

# Clinical and Therapeutic Profile of Undifferentiated Nasopharyngeal Carcinoma in Children and Young Adults: A Retrospective Study

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# Abstract

**Objective:** The aim of our work was to analyze the epidemiological, clinical and therapeutic aspects of nasopharyngeal cancer in children and young adults under 20 years of age.

Patients and Methods: This was a retrospective study of 20 patients diagnosed with undifferentiated nasopharyngeal carcinoma between June 2012 and October 2016 and treated at the radiotherapy department of Hassan II University Hospital in Fez, Morocco.

**Results:** The average age of patients was 13.5 years. The most affected age group was 10 to 15 (14 patients). The male/female ratio was 1, 8:1. The diagnosis is often late with presenting symptomatology dominated by cervical lymphadenopathy in 95% of cases. Fifteen patients were classified T3-T4 and 14 patients were N2-N3 with one bone metastasis. All patients received neoadjuvant chemotherapy followed by concomitant radiochemotherapy. Three patients were lost to follow-up. The acute toxicity was radiation induced mucositis (100%), radiodermatitis (60%), xerostomia (55%), hearing impairement (44%) and trismus (33%). There was good locoregional control in 55%, loco-regional recurrence in 10%, and distant metastases in 15%. The overall survival was 85% and relapse-free survival was 50%. Conclusion: Improving the prognosis of this cancer requires early diagnosis and more accessible and developed medical infrastructures. Recent advances in intensity modulated radiation therapy should be the main treatment technique for all our patients.

**Keywords:** Nasopharynx; Children; Radiotherapy; Chemotherapy; Prognosis

# Introduction

Childhood nasopharyngeal cancer in young adults are common in countries around the Mediterranean where it accounts for 5% to 10% of all pediatric tumors and 18% of nasopharyngeal carcinomas [1,2]. The current management guidelines are similar to those of adults without specific recommendations to this age group. Radiation therapy remains the main treatment modality with concomitant chemotherapy. The squeal of treatment in children and young adults remain the main challenge [3]. Although the stages of the disease are usually advanced in children and young adults, the prognosis remains better compared to adults [4,5]. In this study, we will highlight the clinical and therapeutic aspects of this cancer in 20 children and young adults.

# **Patients and Methods**

This was a retrospective study of 20 patients aged <20 years who had histologically proven nasopharyngeal carcinoma either by nasopharynx biopsy or cervical lymph node biopsy. The study was carried out from June 2012 to October 2016 at the radiotherapy department of Hassan II University Hospital in Fez, Morocco. The patients had a clinical examination, a biopsy of the nasopharyngeal mass or cervical lymphadenopathy, as well as intr-oral assessment. The loco-regional extension assessment was made with CT-scan (15 patients) and/or cervicofacial MRI (5 patients). The distance

J Nucl Med Radiat Ther, an open access journal ISSN: 2155-9619 assessment was done with chest X-ray, abdominal ultrasound and thoracoabdominopelvic CT scan. All patients underwent bone scintigraphy. At the end of this assessment, the patients were classified according to the AJCC 7<sup>th</sup> Edition.

#### **Treatment sequence**

The patients had external beam radiotherapy. The protocol includes induction chemotherapy followed by concomitant radio chemotherapy.

#### Radiotherapy

Radiotherapy was delivered using 3D conformal radiotherapy (3DCRT) technique in 15 patients. The prescribed dose was 70 Gy on tumor and positive lymph nodes and 50 Gy in low risk areas. The Photon beams were 6 MeV and the electron beams were 6,9 or 12 MeV.

