

# A Moroccan Study on the Epidemiology and Outcomes of Nasopharyngeal Carcinoma

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## ABSTRACT

**Background:** Nasopharyngeal carcinoma is a rare malignancy but with high incidence in some regions including the Mediterranean basin. Radiotherapy is the mainstay of treatment, with chemotherapy used in advanced cases. The aim of the study is to describe the epidemiological, clinical and therapeutical features of this disease in Moroccan population.

**Methods:** It is a retrospective study of 141 patients with nasopharyngeal carcinoma treated at Hassan II University Hospital, Morocco from January 2010 to December 2016. Collection of data was obtained through computerized records of patients. Statistical analysis was performed by SPSS software version 23 and the overall survival (OS) was calculated from the date of starting primary therapy to death regardless of cause.

**Results:** 141 patients were reported with a mean age of 49 years old and a sex ratio of 2.4 M/F. Symptoms were cervical lymph nodes (59.57%), epistaxis or nasal obstruction (51.77%) and hearing loss (33.33%). Histological diagnosis was obtained by nasopharyngeal biopsy (89.36%) and the undifferentiated nasopharyngeal carcinoma was the main histological subtype 93.62%. After loco regional and distant imaging, we concluded to 2.13% of stage I, 19.85% of stage II, 41.85% of stage III and 36.17% of stage IV. Treatment was based on an exclusive radiotherapy for patients with small tumors (2.13%) while 61.7% of patients with locally advanced stage received radio-chemotherapy, preceded by induction chemotherapy. Disease free survival at 3 years was 80%.

Surgery was considered for 3 patients with cervical lymph node recurrence and irradiation indicated for 2 patients with local nasopharyngeal relapse. Metastatic patients received platinum-based chemotherapy as first-line therapy and taxanes, gemcitabine, and methotrexate as second-line therapy. The median overall survival was 69.6 months.

**Keywords:** Inflammation; Aging; Cytokines; Delirium; Dementia; Brain; Conditional logic; Boolean

## INTRODUCTION

Nasopharyngeal cancer (NPC) is a unique subset of head and neck cancers. It is a rare malignancy with an annual incidence of 0.7% and a mortality rate of 0.8% according to last global statistics (GLOBOCAN 2018) [1]. However, it is an endemic disease in some regions such as Southern China, Southeast Asia

and North Africa [1]. Morocco is an endemic region of NPC with an incidence of 3.7 cases/100000 according to the cancer registry of Casablanca [2].

In the endemic areas, the histology is dominated by the undifferentiated carcinoma subtype while squamous cell carcinoma is less common but the mechanisms behind this particular geographic distribution remain unclear [1]. The causal

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agents are not yet clearly identified, but It is believed that the Epstein Barr virus (EBV) nuclear antigen may infect the epithelial lining in the nasopharynx and lead to malignant transformation [3]. Other factors were incriminated including genetic susceptibility, early exposure to chemical carcinogens especially salted fish, and preserved food. Additionally, some other environmental factors were associated with NPC such as benzopyrene, benzanthracene, polycyclic aromatic hydrocarbons and formaldehyde [1]. Regarding squamous cell carcinoma in non-endemic areas, smoking and alcohol are the most incriminated risk factors.

The diagnosis of NPC should be based on clinical examination, the Magnetic Resonance Imaging (MRI) or CT scan of the nasopharynx in addition to bone scan and CT of the chest and abdomen for distant extent in locally advanced disease [4]. The confirmation of the diagnosis is obtained by naso-endoscopy with nasopharyngeal biopsy [4]. Therapeutically, management strategy depends mainly on the stage of the disease. Radiotherapy is the mainstay of radical treatment for localized disease because of the radio-sensitivity of these tumors, with better control by using intensity modulated radiotherapy (IMRT) and concomitant cisplatin-based chemotherapy for locally advanced disease. Palliative chemotherapy remains the basis of treatment for metastatic stage [4].

