

## Therapeutic Aspects of Undifferentiated Nasopharyngeal Cancer in Young Adults (Under 40 Years Old)

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DOI: [10.36347/sasjm.2023.v09i06.018](https://doi.org/10.36347/sasjm.2023.v09i06.018)

| Received: 02.05.2023 | Accepted: 07.06.2023 | Published: 10.06.2023

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### Abstract

### Original Research Article

Nasopharyngeal carcinoma (UCNT) is a distinct form of head and neck cancer, endemic in the North African zone, with its high metastatic potential and its relationship with the Epstein-Barr virus. The aim of our study was to assess the clinical and therapeutic aspects of this carcinoma in young adults under 40 years of age. We carried out a retrospective study in the Department of Radiation Oncology between December 2006 and December 2019 with a follow-up of at least 24 months, treatments were based on inducing chemotherapy followed by chemo-radiation depending on the clinical stage (TNM). Of all UCNT patients treated, 75 were Aged under 40 (34.56%), and the median age was 24 years. The diagnosis is often late revealing symptomatology dominated by cervical lymph nodes, and stage IV disease was dominant. Treatment was based on neoadjuvant chemotherapy followed by concomitant radio-chemotherapy in all our patients, Evolution was favorable in 52% of our patients, 13% had a locoregional recurrence, and 16% had distant metastases. Bad prognosis of UCNT is often related to locally advanced stages (stage III and IV) and metastatic recurrence. Therefore, assessing early diagnosis improves its outcome in the young population. Recent radiation technics such as IMRT and VMAT reduce treatment-related toxicity and lead to a better quality of life.

**Keywords:** UCNT, Young adults, North African country, Radiation therapy, Chemotherapy.

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## INTRODUCTION

With a standardized incidence of 1.3 per 100,000 inhabitants, Moroccan adults under 40 years old are at intermediate risk for nasopharyngeal carcinoma, and considered as the first peak of carcinoma incidence especially between the ages of 15 and 20 years.

Eighteen to 30% of nasopharyngeal carcinomas occur before the age of 40 in Morocco, and the most common histological type is undifferentiated carcinoma of nasopharyngeal type (UCNT), accounting for 90% of cases [1].

Due to the deep location of the nasopharynx making surgery a big challenge, radio-chemotherapy remains a standard of treatments in the majority of cases, with a satisfying local control of the disease. Sadly, loco-regional and metastatic relapses are still

frequent, leading to a significant morbidity and mortality, despite remedial treatments proposed [2].

## METHODS

This retrospective study was conducted on a series of 75 patients under the age of 40 years treated for UCNT in the radiation oncology department of Mohamed VI hospital in Marrakesh, Morocco, over a 12-year period between December 2007 and December 2019.

The initial evaluation included a clinical examination and systematic endoscopy with biopsy. Facial MRI was performed in all the patients. Chest X-ray and abdominal ultrasound were performed mainly for extension workup. And the 8<sup>th</sup> edition of TNM (2017) classification was applied for tumor staging.

**Citation:** Zinah Idrissi Kaitouni, Youssouf Mohamed Ammor, Layla Benyouness, Mouna Darfaoui, Issam Lalya, Abdelhamid Elomrani, Mouna Khouchani. Therapeutic Aspects of Undifferentiated Nasopharyngeal Cancer in Young Adults (Under 40 Years Old). SAS J Med, 2023 Jun 9(6): 650-654.

## Treatment of non-metastatic patients

### Neo-adjuvant chemotherapy

Neoadjuvant chemotherapy is performed if evidence of lymph node involvement. The most widely used protocol combines Doxorubicin and Cisplatin (AC), or Epirubicin and cisplatin (BEC) protocol.

