RESEARCH COMMUNICATION

Pediatric Nasopharyngeal Carcinoma: A Review of 27 Cases over 10 Years at Shaukat Khanum Memorial Cancer Hospital and Research Center, Pakistan

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Abstract

Purpose: This study aims to review the clinical features, treatment and outcome of pediatric nasopharyngeal Carcinoma at Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH&RC) over ten years. Methods: Retrospective review of pediatric patients who were diagnosed with nasopharyngeal carcinoma and treated at SKMCH&RC from July 1996 to June 2006. Results: A total of 27 children with NPC were included. The male to female ratio was 4.4:1. The mean age at diagnosis was 14 years (8-18 years). The most common presenting symptom was neck swelling (81.5%, 22/27). The mean duration of symptoms before diagnosis was 10.3 months (3-36 months). The majority of patients (70%, 19/27) presented at stage IV. All received a combination of chemotherapy and radiotherapy. Survival analysis was performed for 22 patients; of these 8 patients died and 4 were lost to follow-up. The median follow-up time of the surviving patients was 53 months (5-116 months). At 5 years, the cumulative overall survival (OS) was 55% while the cumulative EFS was 54% with a flattening of the curve at 2 years. There was a significant difference in OS (p=0.001) and EFS (p=0.057) in patients diagnosed with NPC under 14 years of age (n=11) and those between 14 and 18 years (n=11). Conclusion: In our institutional study, NPC presents late and in advanced stage. The outcome is better in younger children. Our survival rates, while comparable to developing countries, are less than those seen in the developed world. We feel a strong need for collaborative studies in view of small numbers in individual centres.

Key words: Nasopharyngeal cancer - Pakistan - pediatrics - retrospective study - Southeast Asia

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Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy arising from the epithelium of the nasopharynx. It is very rare in children accounting for just 1-5 % of all pediatric cancers (Ayan et al., 2003; Laskar et al., 2004). In some populations, a bimodal age incidence is observed, with a first small peak occurring in late childhood (Commoun et al., 1974; Laskar et al., 2004).

The clinical features and behavior of NPC varies greatly according to age, racial and geographical factors and Epstein-Barr virus (EBV) exposure (Marks et al., 1998; Guo et al., 2009). The most common histological variant in children is undifferentiated carcinoma (WHO Type III), which is associated with an advanced local disease at presentation, and a greater rate of distant metastasis (Sham et al., 1990; Marks et al., 1998; Laskar et al., 2004).

In the past pediatric NPC has been treated with radiotherapy following adult guidelines. However, NPC is very chemo sensitive. The role of chemotherapy is particularly important in children as they can have devastating cosmetic and functional consequences from high dose radiotherapy. This, and the poor overall survival in children treated with radiotherapy alone, has led to the investigation of neoadjuvant, concomitant and adjuvant chemotherapy for the treatment of pediatric NPC (Kim et al., 1989; Laskar et al., 2004; Rodriguez-Galindo et al., 2005; Kupeli et al., 2006; Orbach et al., 2008). There is a dearth of published clinical trials to determine the impact of chemotherapy on the long term disease free survival. Most studies regarding pediatric NPC have been single-institution based and have included a retrospective review of patients accrued over long periods (Commoun et al., 1974; Sham et al., 1990; Zubizarreta et al., 2000; Laskar et al., 2004; Polychronopoulou et al., 2004; Kupeli et al., 2006).

In Southeast Asia, only a few studies have been carried out to determine the incidence, clinical characteristics and treatment outcomes in patients with NPC (Shah et al., 2000; Laskar et al., 2004). The Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH&RC) is

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a tertiary care cancer center in Pakistan that provides care to patient from all over the country as well as neighboring countries. The purpose of this study was to review the clinical characteristics, treatment and outcome of NPC treated at SKMCH&RC in a ten year period, and to compare it with the international data, so as to make a contribution to the clinical aspects of this rare pediatric malignancy.

