RESEARCH ARTICLE

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Epidemiological, Clinicopathological and Prognosis Features of Moroccan Patients with Nasopharyngeal Carcinoma

Amina Gihbid[1,2], Nezha Tawfiq[3], Nadia Benchakroun[3], Zineb Bouchbika[3], Souha Sahraoui[3], Karima Bendahhou[3], Abdellatif Benider[3], Jafar Ibnohoud[4], Amal Guensi[4], Mohammed El Mzibri[5], Rachida Cadi[2], Meriem Khyatti[1]*

Abstract

Proposal: A distinct epidemiology, etiology, clinical characteristics, and therapeutic outcomes characterize nasopharyngeal carcinoma (NPC) from other head and neck cancers. An actualized analysis of NPC patients' features enables a global view of NPC management. Accordingly, the current study investigated the epidemiological and clinical characteristics of Moroccan patients with NPC, as well as their 4-years survival outcomes and influencing prognostic factors. **Methods:** We prospectively analyzed data of 142 histologically confirmed Moroccan patients with NPC between October 2016 and February 2019. Kaplan-Meier and Cox regression analyses were used to assess predictive prognostic factors related to NPC. All analyses were conducted using SPSS version 21 statistical software. **Results:** In the present study, a net male predominance was found, with a mean age of 44±16.3 years old. Advanced stages of NPC were observed in 64.1% of patients, and 32.4% of patients presented with distant metastasis at diagnosis. The 4-years overall survival, locoregional relapse-free survival, distant metastasis-free survival and progression-free survival were 68.0%, 63.0%, 53.9%, and 39.9%, respectively. Age, N category and distant metastasis were identified as the most important independent prognosis factors for NPC in this cohort ($p<0.05$). **Conclusion:** In conclusion, NPC affects young adults and is frequently diagnosed at advanced disease stages, impacting therefore negatively patients survival; which is in line with data from endemic areas for NPC. The current study clearly highlights that a greater attention should be directed to improving the management of this aggressive malignancy.

Keywords: Nasopharyngeal carcinoma- epidemiology- prognosis

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Introduction

Nasopharyngeal carcinoma (NPC) is a highly aggressive head and neck malignancy developed from the nasopharynx epithelium (Mlk et al., 2016). This cancer had a particular worldwide geographic distribution, its highly incident in selected geographic and ethnic populations. High endemic areas for NPC are located in southern parts of China and other parts of Southeast Asia (Malaysia, Indonesia, Vietnam), with an estimated incidence of 25-80 per 100,000 person-year. With an incidence of 16 per 100,000 per year, North African countries, natives of Artic region, Inuit of Greenland and Alaska represent intermediate incidence areas for NPC. The other parts of the world are considered as low incidence areas for NPC, with an incidence less than 1 per 100,000 person-year (Mahdavifar et al., 2016; Chang et al., 2021; Sung et al., 2021). NPC is a multifactorial cancer, involoving a combined and accumulative effect of host genetic, epigenetic, environmental and viral (Epstein Barr Virus (EBV)) risk factors (Jia and Qin, 2012; Perri et al., 2015; Dai et al., 2016).

The deep anatomy of the nasopharynx implies a sophisticated NPC diagnostic strategy, that combines physical examination, guided biopsy and several imaging modalities. Unfortunately, NPC is currently diagnosed at advanced stages, with around 11% of patients diagnosed with distant metastasis (Bossi et al. 2021). Concurrent chemoradiotherapy (CRT) with or without induction chemotherapy (CT) are the standard treatment modalities for these patients. Meanwhile, early stages of NPC are potentially curable with radiotherapy (RT) alone (Lee et al., 2012; Blanchard et al., 2015; Guan et al., 2020). To stage and predict prognosis of NPC, the Union for

*[1]Laboratory of Viral Oncology, Institut Pasteur du Maroc, Casablanca, Morocco. [2]Laboratory of Pathophysiology, Molecular Genetics and Biotechnology, Faculty of Sciences Ain Chock, Hassan II University, Casablanca, Morocco. [3]Mohammed VI Center for Cancer Treatment, Ibn Rochd University Hospital, Casablanca, Morocco. [4]Nuclear Medicine Department, Ibn Rochd University Hospital, Hassan II University, Casablanca, Morocco. [5]Biology and Medical Research Unit, National Center of Energy, Sciences and Nuclear Techniques, Rabat, Morocco. *For Correspondence: meriem.khyatti@pasteur.ma*

International Cancer Control (UICC) classification based on tumor, node, and metastasis evaluation (TNM) is commonly used. Survival of patients is influenced primarily by the stage of the disease and the treatment modality used (Lee et al., 2005). The 5-years overall survival (OS) for advanced NPC stages was reported to be between 25% to 40%, and the advent of intensity-modulated radiotherapy has significantly improved this rate to 80% to 90% (Luo et al., 2016).

