Multimodality Treatment for Pediatric Nasopharyngeal Carcinoma: A Review of 24 patients in Upper Egypt.

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Abstract: Background: Pediatric nasopharyngeal carcinoma (NPC), is rare but mostly presented in advanced stage. Our retrospective study aimed at evaluation of treatment outcome and toxicities. **Patients and methods:** The records of 24 eligible patients with NPC were reviewed during the period from January 2005and January 2015. Patients received 3 courses of chemotherapy regimen that consisted of cisplatin, 5-fluorouracil, with or without methotrexate followed (in non metastatic patients) by radiation therapy or chemo-radiotherapy. OS rates were estimated using the GraphPad prism program. The log- rank test was used to examine differences in OS rates. **Results:** The majority of patients presented with advanced stages (III&IV) (17, 71%), and showed response to treatment (CR&PR) (15, 63%). With a median follow up of 34 months (range: 3-120), the 3-year rate for OS was 58%. Univariate and multivariate analyses revealed that disease stage significantly affected survival.
Conclusion:. The used treatment protocol resulted in favorable outcome, but was associated with late effects. High precision radiotherapy (IMRT or 3DCRT) are needed to improve the cure of advanced or recurrent disease and to reduce long-term morbidities.
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Key words: Childhood nasopharyngeal cancer; Chemotherapy; Radiotherapy; Survival.

1. Introduction:

Nasopharyngeal carcinoma, or lymphoepithelioma, is extremely rare in pediatric patients; only about 3% of all nasopharyngeal carcinomas occur in patients younger than 19 years [1] .This tumor accounts for less than 1% of all pediatric cancers but is responsible for 20% to 50% of all nasopharyngeal malignancies in children [2].

Nasopharyngeal carcinoma presents as a painless mass in the upper neck. The majority of children with nasopharyngeal carcinoma present with advanced-stage disease (stage III or IV) [3].

Survival of patients with T1 and T2 lesions is excellent, with local control rates in excess of 75% to 80%. Prognosis of patients with T3 and T4 lesions is worse, with survival estimates in the 30% to 40% range [1].

Radiotherapy remains the foundation of therapy for nasopharyngeal carcinoma. Patients with T1 and T2 lesions can be adequately treated with radiation alone (doses of 65 to 70 Gy administered as 1.8- to 2.0-Gy daily fractions 5 days a week). Intensity-modulated radiotherapy (IMRT) has recently gained popularity and may improve local control in children while limiting the side effects [4]. For advanced-stage disease, neoadjuvant chemotherapy has been used followed by local radiotherapy or by concomitant chemoradiation. The most commonly used agents include cisplatin, methotrexate, leucovorin, and 5-fluorouracil (5-FU). In a study at St. Jude Children's Research Hospital, 20 of 21 patients with advanced-stage disease were long-term survivors after receiving four pre-radiation courses of these agents followed by radiotherapy [5]. The aim of this retrospective study on pediatric nasopharyngeal carcinoma to report the clinical presentation, treatment outcome, prognostic factors affecting OS and early and late toxicities of treatment.

2. Patients and Methods:

This retrospective study was carried out in the Pediatric Oncology, and Radiotherapy departments, SECI and Clinical Oncology department, Faculty of Medicine, Assiut University as well as Sohag Cancer Center, Ministry of Health after approval of our institute board.

Eligible patients had histologically confirmed nasopharyngeal carcinoma, and were previously untreated. The records of 24 eligible patients were reviewed during the period from January 2005 and January 2015. For each patient, initial staging evaluation was done by history and physical examination; hemogram, routine chemistry profile, local MRI, chest computed tomography (CT) scan with contrast, abdominopelvic ultrasound and bone scan. Histopathologic diagnosis was obtained from presenting mass or lymphadenopathy according to WHO classification .Staging according to The 5th Edition of the American Joint Committee on Cancer

Staging System [6]. Parental consent for treatment was obtained from parents of each patient.

Chemotherapy:

Our patients were given 3 courses (with 4 weeks intervals) of pre-radiation chemotherapy regimen that consisted (from 2005-2009) of methotrexate (MTX, bolus injection of 120 mg/m^2 on day 1), cisplatin (CDDP, 100 mg/m^2 IV infusion over 6 hours on day 1), and 5-fluorouracil (5-FU, 1000 mg/m^2 daily as continuous infusion on days 1 through 5), followed (in non metastatic patients) by radiation therapy, and anther regimen consisted (from 2010-2014) of CDDP (100 mg/m^2 over 6 hours were applied on day 1), and 5-FU (1000 mg/m^2 daily as continuous infusion on days 1 through 5), followed (in non metastatic patients) by concurrent chemo-radiotherapy (with cisplatin 40 mg/m^2/day 1 every week during 7 weeks of radiation).

