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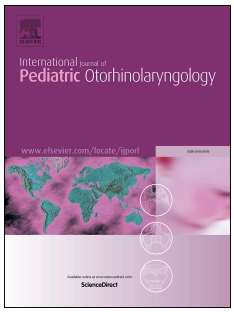

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Treatment outcome of childhood nasopharyngeal carcinoma: a single institution experience

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ABSTRACT

Objectives: Nasopharyngeal carcinoma is a rare malignancy in children. The aim of this study was to provide analysis of children with nasopharyngeal carcinoma treated in a single institution.

Methods and materials: Between 1999 and 2016, fourteen pediatric patients with a diagnosis of undifferentiated nasopharyngeal carcinoma were treated in our institution, and the patients' clinical characteristics, treatment modality, outcome, and toxicity were analyzed.

Results: The median age at diagnosis was 15,5 years. The gender ratio was 1:1. The majority of patients had regionally and/or locally advanced tumors and one had bone metastases at the time of diagnosis. All patients received chemotherapy before radiotherapy, with partial response in thirteen patients and complete response in one. Radiation dose to the primary tumor and involved cervical lymph nodes was 55-60 Gy, uninvolved cervical and supraclavicular regions received prophylactic radiation with dose of 45-50 Gy. Ten patients received adjuvant chemotherapy. Three-year time to progression (TTP) and three-year overall survival (OS) rates were 75% and 73% respectively. Five-year TTP was 65% and OS 63% respectively, and after ten years TTP and OS remained the same. At the end of follow-up period, ten patients were alive, and four died. All of the patients that had distant metastases died. Most common late complications were skin fibrosis and xerostomia.

Conclusions: Multimodal therapy of children with nasopharyngeal carcinoma is associated with long-term survival. It is expected that further advances in the management of these patients, with improved radiotherapy and chemotherapy, will reduce acute and late toxicity and improve quality of life of treated children.

Keywords: children; nasopharyngeal carcinoma; survival; treatment.

1.INTRODUCTION

Nasopharyngeal carcinoma represents approximately 1% of all childhood cancers and 40-50% of all malignancies involving the nasopharynx in children. The incidence of pediatric nasopharyngeal carcinoma (NPC) varies greatly with ethnic and geographic factors [1]. Nasopharyngeal carcinoma shows bimodal age distribution: the first peak is between 10-20 years of age and the second one between 50-60 years. This is not the case in endemic regions (Southeastern Asia and China), where this distribution is unimodal and does not contain a pediatric peak [2].

Etiology and pathogenesis are closely related to Epstein-Barr virus (EBV) infection. Children with NPC differ from their adult counterparts in having a closer association with EBV [3].

According to WHO classification [4], NPC is histopathologically divided into three categories: keratinizing squamous cell carcinoma (WHO type I), non-keratinizing squamous cell carcinoma (WHO type II), and undifferentiated carcinoma (WHO type III). Children with NPC almost always have the undifferentiated variant of disease [5,6].

In many patients, the initial appearance of NPC is a cervical adenopathy, and diagnosis is made with a lymph node biopsy. Primary tumor symptomatology can also present with trismus, painful mass, otitis media, nasal congestion, hearing loss, and cranial nerve paralysis secondary to skull base involvement. Large tumor volumes produce nasal obstruction, bleeding, and nasal voice [7].

Although childhood and adolescent NPC patients usually present with advanced locoregional disease at first diagnosis and a high prevalence of distant metastasis, their outcomes are generally better than adult NPC patients [8].

For all patients, treatment of NPC is administered with the intention of cure. The rarity of NPC in children, and occurrence of the disease in older children and adolescents has led oncologists to follow treatment guidelines established for adults. The main treatment strategy for all cases of locoregional NPC has been high-dose radiotherapy [9].

