Research Article

Paediatric Nasopharyngeal Carcinoma a Rare Entity; Experience from a Tertiary Care Children Hospital

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Abstract:

Background: In the paediatric population, Nasopharyngeal carcinoma (NPC) is a rare tumour of head and neck region arising from epithelial cells of nasopharynx. There is racial, geographical and age wise variability in the incidence of NPC. Most of the cases occur in south east Asia, southern China and Africa while in the rest of the world incidence of NPC is relatively low.

Objective: To determine clinical features, stage of disease at presentation, treatment and outcome in children presenting with nasopharyngeal carcinoma to our hospital.

Methods: Analytical cross sectional study was conducted in The Department of Paediatric Haematology/Oncology, The Children's Hospital and the Institute of Child Health, Lahore. Children less than 18 years who presented to the hospital from Jan 2016 to Dec 2020 with nasopharyngeal carcinoma (NPC) were included in the study. Complete medical record of the patients was reviewed and data including demographic detail, symptoms, treatment and outcome was collected and analysed with SPSS v 19.0.

Results: Thirty children diagnosed with NPC were included in the study. Their mean age was 11.83±1.86 years and male to female ratio was 2.75:1. Majority of children belonged to rural areas. 12(40%) patients had stage III and 18(60%) patients had stage IV disease. Most common symptom at presentation was neck swelling 21(70%) followed by headache 5(16.7%), neurological 2(6.7%), ear 2(6.7%) and nasal symptoms 1(3.3%). 14(46.7%) patients got complete remission and are well, 1(3.3%) patient had residual disease, 13(43.33%) patients died and 2 (6.7%) patients lost follow up. Cumulative overall survival was 44% while cumulative event free survival was 40%.

Conclusion: Nasopharyngeal carcinoma is a rare tumour of head and neck. It is most prevalent in male children. Major symptom at presentation is neck swelling. Children usually present at advanced stage of disease due to which mortality is high.

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Keywords: Carcinoma, Chemotherapy, Nasopharyngeal, Radiotherapy, Paediatric.

Introduction:

In the paediatric population, Nasopharyngeal carcinoma (NPC) is a rare tumour of head and neck region arising from epithelial cells of nasopharynx. There is racial, geographical and age wise variability in the incidence of NPC. Most of the cases occur in south east Asia, southern China and Africa while in the rest of the world incidence of NPC is relatively low.[1] Peak incidence of NPC among children is from 10 to 20 years of age.[2] It represents about 1% of childhood carcinomas.[3] Epstein-Barr virus, family history and HLA class I genotypes are considered important risk factors for NPC.[4] Nasopharyngeal epithelial cells which are infected by Epstein Barr Virus show certain group of latent genes, and it is proposed that these genes transform epithelial cells into malignant cells.[5] Epstein Barr virus BART micro RNAs are also linked to this

transformation.[6] Certain environmental factors have also been considered risk factors for the disease. Use of salted fish, certain herbs and smoking have been related to the high incidence of disease in Southern China.[7] NPC has a long asymptomatic course and these children present with non-specific nasal, auditory or neurological symptoms. The most common presentations are neck mass, epistaxis, nasal blockage, hearing loss and tinnitus. At the time of diagnosis their cancer is in advanced stage and has metastases in lymph nodes.[8] Histopatho-logical evidence of disease from biopsy is required for diagnosis of NPC. Radiological investigations, including Computed Tomography scans and MRIs, are used to find the extent of disease. American Joint Committee on Cancer Staging System is used to stage the cancer, and then treatment is given accordingly.[9] Traditionally radiation therapy (RT) was the treatment for NPC. But now RT is given only for stage I and II disease and for stage III & IV disease combination of chemotherapy (CT) and RT is given. RT is given after induction with CT or concomitant with CT. Overall survival has increased with combination of RT and CT.[10] This study aims to review the clinical profile at presentation, symptoms, treatment and outcome in children presented to our tertiary care children hospital with NPC from Jan 2016 to Dec 2020 and to enhance our knowledge regarding the clinical aspects and outcome of this rare disease.

Methods:

This Analytical cross sectional study was conducted from January 2016 to December 2020 in The Department of Paediatric Haematology / Oncology, The Children's Hospital and the Institute of Child Health, Lahore. A minimum sample size of 27 children was calculated using Open Epi software through formula for single proportion taking paediatric NPC frequency of 11.8% among all NPC cases(13), confidence level of 80% and 8% margin of error. Approval was obtained from hospital ethical committee. Children less than 18 years of age who presented to our hospital from Jan 2016 to Dec 2020 with NPC were included in this study. Patients who had histopathological confirmation of disease were included. Computed Tomography or Magnetic Resonance Imaging of head and neck was used to stage the disease.

