


# Epidemiological Profile and Clinicopathological, Therapeutic, and Prognostic Characteristics of Nasopharyngeal Carcinoma in Northern Morocco

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## Abstract

**Background:** Nasopharyngeal carcinoma is a multifactorial disease mainly affecting the Asian and North African populations including Morocco. This study aimed to determine the epidemiological profile of nasopharyngeal carcinoma in Northern Morocco as well as its clinicopathological, therapeutic, and prognostic characteristics.

**Methods:** 129 patients with nasopharyngeal carcinoma followed at the regional center of oncology of Tangier in the period between April 2017 and July 2019, and diagnosed elsewhere from March 2000 to February 2019, were included in this study. Statistical analysis of the data was realized using Statistical Package for the Social Sciences (SPSS) software.

**Results:** Nasopharyngeal carcinoma (NPC) represented 5% of all cases with a median age of 50. The most affected age group was 40–54 years (41.1%). Of all patients, 65.9% were men and 34.1% were women with a sex ratio of 1.93 (Male/Female). Undifferentiated nasopharyngeal carcinomas were the most common histological type affecting 96.12% of patients. At diagnosis, the majority of patients (82.2%) had an advanced stage of NPC (III, VIa, b, c) including 5.4% of metastatic cases (IVc). Most cases (86%) had lymph node involvement with cervical mass being the most common clinical presentation. 81.4% of patients received radiotherapy combined with chemotherapy. Among these patients, 54.3% had concurrent radiochemotherapy preceded by induction chemotherapy. The 5-year overall survival (OS) was 86.8% for all patients. It represented 91.3% for early stages, 87.9% for locally advanced stages, and 57.1% for the metastatic stage significantly. The disease-free survival (DFS) at 5 years was 87.6% knowing that relapse occurred in 16 cases.

**Conclusions:** Nasopharyngeal carcinoma is a particular disease with a late declaration. It is common in Morocco as is the case in other endemic areas with a high prevalence. Patients' survival is significantly influenced by disease staging.

## Keywords

nasopharyngeal carcinoma, epidemiology, clinicopathology, therapy, survival, prognosis, Northern Morocco

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## Introduction

Nasopharyngeal carcinoma (NPC) is a multifactorial disease resulting from a complex interaction between genetic and environmental factors. It occurs most often in the epithelial cells lining the interior of the nasopharynx which is the highest part of the pharynx where the nasal fossae and the Eustachian tube open.<sup>1</sup>

According to the most recent WHO classification of head and neck tumors published in 2017 (4<sup>th</sup> edition), the histological types of nasopharyngeal carcinomas are defined as keratinizing squamous-cell carcinomas or non-keratinizing carcinomas. The second type is subdivided into differentiated and undifferentiated carcinomas (UCNT).<sup>2</sup> UCNT is by far the most common histological type of NPC in endemic areas (>90%).<sup>3</sup> Nasopharyngeal tumors show a high frequency of metastasis, compared with other cancers of the head and neck, varying between 5% and 41%.<sup>4</sup> The regional and distant lymph nodes, the bone, the lungs, and the liver represent the most common sites of metastasis in this type of cancer.<sup>1,5</sup>

This complex malignancy is distinguished from other cancers of the head and neck by its geographic distribution and its etiology. Although rare in North America and Europe, with age-standardized incidence rates (ASRs) of less than 1 per 100 000 person-year, nasopharyngeal carcinoma is one of the most common cancers in Southern China, Southeast Asia, and North Africa with ASRs of 2–10/100 000-year.<sup>6</sup> NPC has a remarkable sex disparity with a higher risk in males. The sex ratio is 2–3 men per woman.<sup>7,8</sup> In North Africa, nasopharyngeal carcinoma generally affects 2 peaks of age. The first peak is between 10 and 20 years old and the second, the major one, is between 45 and 55 years old. For Chinese and Eskimos, the peak incidence is between 45 and 55 years old.<sup>9,10</sup>

In addition to genetic predisposition and environmental factors such as dietary and toxic substances, the carcinogenesis of the nasopharynx depends on genetic and epigenetic alterations whose effect is added to the activation of oncogenes and signaling pathways following the expression of Epstein Barr virus's (EBV) latent genes.<sup>11</sup>

Nasopharyngeal tumors are radiosensitive and rarely accessible for surgery which makes radiotherapy (RT) the basic therapeutic modality, although the standard curative treatment of this type of cancer is concurrent radiochemotherapy (CRT). The latter has shown several benefits like improving clinical outcomes and patients' survival.<sup>12</sup> CRT can be followed by adjuvant chemotherapy or preceded by induction chemotherapy to treat advanced stages of NPC.<sup>13</sup>

Another particularity of nasopharyngeal carcinoma is that the majority of patients are diagnosed at an advanced stage.<sup>14</sup> The complex anatomy of the nasopharynx and the nonspecific nature of the symptoms such as cervical masses, rhinological signs, and otological signs make this cancer with a late declaration causing a major health problem.<sup>15</sup>

In Morocco, as is the case in other endemic countries, the incidence and prevalence of nasopharyngeal carcinoma are high. However, very few studies have been done in this regard.