Unfortunately, high-dose radiation in children has been associated with significant morbidity among long-term survivors and is sufficient only for local and regional control of disease [3]. Because of the biological characteristics of the tumor, systemic therapy is necessary [10]. There is much concern about treatment related morbidity in young patients, including the possibility that high radiation doses usually lead to significant sequelae and concomitant chemoradiotherapy is usually related to both acute and chronic morbidities. Thus, the optimal treatment modality has not yet been established [11].

In this paper, we wish to report our experience in the treatment of NPC in children treated with a combination of radiotherapy and chemotherapy and related acute and late toxicity.

2. MATERIAL AND METHODS

Data on fourteen pediatric patients with a diagnosis of NPC, treated at the Institute of Oncology and Radiology of Serbia between January 1999 and December 2016, were analyzed.

Institute of Oncology and Radiology of Serbia, Belgrade is the national referral center for the treatment of childhood tumors [12].

Inclusion criteria in this study were patient's age younger than 20 at the time of diagnosis, patients with a confirmed histopathological diagnosis of NPC, and patients with no previous history of malignancy.

Clinical staging of the disease was performed by a complete clinical examination, epipharyngoscopy, computed tomography/magnetic resonance imaging (CT/MRI) of the pharynx, base of the skull and neck, ultrasound of the neck and abdomen, chest X-ray and optionally bone scan. All patients were staged according to the TNM classification system of American Joint Committee on Cancer [13].

The surgical procedure was limited to biopsy in twelve patients, and in two patients a neck dissection was performed additionally.

The primary treatment for all patients was neoadjuvant chemotherapy. For seven patients chemotherapy consisted of neoadjuvant methotrexate (MTX), cisplatin (CDDP) and 5-fluorouracil (5-FU), and adjuvant 5-FU and CDDP. Six patients received chemotherapy according to MD Anderson Hospital protocol: neoadjuvant Cyclophosphamide (Cyc) - Adriamycin (Adr) - Vincristine (Vcr) and adjuvant Cyc - Vcr - Actinomycin D (Act D). In one patient, chemotherapy was administered according to NPC-2003-GPOH protocol: neoadjuvant 5-FU-CDDP-leucovorin.

Six patients received recombinant interferon alpha therapy in the adjuvant setting.

Until 2006, 5 patients received two-dimensional radiotherapy (2D-RT) with two lateral opposing or three-field technique. After that period, three-dimensional conformal radiotherapy (3D-CRT) was introduced, and was delivered to 9 patients. For all patients, radiotherapy was applied using 6 MeV photons, plus electron boost to the neck in cases of conventional therapy, when appropriate. The irradiated volume included the nasopharynx, base of the skull, posterior portion of the maxillary sinus, nasal cavity and the whole neck and supraclavicular region. Radiation dose to the primary tumor and involved cervical lymph nodes was 55-60 Gy (median 57,6 Gy). Uninvolved cervical and supraclavicular regions received prophylactic radiation with a dose of 45-50 Gy. Radiation was given five times a week with a fraction size of 1,8-2 Gy per day.

After the completion of treatment, follow-up examinations were conducted every 3 months for 36 months, every 4 months up to 5 years, followed by yearly examinations according to our protocol. The patients' disease status was assessed by clinical examination and by CT and/or MRI. Endocrine assessment was recommended every 6 months.

Survival was calculated from the date of diagnosis until the date of death or last follow-up. In all patients, acute toxicity and late effects of therapy were evaluated according to the European Organization for the Research and Treatment of Cancer (EORTC) scoring scale [14].

Statistical analysis: The survival analysis was done using the Statistical Package for Social Sciences (SPSS) version 13.0 and the Kaplan-Meier method was used to calculate the actual survival.

3. RESULTS

Fourteen children were included in this study according to the inclusion criteria (Table 1). The median age at diagnosis was 15,5 (range 13-19) years. The gender ratio was 1:1. The median duration of symptoms at an entry to the hospital was 4,5 months (range 2-9).