With this work we report the experience of a Moroccan unit at Hassan II University Hospital, in Fes, Morocco. the aim of this work is to describe epidemiological, clinical, paraclinical, therapeutic and prognostic aspects of this disease in Moroccan patients and discuss our results in comparison with literature.

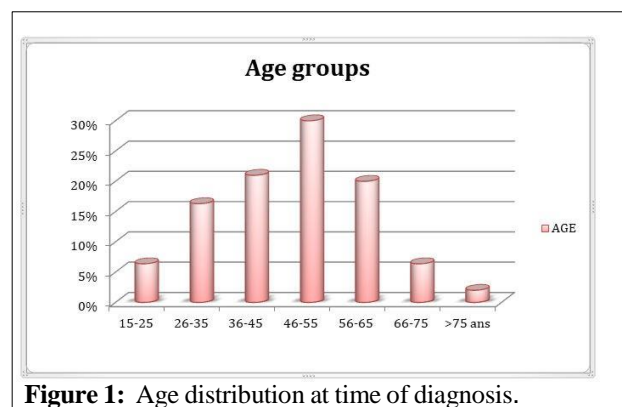
## MATERIAL AND METHODS

It is a retrospective study including patients with nasopharyngeal carcinoma treated in the department of Medical Oncology at Hassan II University hospital in Fes, Morocco from January 2010 to December 2016. Collection of data was obtained through computerized records of patients. Only complete files were included, including Imaging data (CT scan and/or MRI of the nasopharynx in addition to the imaging for the accurate staging (thoraco-abdominal scan and bone scan).

Only histologically proven nasopharyngeal carcinoma was included Statistical analysis was performed by SPSS software version 23 and the overall survival (OS) was calculated from the date of starting primary therapy to death regardless

## RESULTS

One hundred and forty one (141) patients were reported. The mean age was 49 years old with extremes ranging from 16 to 83 years old. The most affected age group was the 46-55 years old group with a remarkable male predominance with a sex ratio (M/F) of 2.4 [Figure 1]. Smoking was present in 40.42% of patients, 6.38% had alcohol consumption, while only 3.54% had a documented EBV infection.



**Figure 1:** Age distribution at time of diagnosis.

The symptoms were dominated by cervical lymph nodes in 59.57% of cases, epistaxis or nasal obstruction in 51.77%, hearing loss in 33.33%, neurological symptoms mainly headache and symptoms related to cranial nerve palsies such as diplopia, facial numbness in 21.98% and ophthalmologic symptoms in 12.05% of patients. The diagnosis was confirmed by naso-endoscopy with nasopharyngeal biopsy in 89.36%, and by cervical lymph node biopsy in 10.64% of cases. Most common histological type was undifferentiated nasopharyngeal carcinoma in 93.62% of cases followed by squamous cell carcinoma in only 6.38% of patients.

All patients had a head and neck computed tomography (CT) to assess the loco-regional extent, and the distant extent was assessed by a chest and abdominal CT in addition to bone scan in 61% of patients. Pet-CT was not performed because of its unavailability in the city. Lymph node involvement was present in 85.8% of patients (N1: 45.39%, N2: 29.79%, N3: 10.64%). According to the 8th AJCC-TNM classification, we had stage I (2.13%), stage II (19.85%), stage III, (41.85%) and stage IV (36.17%). For metastatic patients, the metastases were located by order of frequency in bone (37.25%), lung (15.68%) and liver (11.76%) respectively.

The treatment was adapted according to the stage of the disease, and was based on exclusive radiotherapy for 2.13% of patients with early small tumor (T1N0M0), while 61.7% of patients with a locally advanced stage (T2-T3-T4 and/or N+) received radiation therapy concurrently with chemotherapy based on weekly-cisplatin (40 mg/m<sup>2</sup>), preceded by induction cisplatin-based bi-therapy in most of cases.

Tolerance of radiotherapy was dominated by salivary dysfunction with hyposalivation in 77% of cases, hearing loss in 35% of patients, radiodermatitis was noted in 17% of patients, and hypothyroidism in 5% of irradiated cases. Disease free survival at 3 years was 80%. Three patients who presented cervical lymph node recurrence without distant metastases, underwent lymph node dissection with control of the disease. The indication of re-irradiation was retained in 2 patients with local nasopharyngeal relapse.