Materials and Methods

Study design and patients

We conducted a retrospective review of pediatric NPC at a single institution. Our study population included all biopsy proven cases of NPC in children less than 18 years of age, presenting at SKMCH&RC between July 1996 and June 2006. Patients who did not receive their complete treatment at SKMCH&RC were excluded while patients who received treatment with palliative intent were reviewed but excluded from outcome analysis.

Data collection

The data of 27 patients was retrospectively reviewed from paper charts and Hospital Information System using a structured questionnaire in March 2007 in the Department of Pediatric Oncology at SKMCH&RC. The questionnaire contained details about the patient demographics, clinical presentation, risk factors, staging and grading, treatment received and outcome.

The TNM classification system of American Joint Committee on Cancer (AJCC) staging (Green et al., 2002) was used to determine the disease extent at the time of diagnosis. Clinical examination and reports of initial radiographic studies including CT and MRI were reviewed to determine the stage. Chest x-rays and bone scans were reviewed to evaluate disease spread. The WHO histological grading system was used for grading.

Patients received a combination of chemotherapy and radiotherapy. The timing of chemotherapy (neoadjuvant, concomitant or adjuvant), the agents used and their dosing was reviewed. The dose of radiation given was also noted.

Response evaluation and follow up

End of treatment evaluation as well as any re-evaluation done during treatment was reviewed. This included clinical and radiographic re-evaluation. A complete response (CR) was defined as the disappearance of all evident disease. A decrease of >50% in the size of the tumor was defined as partial response (PR), and a decrease of <50% in the size of the tumor was defined as no response (NR) or stable disease (SD). Progressive disease (PD) was defined as any increase in the size of the tumor or appearance of new lesions. Recurrence/ relapse was defined as reappearance of disease after achieving CR or PR at the end of planned therapy.

Follow up data was collected from medical records for patients who had kept their last scheduled appointment. All other patients were contacted by phone. Patients were considered lost to follow up if they missed two consecutive appointments and were not contactable by phone.

Statistical Analysis

Data analysis was done using Statistical Package for Social Sciences (SPSS) Version 10.

Kaplan-Meier survival curves (Kaplan EL and Meir P, 1958) were used for survival analysis. Log rank analysis was used to compare the survival of the two age groups.

Results

Demographics

A total of 27 children diagnosed with nasopharyngeal carcinoma were included in the study. This formed 38% of pediatric head and neck tumors and <0.01% of all pediatric malignancies at our institution. Of these, 22 were males while only 5 were females, with a male/female ratio of 4.4:1. The age at diagnosis ranged from 8 years to 18 years (mean 14.0+/-2.92 years). 40.7% (n=11) patients were less than 14 years of age while 59.2% (n=16) were between 14 and 18 years of age at diagnosis.

Clinical Presentation

The most common presenting symptom was neck swelling occurring in 81.5% of cases, followed by nasal obstruction (59.3%), epistaxis (33.3%), headache (30%), eye symptoms (18.5%), ear symptoms (14.8%), dysphagia (3.7%), difficulty in breathing (3.7%), difficulty in talking (3.7%) and weight loss (3.7%). The duration of symptoms before presentation ranged from 3 months to 36 months (mean=10.3 months).

Retrospective evaluation revealed WHO Type III disease in 40.7% of cases (n=11) while the histological grade for the rest of the patients could not be ascertained. Most of the patients (n=19, 70.4%) had stage IV disease at presentation. The stage distribution is shown in Figure 1. The EBV status was not formally checked in any of our patients.

Treatment

Of the 27 patients, 22 (81.5%) were treated with a curative intent while the remaining 5 (18.5%) were given palliation only. 50% (n=11) of patients treated with curative intent were less than 14 years of age and 50% (n=11) were between 14 and 18 years. All patients treated with curative intent received a combination of chemotherapy and radiotherapy. In the absence of a specific pediatric chemotherapy protocol, the chemotherapeutic agents used varied, especially in the early period, depending upon the current practice for treatment of adult patients. 14 patients (63.6%) received cisplatin +/- 5-FU neoadjuvant chemotherapy. Some additional agents used included methotrexate (n=3) or epirubicin and bleomycin (n=4). 12 patients (54.5%) received cisplatin+/-5-FU based chemotherapy