After contouring the target volumes (Gross tumor volume (GTV), Clinical target volume (CTV), Planning target volume (PTV)) and organs at risk. A first course of radiotherapy was delivered to the primary tumor areas as well as the microscopic extensions (depending on imaging) and uninvolved nodes up to a dose of 40 Gy. A boost on the nasopharynx up to a total of 7 Gy was delivered. The neck was treated using electron beams up to a dose of 50 Gy or 70 Gy depending the extent of nodal involvement. In No patients, a five-beam technique was used to allow us to give 50 Gy to the neck and nasopharynx without electron beam (Figure 1). Citation: Erraisse MA, Mazghi AE, Bouhafa T, Hassouni K, Youssoufi MA (2018) Clinical and Therapeutic Profile of Undifferentiated Nasopharyngeal Carcinoma in Children and Young Adults: A Retrospective Study. J Nucl Med Radiat Ther 9: 377. doi: 10.4172/2155-9619.1000377



**Figure 1:** (a): Dosimetry example in 3DCRT showing the isodose line of 70 Gy. Parotids (in yellow) are not spared. (b): Dosimetry in IMRT showing the better conformity to the volume with sparing of parotids and brainstem. (c): 5 field's technique isodose of 50 Gy with respect of the spinal cord.

Intensity modulated radiation therapy (IMRT) technique was used in 5 patients. The prescription was made according to the principle of the simultaneous integrated boost (SiB) therapy: A gross tumor volume (tumor+lymphadenopathy) received 70 Gy at 2 Gy per fraction, then the volume at high risk of invasion received 63 Gy at 1.8 Gy per fraction while the low risk volume received a dose of 56 Gy to 1.6 Gy per fraction. In all cases, the contouring was done with respect to pre-chemotherapy tumor volume.

#### Chemotherapy

Induction chemotherapy consisted of Doxorubicin-Cisplatin in 4 patients over 16 years old and Bleomycin-Epirubicin-Cisplatin in the rest. Chemotherapy was administered every 21 days for a total of 3 cycles. The concomitant chemotherapy was made of weekly cisplatin at a dose of 30 mg/m<sup>2</sup>.

# **Treatment monitoring**

Complete remission is defined as total disappearance of any known lesion. Partial remission is defined as decrease of more than 50%.

Patients were seen weekly during chemo radiotherapy. After the end of treatment, they are seen every three months for two years, then every six months until the fifth year and then annually.

# Results

The average annual frequency was 4 new cases per year. The mean age at diagnosis was 13.5 years (from 10 years to 18 years). The peak frequency was between 10 and 15 years old. There were 13 boys (65%) and 7 girls (35%) giving M/F sex ratio of 1.8:1. Lymphadenopathy was present in 19 cases (95%), an otological syndrome in 15 patients (75%), and a rhinological and neurological syndrome in 14 patients (70%). The average time to consultation was 7 months. The diagnosis was confirmed by a nasopharynx biopsy in 15 patients (75%), and a lymph node biopsy in 5 patients (25%). The tumor was classified as T3 and T4

in 30% and 45% of patients respectively. The lymph node involvement was classified as N2 and N3 in 55% and 15% of patients respectively. For the distant extension assessment, we found a patient with a bone metastasis on bone scan. EBV (Epstein Barr Virus) serology was performed in one patient and was positive (Table 1).

Patients Characteristics	Number (%)		
Sex			
Male	13 (65)		
Female	7 (35)		
Age			
≥ 16	4 (20)		
<16	16 (80)		
Symptoms			
Lymphadenopathy	19 (95)		
Nasal obstruction	6 (30)		
Nasal bleeding	10 (50)		
Headache	13 (65)		
Trismus	3 (15)		
Pathology			
UCNT	20 (100)		
Induction Chemotherapy	20 (100)		
T3/T4	15 (75)		
N2/N3	14 (70)		

3DCRT	15 (75)
IMRT	5 (25)

Table 1: Patients characteristics.

### Response to induction chemotherapy

Ten (50%) patients were in complete remission, five (25%) patients in partial remission, and no patients were progressing. However, 5 patients have not had a post-chemotherapy evaluation (25%).

The toxicity secondary to chemotherapy was mainly haematological alone (10%), gastrointestinal alone (10%) and association of more than two toxicity in 15% of cases (haematological or gastrointestinal or renal).

#### Response to radiotherapy

Complete remission was described in 12 patients (60%), partial remission in three patients (15%) and two patients had loco-regional failure (at one year and two years). Distant metastasis occured in three patients (15%).

In this study overall survival was 85% with 15% of deaths (3 patients). The causes of death included hemorrhagic shock secondary to pancytopenia, pulmonary embolism and unexplained cardiorespiratory arrest.