At presentation two patients (14,3%) were in clinical stage (CS) II, nine (64,3%) in CS III and three (21,4%) in CS IV (one in CS IVa, one in CS IVb and one in CS IVc). All of the fourteen patients were histologically diagnosed as undifferentiated type NPC WHO type III.

The majority of patients had regionally and/or locally advanced tumors, and one patient had bone metastases at the time of diagnosis.

All of the patients received neoadjuvant chemotherapy. Three to five courses were given before radiotherapy (median 3). Six children received protocol #1, seven children received protocol #2, and one child received protocol #3 (Table 2). Locoregional response to neoadjuvant chemotherapy was partial in thirteen patients and one patient had a complete response.

Radiation dose to the primary tumor and involved cervical lymph nodes was 55-60 Gy (median 57,6 Gy). Uninvolved cervical and supraclavicular regions received prophylactic radiation with a dose of 45-50 Gy. The mean duration of radiotherapy was eight weeks (range 7-12) with a median number of 30 fractions (range 22-33).

Ten patients received adjuvant chemotherapy in 2-13 courses (median 7). Six patients received recombinant interferon alpha therapy in the adjuvant setting.

After completion of treatment (radiotherapy and adjuvant chemotherapy), complete response was documented in nine patients (64,3%), partial response in two patients (14,3%),

progression of disease in two patients (14,3%, of which one case had distant metastases) and one patient (7,14%) died before a completion of adjuvant chemotherapy (distant progression of disease, treatment-related toxicity and infection).

After the median follow up period of 45 months (range 1-174), 3-year time to progression (TTP) and 3-year overall survival (OS) rates were 75% and 73% respectively. 5-year TTP was 65% and OS 63% respectively, and after 10 years TTP and OS remained the same (Figure 1, Figure 2).

At the end of the follow-up period, ten patients were alive and four died. Of the surviving patients, one had documented locoregional disease and nine were without evidence of disease. All of the patients that had distant metastases died. Cause of death in two patients was a local, regional and distant progression of the disease, in one patient regional and distant progression, and in one patient cause of death was a combination of distant progression of the disease, treatment-related toxicity and infection.

During treatment, twelve patients (85,7%) experienced mucositis grade III or IV and only two (14,3%) patients mucositis gr II. Skin toxicity (dermatitis) was mild (grade I or II) in thirteen (92,8%) cases, while one patient experienced dermatitis grade III. Hematological toxicity was severe in half of the cases (seven patients had neutropenia grade III or IV, and seven had grade I or II). Four patients (28,6%) developed some kind of infection during treatment. Two patients (14,3%) had nausea and vomiting. Nephrotoxicity occurred in one patient (7,1%) and cardiotoxicity in two patients (14,3%) during treatment. One patient (7,1%) experienced veno-occlusive liver disease. (Table 3).

During the follow-up period, most common late complications were skin fibrosis in all patients and xerostomia (92,3%). Four patients (30,7%) developed hypothyreosis, three trismus (23%) and two patients (15,4%) developed sensorineural hearing loss. Empty sella after treatment developed in one patient (7,7%).

Two patients experienced pregnancy and childbirth six and ten years after treatment.

4. DISCUSSION

Pediatric NPC is a disease of adolescents and teenagers rather than young children, in contrast to other pediatric malignancies of nasopharynx like rhabdomyosarcoma [15, 16, 17]. Median age in our study was 15,5, which is in accordance with other series [18, 19].

Most of the large series in pediatric literature showed a wide range of male predominance in NPC [20, 21, 22], except for a publication from England [23] where a close to equal distribution between genders was published. The present study reports an equal gender distribution.

In young patients, the predominant histology of NPC is an undifferentiated variant of disease [11, 24, 25], which was confirmed in our study where all patients were histologically WHO type 3. On the other hand, Daoud et al. [26] reported 56.3% of pediatric patients as undifferentiated carcinoma (WHO type 3), and the remainder had a non-keratinizing variant (WHO type 2).

