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UNDIFFERENTIATED NASOPHARYNGEAL CARCINOMA IN CHILDREN AND ADOLESCENTS: A REPORT OF 68 CASES IN A MOROCCAN CENTER

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ABSTRACT

This study aimed to demonstrate the clinical and therapeutic features of nasopharyngeal carcinoma (NPC) in children and adolescents in Morocco, an intermediate risk area. Sixty-eight newly diagnosed undifferentiated NPC patients younger than 19 years old treated at the National Institute of Oncology Sidi Mohamed Ben Abdellah in Rabat, Morocco, between 2010 and 2016. Patients had a median age of 16 years (range 8-19), with a sex ratio of 2.2. The mean time to presentation was 5.9 months. The main presenting symptom was cervical lymphadenopathy in 77% of cases. Patients with stages I, II, III, and IVa accounted respectively for 1.5%, 10.3%, 44.1%, and 39.7%. Three patients had bone metastases at the time of diagnosis. Forty-four patients received induction chemotherapy before concurrent chemo radiation, 23 patients received concurrent chemo radiotherapy alone with weekly cisplatin, and one patient underwent exclusive radiotherapy. After a mean follow-up of 38 months (range: 14.5 to 65), loco-regional control (LRC) and distant metastasis-free survival (DMFS) were 94.1% and 76.5%, respectively. The 5- and 10- year overall survival (OS) was 87% and 80.1%, respectively. The 5- and 10-year disease-free survival (DFS) was 75.3% and 66%, respectively. At the end of follow-up period, 13 patients (19.1%) were lost to follow-up. Seven patients (10.3%) had died, and 48 patients (70.6%) were alive and without disease. Most common late complications were xerostomia, hearing loss, skin fibrosis, trismus and dental caries. In spite of the majority of children and adolescents with NPC diagnosed at the advanced stage, treatment combining chemotherapy and radiotherapy achieves an excellent local control rate. A higher interval time between symptom onset and consultation (> 6 months), and T stage (T3, T4) were the most relevant prognostic factors in this study.

Keywords: Adolescent, Children, Morocco; Nasopharyngeal carcinoma; Survival; Treatment.

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant tumor arising from the epithelial cells that line the surface of the nasopharynx. According to the Cancer Registry of Greater Casablanca 2008-2012, the global standardized incidence was 2.3 new cases for 100,000 inhabitants per year (1.5 for 100 000 females/year versus 3.1 for 100 000 males/year) (1). It is an unusual malignancy in children, which is only 1% to 5% among all pediatric cancers (2; 3). Its incidence varies between geographical locations. The annual incidence is about 0.1 to 1.5 per million in United States, 1.0 per million in North Africa, 2.0 per million in Southeast Asia, and 2.5 per million in Hong Kong (3). The age distribution of NPC is bimodal, with one peak arising in young adolescents and another peak in patients between 55 and 59 (4). Approximately 20% of NPC occur before the age of 20 (5), and the most common histological type is undifferentiated NPC (UCNT), accounting for 93% of cases (6). Etiology and pathogenesis are closely related to Epstein-Barr virus (EBV) infection. Children with NPC differ from the adult form of the

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disease in having a closer association with EBV and high incidence of locoregionally advanced disease (2). The standard therapy for children with NPC has generally followed the guidelines that have been established for adults. Undifferentiated NPC is very sensitive to radiation. The treatment strategy mainly consists of high-dose radiotherapy. The 5-year survival has been reported as 55% to 90% in most pediatric series with a combination of chemotherapy and radiotherapy. (7; 8; 9). We conducted a retrospective review of all children and adolescents with Undifferentiated NPC treated at the National Institute of Oncology Sidi Mohamed Ben Abdellah in Rabat Morocco, from 2010 to 2016, to investigate the survival and morbidities, as well as the factors associated with clinical outcomes.

MATERIEL AND METHODS

This retrospective study was conducted on a series of 68 children and adolescent treated at the radiation oncology department of National Institute of Oncology Sidi Mohamed Ben Abdellah in Rabat, Morocco, between 2010 and 2016. Inclusion criteria in this study were patient's age younger than 19 at the time of diagnosis, with a confirmed histopathological diagnosis of undifferentiated NPC and with no previous history of malignancy.