Radiotherapy:

All non metastatic patients underwent conventional RT using a two dimensional (2D) technique with 6 MV photons to treat the primary tumor and neck lymph nodes. The patients were immobilized in a thermoplastic cast in the supine position, and were planned using a simulator using two lateral-opposing fields, to irradiate the nasopharynx and upper neck where CTV included the nasopharynx, skull base, pterygopalatine fossa, one third of the nasal cavity and maxillary sinus, and the upper neck lymph nodes with upper border was at 2 cm above zygomatic arch and lower border was at lower border of hyoid bone. The total radiation dose was 61-65 Gy and was given in two phases; first was 45 Gy in 25 fractions over 5 weeks, 1.8 Gy/ fraction. The spinal cord was then excluded and second CTV was irradiated with additional 16-20 Gy/ 8-10 fractions. The lower cervical and supraclavicular LNs were treated using a lower anterior neck field with a midline shield, and irradiated with 45 Gy/25 fractions.

Response to treatment (through clinical examination and radiological studies after treatment):

It was reviewed and recorded according to WHO criteria. 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.

Statistical analysis:

The study cutoff point was January 01, 2015. Overall survival was defined as the interval from end of treatment to the date of death from any cause or to last follow-up. OS rates were estimated using the GraphPad prism program. The log- rank test was used to examine differences in OS rates.

3. Results

Patients' characteristics (Table 1): The median age at the time of study enrollment was 15 years (range: 7-17 years). There were 13 (54%) male patients and 11 (46%) females, with a male to female ratio of 1.2:1. Distribution of T classification was as follows: T2a (21%, n=5), T2b (33%, n=8), T3 (29%, n=7), and T4 (17%, n=4). Disease stage distribution showed that 7 (29%), 7 (29%), 2 (8.5%) and 8 (33.5%) patients presented stages II, III, IVA, and IVC disease respectively.

Treatment outcome

At the end of treatment, complete remission (CR) was achieved in 10 patients (42%), partial response (PR) was in 5 (21%) patients, whereas progressive disease (PD) in 9 (37.5%). Assessment of toxicity profile showed that acute toxicity was well tolerated and included febrile neutropenia that was developed in 10 (42%) patients who were hospitalized and treated, mucositis in 10 (42%), and skin reaction in only 5 (21%) patients. Observed radiation related late effects included xerostomia in 9 (37.5%), neck fibrosis in 7 (29%) and trismus in 6 (25%) patients (Table 2).

Survival analysis

With a median follow up of 34 months (range: 3-120), the 3-year rate for OS was 58.3%. Males had a 3-year OS of 64% compared to 54% of females (P=0.59, HR: 0.698, 95% CI: 0.188-2.60). There was also no significant survival difference according to T classification (p=0.28), and LN status (p=0.07). On the other hand, 3-year OS was significantly higher in patients with non-metastatic disease (78%) than that in metastatic patients (p<0.0001). Furthermore, according to disease stage distribution, 3-year OS rates were 100% (stage II), 86% (stage III), 50% (stage IVA), and 0 (stage IVC) (p<0.0001). Patients who achieved CR, PR, and PD had 3-year OS rate of 100%, 80% and 0 (p <0.0001). Cox-regression multi-variate analysis showed that disease stage was the only independent factor that affected OS (p =0.001, HR: 4.690, 95% CI: 1.84 – 11.95). (Tables 3, 4 and Figures 1, 2).

Fig.(1): OS for patients according to disease stage

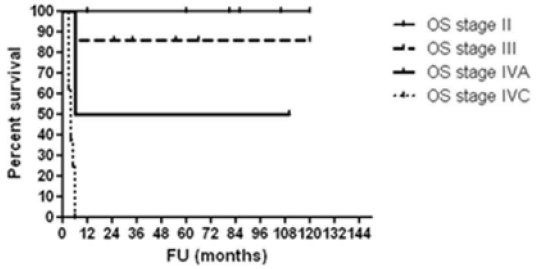

Fig.(2): OS for patients according to response to treatment

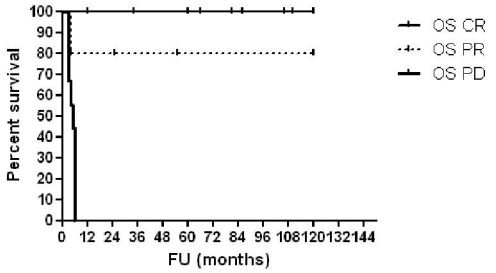

Table 1: Patients' characteristics

Characteristics	NO (%)
Age	
Median	15 years
range	9-17 years
Gender	
Female	11 (45.8)
Male	13 (54.2)
Clinical presentation	
Neck mass	21 (87.5)
Headache	14 (58.3)
Tinnitus	11 (45.8)
Nasal obstruction	10 (41.7)
Epistaxis	7 (29.2)
Others	7 (29.2)
T classification	
T2a	5 (20.8)
T2b	8 (33.3)
T3	7 (29.2)
T4	4 (16.7)
N classification	
N0	3 (12.5)
N1	6 (25)
N2	15 (62.5)
Disease stage	
II	7 (29.2)
III	7 (29.2)
IVA	2 (8.3)
IVC	8 (33.3)

