

## Nasopharyngeal Carcinoma in Children and Adolescents

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### ABSTRACT

**Purpose:** To evaluate the clinicopathological features and the prognostic factors for nasopharyngeal carcinoma in young patients treated at King Faisal Specialist Hospital.

**Materials and methods:** Fifty-four patients  $\leq$  18 years of age, with the diagnosis of nasopharyngeal carcinoma were treated at King Faisal Specialist Hospital during the period between 1975-1996. They accounted for 5% of all patients with nasopharyngeal carcinoma treated within this period. There were 34 males and 20 females; the median age at diagnosis was 14 years. Twenty seven patients (50%) had undifferentiated carcinoma (WHO type III). Fifty two patients (96%) had stage IV disease. Thirty one out of forty patients (78%) in whom parapharyngeal extension could be assessed, had involvement of that region. Eleven patients were treated with palliative intent and were excluded from survival analysis. The survival and prognostic factor analysis focused on the remaining 43 patients treated with radical intent (31 with radiation alone and 12 with chemo-radiotherapy). The total radiation dose ranged from 44-70 Gy. The median follow up was 58 (2.5-216) months.

**Results:** The 5 and 10 year overall survival rates of the whole group were 45% and 39%, respectively. No patients with metastatic disease survived more than 14 months. For the 43 patients treated with radical intent the 5 and 10 year survival rates were 57% and 49%, respectively. The disease free survival (DFS) of 38 patients who attained complete remission (CR) was 68% at 5 and 10 years. In univariate analysis WHO type II tumors, lymph node fixation and persistent disease were poor prognostic factors in terms of overall survival. In multivariate analysis, WHO type II tumors ( $p = 0.04$ ) and patients with persistent disease after initial treatment ( $p = 0.006$ ) were significant adverse factors.

**Conclusion:** The majority of young patients with nasopharyngeal carcinoma present with advanced disease. The response to initial therapy as well as the pathologic subtype were the most important independent prognostic factors affecting overall survival.

**Key Words:** *Pediatric nasopharynx - Radiotherapy - Chemotherapy.*

### INTRODUCTION

Nasopharyngeal carcinoma in children is rare accounting for 1-3% of all pediatric malignancies and 20-50% of all primary nasopharyngeal tumors in this age group [3,12,15,17]. The majority of cases present with advanced stage disease and have undifferentiated carcinoma (WHO type III) tumors [3,8,9,13,16]. The management and treatment outcome are based on retrospective institutional studies with small number of patients accrued over many years, since the rarity of these tumors in children precludes the possibility of randomized trials.

Radiation treatment yields local control rate of 75% to 100% in the recent series [12,13,15,18]. Systemic metastasis remains the main obstacle to cure and is encountered in 30-50% of patients at the time of diagnosis or local relapse [3,9,10,17].

The aim of the present study is to review our hospital's experience in the management of this rare disease entity and to look at the various prognostic factors affecting treatment outcome.

### MATERIALS AND METHODS

We reviewed the hospital records of all patients  $\leq$  18 years of age with the pathologic diagnosis of nasopharyngeal carcinoma treated at King Faisal Specialist Hospital and Research Center (KFSH) in the period from 1975 to

1996. KFSH is a tertiary care hospital and a principal center for oncology in Saudi Arabia.

The endpoints in this analysis were overall survival (OS) defined as the time from histological diagnosis to the date of last follow-up or death and the disease free survival (DFS) for patients who obtained an initial complete response. Disease relapse and survival outcomes were computed according to the methods of Kaplan-Meier and were compared using the Log-rank test.

The American Joint Commission for Cancer (AJCC) 1988 staging system was used in the current study [4].

Out of a total number of 54 patients, 8 with metastatic disease at diagnosis and 3 patients with locally advanced disease and poor performance status, were treated with palliative intent and were excluded from survival analysis. Forty three patients were treated with radical intent (31 with radiation and 12 with combined radiation and chemotherapy). Eleven patients were treated with 3 cycles of chemotherapy before radiation treatment and one patient received concurrent chemo-radiotherapy. The drugs used were Cisplatinum/Adriamycin (6 patients), Cisplatinum/Epirubicin (5 patients) and Carboplatin/5 FU (1 patient). The radiation dose ranged from 44 to 70 Gy. Six out of 43 (14%) patients were treated with a total radiation dose less than 60 Gy. Only one patient was treated with 44 Gy total dose which could be considered a suboptimal dose for radical intent. The remaining 5 patients received doses of 50 Gy or higher. This variation in total dose delivered is attributed to individual variation among treating physicians during the study period.

## RESULTS

Out of 54 patients, 34 were males and 20 females (1.7:1). The age at diagnosis ranged from 6 to 18 (median 14) years.