Patients' complete medical records, including history sheets, laboratory and radiological investigations, treatment charts and follow up charts were obtained from hospital records. Images including MRI and Computed Tomography scans were used to determine the stage of disease as per TNM classification system of American Joint Committee on Cancer staging system.

Data including demographics, clinical presentation, diagnostic investigations, treatment modalities and outcome were recorded in data collection form. Data were entered in SPSS version 19.0 and analysed. Continuous patient characteristics are summarized as mean and standard deviation and categorical patient characteristics are summarized as frequencies and percentages. Pearson Chi-square test was used for continuous variables and student-t test was applied to categorical variables to find out the significance. Kaplan-Meier Curves were used to calculate Cumulative Event Free Survival (EFS) and Cumulative Overall Survival (OS). A p-value < 0.05 was considered significant.

Results:

Thirty children diagnosed with nasopharyngeal carcinoma were included in the study. Their demographic features are presented in Table 1. In our study male to female ratio was 2.75:1, which indicates that this disease is more prevalent in males. Most of the patients belonged to rural areas (areas which does not come within urban boundary) which show some link of the disease with low socioeconomic lifestyle. All the patients were having advanced NPC (Table 1)

Table 1: *Demographic Features and Stage of disease*

Age Mean±SD(range)		**11.83±1.86 (7-15) years**
Gender n (%)	Male	22(73.3)
	Female	8(26.7)
Location n (%)	Rural*	24(80)
	Urban	6(20)
Stage n (%)	Stage I	Nil(Nil)
	Stage II	Nil(Nil)
	Stage III	12(40)
	Stage IV	18(60)

*areas outside the urban boundary

The most common symptom at presentation was neck swelling 21(70%) followed by headache 5(16.7%), neurol-ogical 2(6.7%), ear 2(6.7%) and nasal symptoms 1(3.3%). Treatment was given as per Jude protocol in which CT was followed by RT. Cisplatin and 5 Fluorouracil based 4 cycles of chemotherapy were

Table 2: *Determinants of outcome in paediatric patients with Nasopharyngeal carcinoma*

Determinant		Outcome(n) Rx completed and well	Rx abandoned	Residual disease	Expired	P-Value*
Gender	Male	11	2	1	8	0.530
	Female	3	0	0	5	
Stage of disease	Stage 3	7	1	1	3	0.294
	Stage 4	7	1	0	10	
Residence	Rural	11	1	1	11	0.667
	Urban	3	1	0	2	

*p-value < 0.05 is considered significant

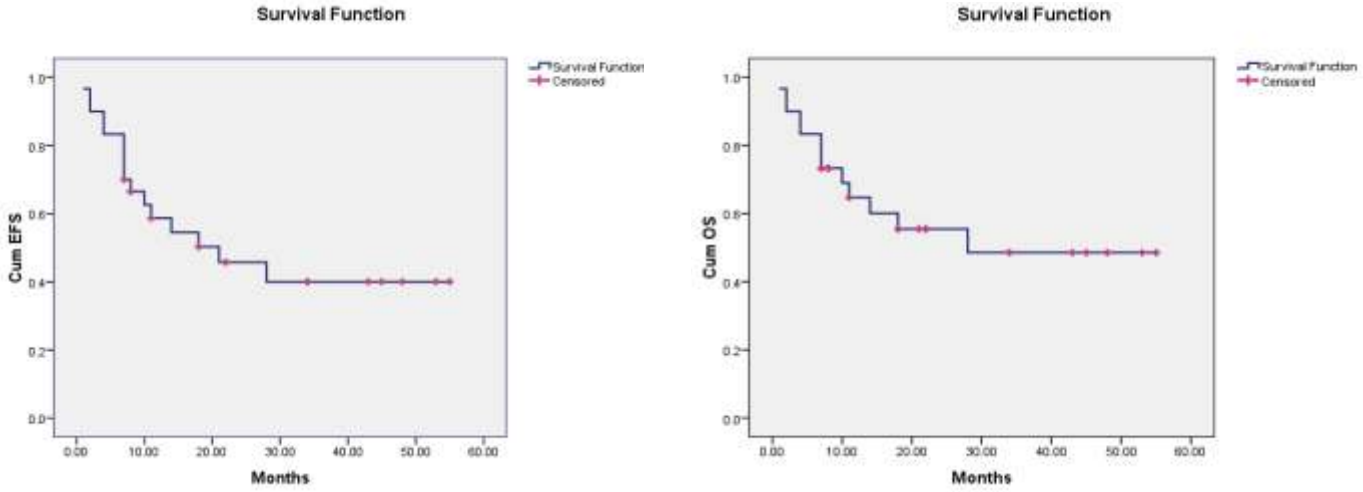

Figure 1: *Kaplan-Meier Curve – Cumulative Event Free Survival (EFS) and Cumulative Overall Survival (OS)*

