherapy cycles, or concurrent chemotherapy and adjuvant chemotherapy. In the PSM cohort, none of the baseline or treatment-related characteristics were found significantly different between the two groups (Table 1).

Comparisons of Survival Outcomes Before and After PSM

To investigate whether juvenile patients with NPC have better prognosis than adult patients, we firstly compared the survival curves of the two complete databases. The median follow-up time of juvenile and adult NPC patients

Table I Clinical Characteristics of 1139 Patients Before PSM and 157 Patients After PSM

Factors	All Cases			Matched Cases		
	Juvenile (n=60)	Adult (n=1079)	P	Juvenile (n=53)	Adult (n=104)	P
Median age (range, year)	16 (10–18)	47 (19–65)		16 (10–18)	47 (24–65)	
Gender			0.686			0.951
Male	46(76.67)	802(74.33)		41(77.36)	80(76.92)	
Female	14(23.33)	277(25.67)		12(22.64)	24(23.08)	
Lymph node biopsy			0.437			0.965
Yes	8(13.33)	110(10.19)		7(13.21)	14(13.46)	
No	52(86.67)	969(89.81)		46(86.79)	90(86.54)	
Histology			0.531			–
WHO Type I	0(0.00)	7(0.65)		0(0.00)	0(0.00)	
WHO Type II/III	60(100.00)	1072(99.35)		53(100.00)	104(100.00)	
T stage			<0.001			0.944
I	4(6.67)	255(23.63)		4(7.55)	7(6.73)	
2	2(3.33)	252(23.35)		2(3.77)	6(5.77)	
3	35(58.33)	305(28.27)		31(58.49)	62(59.62)	
4	19(31.67)	267(24.75)		16(30.19)	29(27.88)	
N stage			0.073			0.873
0	0(0.00)	91(8.43)		0(0.00)	1(0.96)	
I	21(35.00)	399(36.98)		18(33.96)	37(35.58)	
2	26(43.33)	427(39.57)		23(43.40)	41(39.42)	
3	13(21.67)	162(15.01)		12(22.64)	25(24.04)	
Overall stage			0.006			0.798
I	0(0.00)	21(1.95)		0(0.00)	0(0.00)	
II	1(1.67)	194(17.98)		1(1.89)	4(3.85)	
III	30(50.00)	466(43.19)		26(49.06)	49(47.12)	
IV	29(48.33)	398(36.89)		26(49.06)	51(49.04)	
Chemotherapy cycles			0.721			0.735
≤3	18(30.00)	309(28.64)		16(30.19)	26(25.00)	
>3	42(70.00)	770(71.36)		37(69.81)	78(75.00)	
Induction Chemotherapy			0.037			0.487
Yes	58(96.67)	947(87.77)		51(96.23)	102(98.08)	
No	2(3.33)	132(12.23)		2(3.77)	2(1.92)	
Concurrent chemotherapy			0.067			0.685
Yes	39(65.00)	815(75.53)		35(66.04)	72(69.23)	
No	21(35.00)	264(24.47)		18(33.96)	32(30.77)	
Adjuvant chemotherapy			0.609			0.650
Yes	30(50.00)	503(46.62)		26(49.06)	55(52.88)	
No	30(50.00)	576(53.38)		27(50.94)	49(47.12)	
Radiation dose for GTVp(Gy)*	68.87 ±28.86	69.88 ±14.28	0.009	69.70 ±16.56	69.74 ±13.05	0.882

Note: *Calculated in average.

Abbreviations: PSM, propensity score matching; WHO, World Health Organization; GTVp, gross tumor volume of the primary site; Gy, gray.