In metastatic setting (33.1%) the treatment was palliative chemotherapy. First-line chemotherapy was based on the combination of cisplatin and doxorubicin administered in 78% of cases, cisplatin and 5FU in 17% of patients and 5% of patients received carboplatin-5FU because of unfit to

cisplatin. The second line consisted on monotherapies, including gemcitabine, taxanes and methotrexate.

The adverse effects related to chemotherapy were digestive complications especially nausea and vomiting observed in 46% of patients and hematological complications in 29% of cases. For non-metastatic stages, the disease control rate was 41% and for metastatic stages, the objective response rate after a 1st line was 51%. After a median follow-up of 80 months, the median overall survival was 69.6 months.

## DISCUSSION

Our work is a retrospective study describing the main epidemiological, clinical, paraclinical and therapeutic aspects of patients with nasopharyngeal carcinoma treated in medical oncology department at Hassan II University hospital in Fes. Morocco is still an unexplored region with considerable incidence of nasopharyngeal carcinoma and limited available data. Therefore, it should be explored more intensively.

Nasopharyngeal carcinoma is a rare cancer in western countries where the adjusted incidence is very low, while the incidence is remarkably high in endemic regions including southern parts of China, Southeast Asia, the Mediterranean basin and Alaska [1].

Our study showed that the average age of our patients was 49 years, with almost 30% of patients aged between 46 and 55 years, which is consistent with national data from the cancer registry of Casablanca (2008-2012) [2], and also with worldwide data showing that the peak of incidence varies according to incidence area. In high-risk areas (South-East Asia), the peak frequency was between 50 and 59 years, while in low-risk countries (USA), the peak is found in the age over 65 years [5].

Incidence in Africa suggests a bimodal age distribution with a first peak at age 16 and a second peak at age 40-50 years [6,7].

In our series, there was a remarkable male predominance with a sex ratio of 2.4 and which is also concordant with data from Moroccan cancer registry [2], in addition to worldwide data showing a sex-ratio (M/F) ranging between 2 and 3 [1,8].

Etiologic factors are not yet completely identified for NPC but several risk factors were incriminated including EBV infection, genetic susceptibility, early exposure to chemical carcinogens especially salted fish, and preserved food. Other environmental factors also were found to be associated with NPC such as benzopyrene, benzantracene, polycyclic aromatic hydrocarbons and formaldehyde [9]. In areas where EBV is not endemic, like the United States, smoking and alcohol are found to be risk factors [9].

Clinically, cervical lymphadenopathies are the most frequently reported. Several authors reported that at the time of diagnosis, 70% to 80% of patients had cervical lymph nodes [10,11].

Diagnosis is confirmed by the biopsy of the nasopharyngeal mass in nasopharyngoscopy and less through biopsy of neck lymph nodes. This finding is concordant with data reported by the American Society of Clinical Oncology showing that the undifferentiated type is more common in intermediate to high risk areas [12].

For accurate staging, workup should include the imaging of head and neck by CT scan. Magnetic Resonance Imaging (MRI) is useful to optimize staging especially for the evaluation of the skull base invasion in case of advanced tumors. Further exams including chest CT scan and bone scintigraphy should be performed. Positron Emission Tomography (PET)-CT is also preferred for more accurate staging to avoid misdiagnosing distant metastases before starting curative treatment [13]. Other exams are useful to complete the work-up in some cases including visual examination, and evaluation of cranial nerve function, circulating EBV-DNA in plasma and finally hemogram and ionogram [13].

The work-up in our series showed more advanced stages of nasopharyngeal cancer with 41, 85% of stage III and 36,17% of stage IV.

The goal of treatment is to ensure local control of the disease and prevent distant metastases with good management of toxicities. For metastatic disease, the aim is to control the symptoms and prolong survival with a good quality of life.