### Radiotherapy

Loco regional treatment was provided by external beam radiotherapy, delivered by a linear accelerator of 4 to 6 Mev. The patients received 3D conformational radiotherapy by four opposite lateral fields, and a front field for lymph nodes radiation. The prescribed dose was 70 Gy on the tumor and 50 Gy on the lymph node, at a rate of 2 Gy per session up to 5 sessions per week. Lymph nodes prescribed dose varied between 45 and 65 Gy.

### Treatment of de novo metastatic cancer

The therapeutic protocol consisted of a BEC type chemotherapy combining bleomycin, Epirubicin and Cisplatin. The cycles were repeated every 28 days. An assessment was made after three to six cycles. In the event of a good response, radiotherapy to the cavum and cervical lymph node areas was administered using the same procedures as those described for patients with non-metastatic cancer. In case of solitary bone metastasis, radiotherapy of the metastatic site has been indicated according to a hypo-fractionated scheme (30 Gy in ten sessions) at the same time as locoregional irradiation.

### Relapse and failure treatment:

Patients with locoregional or distant relapse received salvage chemotherapy (cisplatin, bleomycin, 5-fluoro-uracil) followed by either re-irradiation in the event of a locoregional relapse, or radiotherapy of the metastatic site in case of bone metastasis.

### Response evaluation and follow up:

The at the end of neoadjuvant chemotherapy, a clinical evaluation associated or not with a CT examination was performed. Three months after the end of radiotherapy, the patients underwent an evaluation by an examination of the cavum and neck with biopsy in case of suspicious lesion as well as imaging of the cavum by CT scan and / or MRI. The patients were subsequently followed all three months during the first two years, every six months up to five years, then annually. An examination of the cavum with a biopsy in case of suspicious lesion as well as imaging of the cavum and neck (CT or MRI) were indicated at an annual rate. A thyroid biological assessment was requested at each consultation. When an endocrine disorder occurs, patients have been referred to an endocrinology consultation for a supplement support.

### Treatment Toxicity

Acute toxicity has been assessed according to the WHO scale. Late toxicity was reported according to

the Radiation Therapy Oncology Group (RTOG) and subjective-objective- management-analytic-late effects of normal tissues (SOMA LENT) scales and was evaluated in patients with non-metastatic cancer during of the initial diagnosis, regularly monitored and not relapsing during the year following the end of treatment.

### Statistical analysis

Survival curves were calculated using the Kaplan - Meier and compared using the Log-rank test. Chi2 test was used for comparison of different prognostic factors. Statistical analysis was performed using SPSS 11 software. Overall survival was calculated from the date of diagnosis to the latest news or death. Disease-free survival was calculated from the date of full remission until the onset of local or distant relapse, secondary tumor or the date of the last news.

## RESULTS

### Patients Characteristics

Patients under 40 treated for UCNT represented 34.56% of all patients treated for nasopharyngeal carcinoma during the same period. The mean age was 24.87 years (9–40 years). The sex ratio was 1.14. Histologically, 80% of the tumors were undifferentiated (grade 3 according to WHO) and 10.66% poorly differentiated (grade 2). 77.4% of the patients had locally advanced tumors (T3-T4). In 69 patients, the lymph nodes were initially involved, stage N2 or N3 in 57% of cases (Table 1). Two cancers had already lung metastasis.

**Table 1: Patients characteristics**

		N (%)
Sex	Male	40 (53%)
	Female	35 (47%)
Age	Median	24 years
Patient complain	Neck nodes	66 (80%)
	Blocked nose	30 (40%)
	Headache	30 (40%)
	Hearing loss	27 (36%)
Histological type	UCNT	75
T Classification	T1	4 (5%)
	T2	13 (17%)
	T3	20 (27%)
	T4	38 (51%)
N Classification	N0	6 (8%)
	N1	12 (16%)
	N2	39 (52%)
	N3	18 (24%)
M Classification	M0	73 (97%)
	M1	2 (3%)

**Treatment outcomes:** 59 patients underwent Neo-adjuvant chemotherapy, and all patients underwent concomitant chemo-radiotherapy (except 3 patients lost to follow-up before starting radiotherapy and 2 with de novo metastatic cancer). Oncological response was

assessed 6 months after radiotherapy by a cavum CT. Complete pathological response could not be proved as some patients presented thickening of the nasopharyngeal wall, and couldn't be determined whether this was a partial response or fibrosis. The outcome showed - except 13 patients lost to follow up and one death – a complete response rate of 56.10%,

and a partial response rate of 21.90%, and a failure rate of 4.29%.