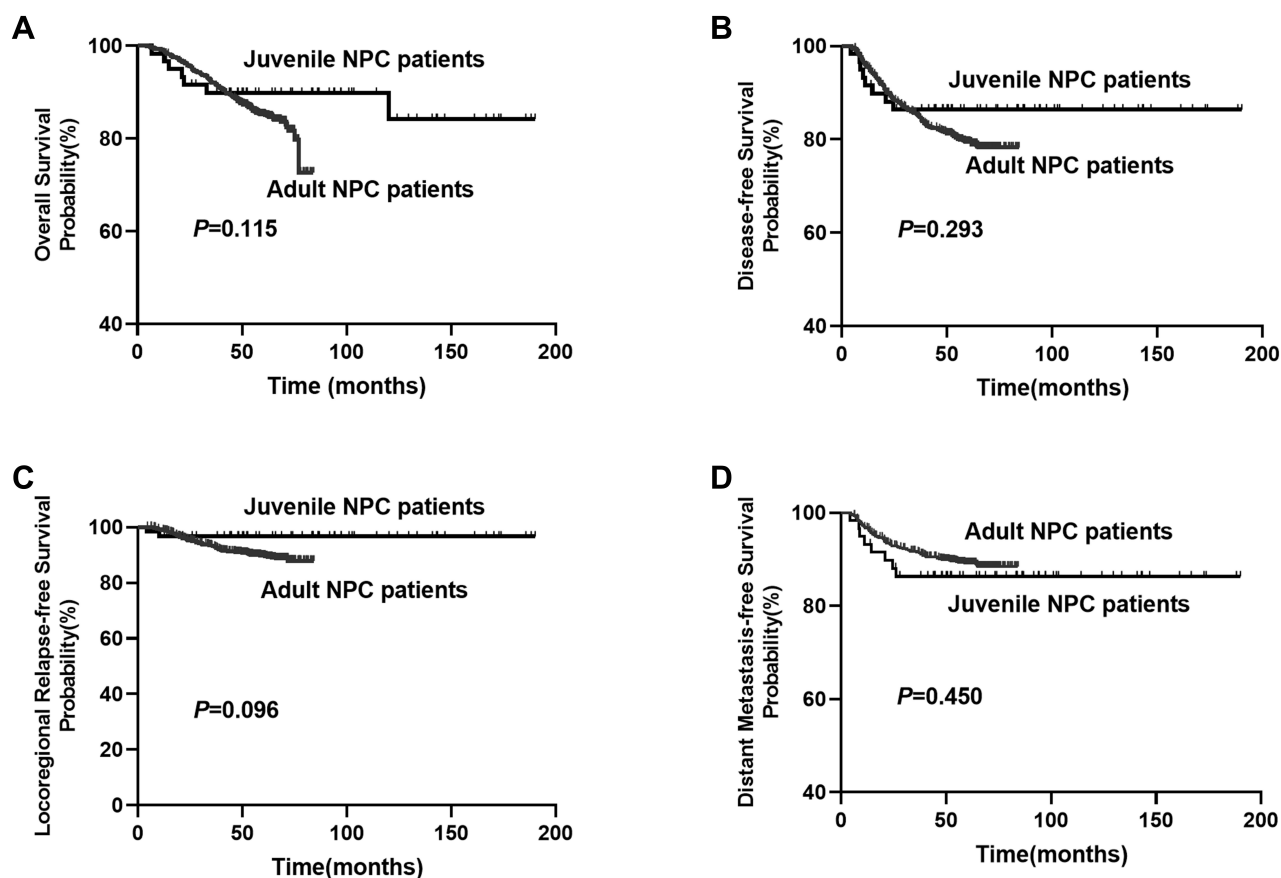


Figure 1 Comparison of overall survival (A), disease-free survival (B), locoregional relapse-free survival (C), and distant metastasis-free survival (D) curves between 60 juvenile and 1079 adult patients with NPC.

Abbreviation: NPC, nasopharyngeal carcinoma.

was 83.6 (range: 6.8–190.2) months and 61.1 (range: 4.5–84.3) months, respectively. No significant between-group differences were observed with respect to 5-year OS (88.07% vs 85.08%, $P = 0.115$), DFS (86.2% vs 79.08%, $P = 0.293$), LRFS (96.6% vs 89.38%, $P = 0.096$), or DMFS (86.1% vs 88.94%, $P = 0.450$) (Figure 1).