Disease free survival at 3 years was 50%.

# Toxicity

The acute and late toxicities for both 3DCRT and IMRT are summarized in Table 2.

	3DCRT	IMRT	
	Number (%)	Number (%)	
Acute Toxicity			
Mucosa	15 (100)	5 (100)	
Skin	9 (60)	3 (60)	
Late Toxicity			
Fibrosis	8 (53,3)	3 (60)	
Xerostomia	11 (73,3)	2 (40)	
Hearing impairement	6 (40)	1 (20)	

 Table 2: Acute and late toxicity after chermoradiotherapy.

# Discussion

The incidence of nasopharyngeal cancer varies by region [6]. In endemic countries, the peak age is around the 5<sup>th</sup> and 6<sup>th</sup> decade, while in the Mediterranean basin, there is a second peak of age between 10 and 20 years with an incidence between 2%-18% [1].

The locally advanced stages are characteristic presentation of this form of cancer with a rate that varies between 30% and 92% according to the different pediatric series [7]. In our series, there was 75% of T3-T4. This is probably due to the nonspecificity of the symptoms such as

nasal obstruction, epistaxis, hearing losses which are also present in benign conditions. The lack of access to care and diagnostic means in developing countries such as Morocco is also contributory.

Undifferentiated carcinoma of the nasopharynx is radiosensitive. Radiotherapy alone in children with advanced stage has a 5-year survival rate of 20% to 40% [8] The low survival and frequency of metastatic relapses in these stages led to the combination with chemotherapy according to different protocols (induction, concomitant, adjuvant) but still without standardized scheme given the small series of children [9].

The choice between concomitant or sequential radio chemotherapy has not yet been standardized due to the lack of randomized clinical trials [10]. In our series, patients received induction chemotherapy followed by concomitant chemo radiotherapy. This is due to the significant improvement of survival by this modality in randomized clinical trials in adults but also in a prospective Italian study in children [11-13].

Venkitaraman and colleagues in 2007, found that the radio chemotherapy combination was associated with a better three-year disease-free survival rate compared to exclusive radiotherapy (82% vs. 40%, p=0.001) [14]. Primary tumor volume is highly significant in evaluating local control, distant metastasis and overall survival [15]. In retrospective series, the radiotherapy dose greater than 66 Gy gave had a better disease free survival [16,17]. In our series all our patients had 70 Gy as a curative dose.

# Conclusion

Most children and adolescents have locally advanced nasopharyngeal carcinoma. The radio chemotherapy has given good results. Reducing distant metastasis and late toxicity using new protocols and IMRT are future directions in the management of these cancers. Adaptive radiotherapy needs to be evaluated to minimize sequelae. Radiotherapy and chemotherapy protocols should be standardized through randomized, multicenter studies.

# Limitations

Our serie is relatively small because of disease rarity in children even if Morocco is an intermediate endemic country like other northafrican ones. It was about 4 patients every year. The doses are 70 Gy with concomittant cisplatin for all patients unless the dose constraints to OAR such as brainstem couldn't be respected. This protocol was also reported in other series. Our doses are high because of the locally advance stages of our patients.

#### Patient evaluation

Actually, there was CR after chemotherapy in 10 patients and CR after radiotherapy in 12 patients. There was PR after chemotherapy in 5 patients and PR in three patients after radiotherapy (two of the initial 5 completed CR).

# According to WHO

Complete remission is defined as total disappearence of any known lesion. Partial remission is defined as decrease of more than 50%. Concerning the induction chemotherapy toxicity, unfortunately we only have data on whether it's hematological, gastrointestinal or renal. Citation: Erraisse MA, Mazghi AE, Bouhafa T, Hassouni K, Youssoufi MA (2018) Clinical and Therapeutic Profile of Undifferentiated Nasopharyngeal Carcinoma in Children and Young Adults: A Retrospective Study. J Nucl Med Radiat Ther 9: 377. doi: 10.4172/2155-9619.1000377

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We don't have details because we assume that most of hematological are for example neutropenia.

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