ORIGINAL RESEARCH

Outcomes and Experiences of Child-Bearing Women with Nasopharyngeal Carcinoma

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Purpose: Nasopharyngeal carcinoma (NPC) is more common among women in Southeast Asia. An important issue is whether it is safe for them to bear children after treatment and when it is safe to do so. We conducted this study to explore the relation between fertility and prognosis in child-bearing women with NPC.

Patients and Methods: Child-bearing women were defined as young women between the ages of 18 and 30. A total of 127 eligible child-bearing NPC patients were identified from December 2003 to December 2014. The patients were divided into two groups, depending on whether or not they had post-therapeutic births. The Kaplan–Meier method was used for survival analyses. The Log rank test was used to compare two survival curves and the independent significances of different prognostic factors were assessed by Cox proportional hazards regression analysis.

Results: The 5-year overall survival (OS) and disease-free survival (DFS) in the Childbirth group were significantly higher than those in the Non-Childbirth group (100% vs 88.8%, P = 0.026 and 100% vs 77.5%, P = 0.007, respectively). In the Childbirth group, no difference was found in the 5-year DFS between different birth interval times, from 1 to 5 years after treatment. The clinical stage was identified as the risk factor of OS (HR = 101.725, 95% CI: 2.160–4790.910, P = 0.019), and consequent childbirth after treatment was associated with favorable DFS (HR = 0.148, 95% CI: 0.034–0.643, P = 0.011).

Conclusion: Post-therapeutic birth did not increase the mortality risk of child-bearing women with NPC. There was no significant correlation between the subsequent birth time window after treatment and the prognosis.

Keywords: nasopharyngeal carcinoma, fertility, child-bearing mortality risk, post-treatment

Introduction

Nasopharyngeal carcinoma (NPC) is one of the most common cancers and it occurs with much greater frequency in Southern China.[1] The risk for males is two to three times higher than that for females.[2,3] Radiotherapy (RT) is the main treatment for NPC,[1–3] and intensity-modulated radiation therapy (IMRT) can achieve excellent 5-year local control rates, ≥90% for T3 disease and 74%–80% for T4 disease.[4] Chemotherapy has made a small, but significant, contribution to improve overall survival (OS) and event-free survival.[5] Concurrent chemoradiotherapy has been the standard treatment for advanced NPC.[5–7] It was reported that women showed better survival outcomes than men and the survival of patients younger than 40 years old was better than older patients.[8] As the probability of survival improves, female NPC patients of child-bearing age may consequently consider conception after recovery.

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However, cancer treatments may cause gonadal toxicities,[9,10] which is especially emphasized in female patients of child-bearing age.[11] In previous studies, among 24 females who treated for Hodgkin's disease in childhood, 17patients (70.8%) had normal gonadal function with regular menstrual periods.[12] Besides, chemotherapy has a negative influence on pregnancy outcomes[13] and increases the incidence of neonatal neutropenia.[14] It was unclear whether subsequent child-bearing would increase the mortality risk of women with carcinoma. Related studies are rare and no investigator has yet answered the question. This retrospective analysis is aimed at exploring the relation between fertility and prognosis in child-bearing patients with NPC. It aims to provide further reference for this subgroup of patients who plan to have children after treatment.

Patients and Methods
Patient Characteristics

The characteristics of the patients are presented in Table 1. From December 2003 to December 2014, a total of 127 female NPC patients of child-bearing age, diagnosed in Fujian Cancer Hospital, were enrolled. The main inclusion criteria consisted of the following: (i) histopathology confirmed primary NPC patients; (ii) complete clinical information and medical history, adequate clinical examination, and laboratory data; (iii) received entire treatment in our center (radical IMRT or two-dimensional conventional radiotherapy, with or without chemotherapy); (iv) absence of distant metastasis before, or during, treatment; (v) no evidence of carcinoma from another source or other severe disease; (vi) complete follow-up data; and (vii) patients no more than 30 years old. Patients were reclassified according to the eighth edition of the American Joint Committee on Cancer staging system. For every eligible female NPC patient, the year of completion of the treatment and subsequent years were screened for live births. Patients were divided into the Childbirth group and Non-Childbirth group, dependent on whether they had post-therapeutic births. The data included age; tumor, node, metastasis (TNM) stages; details of the chemotherapy and radiotherapy; details of the childbirth; and date of death. Data of this study were collected in a manner that the subjects could not be identified, so that no informed consent was required. The retrospective analysis received approval from the ethics committee of the Fujian Cancer Hospital

(YKT2019-027-01) and was conducted in accordance with the Declaration of Helsinki.