We extracted data on the clinical features, histopathology, imaging findings, treatment, and outcomes, to identify the long-term survival and morbidities, as well as the factors associated with survival. All tumors were restaged according to the TNM-classification of the International Union against Cancer (UICC) and the American Joint Committee of Cancer (AJCC). This system was updated to the VIIIth edition in 2017 (10) (from the VIIth edition in 2010). All patients received three-dimensional conformal radiotherapy (3D-CRT) using 6 MeV photons, plus electron boost to the neck when appropriate. Radiation dose to the primary tumor and involved cervical lymph nodes was 70 Gy. Uninvolved cervical and supraclavicular regions received prophylactic radiation with a dose of 56-60 Gy. Radiation was given five times a week with a fraction size of 2 Gy per day. After the completion of treatment, follow-up examinations were conducted every 3 months for 24 months, every 6 months up to 5 years, and every year thereafter. Physical examination was performed at every visit, CT or MRI 3 months after treatment and then yearly. Survival was calculated from the date of diagnosis until the date of death or last follow-up. Late toxicities were evaluated according to the European Organization for the Research and Treatment of Cancer (EORTC) scoring scale (11). Overall survival (OS), disease-free survival (DFS), loco-regional control (LRC) and metastasis-free survival (MFS), were calculated using Kaplan-Meier analysis, in which survival differences were compared with the log-rank test. Prognostic factors were analyzed using the Cox proportional hazards regression model. A difference with a value of <0.05 was considered to be statistically significant. All calculations were carried out using Statistical Package for Social Sciences (SPSS) version 22.0 software.

RESULTS

Patient characteristics (Table I)

The median age at diagnosis was 16 (range 8-19) years. The gender ratio was 2.2. The median time from initial presentation to entry to the hospital was 5.9 months (range 3– 8 months). The most common presenting symptoms were neck mass followed by nasal symptoms, auditory symptoms and neurological symptoms (Table 1). Nasal endoscopy with biopsy was performed in all patients. Histological diagnosis was undifferentiated type NPC WHO type III in all cases. Local staging comprised CT scan for 62 patients (93.9%) and MRI in 8 (13.1%). Distant staging, comprising chest X-ray in 49 (86%), abdominal ultrasound in 45 (81.8%), thoracic abdominal CT scan in 36 (69.2%), and scintigraphy in 41 (78.8%). After this workup, cancer-staging distribution was stage I-II, III, and IVA in 11.8%, 44.1%, and 39.7%, respectively. Three patients (4.5%) had bone metastases (stage IVB) at the time of diagnosis with no other distal metastases (**Table I**).

JMSR
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Table I: Patients characteristics (n = 68).

Characteristic	n (%)
Age	
Median	16
Gender	
Female	21 (30.9)
Male	47 (69.1)
Presenting complaint	
Neck mass	50 (76.9)
Nasal obstruction	51 (78.5)
Epistaxis	27 (30.2)
Tinnitus/hearing loss	47 (72.3)
Headache	31 (47.7)
Cranial nerve palsies	9 (15.6)
Weight loss	6 (9.2)
T stage	
T1	4 (6)
T2	24 (35.8)
T3	21 (31.3)
T4	18 (26.9)
N stage	
N0	5 (7.5)
N1	10 (14.9)
N2	42 (62.7)
N3	10 (14.9)
M stage	
M0	64 (95.5)
M1	3 (4.5)
TNM stage	
I	1 (1.5)
II	7 (10.3)
III	30 (44.1)
IVA	27 (39.7)
IVB	3 (4.5)

Treatment protocol and response

All patients received conventional radiotherapy. Radiation dose to the primary tumor and involved cervical lymph nodes was 70 Gy. Uninvolved cervical and supraclavicular lymph nodes received a radiation dose of 56-66 Gy. A daily dose of 2 Gy was delivered 5 days a week. The mean duration of radiotherapy was 54.6 days (range 42-81 days).

Forty-four patients (64.7%) received induction chemotherapy before concurrent chemoradiation, 23 patients (33.8%) received concurrent chemoradiotherapy alone, and one patient (1.5%) received exclusive radiotherapy. The 3 patients who had bone metastases at the time of diagnosis received 4 cycles of adriamycin-cisplatin, after complete remission of the secondary lesions, they underwent radiotherapy to the nasopharynx. One of them died 1 month after completion of radiotherapy, and 2 others are alive and without disease.

Three cycles of doxorubicin-cisplatin administered at three-week intervals was the most commonly used induction chemotherapy regimen (81.9%). Bleomycin/epirubicin/5-fluorouracil regimen was administered to a small minority of patients 7 (9.7%). Weekly cisplatin protocol was the regimen used concurrently with radiotherapy for 3 to 7 cycles (median of 5). Forty-seven (74.6%) patients concluded the entire cycles of chemotherapy (neoadjuvant and/or concurrent) and 16 patients (25.4%) could not complete the prescribed treatment due to therapy-induced complications.