We note the absence of epidemiological studies and cancer registries in Northern Morocco. This study aimed to determine the epidemiological profile and the clinicopathological, therapeutic, and prognostic characteristics of nasopharyngeal carcinoma in Northern Morocco in order to better understand this complex disease.

## Materials and Methods

### Study Population

This epidemiological and clinical study was conducted on patients diagnosed with nasopharyngeal carcinoma in Northern Morocco. All NPC patients followed and/or treated at the regional center of oncology of Tangier (Ahmed Ben Zayed Al Nahyan center of cancer treatment), since its opening, during the period between April 2017 and July 2019 were included in this study. Patients in our cohort were either treated, followed after relapse, or continued their treatment at the regional center of oncology of Tangier during the follow-up time.

It is a retrospective descriptive study of 129 NPC patients diagnosed elsewhere from March 2000 to February 2019. Patients' diagnosis was confirmed by a nasopharynx or a neck lymph node biopsy. The extent of NPC was determined by imaging techniques such as magnetic resonance imaging (MRI) and computerized tomography (CT).

### Data Collection

Data were collected from medical records of NPC patients in the regional center of oncology of Tangier, which is the only public center for cancer treatment in the Tangier-Tetouan region (North), using detailed technical sheets. The collection of epidemiological, clinicopathological, therapeutic, and prognostic data was then classified and managed in a database of Statistical Package for the Social Sciences (SPSS) software. Patients lost to follow up were afterward contacted by phone to find out the evolution of the disease. Among the 39 lost to follow-up patients, only 24 were reachable.

### Statistical Analysis

All statistical analysis was performed using SPSS software version 23 designed for analysis of scientific projects (SPSS, RRID: SCR\_002865). Descriptive analysis of our cohort was carried out to represent the results significantly for good interpretation. Quantitative variables were presented as central tendency indicators, like the mean and the median, or/and dispersion indicators such as the standard deviation. Ordinal and nominal qualitative variables were presented as frequencies or percentages. In this case, we only calculate the mode. T-test for independent samples was used for statistical significance. The survival rate was analyzed with the Kaplan–Meier method.<sup>16</sup> During this analysis, overall survival (OS)

was calculated from the date of diagnosis until the date of last news or the date of death. Live and lost to follow-up patients represented censored data while deceased patients represented uncensored data. Disease-free survival (DFS) was calculated from the date of diagnosis until the date of last news or the date of relapse. In this case, uncensored data were relapse cases. Overall survival was compared afterward to patients' age, sex, and stage of nasopharyngeal carcinoma using the Log Rank test, the most popular non-parametric test for comparing two or more survival curves. The level of significance was set at  $P\text{-value} \leq 0.05$ .

The missing values of this study were treated using 10% as the threshold. Variables with less than 10% missing data were replaced by the mode for qualitative variables and by the mean or the median for quantitative variables. Variables with more than 10% missing data were excluded from the study.

### Variables Definition

In this study, a wide range of variables were collected and analyzed. Prevalence, patients' age (divided into categories), sex, and origin were grouped into epidemiological data. The clinicopathological data included symptoms, histological types, TNM classification (7<sup>th</sup> edition), and cancer stages. Treatment data included treatment types (radiotherapy, chemotherapy, and surgery). For chemotherapy (neoadjuvant, concurrent, and palliative) and radiotherapy (curative and palliative), variables including chemotherapy regimens, and radiotherapy total dose, fractions, and duration were studied. Relapse data included variables such as relapse types (locoregional and metastatic), common sites, treatment-relapse interval, and treatment after relapse. The date of diagnosis and last news as well as the evolution data divided to under control, in treatment, death, and lost to follow-up were used in survival analysis.

### Ethical Aspects

This retrospective study was approved by the regional health directorate and the regional center of oncology of Tangier in Morocco although it did not require ethical board approval. All patients included in this study gave their informed verbal consent prior to their inclusion as instructed by these committees. In addition, the confidentiality of information collected and the anonymity of patients were ensured.

## Results

### Epidemiological Profile

Regarding the prevalence, nasopharyngeal carcinoma represented 5% of all cases recorded between 2017 and 2019 at the regional center of oncology of Tangier. During this period, 2583 cases of all cancers were recorded, including 129 cases of nasopharyngeal cancer.