Table 2: Treatment outcome

Characteristics	NO (%)
Response to treatment	
CR	10 (41.7)
PR	5 (20.8)
PD	9 (37.5)
Acute toxic effects	
Febrile neutropenia	10 (41.7)
Mucositis	10 (41.7)
Skin reaction	5 (20.8)
Late toxic effects	
Xerostomia	9 (37.5)
Neck fibrosis	7 (29.2)
Trismus	6 (25)

Table 3: Univariate analysis of prognostic factors that might affect OS

Variable	3-year OS	*P* value
Gender		0.59
Females	63.6%	HR: 0.698
Males	53.8%	95% CI:0.188-2.60
T classification		0.28
T2a	100%	
T2b	62.5%	
T3	42.9%	
T4	25%	
N classification		0.07
N0	66.7%	
N1	100%	
N2	40%	
M classification		<0.0001
M0	77.8%	
M1	0	
Disease stage		<0.0001
II	100%	
III	85.7%	
IVA	50%	
IVC	0	
Response to treatment		<0.0001
CR	100%	
PR	80%	
PD	0	

Table 4: Cox regression multivariate analysis

Variable	Significance
Disease stage	*P*=0.001, HR: 4.690, 95% CI: 1.84 – 11.95
T Classification	*P* =0.286
N Classification	*P* =0.235
M Classification	*P* =0.369
Response to treatment	*P* =0.173

4. Discussion:

In childhood nasopharyngeal carcinoma, as a rare pediatric malignant disease, the number of patients that could be eligible for a prospective trial within a reasonable period of time will never be satisfactory for statistical analysis. Therefore, the

retrospective nature of the current study could be justified to answer on the efficacy of multimodality therapy used for treatment of that disease [7].

The current study revealed that the median age of our patients was 15 years with male predominance. This was in agreement with reported studies [8-10].

The present study showed that the vast majority (71%) of patients presented with advanced disease (stages III &IV), and 87.5% had palpable neck nodes. This is confirmed by many studies which report that the majority of pediatric patients presented with advanced stages and were associated with high rate of distant metastases [3, 11, 12].

For advanced-stage disease, some studies have investigated the use of neoadjuvant chemotherapy followed by local radiotherapy in small numbers of children with nasopharyngeal carcinoma, with the most commonly used agents include cisplatin, methotrexate, and 5-fluorouracil (5-FU) [11, 13]. More recently, the administration of neoadjuvant chemotherapy with chemoradiotherapy has gained popularity [14-18]. Accordingly, in our retrospective study, patients were treated by neoadjuvant chemotherapy followed by radiation therapy. In recent years (from 2010 and thereafter), our patients were treated with neoadjuvant chemotherapy followed by chemo-radiation. This treatment protocol resulted in achievement of tumor response to treatment (CR&PR) in the majority (62.5%) of patients. This is matched with results showed by Casanova *et al.* [7], who reported 89% CR rate.

After a median FU of 34 months, the 3-year OS rate was 58%, with disease stage was the independent prognostic factors affecting survival by cox-regression multivariate analysis (P=0.001, HR: 4.690, 95% CI: 1.84 – 11.95). This is confirmed in the literature, where the prognosis of patients with advanced stages is worse, with survival estimates in the 30% to 40% range [9, 19]. Although high-dose radiotherapy in pediatric malignancy can be curative it has been associated with significant morbidity among long-term survivors [20, 21].

In our study, acute treatment related complications were well tolerated and the incidence of common late radiation related toxic effects, such as xerostomia, neck fibrosis, and trismus, were comparable to that found in many reports [7-10].

In a study conducted by Liu *et al.,* [10] who compared 2D and IMRT, it has been shown that the use of IMRT resulted in a significant reduction of trismus (p= 0.03) and G2 xerostomia (p = 0.02) because of IMRT allows for the delivery of high doses to the target area while sparing the surrounding critical structures and offers superior target coverage compared with conventional radiotherapy and 3D-CRT in improving therapeutic ratios.

Conclusion:

Most children with nasopharyngeal carcinoma had advanced diseases at presentation. The treatment protocol of our study resulted in high response rate (63%) and had favorable OS rate, but was associated with radiation related late effects. Univariate and multivariate analyses showed that disease stage significantly affected OS. High precision radiotherapy (IMRT or 3DCRT) are needed to improve the cure of advanced or recurrent disease and to reduce long-term morbidities.

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