Response to treatment was assessed 3 to 6 months after completion of treatment based on clinical examination and imaging. Complete response was documented in 47 patients (74.6%), partial response in 5 patients (7.9%), stable disease in 7 (11%), progressive disease in 3 patients (4.8%) (02 cases had loco-regional progression and one had distant progression of disease), one patient (1.6%) died before a completion of radiotherapy (treatment-related toxicity).

The median follow-up time was 38 months (range 14.5-65 months). Thirteen patients (19.1%) were lost to follow-up. Seven patients (10.3%) had died, and 48 patients (70.6%) were alive and without disease.

The 5 and 10 year OS was 87% and 80.1% respectively. The five- year and 10-year DFS was 75.3% and 66% respectively (**Figures 1, 2**)

JMSR
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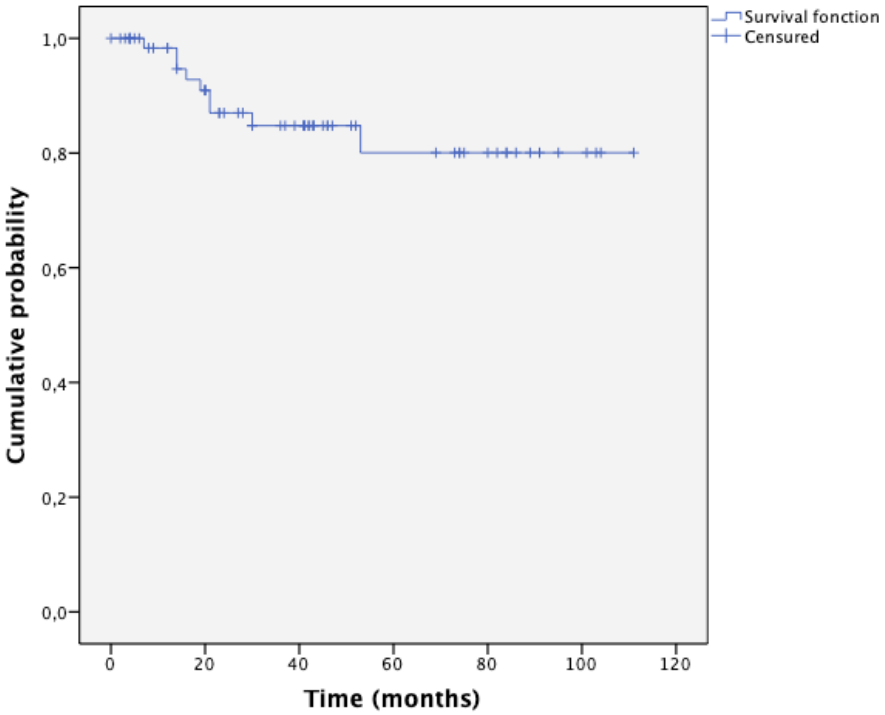

Figure 1. Kaplan-Meier curve illustrating overall survival (OS) of 68 children with nasopharyngeal carcinoma after a median follow up of 52 months