In our cohort, patients' age ranged from 10 to 88 years, with a pic incidence at 40–54 years old. The mean age was  $47 \pm$

**Table 1.** Epidemiological Profile and Clinicopathological Characteristics of NPC Patients in Our Cohort.

Patient characteristics	N = 129 (%)
<b>Age distribution</b>	
10–24	15 (11.6)
25–39	23 (17.8)
40–54	53 (41.1)
55–69	33 (25.6)
≥70	5 (3.9)
<b>Sex</b>	
Male	85 (65.9)
Female	44 (34.1)
<b>Origin</b>	
Urban	111 (86)
Rural	18 (14)
<b>Histological types</b>	
Undifferentiated carcinomas	124 (96.12)
Non-keratinizing squamous	3 (2.33)
Keratinizing squamous	2 (1.55)
<b>cTNM classification</b>	
T1	6 (4.7)
T2	45 (34.8)
T3	46 (35.7)
T4	32 (24.8)
N0	18 (13.9)
N1	37 (28.7)
N2	60 (46.5)
N3	14 (10.9)
M0	122 (94.6)
M1	7 (5.4)
<b>Cancer stage</b>	
I	0 (0)
II	23 (17.8)
III	60 (46.5)
Iva	26 (20.2)
IVb	13 (10.1)
IVc	7 (5.4)

14.9 years with 47.7 for men and 45.7 for women. The median age of patients was 50 years (50 for men and 51 for women). Forty-one and one tenth percent (41.1%), 25.6%, and 11.6% of NPC patients were aged between 40 and 54, 55 and 69, and 10 and 24 years, respectively. Only 3.9% were aged 70 years or more. In this study, the gender difference was remarkable. Of the 129 patients, 85 were men (65.9%) and 44 were women (34.1%) with a sex ratio of 1.93 (Male/Female). The majority of patients lived in urban areas (86%) compared to rural areas (14%) as shown in [Table 1](#).

### Clinicopathology

Patients in our cohort had several clinical signs at the time of diagnosis; the most common were cervical mass (65.1%), rhinological signs (64.3%), otological signs (59.7%), and headaches (27.1%), respectively.

Table 1 shows the other clinicopathological characteristics of NPC patients. Undifferentiated carcinoma nasopharyngeal type (UCNT) was the most common histological type in our cohort, representing 96.12%. Differentiated non-keratinizing squamous and keratinizing squamous were rare, representing 2.33% and 1.55%, respectively. Regarding cTNM classification, analysis of the size and extension of the tumor (T) in patients showed that 35.7%, 34.8%, 24.8%, and 4.7% of tumors were classified T3, T2, T4, and T1, respectively. Among all patients, 86% had lymph node involvement (N1, N2, and N3). 5.4% of patients were metastatic (M1) at the time of diagnosis. The most common sites of metastasis were bone, liver, lymph nodes, and lung. By grouping this data into stages, 82.2% of patients had an advanced stage (III, IVa, IVb, IVc) of nasopharyngeal carcinoma at the time of diagnosis, while 17.8% had an early stage (II). None of these were classified as stage I. Regarding sex, 68.2% of female patients had locoregional advanced NPC (III, IVa, IVb) at diagnosis, whereas 81.2% of males had locoregional advanced stage. NPC stages compared to males and females had a  $p$ -value ( $P = .001 < .05$ ) statistically significant.

### Initial Treatment

In this study, the majority of patients (81.4%, 105 individuals) received radiotherapy combined with chemotherapy (CT), whereas 14.7% (19 individuals) received chemotherapy alone and 1.6% (2 individuals) received radiotherapy alone. 2.3% (3 individuals) of patients did not receive any treatment during the follow-up time. Regarding surgery, only 2 patients have been operated during their treatment with palliative surgery.

Among the patients treated with radiotherapy combined with chemotherapy, 54.3% (57 patients) received induction chemotherapy before the CRT, while 44.7% (47 patients) had CRT directly. All metastatic patients (5.4%) received a palliative treatment including 6 with palliative chemotherapy and 1 with palliative chemotherapy and radiotherapy as shown in Table 2.

The most widely used drugs in neoadjuvant (induction) and palliative chemotherapy were platinum-based combinations including cisplatin–anthracycline. Single drug protocols such as gemcitabine and taxanes were also used in palliative chemotherapy. Regarding concurrent chemotherapy, cisplatin was the most used drug in our study.

Radiotherapy was delivered using Volumetric Modulated Arc Therapy (VMAT), an arc-based approach of Intensity Modulated Radiotherapy (IMRT). The majority of patients in our cohort received a total dose of 70 Gy in 35 fractions of curative radiotherapy. The period of radiation varied from 2 to 88 days with a mean of 54.54 days during the follow-up time.

### Relapse

In our cohort, nasopharyngeal cancer relapse occurred in 16 cases (12.4%) including 7 cases (5.4%) with metastatic

relapse, 5 cases (3.9%) with locoregional and metastatic relapses, and 4 cases (3.1%) with locoregional relapse. The bone was the most common metastatic site after relapse (66.6%). 15 patients of the 16 cases with relapse (93.8%) had an advanced stage of nasopharyngeal carcinoma at diagnosis. The period between the end of treatment and cancer relapse varied between 11 and 1825 days with a mean of 588.27 and a median of 310.50 days. Among these patients, 10 received after relapse treatment by the follow-up time, including 6 cases treated with palliative chemotherapy and radiotherapy, 3 cases treated with palliative chemotherapy, and one case treated with palliative radiotherapy.