Radiotherapy remains the mainstay of radical treatment for localized and locally advanced stages using a total dose of 65 to 70 Gy with a fractionation of 1.8 to 2 Gy per day. Intensity Modulated Radiotherapy (IMRT) delivery techniques allow the improvement of dosimetric coverage of the primary tumour volume, with less toxicities and better quality of life. For stage I disease, radiation therapy alone is the standard of care. Before 1990, exclusive radiotherapy was the standard treatment for all patients with nasopharyngeal even with locally advanced stage. Then Al-Sarraf and al have shown in a phase III study that chemoradiotherapy is superior to radiotherapy alone for patients with advanced nasopharyngeal cancers with significant improvement of Event Free Survival (EFS) and Overall Survival (OS).

These findings were confirmed by a meta-analysis of 8 randomized trials and 1753 patients that demonstrated a reduction of 18% in the risk of death with an absolute survival benefit at five years of 6% in favor of adding chemotherapy to the radiation therapy especially in when given in concomitance. The role of systemic chemotherapy is to prevent and reduce the distant recurrence of NPC. Therefore, bimodal treatment by concurrent cisplatin with radiotherapy became the standard of care for locally advanced stages.

Regarding the roles of neo-adjuvant and adjuvant chemotherapy, they were explored in few trials and still controversial with no proven survival benefit. However an improvement of response rate and EFS was confirmed with neo-adjuvant chemotherapy, but data were not strong enough to make it highly recommended. Then, it remains an option to use the combination of cisplatin and fluorouracil in the neo-adjuvant setting especially in selected cases with T3-T4 and/or N+ disease.

Additional adjuvant chemotherapy is more toxic and its benefit is still unproven. Therefore, adjuvant cisplatin and 5-fluorouracil might be discussed for fit patients.

In our series, exclusive radiotherapy for 2.13% of patients with stage I tumor, while the majority (61.7%) of patients who had

locally advanced disease (stages III, IVA, IVB) received radiation therapy concurrently with chemotherapy based on cisplatin, preceded in most cases by induction cisplatin-based chemotherapy.

In case of recurrent disease confined to primary site, re-irradiation is an option to be considered. This option was considered in 2 patients of our series.

Regarding the role of surgery, it is limited in the management of NPC. It takes more place in case of residual or recurrent neck disease and consists mainly in neck dissection. Three of our patients underwent surgery for cervical lymph nodes recurrence.

For metastatic disease (stage IVC), platinum-based combination chemotherapy is recommended. Regimens can include cisplatin with 5FU or paclitaxel, or gemcitabine. Imaging should be repeated to assess the response to treatment. For second line treatment, Single centre studies have shown an activity with gemcitabine, capecitabine, and taxanes in monotherapy or in combination with platinum.

In our study, patients received platinum-based chemotherapy in first line and subsequent lines were mainly based on monotherapy by taxanes, gemcitabine, capecitabine and methotrexate. In our series, drugs received in metastatic setting were concordant with literature. Patients received in first-line combination of cisplatin and doxorubicin in 78% of cases, cisplatin and 5FU in 17% of patients and 5% of patients received carboplatin-5FU because of unfitness to cisplatin. While second line consisted on single agents with gemcitabine, taxanes and methotrexate.

Until now, There is no strong evidence to use targeted therapies or immunotherapy in NPC outside clinical trials. Immunotherapy against EBV antigens might be promising and is under investigation [13]. The median overall survival was 69.6 months after a median follow up of 80 months.

## CONCLUSION

Nasopharyngeal carcinomas represent a specific entity different from the rest of head and neck cancers. The prognosis in our series might be relatively compromised because of the frequency of locally advanced and metastatic stages.

Based on our data and literature, curative radiotherapy and cisplatin-based chemotherapy for non-metastatic stages as well as

chemotherapy for metastatic stages yielded high levels of objective response as well as long survivals. The improvement of the prognosis of this cancer in Morocco and endemic regions must go through an early diagnosis and multidisciplinary care in addition to more extensive studies.

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