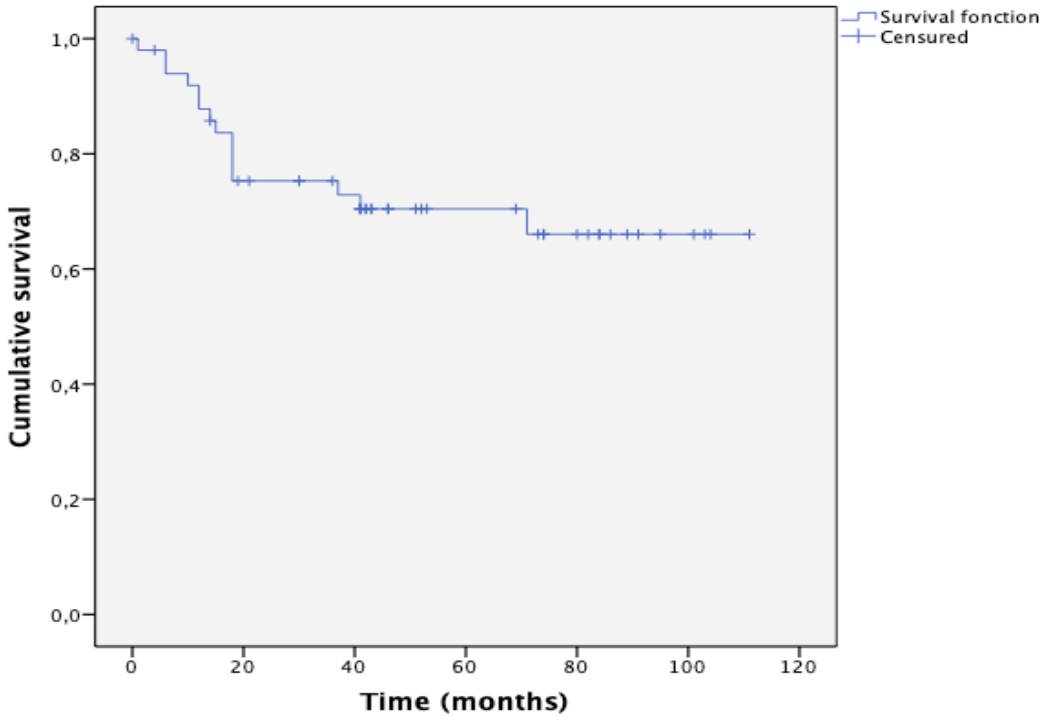

Figure 2. Kaplan-Meier curve illustrating metastasis-free survival (MFS) of 68 children with nasopharyngeal carcinoma after a median follow up of 52 months.

JMSR
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For the univariate analysis, the statistically significant prognostic variables were age < 10 years, the interval time between symptom onset and consultation > 6 month, and T3-T4 stage. N stage was not a prognostic factor in this study. Gender and treatment protocols demonstrated no significant influence on survival.

For the multivariate analysis, only higher interval time between symptom onset and consultation (> 6 months), and T stage (T3-T4) were significant prognostic factors for survival with p values of 0.04 and 0.03 respectively. LRC and DMFS were obtained in 94.1% and 76.5% respectively.

Identifiable recurrence occurred in 15 (29.4%) patients during the follow-up period. The median time interval from the end of the treatment to the diagnosis of first recurrence was 15 months (range 10–18 months), with 97% of the recurrences occurring in two first years. A total of 3 patients (5.9%) had locoregional recurrence, and 12 cases (23.5%) had distant metastases. The organs affected by distant metastasis were bone (80%) and liver (50%).

Most common late complications were grades 2-3 xerostomia in 42 patients (85.7%), 36 patients (75%) experienced hearing loss, neck fibrosis was observed in 36 cases (55.4%), trismus in 27 cases (58.7%), dental caries in 12 cases (29.3%), and one patient experienced growth retardation.

DISCUSSION

Nasopharyngeal carcinoma is neoplasm arising from epithelial cells of the nasopharynx. It is a rare malignancy worldwide, but it is endemic in a few areas including Southern China, Southeast Asia and North Africa. The age distribution of NPC is bimodal, with one peak arising in young adolescents and another one in patients between 55 and 59 years of age (4). However, NPC is exceedingly rare in children. An estimated 5% of primary malignant tumors in children originate in the area of the head and neck (12), while nasopharyngeal carcinoma constitutes about 2% of head and neck malignant tumors in children (13). The etiology of NPC is multifactorial caused by an interaction of the oncogenic gamma-herpes virus EBV, environmental, and genetic factors, in a multistep carcinogenic process (14). A monoclonal EBV infection is found in more than 98% of pre-invasive lesions (15).

Young patients with NPC frequently present with symptoms resulting from mass effect. Nasal symptoms, such as epistaxis and nasal obstruction are almost always present. Secondly, auditory symptoms such as hearing loss and tinnitus occur, which are related to dysfunction of the Eustachian tube caused by latero-posterior extension of the tumor into the paranasopharyngeal space. Thirdly, cranial nerve palsies are present, commonly affecting the fifth and sixth cranial nerves and resulting from upward extension of the tumor leading to skull base erosion; patients also might experience headache, diplopia, facial pain and numbness (16). Since nasal and auditory symptoms are non-specific, majority of NPC in children are diagnosed in locally advanced stages, with lymph node metastases occurring in up to 90% of patients (given the rich lymphatic drainage of the nasopharynx), and about 5-11% of children, distant metastases are detected at diagnosis involving bones (67%), liver (30%), lungs (20%), bone marrow (23%) (2; 17)

Since there is a strong association between the histology of undifferentiated carcinoma, Epstein-Barr virus infection (18), and the high rate of advanced disease status, nasopharyngeal carcinoma in children is distinguishable from the adult form by its close association with Epstein-Barr virus (EBV) infection, a higher rate of undifferentiated histology, and a greater incidence of advanced locoregional disease (19). Despite an elevated incidence of advanced loco-regional disease in children and young adults compared with older adults with nasopharyngeal carcinoma, the overall survival rates are not significantly different between these population groups. Several studies have found that children and adolescent NPC patients have superior results compared with adult NPC patients, with 5-year overall survival (OS) rate 71% in young vs 58% in adults, (p = 0.03) (20).