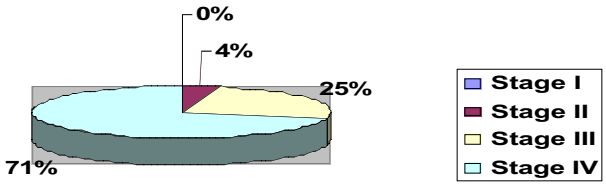

Figure 1. Stage Distribution of the Patients

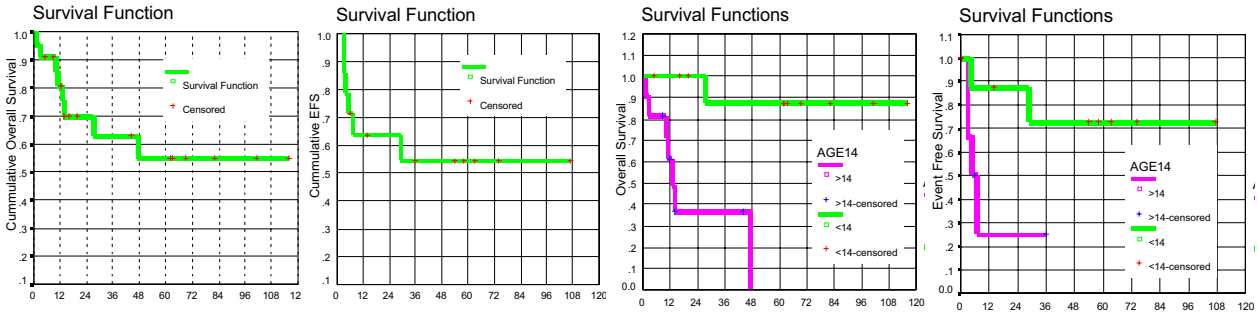

Figure 2. Kaplan-Meier Curves (Months). a) Cumulative Overall Survival; b) Cumulative event free survival; c) Comparison of overall survival in patients under 14 years (green line) and between 14 and 18 years (purple line) (p=0.001); d) Comparison of event free survival in patients diagnosed with nasopharyngeal carcinoma under 14 years (green line) and between 14 and 18 years (purple line) (p=0.057)

concomitant with radiotherapy. Only 7 patients (31.8%) received cisplatin+/-5-FU based adjuvant chemotherapy. The mean dose of radiation given was 65.2Gy (30-76Gy).

Complications

Mucositis was the only significant immediate complication which was observed in 18 patients (66.6%), followed by xerostomia and nephrotoxicity which were observed in 3 patients (11.1%) and 2 patients (7.4%) respectively. The only long term complication was growth hormone deficiency in 1 patient (3.7%).

Outcome

Survival analysis was done on 22 patients after exclusion of patients treated with palliative intent (see Figure 2). Of these, 8 patients died. The median follow-up time of the surviving patients was 53 months (5-116 months). 4 patients were lost to follow-up. At 5 years, the cumulative OS was 55%. A total of 14 patients achieved remission; of which 6 patients relapsed. The cumulative EFS at 5 years was 54% with a flattening of curve at 2 years.There was a significant difference in the OS (p=0.001) and the EFS (p=0.057) in patients diagnosed with NPC under 14 years of age and those between 14 and 18 years.

Discussion

The incidence of pediatric nasopharyngeal carcinoma varies considerably according to geographical and racial factors. The geographical pattern of incidence suggests a unique interaction between environmental and genetic factors (Chan et al., 2002; Ayan et al., 2003). The exact incidence of pediatric NPC in Pakistan is unknown. At our instiiution, NPC constituted only 1.7% of all pediatric solid tumors and those paediatric cases accounted for 11.8% of all nasopharyngeal carcinomas. Lasker et al reported that NPC constitutes 1.5% of all pediatric cancers seen at their hospital in India (Laskar et al., 2004). Similarly; Shah et al have reported that NPC constituted 1.9% of all pediatric cancers in Karachi, Pakistan (Shah et al., 2000).