Treatment

All the therapeutic schemes regarding chemotherapy and radiotherapy were based on the clinical TNM stages, physicians' absolute discretion, and patients' choices.

Radiotherapy

Thirty-nine patients were treated with two-dimensional conventional radiotherapy, with a 1.8 or 2 Gy daily fraction and 5 fractions per week. Phase 1 of the conventional radiotherapy consisted of two fields of 36–40 Gy and the fields were then reduced off-cord to 50 Gy. Phase 2 brought a total dose of 68–72 Gy to the nasopharynx. Node negative patients received 50–54 Gy to the neck and node-positive patients were boosted to 66–70 Gy at the positive lymph node region. The other 88 patients received intensity-modulated radiotherapy, with a prescribed dose of 70 Gy in 31–35 fractions, at 2.0–2.25 Gy/fraction, to the planning target volume of the gross primary tumor volume and the nodal gross tumor volume. The target volume and radiotherapy dose were implemented using institutional treatment protocol as previously reported.[15] Gross tumor volume (GTV) was outlined according to the information from computed tomography (CT) and magnetic resonance (MR) images and visible tumor. Clinical target volume 1 (CTV-1) was defined as the high-risk region including the GTV and 6 mm margin for potential microscopic disease. Clinical target volume 2 (CTV-2) was designed for regions potentially involved including nasopharyngeal cavity, maxillary sinus, pterygopalatine fossa, posterior ethmoid sinus, parapharyngeal space, skull base, anterior third of clivus and cervical, vertebra, inferior sphenoid sinus and cavernous sinus. Organs at risk (OARs) include brain stem, spinal cord, optic nerve, parotid and so on.

Chemotherapy

For patients at stage II–IV B, the concurrent chemotherapy regimen comprised two cycles of platinum-based chemotherapy (80mg/m2, on day 1, every 3 weeks). Patients at stages III–IV underwent two cycles of neoadjuvant chemotherapy which consisted of gemcitabine (1000 mg/m2, on days 1 and 8) plus cisplatin (80 mg/m2, on day 2); or paclitaxel (135 mg/m2, day 1) plus cisplatin (80 mg/m2, day 2). Concurrent platinum-based chemotherapy was administered to every patient as a standard treatment.

Table 1 Patients and Tumor Characteristics

Characteristics	n (%)	Childbirth Group n(%)	Non-Childbirth Group n(%)	P-value
Age,years Median (Range)		23 (19–30)	26 (18–30)	0.229
T-stage T1 T2 T3 T4	 13 (0.2) 30 (23.6) 59 (46.5) 25 (19.7)	 4 (10.5) 7 (18.5) 23 (60.5) 4 (10.5)	 9 (10.1) 23 (25.8) 36 (40.4) 21 (23.7)	0.155
N-stage N0 N1 N2 N3	 9 (7.1) 72 (56.7) 28 (22.0) 18 (14.2)	 4 (10.5) 21 (55.3) 6 (15.8) 7 (18.4)	 5 (5.6) 51 (57.3) 22 (24.7) 11 (12.4)	0.461
Clinical stage I II III IVa	 1 (0.8) 27 (21.3) 60 (47.2) 39 (30.7)	 0 (0) 6 (15.8) 22 (57.9) 10 (26.3)	 1 (1.1) 21 (23.6) 38 (42.7) 29 (32.6)	0.352
Radiation therapy technique CRT IMRT	 39 (30.7) 88 (69.3)	 12 (31.6) 26 (68.4)	 27 (30.3) 62 (69.7)	>0.999
Treatment method RT alone RT+AC CCRT NACT+RT NACT+RT+AC NACT+CCRT NACT+CCRT+AC	 5 (3.9) 2 (1.6) 3 (2.4) 25 (19.7) 33 (26.0) 29 (22.8) 30 (23.6)	 2 (5.3) 0 (0) 0 (0) 8 (21.1) 12 (31.6) 9 (23.7) 7 (18.3)	 3 (3.4) 2 (2.2) 3 (3.4) 17 (19.1) 21 (23.6) 20 (22.5) 23 (25.8)	0.715
Reproductive history before treatment 0 1 2 3	 70 (55.1) 49 (38.6) 7 (5.5) 1 (0.8)	 26 (68.4) 11 (28.9) 1 (2.7) 0 (0)	 44 (49.4) 38 (42.7) 6 (6.7) 1 (1.2)	0.232