**Follow up:** After a 23-month follow-up, 39 patients remained in complete remission, locoregional recurrence occurred in 10 patients (after a mean delay of 20.9 months) (Table 2).

**Table 2: Patients characteristics in relapse or progressive disease**

Relapse site	Time to relapse (Months)	Age	Sex	Histological type	Relapse treatment
Nasopharynx	2	32	M	UCNT	Chemotherapy
Nasopharynx	8	26	F	UCNT	Chemotherapy
Nasopharynx	4	21	M	UCNT	Chemotherapy
Nasopharynx	6	40	F	UCNT	Chemotherapy
Right cervical node	18	18	M	UCNT	Chemotherapy
Left cervical node	30	38	F	Undifferentiated Carcinoma	Chemotherapy
Left cervical node	34	31	F	Undifferentiated Carcinoma	Chemotherapy
Left cervical node	60	29	F	Undifferentiated Carcinoma	Chemotherapy
Bilateral cervical nodes and Nasopharynx	46	9	M	UCNT	Chemotherapy
Nasopharynx	1	40	M	UCNT	Chemotherapy

12 patients had secondary metastases, the locations involved liver in 4 patients, bone in 7 patients, and brain in one patient. The average delay was 20 months (6 months-36 months). All the patients received palliative chemotherapy, and 4 of them received palliative bone and whole brain radiation therapy.

#### Treatment toxicity

Complications related to chemotherapy were dominated by digestive complications that were present in all patients. The other complications were less frequent: 8% pulmonary toxicity, 8% alopecia, hematological toxicity in 3 patients and renal failure in one patient.

The acute toxicity of radiotherapy was represented mainly by mucositis in 41 patients, and radiation dermatitis in 27 patients. The late sequelae were dominated by xerostomia in 35 patients, trismus in 4 patients, and 8 patients experienced hearing loss.

## DISCUSSION

Management of young adults with nasopharyngeal carcinoma must be based on the most appropriate treatment option that has been most extensively validated by clinical trials. It remains frequent in the adult population around the Mediterranean rim, with rates between 10 and 18% of all patient presenting UCNT [2].

24% of patients were smokers, approximately same as published in the literature for adult populations. This finding tends to suggest a correlation between smoking and nasopharyngeal carcinoma in our series. This correlation was demonstrated in a Chinese adult population with an adjusted odds ratio (OR) of 1.67,

with a correlation between the duration of smoking (years), intensity of exposure (pack-years) and the development of nasopharyngeal carcinoma with P-values of 0.001 and 0.018 respectively [3].

Treating this young population is still challenging due to the late diagnosis and lymph nodes that are frequently involved as described in the latest series. Indeed 66% of our sample had stage IV disease, and 27% had stage III. This is mainly explained by inadequacy of health infrastructure, low socioeconomic level and ignorance of this malignant disease. Metastatic cervical lymphadenopathy is often mistaken for tuberculosis, especially in young people.

Radiotherapy is mandatory due to high sensitivity of nasopharyngeal carcinomas, particularly UCNT, leading to a satisfying outcome [4]. Concomitant chemotherapy in case of extensive lymph node involvement (N2-N3) or, with a large tumor volume Allows to strengthen locoregional control. 59 patients with non-metastatic cancer (85%) received cisplatin based chemotherapy, followed by CT-RT. This strategy was based on neoadjuvant chemotherapy results observed in adults showing a significant improvement in disease-free survival [5]. Lymph node response rate was 88% with a complete response in 21% of cases, this rate varies from 10 to 86% in the literature [6].