Majority of NPC in children are diagnosed in locally advanced stages, with lymph node metastases occurring in up to 90% of patients [27]. About 85% of our patients presented in

advanced clinical stages III or IV, similar to other reports [28, 29]. The main factor for late diagnosis and advanced stage of disease may be nonspecific symptoms (nasal obstruction, headache, otitis media), but also delayed diagnosis due to socioeconomic factors in a developing country like Serbia may also play a role. Advanced tumor stage and advanced nodal disease are reported to be associated with adverse outcome [30, 31, 32].

It is well known that NPC is a radiosensitive cancer, but treatment with radiotherapy alone is associated with poor outcome in pediatric patients with advanced NPC with a 5-year survival rate between 20 and 40% [33, 34]. The poor OS and high incidence of systemic failure in patients with locally advanced NPC have led to the investigation of early combined therapy (chemotherapy before, concurrently with, or after radiotherapy) to improve survival in childhood NPC. Unfortunately, due to the small sample sizes of childhood nasopharyngeal carcinoma, standardized chemotherapy combinations or treatment schedules are not yet available [35].

In recent years, most pediatric patients with NPC have received a combination of chemotherapy and radiotherapy with various regimens worldwide, usually containing cisplatin and often 5-fluorouracil. Reported survival rates vary between 55% and 90% for OS and between 60.6% and 77% for disease-free survival (DFS) and event-free survival (EFS) [36]. Ayan et al. [6] reported a long-term survival rate of 52% in patients treated with chemotherapy before radiotherapy.

In our study of 14 children treated with combined chemotherapy and radiotherapy, 3-year TTP and 3 years OS rates were 75% and 73%, 5-year and 10-year TTP and OS 65% and 63%, respectively. These rates were comparable with other series reported in the literature.

Similar to our results, Daoud et al. [26] reported 5-year OS rate 56% in a study from 2003, and Selek et al. [37] reported 5-year OS rate 69% in 2005.

Optimal radiation dose in pediatric NPC has not been established, particularly when combined with chemotherapy. In reports of Ingersoll [38], Ayan [6] and Afqir [1], improved local control with higher doses (≥60 Gy) was reported. Excellent local control has also been reported with a radiation dose of 59,4 Gy [3]. Variety of applied radiotherapy doses (35-65 Gy) has also shown adequate local control [39]. According to our results, radiotherapy doses of 55-60 Gy to the gross disease and elective nodal doses of 45-50 Gy, in combination with applied chemotherapy, seemed to be enough for satisfactory locoregional control. We propose this dose range especially for responders to pre-irradiation chemotherapy.

In our series, distant metastases occurred in all patients who died of disease. In general, distant metastasis remain the major pattern of failure. Therefore, early systemic treatment is necessary for NPC [40, 41, 42].

Data of the long-term side effects in young patients with NPC are scarce. Most common late effects in the current study were neck fibrosis, xerostomia, hypothyreosis and sensorineural hearing loss similar to other reports [19, 25, 33].

It has been consistently reported that higher radiation doses in children are of particular concern owing to the associated long-term morbidity [6, 43]. Lu et al. found that the incidences of sequelae (grade I–IV) in patients with high radiation dose >66Gy were apparently higher than those in patients with low radiation dose ≤66 Gy [44].

Second malignancies have been reported as a consequence of high-dose radiotherapy with or without chemotherapy [45, 46]. Wolden et al. [47] reported two cases (6%) of secondary

cancer among 33 children, after a median latency of 8 years after treatment. Both cases were salivary mucoepidermoid carcinomas. One occurred in the base of tongue, and the other occurred in the parotid gland. Liu et al. [8] reported six cases (3,8%) of 158 treated children who developed second malignant tumors in the radiation field 38-123 months after radiotherapy. None of our patients developed second malignancies. Pao et al. [32] also reported no second malignancies during 11 years (range 4-20) of follow-up in a series of 29 children with NPC. Long-term follow-up of patients is crucial for early detection of second malignancies as many depend upon complete surgical resection for cure. Patients also require long-term monitoring for dental, endocrinological, and psychological problems [47].