Standard therapy for NPC in children has generally followed the guidelines established for adults. Since undifferentiated NPC is a very radiosensitive cancer, radiotherapy is the mainstay treatment modality for non-metastatic disease and high dose radiation to the nasopharynx and involved cervical nodal regions is the mainstay of treatment of loco-regional NPC. Currently, IMRT is the most widely used technique. It has reduced the 5-year occurrence rates of loco-regional failure for newly diagnosed and non-metastatic nasopharyngeal carcinoma to 7.4% (21). However, this treatment appears to control the primary tumor, but shows no benefit for preventing the appearance of distant metastasis. The prognosis of children with advanced NPC (Stages III and IV) treated with radiation therapy alone is poor, with a 5-year survival rate between 20 and 40% (2). No standard total radiation dose applied to the tumor has been established. High dose radiotherapy-related morbidities in children are also a great concern among long-term survivors, including xerostomia, hearing loss, neck fibrosis, hypothyroidism, osteoradionecrosis of the skull base, temporal lobe necrosis, delayed bulbar palsy, hypopituitarism, dental problems, secondary cancers in the radiation

field has also been described (22). In our series, although some patients developed xerostomia, skin fibrosis, trismus, hearing loss, dental caries, and growth retardation, no osteoradionecrosis or development of new malignancy was reported.

The poor OS and high incidence of systemic failure in patients with locally advanced NPC have led to the investigation of early combined therapy (neoadjuvant, concurrent, or adjuvant chemotherapy) to improve survival in childhood NPC.

Compared with adjuvant sequencing, induction chemotherapy is better tolerated and eradicates micrometastases earlier; therefore, induction chemotherapy followed by concurrent chemoradiotherapy may represent a promising treatment strategy for nasopharyngeal carcinoma in the IMRT era (23; 24).

Single-agent studies have shown that adriamycin, epirubicin, cisplatin, and bleomycin are the most active agents for treatment of NPC (25). Unfortunately, due to the small sample sizes of childhood nasopharyngeal carcinoma, standardized chemotherapy combinations or treatment schedules are not yet available. Platinum-based chemotherapy has gained popularity, including BEP (Bleomycin, Epirubicin, Cisplatin), PF (Cisplatin, Fluorouracil), MPF (Methotrexate, Cisplatin, Fluorouracil), and PMB (Cisplatin, Methotrexate, Bleomycin). According to data from different studies, the survival rate was around 40 to 90% when a combination of different chemotherapy regimens and radiotherapy are utilized (26; 27; 28). Although cure rates in childhood NPC have improved with recent advances in radiotherapy, around 20 to 50% of patients still suffer from recurrent or metastatic disease. These issues highlight the importance of close follow-up. After the end of treatment patients should be followed-up at regular intervals and observed for recurrences and late complications of therapy. MRI and EBV-serology/DNA are the main diagnostic modalities for the detection of relapse. MRI is superior to CT for diagnosing local residual/recurrent nasopharyngeal carcinoma (29). Twelve weeks after the completion of radiotherapy is considered the appropriate timepoint for initial assessment of residual disease, treatment induced inflammation would have largely resolved and most tumours would have regressed (29; 30).

The therapeutic outcomes of this study and a review of the literature show that the prognosis for children and adolescents with NPC can be improved with a combination therapy protocol. Local radiotherapy combined with multiagent chemotherapy is effective in achieving satisfactory OS and DFS in children and adolescent with NPC. However, distant metastasis remained the major pattern of failure in the present series occurring over a short period after treatment.

The main limitation of our study is a retrospective design, including the inability to collect accurate patient information in the medical record and avoid missing data; some patients were also lost of follow-up after the treatment.

CONCLUSION

Most childhood and adolescence NPC patients had local advanced diseases at first diagnosed.

The therapeutic outcomes of radiotherapy combined with chemotherapy in this study were excellent. Reducing distant metastasis with new therapeutics and late toxicities with intensity-modulated radiotherapy will be the future directions for the treatment of children and adolescent NPC.

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None.

CONFLICT OF INTEREST:

The authors declare no conflict of interest in this study.

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