### Survival

The mean of patients' follow-up from diagnosis was 28.6 months with extremes between 1 and 220 months. The mean of non-metastatic patients' follow-up was 29.7 months, while the mean of metastatic patients was 9.8 months. The 5-year overall survival (OS) was 86.8% knowing that the event (death) occurred 17 times (14 men and 3 women). The OS at 5 years was 91.3% for early stages (I, II), 87.9% for locally advanced stages (III, IVa, IVb), and 57.1% for the metastatic stage (IVc) with a  $P$ -value of .002 ( $< .05$ ) statistically significant. Regarding sex, the 5-year OS was 83.5% for males and 93.2% for females with a  $p$ -value = .053 ( $\geq .05$ ) weakly significant. Regarding the age groups 10–24, 25–39, 40–54, 55–69 and  $\geq 70$ , the OS at 5 years was 93.3%, 91.1%, 83%, 87.9%, and 80%, respectively, with a  $p$ -value = .71 ( $> .05$ ) not statistically significant (Figures 1–4). The 5-year DFS was 87.6% knowing that the event (relapse) occurred in 16 cases (Figure 5).

### Discussion

Knowing that this is the first epidemiological and clinical study of nasopharyngeal carcinoma in Northern Morocco with the absence of a cancer registry, these results give an idea of the epidemiological profile and the clinical characteristics of this type of cancer in Morocco and particularly in Northern Morocco.

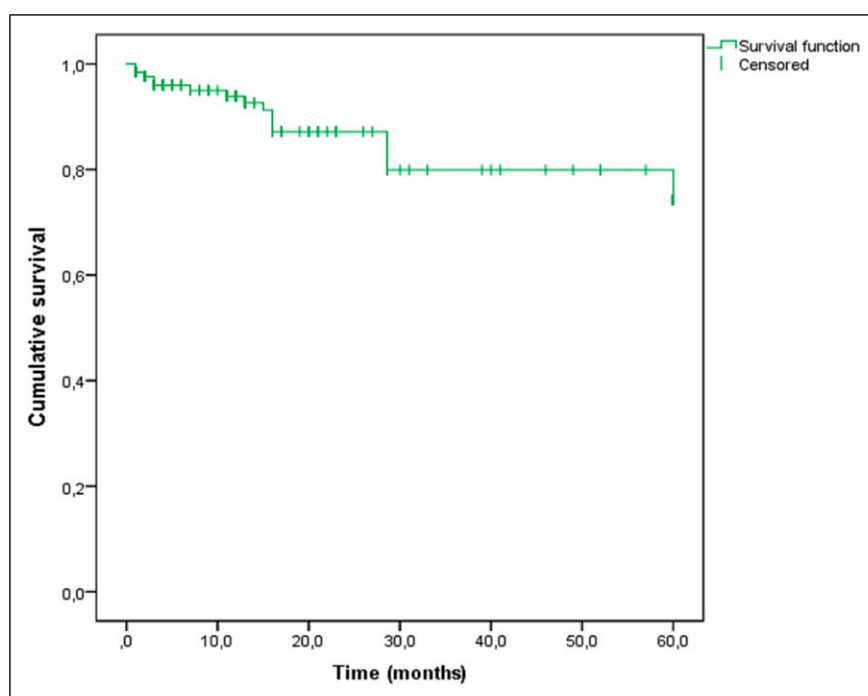
### Epidemiological Profile

In Morocco, as is the case in other endemic areas, nasopharyngeal carcinoma is one of the most common cancers with a high prevalence. In this study, NPC represented 5% of all cases reported between 2017 and 2019. This result gives an idea about the prevalence although it included all patients recorded at the regional center of oncology of Tangier during that period even if some of them were diagnosed way before.

Our prevalence is higher than that found in Casablanca (1.8%) during the period from 2008 to 2012 (Cancer registry of Casablanca 2008–2012) and almost similar to that found by Arfaoui et al (4.9%) in Rabat between 1994 and 2004.<sup>17,18</sup>

**Table 2.** Initial Treatment of NPC Patients During the Follow-Up Time.

Treatment type		Frequency	Percentage %
Radiotherapy and chemotherapy	Concurrent	47	44.7
	Neoadjuvant and concurrent	57	54.3
	Palliative	1	1.0
	Total	105	100.0
Chemotherapy alone	Neoadjuvant alone	13	68.4
	Palliative	6	31.6
	Total	19	100.0
Radiotherapy alone	Total	2	100.0
No treatment	Total	3	100.0