PSM was used to minimize the influence of confounding variables. After PSM, a total of 157 cases including 53 juveniles and 104 adults were eligible for further analysis. The OS, DFS, and LRFS of juvenile patients were significantly better than that of their adult counterparts ($P = 0.005$, $P = 0.027$, and $P = 0.024$, respectively). However, the DMFS was still comparable in the PSM cohort ($P = 0.372$) (Figure 2).

Late Toxicity

Excluding the six patients who were lost to follow-up and the seven patients who died, 47 jNPC patients were included in the analysis of long-term toxicity (Table 2). Nearly half of the

patients (23/47, 48.9%) suffered varying degrees of sequelae. The most commonly recorded sequelae were cervix fibrosis, ototoxicity, and xerostomia (all were 11/47, 23.4%). Fortunately, 91.3% (21/23) of these patients had \leq grade 2 toxicity, while none of these had grade 4 toxicity. Two patients developed grade 3 ototoxicity, which was confirmed to have a negative impact on the quality of life.

Discussion

There are limited comparative studies of survival outcomes between juvenile and adult NPC. To the best of our knowledge, there was no robust evidence to prove the conjecture that jNPC has better prognosis than aNPC in the IMRT era. In the present study, the two cohorts presented an imbalanced proportion in T stage, clinical stage, induction chemotherapy, and radiation dose for GTVp prior to PSM. In addition, no significant difference was found in OS, DFS, LRFS, or DMFS. After PSM analysis, the difference in characteristics between the two groups was eliminated. Moreover, significant differences emerged with respect to OS, DFS, and