With better treatment outcomes and longer survival, quality of life of treated children becomes more important. Several studies have demonstrated advantages of Intensity Modulated Radiotherapy in children with NPC due to decreased radiation-induced toxicity [48,49].

Results of our study, together with data from other studies, demonstrates the importance of a long-term follow-up in pediatric NPC patients.

Our experience indicates that combined modality approach based on administered chemotherapy protocols (neoadjuvant and adjuvant in selected cases) and radiotherapy is effective treatment with acceptable toxicity.

Multi-institutional and international cooperative group studies are needed to define the new strategies for this rare disease.

5. CONCLUSIONS

Children with NPC treated with multimodal therapy have long-term survival, so there is a need for long-term follow-up and analysis of expected late effects. It is expected that better risk and response adapted treatments with modern radiotherapy and chemotherapy will reduce acute and late toxicity, which will substantially improve quality of life of treated children.

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Table 1: Clinical characteristics, treatment and survival of 14 children with nasopharyngeal carcinoma

Case No.	Age/Sex	Date of diagnosis	CS	Radiotherapy dose(Gy) primary tumor/lymph nodes	Chemotherapy protocol	Relapse date/site	Current status
1	16/f	Oct 1999	II	60	#1	NA	NED
2	16/f	June 2000	IVb	60	#1	Feb 2002 Lung, local progression	DOD (Sept 2003.)
3	19/m	Dec 2000	IVc	60	#1	NA	DOD (Aug 2001)
4	15/f	Jan 2002	III	60	#1	NA	NED
5	13/m	March 2004	III	55	#2	NA	NED
6	14/f	July 2004	III	55	#2	NA	NED
7	15/m	Nov 2004	II	55	#1	Jan 2007 Locoregional progression	DOD (Sept 2009)
8	16/m	Nov 2004	III	55	#2	NA	NED
9	13/f	May 2008	III	55	#2	NA	NED
10	16/m	Oct 2008	III	55	#2	Nov 2009 Bone, lung	DOD (June 2011)
11	15/m	Apr 2011	III	59,4	#2	NA	NED
12	16/f	June 2011	IVa	59,4	#1	Oct 2012 Regional progression	SD
13	18/f	June 2012	III	55,8	#2	NA	NED
14	13/m	Nov 2012	III	59,4	#3	NA	NED

CS- clinical stage

NA- not available

NED- no evidence of disease

DOD- dead of disease

SD- stable disease

Table 2: Chemotherapy regimens

#1	MD Anderson Hospital protocol: Neoadjuvant Cyc-Adr-Vcr + adjuvant Cyc-Vcr-Act D
2#	Neoadjuvant MTX-CDDP- 5-FU + adjuvant 5-FU -CDDP
3#	NPC-2003-GPOH protocol: Neoadjuvant 5-FU –CDDP- leucovorin

Cyc- Cyclophosphamide

Adr- Adriamycin

Vcr- Vincristine

Act D- Actinomycin D

MTX- Methotrexate

CDDP- Cisplatin

5-FU- 5-fluorouracil

Table 3: Treatment toxicity among 14 children with nasopharyngeal carcinoma

Toxicity	Number of patients
Acute	
Mucositis	14/14
Dermatitis	14/14
Neutropenia	14/14
Infection	4/14
Cardiotoxicity	2/14
Nephrotoxicity	1/14
Veno-occlusive liver disease	1/14
Late	
Fibrosis	13/13
Xerostomia	12/13
Hypothyreosis	4/13
Trismus	3/13
Sensorineural hearing loss	2/13
Empty sella	1/13