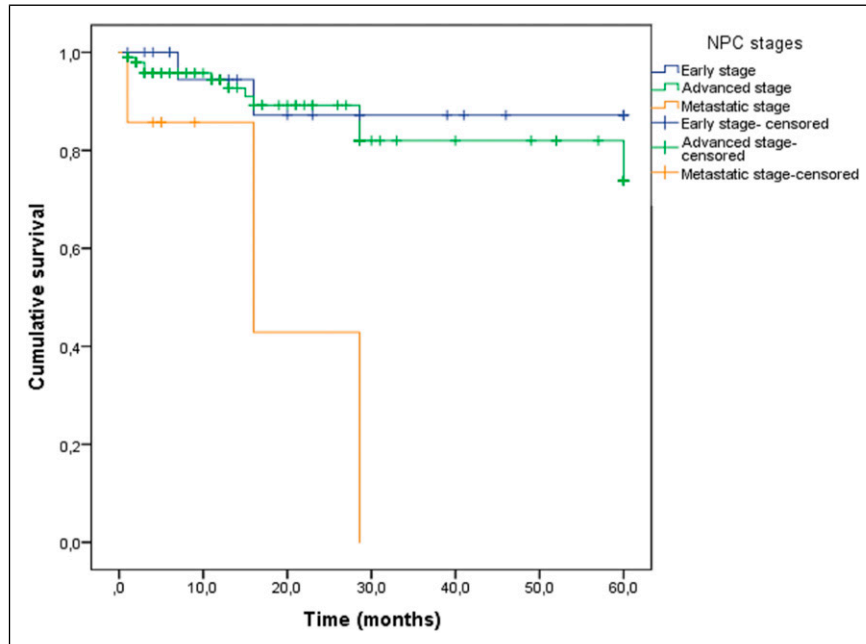
**Figure 1.** Overall survival at 5 years.

Internationally, the prevalence of nasopharyngeal carcinoma was 3.2% (3-year period) according to the International Agency for Research on Cancer (IARC) which is lower than the prevalence of this study.<sup>6</sup> These results confirm that Morocco is one of the regions at risk for this type of cancer.

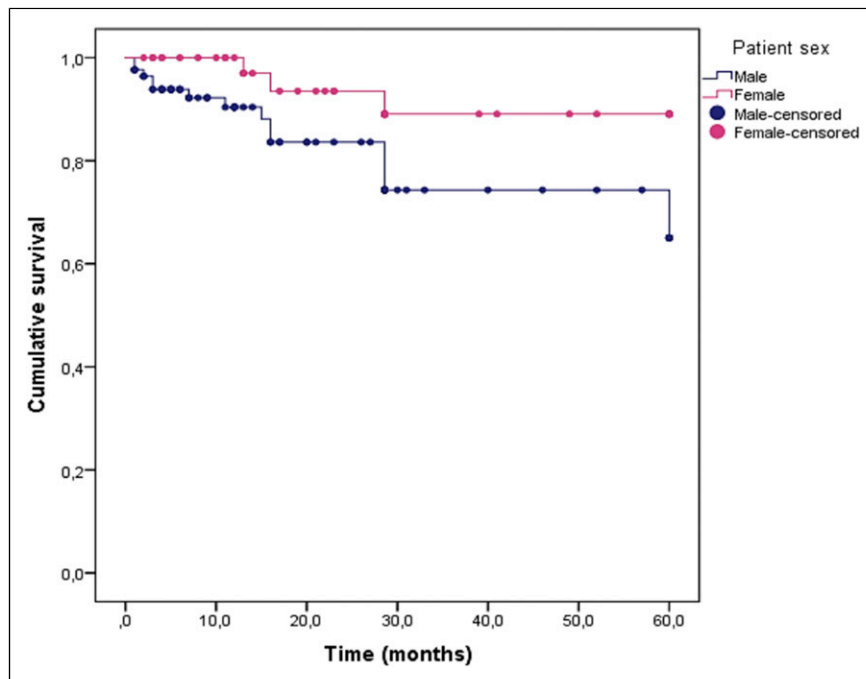
In our cohort, patient's ages ranged from 10 to 88 years with a median of 50 years old. Abdullah et al found a median age of 51 years in a study of 266 NPC patients, whereas Alami et al found a median age of 47 years in a study of 163 NPC patients.<sup>19,20</sup> The most common age group in this study was 40–54 years. These results converge at the national level with

Arfaoui et al.'s study and internationally with the results of IARC.<sup>9,17</sup> Unlike the majority of cancers, nasopharyngeal carcinoma also affects young people.<sup>21,22</sup> 11.6% of patients in our cohort were between 10 and 24 years old at diagnosis, knowing that children under 15 are normally treated in pediatric centers except for some rare cases. Without this condition, the percentage of young NPC patients could be greater. These results are similar to what Daoud et al. found.<sup>23</sup> This might be explained by the genetic predisposition which contributes to the development of NPC at a younger age.

The sex disparity was remarkable in this study with a higher risk for males and a sex ratio of 1.93 (M/F). These



**Figure 2.** Overall survival at 5 years regarding NPC stages. NPC: Nasopharyngeal carcinoma.



**Figure 3.** Overall survival at 5 years regarding sex.

results are consistent with the literature data.<sup>24,25</sup> The sex difference may be due to the great exposure of men to NPC risk factors including toxic substances and occupational factors such as wood dust and chemical fumes.<sup>26,27</sup> Further studies on this level should be done.