The common presenting symptoms were enlarged neck nodes (94%), nasal obstruction (56%), headache (48%) and earache (20%). Twenty seven out of 54 patients (50%) were found to have fixed nodes. Eight patients (15%) presented with metastatic disease mainly in the bones.

Ninety six percent of the patients had stage

IV disease. Thirty seven patients had T3/T4 and 49 patients had N2/N3 disease (Table 1). In 3 patients the primary tumor size could not be assessed; they were labelled as Tx.

Ninety three percent of patients had good performance status (PS 1 & 2). Twenty seven (50%) patients had WHO type III (undifferentiated carcinoma) tumors. Tumor extension to the parapharyngeal space could be assessed in 40 patients and was involved in 31 (78%) of them. The median follow up was 58 (2.5-216) months.

The 5 and 10-year overall survival rates for the whole group were 45% and 39% respectively. Of the 8 patients with systemic metastases, none survived more than 14 months.

The 5 and 10-year survival rates for radically treated patients (N=43) were 58% and 49%, respectively. Thirty eight patients (88%) attained complete remission (CR) and had a 5 year OS (64%) compared to no survivors among 5 patients with persistent disease after initial therapy ( $p = 0.00001$ ). None of the patients with persistent disease survived beyond 15 months.

The 5-year OS for patients with mobile cervical lymph nodes (21 patients) was 62% compared to 44% in those with fixed nodes (19 patients). This difference was statistically significant ( $p = 0.01$ ).

Patients with WHO type III tumors had 5-year OS rate of 84% compared to 36% for those with WHO type II tumors ( $p = 0.03$ ). Total irradiation dose ( $\geq 60$  Gy versus  $< 60$  Gy), initial tumor size (T1 + T2 versus T3 + T4) and parapharyngeal extension had no significant impact on the overall survival results.

For 38 patients who achieved CR, the 5-year DFS was 69%. The site of first relapse was systemic metastasis, with no locoregional failure.

Patients with WHO type III tumors had a 5-year DFS of 89% compared with 51% for WHO type II tumors ( $p = 0.01$ ). Patients who received chemotherapy (N=9) had a DFS of 100% compared with 61% ( $p = 0.05$ ) in no chemotherapy patients who did not receive chemotherapy (N=29).

Neither T stage, parapharyngeal extension nor lymph node fixation had any impact on

DFS. Also, there was no significant difference in DFS between males and females (82% versus 50%,  $p = 0.09$ ), nor for patients treated with radiation dose > 60 Gy compared to those who received < 60 Gy (72% versus 60%). Multivariate analysis revealed WHO type II tumors ( $p = 0.04$ ) and persistent disease after initial treatment ( $p = 0.006$ ) as the only independent prognostic factors that negatively influenced the OS.

*Side effects of treatment:*

Short to median term xerostomia was the most common side effect, observed in 36/43 (84%) patients. It was mild in 26, moderate in 8 and severe in 2 patients. Trismus occurred in 8/43 (19%) patients (7 patients had mild trismus, one patient severe trismus). Laryngeal stenosis and perichondritis occurred in 1 patient 6 years following radical radiation treatment to a dose of 60 Gy. One patient developed renal toxicity while receiving neoadjuvant chemotherapy (Cisplatinum/Adriamycin). There were no reported second malignancies in this study.

Table (1): Distribution of patients by T and N stage.

Stage	T <sub>x</sub>	T <sub>1</sub>	T <sub>2</sub>	T <sub>3</sub>	T <sub>4</sub>	Total
N <sub>0</sub>	0	0	1	1	1	3
N <sub>1</sub>	0	0	0	0	2	2
N <sub>2</sub>	1	4	5	6	12	28
N <sub>3</sub>	2	1	3	9	6	21
Total	3	5	9	16	21	54

8 Patients M<sub>1</sub>

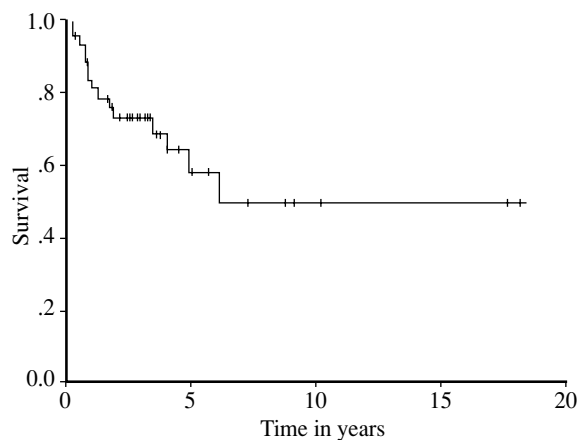


Fig. (1): The overall survival for patients treated with radical intent (43 patients).