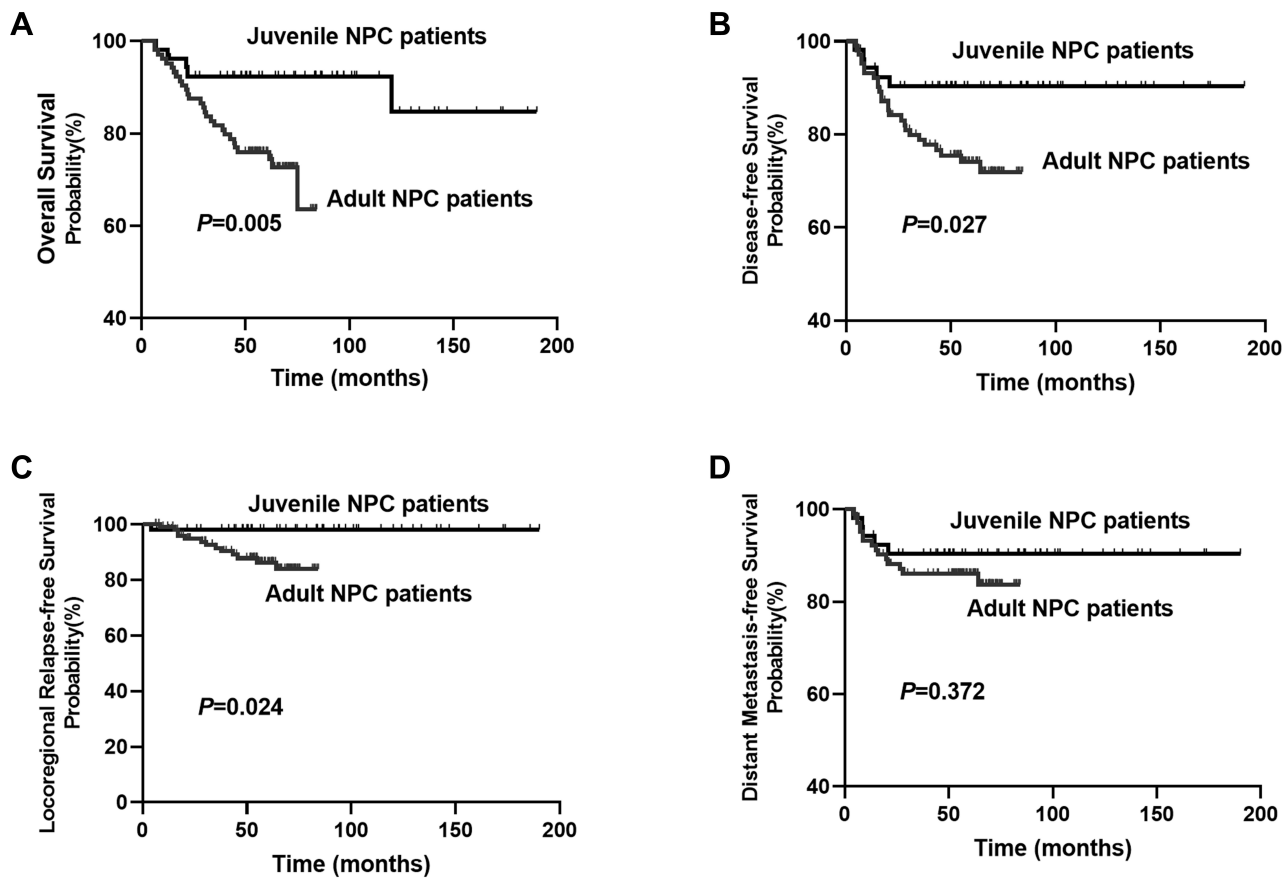


Figure 2 Comparison of overall survival (A), disease-free survival (B), locoregional relapse-free survival (C), and distant metastasis-free survival (D) curves between 53 juvenile and 104 adult patients with NPC after PSM.
Abbreviations: NPC, nasopharyngeal carcinoma; PSM, propensity score matching.

LRFS. Our present research represents the first study to demonstrate better OS of patients with jNPC as compared to aNPC in China. Furthermore, we observed relatively mild long-term toxicity in the juvenile patients; apart from two

cases with severe ototoxicity, all of the recorded adverse effects were \leq grade 2.

Prior to PSM analysis, none of the survival outcomes showed a significant between-group difference. Similar

Table 2 The Frequency of Late Toxicities in Juvenile Patients with NPC

Late Toxicities	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Xerostomia	36(76.6)	7(14.9)	4(8.5)	0	0	0
Brain damage	47(100)	0	0	0	0	0
Cervix Fibrosis	36(76.6)	5(10.6)	6(12.8)	0	0	0
Trismus	46(97.9)	0	1(2.1)	0	0	0
Dysphagia	46(97.9)	1(2.1)	0	0	0	0
Hoarseness	47(100)	0	0	0	0	0
Dental caries	47(100)	0	0	0	0	0
Ototoxicity	36(76.6)	5(10.6)	4(8.5)	2(4.3)	0	0
Blurred vision	46(97.9)	1(2.1)	0	0	0	0
Hypothyroidism	47(100)	0	0	0	0	0
Amenorrhea*	10(100)	0	0	0	0	0

Note: *Amenorrhea was evaluated only for the ten female patients.

Abbreviation: NPC, nasopharyngeal carcinoma.

results were reported by Daoud et al,^{10,11} who found comparable prognosis of jNPC and aNPC. However, it is noteworthy that the two groups in our study showed considerable differences in clinical characteristics. Compared to adult patients with NPC, jNPC patients had more advanced T stage ($P < 0.001$) and overall stage ($P = 0.006$), which may theoretically lead to poorer prognosis. Besides, greater usage of induction chemotherapy in jNPC patients (96.67% vs 87.77%, $P = 0.037$) may have had an effect on the prognosis, which was also a consequence of high occurrence of locally advanced stage. Thus, it would be hard to draw a reliable conclusion by comparing the two cohorts directly. The statistical method should be optimized to eliminate the confounding effects.

To minimize the systematic error caused by the sample structure, we adopted the PSM method; it is defined as the conditional probability that an individual is affected by a certain independent variable after controlling the observed covariates.²¹ To implement the PSM, we firstly performed logistic regression based on the factors that may influence the outcomes, which allowed us to calculate the propensity score of each patient. By awarding each patient a propensity score according to the characteristics, multiple covariates can be turned into a single one, and thus the combined influences of multiple covariates could be exerted. In addition, the subjects were finally matched on the propensity scores. To minimize the loss of data during the process of matching and make the most of our large database, 1:2 PSM was performed. Finally, the quality of the matching was assessed by comparing each factor between two groups with Log rank test. The two groups were not balanced until P value of each factor was >0.05 . This method was of great help to eliminate the imbalanced potential confounding variables, especially for the high-quality database with a large cohort of patients. It also helps adjust the distinctly imbalanced samples for comparison,²² such as the imbalanced characteristics of the juvenile and adult patients with NPC in our study. Besides, by setting patients with similar characteristics into treated group and control group, the PSM method can simulate the process of the experimental method.²³ Therefore, the PSM method can help obtain more reliable causal relationships between the intervention and survival outcomes.