Our results showed a predominance of urban origins (86%) over rural origins (14%) which converge with the results of Wei et al. in China.<sup>28</sup> This could be explained by the difficulty of access to diagnosis and treatment in rural areas and the urbanization of Moroccan people.



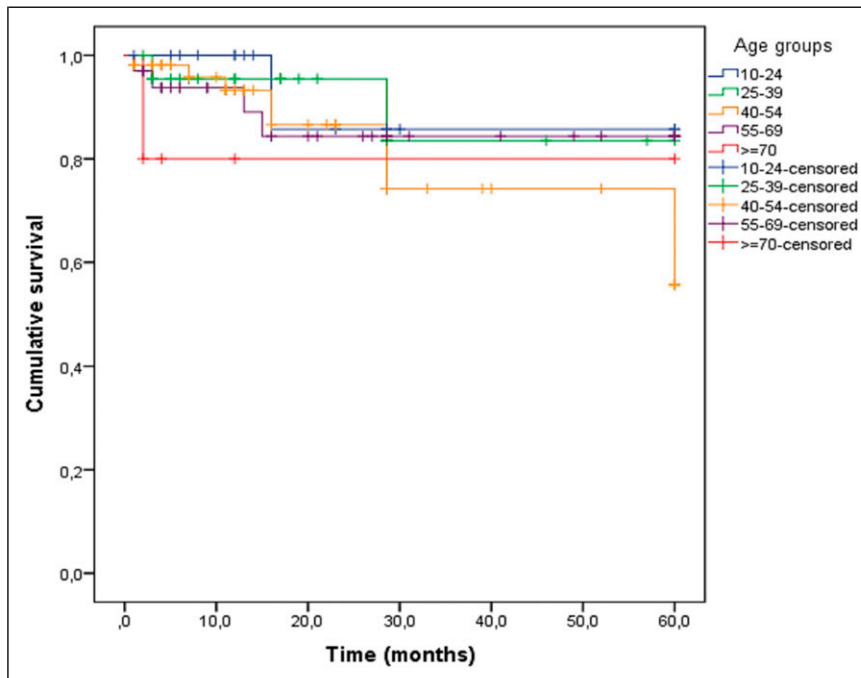


Figure 4. Overall survival at 5 years regarding age groups.

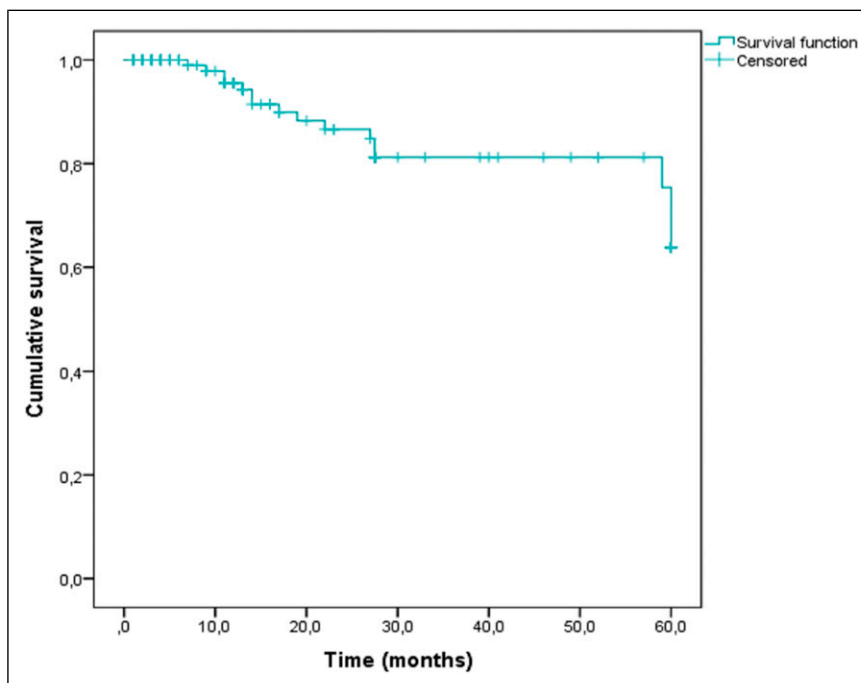


Figure 5. Disease-free survival at 5 years.

**Clinicopathology**

In the early stages of the disease, nasopharyngeal cancer may not cause any symptoms. Clinical signs of NPC appear as the tumor grows in nearby tissue. Cervical mass caused by

lymphadenopathy was the most common symptom in this cohort, followed by rhinological signs, including nasal congestion and epistaxis, otological signs such as hearing loss and tinnitus, and headaches. Other symptoms such as eye signs, neurological signs, and weight loss have been reported less

frequently. These results converge with the literature data.<sup>15,24</sup> The non-specificity of the symptoms and the complex anatomy of the nasopharynx make the diagnosis of NPC difficult which could explain why most patients are diagnosed at an advanced stage.