Concomitant chemo-radiotherapy in adult UCNT was first assessed in the American trial of Intergroup 0099 showing a significant improvement in disease-free survival and overall survival compared to radiotherapy alone [1]. These results were confirmed by another Asian study which demonstrated the superiority of concomitant chemo-radiotherapy over radiotherapy

alone. Making it the standard of treatment for locally advanced UCNT in young adults [7].

If most centers consider that concomitant chemo-radiotherapy constitutes the standard treatment for advanced tumors, the value of primary chemotherapy followed by CT-RT is still in debate, in particular the adjunction of taxanes. This molecule has already proven its effectiveness in oral and pharyngeal tumors [8]. As of UCNT, they are still studied in several randomized trials for both adult and childhood.

All patients who underwent radiotherapy received a dose greater than or equal to 70 Gy, which may explain the low rate of local recurrence (only one case). The optimal dose of radiotherapy in childhood UCNT remains to be determined, particularly after neoadjuvant chemotherapy. Analyses of the old series have shown that doses below 50 Gy were associated with high rates of local relapse. In most recent series, the doses ranged from 50 to 70 Gy [6]. In a retrospective multicenter analysis of 165 patients under 18 years of age, irradiation at doses greater than or equal to 66 Gy resulted in a better five-year locoregional recurrence-free survival rate (90% vs. 73%;  $p = 0.01$ ) [9].

Acute toxicities are generally transient and are dominated by mucositis and radiation dermatitis [6]. Late toxicity often leads to management problems. The most frequent toxicity is xerostomia (Nearly all our patients experienced it), Rates goes from 48 to 100% in the literature [6]. Endocrine disorders are the most severe late toxicities, one third of our patients Hypothyroidism, however it was subclinical in 69.2% of cases. Daoud *et al.* found in a prospective study involving 47 patients with UCNT, a hypothyroidism rate of 29%, half of which was subclinical. Neurological toxicity is rare (only 5 in our sample) and often correlated with the dose and hyper fractionating of radiotherapy and the young age of patients [10] Two of our patients had secondary cancers which occurred five and ten years after radiotherapy. Secondary tumors can be observed after a delay of up to 25 years and are dominated mainly by sarcomas [11].

Innovative radiotherapy techniques, including velocity and intensity-modulated irradiation (VMAT, IMRT), are promising and could reduce treatment toxicity. In adult UCNT, IMRT has been shown to significantly reduce xerostomia [12]. In children, it has been validated in the treatment of several tumor sites such as SNC.

Due to the particular biological profile of juvenile UCNT, some authors have proposed immunotherapy. In a prospective multicenter study including 59 patients aged less than or equal to 25 years, adjuvant immunotherapy with interferon beta

was administered for a period of ten months after neoadjuvant chemotherapy and radiotherapy. With a mean follow-up of 48 months, overall survival and disease-free survival were 95 and 91%, respectively. Otherwise, the combination of radiotherapy with targeted therapies, in particular Cetuximab in the treatment of head and neck cancers has proven its effectiveness [13]; this therapeutic route, which seems to be promising, has not yet been validated in nasopharyngeal cancers.

## CONCLUSION

In our country, UCNT in the young population is a relatively common tumor. Its treatment is based on the combination of chemotherapy and radiotherapy, mainly in advanced stages. However, metastatic relapses represent a frequent and early mode of failure.

Even if the optimal irradiation dose remains a subject of controversy, high doses are associated with excellent local control rates with, however, an increase in late toxicity which may affect the quality of life of young patients. For that purpose, innovative radiotherapy techniques seem promising and could resolve toxicity issues.

**Acknowledgment:** Statistic department of Hematological and oncological center, University Teaching Hospital Mohamed VI, Marrakesh, Morocco.

**Conflict of interest:** The authors declare no conflict of interest.

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