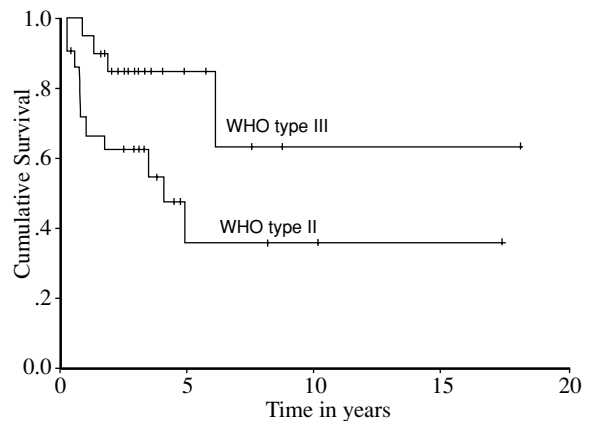


Fig. (2): The overall survival according to pathology, patients with WHO type III tumors had a significantly better 5 year OS (84%) in comparison to those with WHO type II tumors (36%) with a  $p$  value of 0.03.

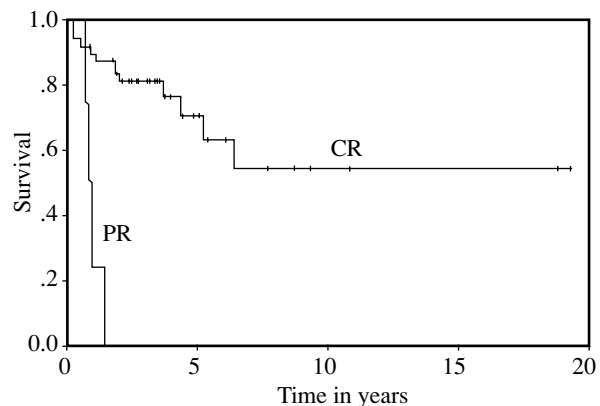


Fig. (3): Overall survival according to response to treatment, patients in CR had a significantly better 5-year OS (64%) in comparison to those with PR (0%) with a  $p$  value of 0.00001.

**DISCUSSION**

In the present study, nasopharyngeal carcinoma constituted 5% of all childhood malignancies and 5% of all nasopharyngeal carcinomas. The higher incidence in comparison with Europe and North America is consistent with other reports from the Middle East [19]. Most of our patients presented with stage IV disease, in accordance with other series [2,5,6,7,9,11,14]. Despite the advanced stage of the disease, patients treated with radical intent have a higher survival rate than their adult counterpart [9,12]. In the current study, the 5-year DFS for the 38 patients who were treated radically and achieved CR was 69% and remained unchanged to 10 years. This is similar to the results recently re-

ported by Memorial Sloan-Kettering hospital group [18].

A high percentage of patients develop distant metastases up to 80% in some reports [19]. In the present study, 29% of patients developed distant metastases after achieving CR and none of these had evidence of locoregional failure. Several authors advocate the use of systemic adjuvant chemotherapy in an attempt to reduce the incidence of distant metastases [6,11,18]. Wolden found that combined modality therapy significantly increased the freedom from distant metastases, to 84% compared with 43% in patients who received radiation alone [18]. The combined M.D. Anderson and Stanford experience reported a better 5-year survival rate in 14 patients who received adjuvant chemotherapy in comparison to 43 patients treated with radiation alone (60% versus 50%), with a corresponding lower distant metastasis rate in patients who received adjuvant chemotherapy [9]. Optimal adjuvant chemotherapy treatment and its sequencing remains to be determined. In the adult nasopharyngeal carcinoma, combined modality treatment using concurrent chemotherapy has improved both progression free and overall survival [1], this may also be true for the pediatric counterpart. None of the 12 patients who received chemotherapy in the present study developed distant metastases.

The local control rate in the present study (88%) was quite comparable to other series [9,12,13,15,18,19]. There was no difference of statistical significance between patients who received radiation dose < 60 Gy and those who received  $\geq$  60 Gy. These results would suggest that a dose of 60 Gy need not to be exceeded, but the optimal dose remains to be determined.

In the present study, there was a higher percentage of WHO type II tumors (50%) in comparison to the 10-27% incidence reported in the literature [3,9,12,18]. Patients with WHO type III tumors had significantly better 5-year survival rates than those with WHO type II tumors. This finding is consistent with the experience at M.D. Anderson and Stanford where patients with WHO type III tumors had a 53% 5-year survival rate compared to 43% for patients with WHO type II tumors [9]. In the current study, failure to achieve CR following initial treatment was the most important prognostic factor. This finding emphasizes the importance of treatment

strategies which intensify initial treatment.

In conclusion, most young patients with nasopharyngeal carcinoma presented with advanced stage disease. Treatment results in KFSH are comparable to those reported from Europe and north America. Initial response to treatment and WHO pathologic subtype were found to be significant prognostic factors and are consistent with the need for the use of chemotherapy in addition to radiation treatment. Optimal radiation dose and its sequencing with chemotherapy remains to be defined.

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