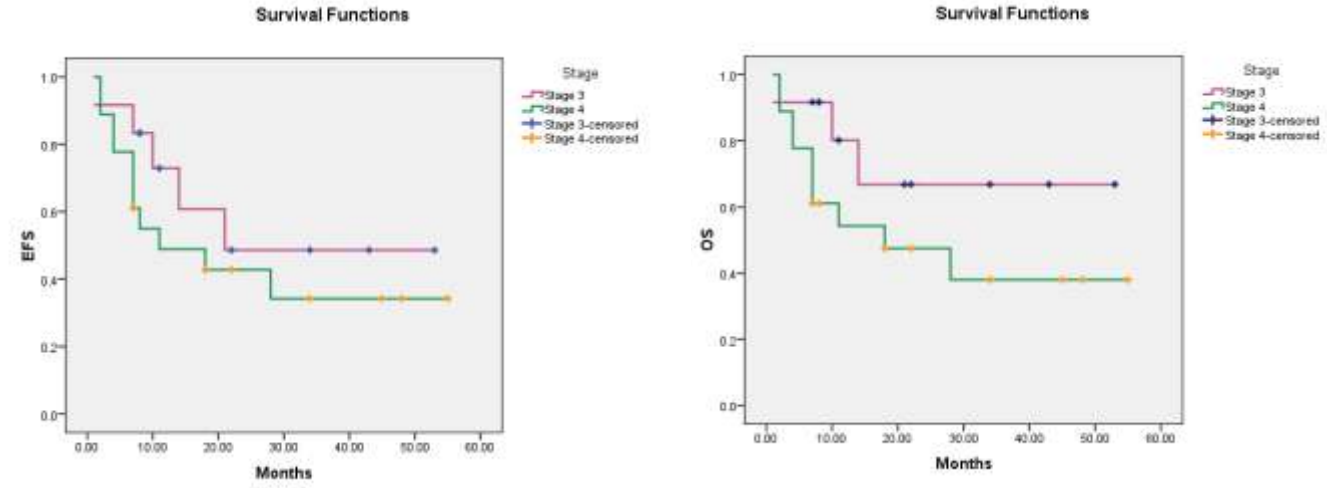

Figure 2: *Kaplan-Meier Curves – Comparison of Event Free Survival (EFS) and Overall Survival (OS) between Stage III and Stage IV disease*

given. After that radiotherapy was given with phase 1(44 Gy in 22 fractions), phase 2(26 Gy in 13 fractions) and for anterior neck 50 Gy in 25 fractions.

9(30%) patients died before the completion of CT. 2(6.7%) patients left the treatment incomplete during CT and we lost communication with them. 19(63.3%) patients received both CT and RT. 4 more patients died during course of disease. 14(46.7%) patients got complete remission and are well, while 1(3.3%) patient got incomplete remission and has residual disease. 12 patients had stage III and 18 patients had stage IV disease. 3 patients with stage III and 10 with stage IV died. One patient from each group abandoned treatment. None of the patients has reported relapse of the disease yet. At the end of study 15 (50%) patients are alive with one patient having residual disease. Table 2 describes outcome in relation to gender, residence and stage of disease. None of these is found to be significant.

At end of 5 years cumulative Event Free Survival (EFS) was 40% while Cumulative Overall survival (OS) was 44% as shown in figure 1. Similarly figure 2 shows comparison between stage III and stage IV disease in terms of EFS (p=0.356) and OS (p=0.171).