Most studies on pediatric NPC have pointed towards a male preponderance of the disease (Ayan and Altun, 1996; Zubizarreta et al., 2000; Laskar et al., 2004; Kupeli et al., 2006). Our study was also consistent with a predominant male preponderance, the male to female ratio being 4.4:1. In our study, age at diagnosis had a significant impact on the OS and EFS, with patients less than 14 years of age at diagnosis faring better than those between 14 and 18 years. Laskar et al (2004) and Ozyar et al (2006) have shown a similar impact of age on OS and EFS.

The most common presenting symptom of NPC is cervical lymphadenopathy, followed by nasal, aural and neurological symptoms (Zubizarreta et al., 2000; Chan et al., 2002; Ayan et al., 2003; Laskar et al., 2004; Polychronopoulou et al., 2004). Most of the patients in our study presented with Stage IV disease with neck swelling being the commonest mode of presentation. Advanced stage of disease, particularly invasion of the base of the skull and cranial nerve involvement, is associated with an adverse outcome, so early recognition is of prime importance in improving treatment outcome (Gasparini et al., 1988; Ozyar et al., 2006). This highlights the need of thorough knowledge of the common modes of presentation and a high index of suspicion on part of clinicians. As majority of our patients presented at a very advanced stage of disease, the comparison between the outcomes at different stages was not possible.

There is considerable debate over the optimal dose of radiotherapy in pediatric NPC particularly when combined with chemotherapy (Ayan and Altun, 1996; Commoun et al., 1974; Laskar et al., 2004; Orbach et al., 2008). All patients treated with a curative intent in our study, were given a combination of radiotherapy and chemotherapy. The radiation doses given to our patients varied between 30-76Gy. Since most of our patients received high radiation doses (mean radiation dose 65.2Gy), thus the difference in the OS and EFS with high and low radiation doses could not be ascertained. It has been consistently reported that higher radiation doses in children are of particular concern owing to the associated long term morbidity (Kim et al., 1989; Ayan and Altun, 1996; Ulger et al., 2007). In our study, only 1 patient had a long term complication. This may be because some complications like hypothyroidism (Ulger et al., 2007) are often sub clinical and may not have been addressed.

A number of studies have demonstrated improvements in the OS and/or EFS with the use of combination chemotherapy with radiotherapy (Gasparini et al., 1988; Ayan and Altun, 1996; Laskar et al., 2004; Ozyar et al., 2006). All of our patients received chemotherapy in

addition to radiotherapy. However, comparison between different regimens of chemotherapeutic agents was not possible due to small numbers in each group. The 5 year OS of 55% and EFS of 54% in our study is very close to that reported by Laskar S et al in India (2004), while experience at St Judes Children Research Hospital USA has shown a 4 year OS and EFS in the range of 75% and 77% respectively (Rodriguez-Galindo et al., 2005). Similarly, Ozyar et al (2006) have shown OS of 77% and EFS of 68% at 5 years in a Rare Cancer Network study involving 8 different countries. Majority of patients in their study also presented with advanced stage disease; so late presentation cannot be considered the reason for the difference in outcome. Rodriguez-Galindo et al (2005) reported that 65% of their patients tested EBV positive on serology. The EBV status of our population was unknown but Shah et al (2000) have shown that majority of cases of NPC in their study were EBV negative, pointing to a different etiology of this disease in our region. This difference in the nature of disease may be responsible for the worst outcome in spite of similar treatment strategies.

In our institutional study, pediatric NPC presents very late, with most of the patients presenting at an advanced stage of disease. Our survival rates, while comparable to developing countries, are still less than those seen in the developed world. Further studies to better define the risk factors and etiological agents related to NPC in our region are important to improve our understanding of the nature of this disease and better design its treatment.

As pediatric NPC is an extremely rare tumor, it is imperative that large collaborative, multicenter studies be carried out, so that uniform treatment strategies can be developed, which may help achieve further improvement in the outcome of this rare pediatric malignancy. In view of the consistent finding of advanced stage , late presenting disease in developing countries , it would furthermore be very useful to have regional collaborative studies looking at the causes of delay in presentation and the potential role of simple public awareness campaigns in improving outcome.

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