Figure 1. Time to progression rate of 14 children with nasopharyngeal carcinoma

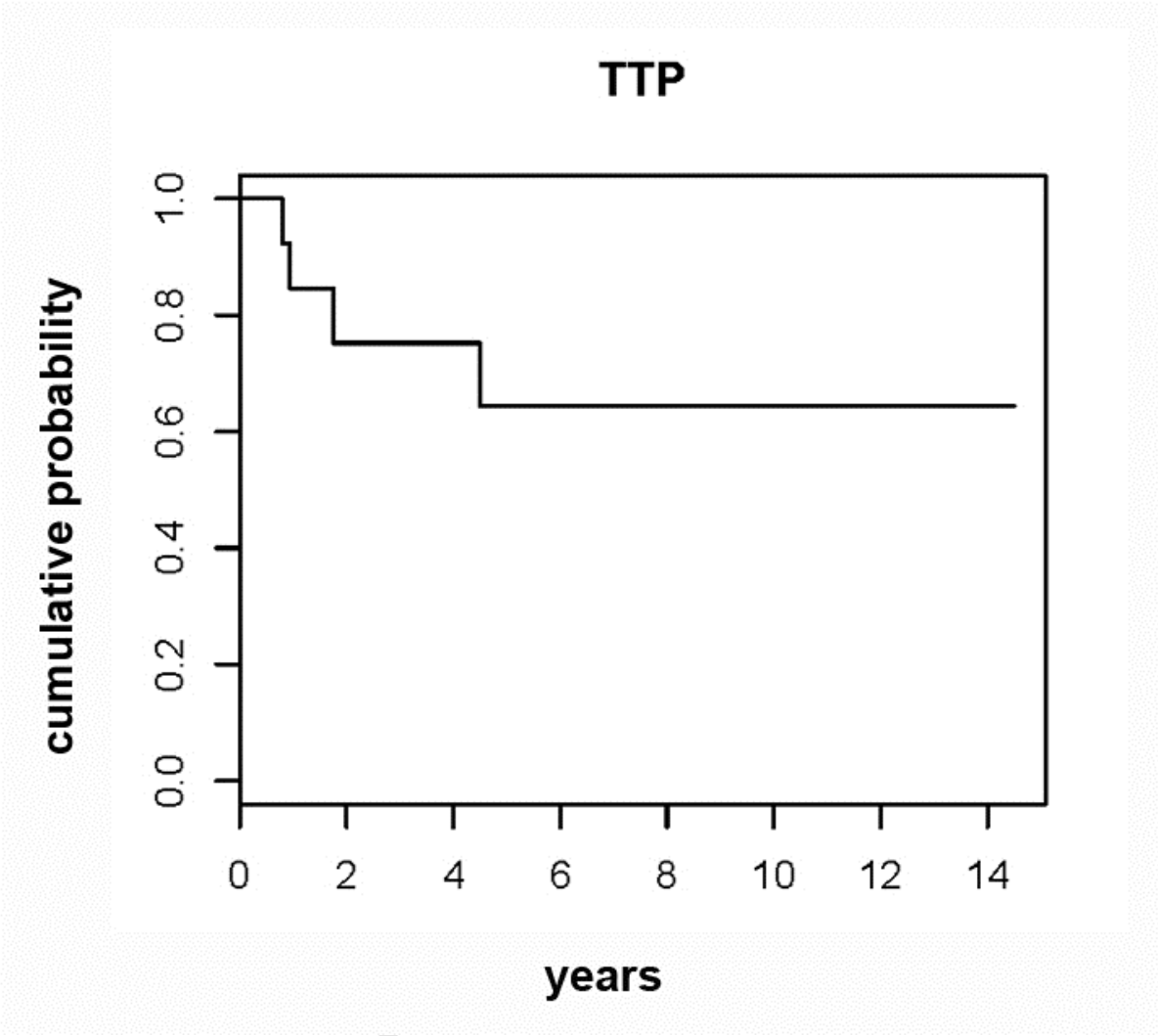

Figure 2.Overall survival rate of 14 children with nasopharyngeal carcinoma