Discussion:

NPC is rare malignant carcinoma of head and neck. There is racial, geographical and age wise variability in its incidence. Its incidence is 2-3 times higher in male children than in females. Similar to our study many other studies reported this observation that NPC incidence is higher in males.[11,12] In our study male to female ratio was 2.75:1. This ratio was 4.4:1 in the study conducted in a local cancer hospital by Haleema Saeed et al.[13] A study conducted in a tertiary care hospital in Eastern India demonstrated the occurrence of disease between the male and female children at ratio of 2.2:1. In this study 14 (66.7%) were boys and 7 (33.3%) were girls.[14] A study conducted in Malaysia showed male to female ratio of 2.4 : 1 among children presented with NPC.[15] This male to female predominance is also found in adult patients. In a study male to female ratio in adult patients was 2.8:1.[16]

In adults most cases of NPC are presented in fifth and sixth decade of life, while in children peak presentation of cases is reported between 10-20 years of age. In our study mean age of patients was 11.83 years and ranged from 7 to 15 years. Haleema Saeed et al. found that the age range at diagnosis was from 8 to 18 years and mean age was 14.0 years.[13] In Malaysian study mean age of presentation was 18.3 years.[15] In the Indian tertiary care hospital, mean age of children presented with NPC was 13.28 years.[14]

Most patients who presented to us belonged to rural areas. A retrospective cohort study from USA also stated that paediatric age group patients largely belonged to rural areas which shows some association with low socioeconomic status.[17]

These children have long asymptomatic course and present with symptoms like neck swelling, nasal, ear and neurological symptoms. In our study most common symptom was neck swelling followed by headache, neurological, nasal and ear symptoms. Haleema Saeed et al. described that most common symptoms at presentation in their hospital were neck swellings (81.5%), nasal obstruction (92.6%), epistaxis (33.3%) and headache (30%). (13) In the Indian and Malaysian study, they also observed that most common clinical presentations in children were neck swelling and nasal symptoms.[15] While in adult patients as compared to children, otologic and nasal symptoms were more common than neck swelling.[18,19]

Most of the children in our study presented with advanced disease, with 60% having stage III and 40% stage IV disease. In another local cancer hospital study, 71% children had stage IV, 25% had stage III and 4% had stage II disease. Radhakrishna V et al. described that 1/37 (3%), 2/37 (6%), 13/37 (35%), and 21/37 (57%) patients had stage I, II, III and IV disease respectively, in their hospital.(20) Li Y et al. reported 38.5% patients with stage III and 61.5% with stage IV disease in their study.

RT is the treatment of choice for stage I and II disease. It has been used successfully with good 10 years survival in initial stages of disease. CT is given in advanced cases. Recent studies have demonstrated that combination of CT and RT is superior to single modality and provides better survival in advanced disease. The chemotherapy includes methotrexate, bleomycin, 5 Fluorouracil and cisplatin. Chemo-radio-therapy is being given as

concurrent therapy or after induction chemotherapy. A recent large study compared concurrent chemo radiotherapy with induction chemotherapy followed by chemo-radiotherapy and found no overall survival difference. [21] A French retrospective study also did not show any difference between these two regimens. This study also showed some promise with maintenance ß-Interferon therapy that no relapse was observed after its use.[22] Traditionally NPC in children was treated with RT doses comparable with adult doses i.e. from 60 to 70 Gy. Due to the risk of late side effects of RT, recent studies advocate radiation dose reduction strategy after induction chemotherapy.[23] Radiation of 50 Gy is often desirable for neck lymph nodes.

In our study, four cycles of CT were followed by RT, and 15 (50%) patients are alive till the end of study. One of these patients had the residual disease. Cumulative OS at 5 years was 44% while cumulative EFS at 5 years was 40%. Deaths were associated with treatment related mortality (TRM) including febrile neutropenia and electrolyte imbalance and sequelae of advanced metastatic disease. Haleema Saeed et al. reported 55% overall cumulative survival. Their 22 patients received combination CT and RT. 8 patients died and remission occurred in 14 patients, out of which 6 patients later relapsed.[13] Li Y et al. described overall 5 years survival 83.7% in induction chemotherapy plus chemo radiotherapy group and 74.6% in concomitant chemo radiotherapy group. Statistically both groups were no different (p=0.153).[21]

As this is a rare disease only thirty patients with confirmed NPC presented to us during the study period. A multicentre study with large sample size should be conducted in our country to get consolidated results. It will improve our understanding of the disease and help us in developing a consensus regarding treatment. Neoadjuvant therapy like ß-Interferon should also be studied as it has resulted in improved outcome in studies from developed countries.

Conclusion:

Children who presented to us with nasopharyngeal carcinoma had stage III and stage IV disease. Most of the children affected by the disease belonged to rural areas and were males. Major symptom at presentation was neck swelling followed by headache and neurological symptoms. Mortality was high with stage IV due to advanced disease. Overall and event free survival was less than fifty percent.

Ethical Approval: Given

Conflict of Interest: The authors declare no conflict of interest.

Funding Source: None

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