Abbreviations: CRT, conventional radiotherapy; IMRT, intensity-modulated radiotherapy; RT, radiotherapy; AC, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; NACT, neoadjuvant chemotherapy.

Neoadjuvant and/or adjuvant chemotherapy were applied, according to the physician's discretion. Neoadjuvant or adjuvant chemotherapy consisted of gemcitabine with cisplatin or paclitaxel with cisplatin. Chemotherapy was repeated every 3 weeks.

Follow-Up and Statistical Analysis

The data were collected every 3 months within the first 2 years and every 6 months thereafter. The follow-up period was from the diagnosis to the end of the follow-up or the date of death. The final date of the follow-up was

January 2020. The pretreatment and treatment data were calculated and compared using Chi-square or Fisher's texts and then processed using GraphPad Prism 8 software and R tool (Version 3.6.1). The Kaplan–Meier method was used for the survival analyses. The Log rank test was used to calculate the significance of the differences between the two survival curves. Cox proportional hazards regression analysis was used to assess the independent significance of different prognostic factors. Any difference was considered to be statistically significant if the p value was <0.05, based on two-sided tests. The primary clinical endpoint was OS and progression-free survival, defined as the date from diagnosis to death from any cause, or to disease progression or death from any cause, whichever occurred first.

Results

Patient Characteristics

A total of 127 consecutive patients at child-bearing age, with stage I–IVa NPC, were enrolled in the study. From the entire cohort, 38 patients had post-therapeutic births and were assigned to the Childbirth group, and 89 patients without post-therapeutic births were assigned to the Non-Childbirth group. All patients in the Childbirth group gave birth at least 1 year after treatment. Basic characteristics of all patients are presented in Table 1. For the entire cohort, the median age was 25 (range 18–30) years old. The median age was 23 (range 19–30) years old for the Childbirth group and 26 (range 18–30) years old for the Non-Childbirth group, respectively. There were no significant differences between the two groups in the age distribution (P = 0.107), T stage (P = 0.155), N stage (P = 0.461), clinical stage (P = 0.352), radiotherapy technique (P>0.999), treatment method (P = 0.715), and reproductive history before treatment (P = 0.232). The majority of the patients in both groups were at stages III–IV (84.2% vs 75.3%).

Influence of Post-Therapeutic Birth on Survival Outcomes

The median survival period of the Childbirth group was 11.0 years and only one patient died, while the median survival period in the Non-Childbirth group was 8.3 years, from which 15 patients (16.9%) died during follow-up. During the follow-up, relapse and metastasis occurred to one of the patients in the Childbirth group. Additionally, 2 patients (2.2%) experience a relapse, 11 patients (12.4%) had metastasis, and 3 patients (3.4%) had both a relapse and metastasis in the Non-Childbirth group. Between the Childbirth and Non-Childbirth groups, statistically significant differences were found in the 5-year OS rate and 5-year disease-free survival (DFS) (100% vs 88.8%, P = 0.026 and 100% vs 77.5%, P = 0.007, respectively) (Figure 1).