In this study, undifferentiated carcinoma (UCNT) was the most common histological type of nasopharyngeal cancer with 96.12% of cases. These results are consistent with all studies like Bahannan A et al and Wided BA et al confirming that UCNT is the predominant type of NPC in endemic areas.<sup>29,30</sup> Several studies showed that UCNT and non-keratinizing squamous have better prognosis and are more responsive to radiation than keratinizing squamous-cell carcinoma although the latter is more common in non-endemic areas such as the United States of America.<sup>31,32</sup>

Thirty-five and seven tenth percent (35.7%), 34.8%, 24.8%, and 4.7% of tumors in our cohort were classified T3, T2, T4, and T1, respectively. Of the 129 patients, 86% had lymph node involvement. In a study of 83 NPC patients in Taiwan, Liu et al found that 42% of patients had T2 tumors, 28% had T4, 23% had T1, and 7% had T3. Of the 83 patients, 77% had lymph node involvement.<sup>33</sup> Bahannan et al and Raissouni et al found cervical nodal metastasis in 78.9% and 80% of patients, respectively.<sup>25,30</sup> T-stage and N-stage were shown to be significant prognostic factors in NPC.<sup>33,34</sup> In this study, 5.4% were metastatic at the time of diagnosis with bone, liver, lymph node, and lung being the most common sites of metastasis. These results are similar to the literature data.<sup>1,35</sup>

One of the particularities of NPC is that the majority of patients are diagnosed at an advanced stage. In this study, 82.2% of patients had an advanced stage (III, IVa, IVb, IVc) of nasopharyngeal carcinoma including the metastatic stage (5.4% IVc). Marnouche et al and Mak et al also found a high percentage of patients with an advanced stage of NPC (85.5% and 66.1%, respectively).<sup>14,36</sup> These results confirm that NPC is a late declaration cancer. The detection of anti-EBV antibodies and other serological markers such as Cyfra 21 can predict this type of cancer, hence their usefulness in early diagnosis.<sup>37,38</sup> More studies at this level should be done. In this study, only 68.2% of females had locoregional advanced NPC, compared to 81.2% of males who had locoregional advanced disease. This difference in NPC stages between men and women was statistically significant which might result in a better prognosis for female patients compared to males.

### Treatment Modalities

Nasopharyngeal carcinoma is a radiosensitive tumor which makes radiotherapy the first choice for treating early stages. Many studies have shown that the addition of chemotherapy to radiotherapy has several benefits including improved clinical outcomes and survival in patients with locally advanced stages of NPC.<sup>12,39</sup> In this study, 81.4% of patients received an initial treatment of radiotherapy (RT) combined with chemotherapy (CT). Among these patients, 54.3% received induction

chemotherapy before the CRT. Wang et al and Tan et al performed a meta-analysis in which they confirmed that the addition of induction chemotherapy to CRT to treat advanced stages of NPC improves overall and progression-free survival.<sup>13,40</sup>

In our cohort, patients without treatment (2.3%) and patients treated with chemotherapy (14.7%) or radiotherapy alone (1.6%) are either lost to follow-up or have not yet started or completed their treatment by the follow-up time.

According to several studies, palliative chemotherapy and radiotherapy as well as surgery in some cases play an important role in controlling the disease and prolonging the survival of patients with recurrence or metastasis.<sup>15,41</sup> In this study, 17 patients (13.18%) including 7 metastatic cases and 10 relapse cases received palliative treatment, mainly CT and RT. Only 2 patients have been operated during their treatment (palliative surgery).

The most used CT protocols in this study were platinum-based drugs such as cisplatin combined with anthracycline for neoadjuvant and palliative CT and cisplatin alone for concurrent CT. Zhou et al. found that docetaxel, cisplatin, and fluorouracil (TPF)-based induction CT plus CRT results in better survival outcomes with manageable toxicities compared with CRT alone or double-drug based induction CT.<sup>42</sup> Zhang et al. showed that the addition of gemcitabine and cisplatin induction CT to cisplatin CRT improves patients' survival.<sup>43</sup>

Radiotherapy dose is usually 2 Gy per fraction, 5 days per week with a total dose of 70 Gy in 49 to 50 days. In our series, the majority of patients received a total dose of 70 Gy in curative RT (VMAT-IMRT). The treatment period varied from 2 to 88 days with a mean of 54.54 days by the follow-up time. Interruption during RT treatment has been reported to reduce local control and survival of patients.<sup>44,45</sup> These delays can be due to the treatment tolerance and/or logistic issues.

