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Nasopharyngeal carcinoma in children and adolescents in an endemic area: A report of 185 cases

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ABSTRACT

Background: This study aimed to demonstrate the clinical and therapeutic features of nasopharyngeal carcinoma (NPC) in children and adolescents in Southern China, an endemic area.
Patients and methods: A total of 185 newly diagnosed NPC patients younger than 21 years old in the Sun Yat-sen University Cancer Center from 1993 to 2011 were retrospectively analyzed. Overall survival (OS) rate estimates and Kaplan–Meier survival curves were calculated. Cox proportional hazard ratios (HRs) were used to identify independent prognostic factors for survival. Chi-square test was used to compare the incidence of sequelae and the stage distribution between different subgroups.
Results: Most patients were male (71.4%). The main presenting symptoms were neck mass (44.9%), tinnitus/hearing loss (36.2%), bloody nasal discharge (22.7%), headache (22.2%), and nasal obstruction (20.0%). Stage I, II, III, and IV patients accounted for 1.1%, 8.1%, 43.8%, and 47.0%, respectively, of the total number of patients included in the study. All patients were treated by radiotherapy: 39 Gy–84 Gy to primary tumors (median, 68 Gy) and 36 Gy–74 Gy to cervical lymph nodes (median, 60 Gy); 84.3% of the patients were treated by chemotherapy either. The complete response rate was 94.1%. The 5-, 10-, and 15-year survival rates were 78% ± 4%, 70% ± 5%, and 66% ± 6%, respectively. Tumor node metastasis (TNM) stage was the statistically significant predictor of distal metastasis and OS. Distal metastasis was the major pattern of treatment failure. The main long-term complications of therapy were xerostomia (47.0%), hearing loss (28.1%), neck fibrosis (24.3%), trismus (12.4%), glossolalia (7.0%), and radiation encephalopathy (5.4%). The incidences of these morbidities were significantly higher in the high radiation dose (more than the median) group than in the low radiation dose group (less than or equal to the median), while no differences in survival were observed.
Conclusions: In spite of the majority of patients diagnosed at the advanced stage, children and adolescents with NPC had excellent survival except metastatic disease. The TNM stage was the most relevant prognostic factor. A higher radiation dose (>68 Gy) could not improve survival but could increase long-term morbidities.

1. Introduction

Nasopharyngeal carcinoma (NPC) is a rare tumor in children and adolescents in industrialized countries. In Europe and the United States, it represents approximately 1% of all childhood cancers [1]. The annual incidence is about 0.5 per million children/adolescents in the United States [2]. However, NPC is more common in the young Chinese population. According to the Hong Kong cancer registry, NPC is the fourth most common malignant neoplasm (after bone, brain, and hemic malignancies) in males and the fifth most common malignant neoplasm (after bone, brain, thyroid, and hemic malignancies) in females during the second decade of life [3]. In individuals aged <30 years old, the incidence of NPC is about 1.6–3.0 per million [4].

The treatment approaches for children and adolescents with NPC were generally extrapolated from adult protocols because of the lack of clinical trials in these populations. However, the biological and clinical features of this tumor in children may vastly differ from adults, hence requiring a better understanding of this particular condition and improving patient management. Generally, compared with that in adults, NPC in children has several characteristics: undifferentiated carcinoma is the most common histologic type; advanced locoregional disease presents in most patients at first diagnosis with a higher prevalence of distal metastasis; the tumor is more closely associated with the Epstein-Barr virus (EBV); and young patients are at a higher risk of developing therapy-related complications [1,2,5–13]. As most published series are small and have short follow-ups, the

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long-term outcome of children and adolescents with NPC has not been well characterized, especially in endemic areas. Therefore, we conducted a retrospective review of all children and adolescents with NPC treated at our institution (a large cancer center in south China) during the past 19 years to investigate the clinical features, long-term survival, morbidity, and factors associated with prognosis.

2. Patients and methods

2.1. Clinical review

We reviewed the medical records of all NPC patients younger than 21 years old who were treated in the Sun Yat-sen University Cancer Center between 1993 and 2011. The subjects were retrospectively identified in our institutional database. We extracted data on the presenting features, histopathology, imaging findings, treatment, outcome, and late morbidities.

As NPC staging has evolved over the past decades, we attempted to re-stage all patients according to the most recent version of the American Joint Committee on Cancer (AJCC 7) NPC staging classification using the available clinical information and the original radiology reports.

Additionally, with the changes in the diagnostic standard and classification methodology over the past decades, only the pathologic type of patients diagnosed after 2002, from which the WHO classification of NPC [14] was adopted in our institution, was recorded and analyzed.