No difference was found in the 5-year DFS between different intervals, from the end of the treatment to the subsequent birth in the Childbirth group (Figure 2). To explore the impact of childbirth history before treatment, patients in the Non-Childbirth group were further divided into two subgroups. However, no significant differences were observed in the 5-year OS rate (88.9% vs 88.6%, P = 0.420) and 5-year DFS (82.2% vs 70.5%, P = 0.911) between the subgroups with and without a history of childbirth. Among the 45 patients with a history of childbirth in the Non-Childbirth group, 38 (84.4%) had one birth, 6 (13.3%%) had two births, and 1 (2.2%) had three births. No statistical difference was observed in the 5-year OS rate and 5-year DFS (P = 0.151 and P = 0.113, respectively).

Multivariate Analyses of the Survival

Variables, including age, T stage, N stage, clinical stage, reproductive history, chemotherapy, and radiotherapy, were
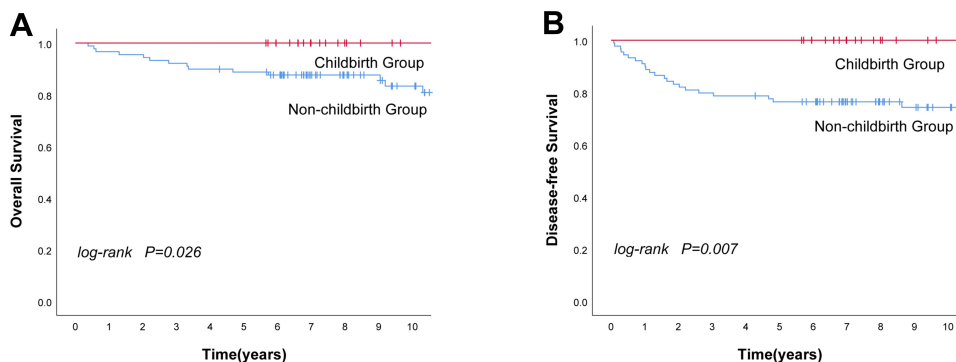

Figure 1 Kaplan–Meier survival curves for the female patients with NPC in the Childbirth group and Non-Childbirth group. (**A**) overall survival, (**B**) disease-free survival.
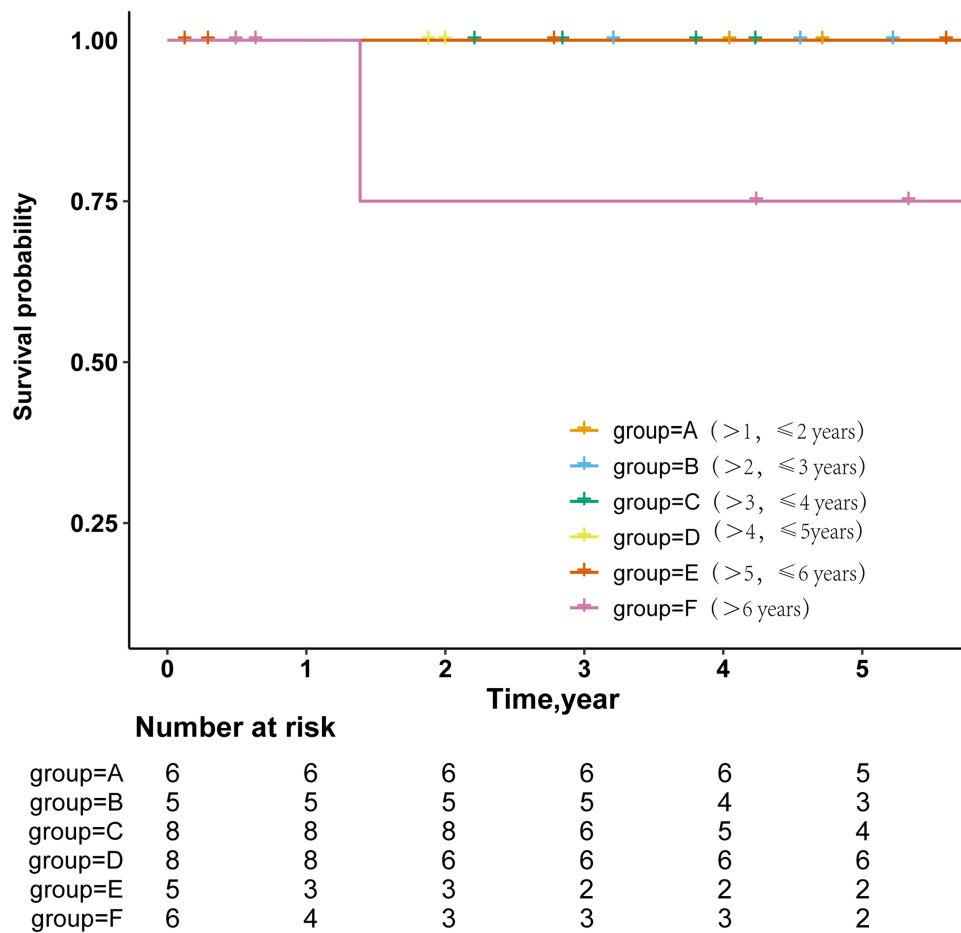
Figure 2 Kaplan–Meier survival curves for the female patients with NPC in different intervals between the accomplishment of treatment and subsequent birth.