After using the PSM method, the clinical features of the two groups were well balanced. A remarkably better survival was observed in juvenile group in OS, DFS and LRFS, but DMFS was still similar. Chen et al¹⁶ also conducted a PSM study for comparing juvenile and adult patients with NPC. However, they did not observe a significant between-group difference with respect to OS, which was different from our

study. This discrepancy may be attributable to the single-center scope of the study, which may have introduced an element of bias. Multi-center studies may provide more robust evidence in this respect. Furthermore, the median age of patients in the adult group in their study was only 31 years, which is relatively low and may consequently narrow the gap of survival between the two groups. However, it is noticeable that the DMFS curves of the two groups were similar, which indicated that distant metastasis remained the major treatment failure pattern in the juvenile population. Based on micrometastasis theory,²⁴ it is presumed that the insufficient intensity of chemotherapy may account for distant metastasis. Till date, prospective studies have confirmed the safety and efficacy of cis-platinum plus 5-FU regimen (PF regimen) for induction-concurrent chemotherapy for jNPC.^{25,26} In addition, tentative exploration of interferon- β as adjuvant treatment has also made a breakthrough.² Further studies are expected to reveal the appropriate cycles of chemotherapy and the safety and long-term efficacy of interferon- β ; this would help determine the optimal chemotherapy strategy for jNPC.

As for the complications of jNPC, nearly half of the patients (48.9%) developed sequelae; cervix fibrosis, ototoxicity, and xerostomia were the most common side effects. Fortunately, most of the sequelae were mild, which coincided with the reports of late toxicity in the IMRT era and represented a great improvement compared with the 2D-CRT era.^{13,27,28} However, we should be on the alert for the two cases with grade 3 ototoxicity, whose life quality was deeply affected. Since the juvenile patients achieved a better LRFS than adults, the present radiation dose might be adequate for local control of the tumor. Consequently, an appropriate decrease could be tried in the near future, with the purpose of protecting the organs at risk and lowering the incidence of severe late effects. Several recent studies have shown that for jNPC patients who show complete response (CR) or partial response (PR) to induction chemotherapy, the local radiation dose may be safely reduced to <60 Gy,^{2,29} this may provide some suggestions for improvement in the future treatment strategies. In addition, the role of radiation protective agents such as Amifostine in jNPC patients remains largely unknown, which is required to be revealed by the further clinical trials. Apart from radiotherapy, platinum-induced ototoxicity is another concern; it has been shown to correlate with accumulated platinum dose and genetic susceptibility.^{30,31} Therefore, hearing tests should be conducted before and during the treatment to recognize the side effect and

institute timely changes in the treatment plan; chemotherapy drugs with lower ototoxicity should also be considered.

Some limitations of our study should be considered while interpreting the results. Owing to the rarity of jNPC, data of juvenile group pertained to a time span of 15 years, which was much longer than that for adults; this may lead to inevitable influences on survival outcome comparison. However, the jNPC patients possessed better prognosis as compared to the aNPC patients even if the much longer time span possessed by the jNPC patients, which indirectly supported the current results. Besides, this was a single-center study; well-designed multicenter studies should be conducted for more robust evidence.

Conclusion

In the era of IMRT, Chinese patients with jNPC showed a better prognosis than their adult counterparts, as assessed using the PSM method. However, distant metastasis remained the main treatment failure pattern. Complications encountered in juvenile patients were relatively mild; however, severe ototoxicity remains a concern in these patients.

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Disclosure

None of the authors have any conflicts of interest to disclose for this work.

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