The use of IMRT to target the tumor more precisely by increasing the radiation dose seems to be more promising than conventional RT in treating nasopharyngeal carcinoma. Several studies have shown that it contributed to an absolute improvement in locoregional control and survival as well as lower incidence of toxicities.<sup>46</sup> Recent studies and clinical trials focus nowadays on new treatment modalities such as immunotherapy, gene, and targeted therapies. Regarding this latter, monoclonal anti-EGFR antibodies such as cetuximab and nimotuzumab are among the most studied targeted therapy. Adoptive transfer of autologous EBV-specific cytotoxic T cells and inhibition of checkpoints such as PD-1 and CTL-4 to activate the immune system are used as immunotherapy strategies.<sup>47-49</sup> Significant cytotoxicity mediated by apoptosis was obtained using a technique of gene therapy that consists of introducing a viral vector (adenovirus) containing a transgene which, its expression, is under the transcriptional regulation of the latent origin of the replication of repeated sequences (oriP) of the Epstein Barr virus.<sup>50</sup>

### Recurrence

Among all patients, 12.4% presented NPC recurrence with a higher rate of metastatic relapses compared to locoregional



relapses. Like other studies, the most common site of metastatic recurrence in our cohort was the bone. These results are similar to the literature data.<sup>51,52</sup> In this study, the median interval between the end of treatment and NPC relapse was 310.50 days. When this period is less than 90 days (1 case), the tumor is said to be resistant to treatment. Therapeutic failure and NPC recurrence may be due to the presence of hypoxic tumors which are known to be radioresistant.<sup>53</sup>

### Survival Functions

With a mean follow-up of 28.6 months, the overall survival (OS) of all patients at 5 years was 86.8%. Marnouche et al. found a 5-year OS of 68%.<sup>14</sup> Internationally, Mak et al found a 5-year OS of 70.7% in Singapore, whereas Anne lee et al reported a 5-year OS of 75% in Hong Kong.<sup>36,54</sup> In our cohort, the DFS at 5 years was 87.6%. Marnouche et al. reported a 5-year DFS of 81.1% in Rabat Morocco.<sup>14</sup> In Malaysia, Phua et al found a poor DFS of 48.4%.<sup>55</sup> According to several studies, the OS and DFS improve when patients are treated with IMRT instead of conventional RT and with concurrent radiochemotherapy instead of RT alone.<sup>12,56</sup>

The five-year overall survival in our cohort for early stages, locally advanced, and metastatic stages was 91.3%, 87.9%, and 57.1%, respectively, which confirm that NPC stages influence significantly patients' survival. These results were consistent with those of several studies showing that the NPC stage is the most important prognostic factor for NPC.<sup>20,54,55</sup> Regarding sex, the 5-year overall survival was higher in women (93.2%) compared to men (83.5%) with p-value weakly significant. These results were similar to the literature data showing a female advantage with a higher survival.<sup>57,58</sup> Lu et al and OuYang et al suggest that the favorable prognosis of female NPC patients is not only attributed to the early diagnosis and treatment but might also be attributed to some intrinsic biologic factors of female patients such as the hormonal differences.<sup>57,58</sup>

In this study, OS at 5 years was lower for patients aged 70 years or more (80%) and for the age group 40–54 years (83%) which is the most affected age category. The age groups 10–24, 25–39, and 55–69 had an OS of 93.3%, 91.1%, and 87.9%, respectively, with p-value not statistically significant. In an Indonesian study, Hutajulu et al. showed that age was an independent predictor for the OS.<sup>59</sup>

The limited data accessibility and the study size are considered as the limitations of the study although the latter represents the first study of its kind in Northern Morocco. It relates to the national plan for the prevention and control of cancer.

### Conclusion

It is becoming more and more difficult to ignore the role of nasopharyngeal cancer in Morocco, as is the case in other endemic areas, hence the importance of carrying out

epidemiological studies and establishing cancer registries. NPC remains a complex malignancy with a late declaration, representing one of the most frequent cancers in Morocco and particularly in Northern Morocco. It is characterized by its epidemiological profile and its clinicopathological, therapeutic, and prognostic factors. Being the first of its kind in Northern Morocco, this study will contribute to the understanding of this type of cancer by improving the prevention and patients' follow-up. It will also allow us to study the molecular and genetic part of nasopharyngeal carcinoma to subsequently improve therapeutic pathways and early diagnosis of this disease.

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### Abbreviations

CRT, concurrent radiochemotherapy; CT, chemotherapy; DFS, disease-free survival; EBV, Epstein Barr virus; IARC, International Agency for Research on Cancer; IMRT, intensity modulated radiotherapy; NPC, nasopharyngeal carcinoma; OS, overall survival; RT, radiotherapy; SPSS, Statistical Package for the Social Sciences; UCNT, undifferentiated carcinoma nasopharyngeal type; WHO, World Health Organization.

### Ethics Statement

My co-authors and I confirm that our study uses information from patients of the regional center of oncology of Tangier, but we did not collect the information from the patients ourselves. So, the study did not require interaction with patients.

### Data Accessibility Statement

The datasets generated and analyzed during the current study are not publicly available due to the confidentiality of patient data and ethical restrictions but are available from the corresponding author on reasonable request.

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