analyzed using multivariable analysis (Table 2). The clinical stage was found to be a risk factor of the OS (HR = 101.725, 95% CI: 2.160–4790.910, P = 0.019), and consequent childbirth after treatment was associated with favorable DFS (HR = 0.148, 95% CI: 0.034–0.643, P = 0.011).

Discussion

The overall prognosis of NPC has been dramatically improved, owing to the advancements in patient management, including the improvement of RT technology, the broader application of chemotherapy, and staging systems

Table 2 Cox Regression Model of Multivariable Analysis for OS and DFS

Variables	OS		DFS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	5.139 (0.281–94.000)	0.270	4.995 (0.501–49.798)	0.170
T-stage	0.735 (0.060–8.950)	0.809	0.928 (0.143–6.011)	0.937
N-stage	0.392 (0.139–1.176)	0.095	0.552 (0.218–1.397)	0.210
Clinical stage	101.725 (2.160–4790.910)	0.019	12.869 (0.762–217.288)	0.077
NACT	0.453 (0.077–2.666)	0.382	0.768 (0.196–3.004)	0.704
CC	0.590 (0.181–1.919)	0.380	0.915 (0.376–2.224)	0.844
AC	1.625 (0.495–5.335)	0.424	1.029 (0.427–2.475)	0.950
RT	0.593 (0.081–4.314)	0.605	0.630 (0.127–3.105)	0.570
Reproductive history before treatment	0.779 (0.243–2.501)	0.675	0.545 (0.212–1.403)	0.208
Reproductive history after treatment	0.135 (0.016–1.109)	0.062	0.148 (0.034–0.643)	0.011

Abbreviations: NACT, neoadjuvant chemotherapy; CC, concurrent chemotherapy; AC, adjuvant chemotherapy; RT, radiotherapy.

with improved accuracy.[4] Besides, Epstein-Barr virus (EBV) DNA has been used as tumor marker for NPC. The previous study has revealed that survival outcomes were significantly better in patients with undetectable EBV DNA level between pre-IMRT and mid/post IMRT.[16] A previous randomized Phase 3 trial of gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma suggested that induction chemotherapy, added to chemoradiotherapy, had a significantly positive impact on recurrence-free survival and OS among patients with locoregionally advanced NPC.[17] Similarly, Yang's study came to the same conclusion—induction chemotherapy, followed by concurrent chemoradiotherapy, provided better DFS, distant metastasis-free survival and OS, compared with concurrent chemoradiotherapy alone in locoregionally advanced NPC.[18] Moreover, the widespread application of IMRT has contributed to improved survival.[19] With the combined use of IMRT and the addition of induction therapy and concurrent chemoradiotherapy, survival outcomes have been substantially improved in patients with NPC.