2.2. Statistical methods

The cases that had indeterminate pathologic diagnosis, incomplete treatment information, and no radiotherapy (RT) were excluded from the analysis.

Overall survival (OS) was defined as the time interval from the date of diagnosis to the date of death from any cause or to the date of last contact. Only the morbidities that occurred or persisted six months after treatment and made patients uncomfortable or inconvenienced them for most of the day were recorded and analyzed in this study. For example, glossolalia was recorded if the patient's words could not be understood by strangers; xerostomia was recorded if the patient had difficulty swallowing without water; trismus was recorded if the patient had difficulty eating solid food; tinnitus/hearing loss was recorded if the patient had difficulty communicating when using normal speaking voice; and neck fibrosis was recorded if the patient constantly felt neck stiffness. OS was estimated using the Kaplan–Meier method. Differences in OS were examined by exact log-rank test. Prognostic factors were analyzed using the Cox proportional hazards regression model. Chi-square tests were used to compare the incidences of RT morbidities and the stage distribution between different subgroups. Statistical significance was assumed for a two-tailed P value < 0.05.

3. Results

3.1. Patient characteristics (Table 1)

A total of 185 eligible cases were identified from 1993 to 2011. Seven patients were excluded: two patients with unknown radiation dose, 3 patients without distal metastasis who were referred to other hospitals, one patient with distal metastasis who quit his treatment, and one patient without any follow-up information after treatment. The median age at diagnosis was 17 years (range, 8–20 years). Most patients were male (71.4%). Thirty-one patients (16.8%) had a family history of cancer, among which nine cases had NPC. Two patients had a history of smoking (ten years for one patient and three years for the other). None were found to suffer from alcoholism. The median time interval between the first presentation and diagnosis was three months (range, 0.3–30 months). The most common presenting symptom was neck mass, followed by tinnitus/hearing loss, bloody nasal discharge, headache, and nasal obstruction. The majority of patients had advanced T stage, regional lymph node metastases, and high AJCC stage. Five patients (2.7%) had distal metastases (stage IVC) at diagnosis. Among the 126 cases diagnosed after 2002, 123 of them (97.6%) were of WHO type III, and the remaining 3 cases (2.4%) were of type II.

Table 1
Patient characteristics.

Characteristic	n (% or range)
Gender	
Male	132 (71.4)
Female	53 (28.6)
Age, years(median)	17 (8–20)
Presenting symptom	
Neck mass	83 (44.9)
Tinnitus/hearing loss	67 (36.2)
Nasal bloody discharge	42 (22.7)
Headache	41 (22.2)
Nasal obstruction	37 (20)
Facial numbness	2 (1.1)
Mandible/neck pain	2 (1.1)
Symptoms duration prior to diagnosis; months (median)	3 (0.3–30)
Pathologic type[a]	
Squamous cell carcinoma	3 (2.4)
Undifferentiated nonkeratinizing carcinoma	123 (97.6)
T stage	
T1	5 (2.7)
T2	33 (17.8)
T3	86 (46.5)
T4	61 (33.0)
N stage	
N0	12 (6.5)
N1	57 (30.8)
N2	80 (43.2)
N3	36 (19.5)
TNM stage	
I	2 (1.1)
II	15 (8.1)
III	81 (43.8)
IVA/IVB	82 (45.1)
IVC	5 (2.7)

[a] 59 patients diagnosed before 2003 when WHO classification was not used in our institution were excluded herein.

Quantitative pretreatment EBV–DNA levels were available for 49 patients: the level was 0 for 4 patients, $\leq 10^3$ for 4 patients, and $>10^3$ for 41 patients, with a positive rate of 83.7% (cut-off value, 10^3). However, the small number of patients hindered any correlation with stage or prognosis and difference from adults. After treatment, EBV–DNA level was undetectable in 35 patients, detectable but only $\leq 10^3$ in 3 patients, persistently positive in 2 patients with metastatic disease, and unavailable for 4 patients.

3.2. Treatment protocol and response

All patients received RT, with 65.9% of them receiving conventional radiotherapy (CRT) and the remaining patients (34.1%) receiving intensity modulated radiation therapy (IMRT). The median radiation dose was 68 Gy (range, 39 Gy–84 Gy) to the primary lesion and 60 Gy (range, 36 Gy–74 Gy) to the cervical lymph node. A daily dose of 1.8 Gy–2.0 Gy was delivered five days a week by conventional fractionation.