In Eastern and Southeastern Asia, delivering a baby is of great traditional importance. The continuity of ethnicity is one of the key points in the traditional concepts of these regions. As traditional societies modernize, many women are choosing to have children later in life. Therefore, some female patients with NPC were nulliparous before diagnosis. Thus, whether and when to bear children after treatment are important issues for NPC patients, as female NPC patients have satisfying recoveries.

In our cohort, patients from the Childbirth group experienced significantly better outcomes, regarding the 5-year OS rate and 5-year DFS, than those of the Non-Childbirth group. Multivariate analysis shows that subsequent birth after treatment was indicative of decreased risk in terms of DFS. The data suggest that having a post-therapeutic birth is a factor for a better prognosis. A previous study on the effect of post-therapeutic birth shows that the actual survival of women who give birth after breast cancer seemed unexpectedly high, which suggests that successful pregnancy may have in some way been protective for breast carcinoma patients.[20] Similarly, our study indicates that a successful pregnancy may have the same positive influence on NPC patients. Moreover, the result of the study is generally similar to previous studies, which indicated that childbirth itself may not negatively influence the survival outcomes in patients with pregnancy-associated NPC.[21,22] One woman, who

wished to become pregnant after her NPC treatment, generally had a satisfying body recovery. The previous study about childbearing and survival after breast carcinoma in young women also has revealed that relatively healthier women are more likely to become pregnant than women with adverse disease sequelae or poor prognosis,[23] which is called "healthy mother effect" and it may account for the result that patients who had delivered a child had a better prognosis.

An earlier study showed that reproductive history was a factor that contributed to a worse prognosis in patients with breast cancer.[24] To further investigate the influence of childbirth, we divided the Non-Childbirth group into two subgroups, based on their reproductive history before treatment. The survival outcomes of the 5-year OS rate (88.9% vs 88.6%, P = 0.420) and 5-year DFS (82.2% vs 70.5%, P = 0.911) between the two subgroups had no significant difference. For female NPC patients of childbearing age who did not deliver a child after treatment, reproductive history was not a prognostic factor. The influence of reproductive history on female NPC patients seems to be less significant than for other types of cancer, such as breast cancer. Contrary to an earlier study, which indicated that women who had three pregnancies had a significantly increased risk for NPC, compared with those who had two pregnancies,[25] no statistical difference was observed in the current study. Owing to the lack of data on abortions that may happen to women who were parous, or had an unsatisfying recovery after the treatment, patients without completed pregnancies were not identified in our cohort, which led to this difference.

Women delivering infants with different interval times, from 1 to 5 years after the treatment, showed no difference in the 5-year DFS (100%). This suggests that delivering from 1 to 5 years after treatment had no influence on prognoses. NPC patients who gave birth more than 6 years after treatment had the result of a worse DFS. However, this result is open to discussion because the sample size of patients in this subgroup is too small to draw a convincing conclusion. Furthermore, most of the patients were beyond the optimal age for childbearing and were not willing to be pregnant. Unfortunately, our cohort lacks the data on women who delivered within 1 year after treatment. A previous study showed that women fertilized during initial treatment had worse prognoses than those fertilized at least 2 years after radiation therapy,[26] indicating that childbearing within 1 year of the treatment is not recommended. In the earlier finished study,

Xu B's research has confirmed that NPC is a high expression tumor of estrogen receptors (ER) and progestogen receptors (PR); the positive intensity of ER and PR was associated with the negative influence of NPC.[27] This suggests that the level of these hormones may influence the prognoses of patients who had post-therapeutic births in different interval times.

Conclusion

The results of this study demonstrate that post-therapeutic birth does not increase the mortality risk of child-bearing patients with NPC. Multivariate analysis showed that having a post-therapeutic birth was a significant prognostic factor in female NPC patients for a better DFS. Further analyses indicated that an applicable interval time between the completion of treatment and subsequent birth is 1–5 years. Based on this study, post-therapeutic birth is not associated with a worse prognosis. In contrary, successful pregnancy and post-therapeutic birth may have in some way been protective to patients. The final decision on whether to deliver a child or not entirely depends on the choice of individual patient and her family.

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Disclosure

The authors report no conflicts of interest in this work.

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