In Morocco, as it is the case in endemic areas for NPC, management of NPC is one of the greatest clinical challenges faced by oncologists, and many efforts are made to ensure an early diagnosis and to optimize treatment approaches for a better management of this aggressive malignancy. In this field, an actualized analysis of epidemiologic, clinico-pathological, prognostic and biologic features of NPC will be of a great interest to better understand cancer evolution and to analyze the strengths and weaknesses of the existing strategy for better management of NPC in our country. Thus, the clinical data from Moroccan NPC patients were prospectively analyzed in order to evaluate epidemiological characteristics, 4-years patient survival and influencing prognostic factors.

Materials and Methods

Patients

From October 2016 to February 2019, 142 histologically confirmed patients with NPC were enrolled prospectively in the present study. Recruitment and treatment of these patients were carried out at Mohammed IV Center for Treatment of Cancer, Ibn Rochd University Hospital of Casablanca, Morocco. The study protocol was approved by the Ethics Committee of Ibn Rochd University Hospital, Casablanca – Morocco. Informed consents were obtained from all patients. For those under 18 years of age, consents were obtained from their parents and/or legal guardians.

Socio-economic data (age, sex, childhood habitat, familial history of cancer, tobacco habits, alcohol consumption) were collected by face-to-face interviews and clinical information including (histological type, clinical presentations, TNM classification, disease stage, management timeline, imaging data, treatment regimens and survival patient's outcome) were retrieved from patients' medical records. Family history of cancer was considered when a first-degree relative (father, mother and siblings), and/or when a second-degree relative (such as grandparents, uncles, aunts, distant cousins or niece on one side or on the other of the family) had a prior history of any type of cancer. Patients were characterized as smokers when they were past or current smokers, and as drinkers when they were drinker's during the last 5 years or present drinkers.

The histopathological classifications were confirmed on the basis of the World Health Organization (WHO) criteria for Head and Neck Tumours ; NPCs were grouped into keratinizing squamous cell carcinoma (KSCC), non-keratinizing differentiated carcinoma (NKDC) and non-keratinizing undifferentiated carcinoma (NKUC). Furthermore, all patients were staged according to the 7th edition of the UICC/AJCC system. The date of treatment was defined as the time between histological diagnosis and the start date of the first treatment.

Follow-up and survival endpoints

For all patients, follow-up evaluations were performed every 3 months within the first year, every 6 months for the following 2 years, and annually thereafter. During the follow-up period, patients were regularly re-examined by medical consultation, nasopharyngoscope, head and neck MRI and/or CT, thoracic, abdominal and pelvic CT, and [^{18}F]-FDG-PET/CT.

The follow-up period was considered as the date of the first consultation in the center to either the date of death or the date of loss to follow-up or till March 31, 2021. OS was defined as the interval from the date of diagnosis to the date of death from any cause or last follow-up. Locoregional relapse-free survival (LRRFS) was defined as the interval from the date of diagnosis to the first confirmed radiological or histological locoregional relapse, death from any cause, or last follow-up. Distant metastasis-free survival (DMFS) was defined as the interval from the date of diagnosis to the first confirmed radiological or histological distant metastasis, death from any cause, or last follow-up. Progression-free survival (PFS) was defined as the time from the diagnosis to the progression of the disease, death, or last follow-up.

Statistical analysis

The epidemiological and clinical characteristics of the studied NPC patients are presented as mean values, ranges and percentages. Survival rates were determined using Kaplan-Meier method, and survival differences were compared using the log-rank test. Univariate and multivariate Cox proportional hazards regression models were used to assess prognostic factors of NPC; hazard ratios (HRs) and their 95% confidence intervals (CIs) were reported. Variables with significant differences in the univariate analysis were entered into multivariate regression models. All analyses were conducted using SPSS version 21 statistical software (IBM Corporation, Armonk, USA). Results were considered statistically significant when the p-value was less than or equal to 0.05.

Results

Sociodemographic characteristics

The age of the 142 NPC patients enrolled in the present study ranged from 12 to 80 years, with a mean age of 44.0 ±16.3 years and a male to female (M:F) sex ratio of 1.6. The age distribution of our NPC patients showed a bimodal distribution, with a first peak occurring at 12-21 years and the second at 43-52. We observed a M:F sex ratio of 1.2 for NPC patients under 30 years of age, and of 1.8 for patients above 30 years. The cohort consisted of 52.1% patients with urban childhood habitat, and 47.9% of patients with rural childhood habitat. Of these patients, 19.0 % were smokers and 14.1% were alcohol consumers; the combination of alcohol consumption and smoking was observed in 4.9% of patients. A family history of cancer was found within 22.5% of patients, among them,

Table 1. Socio-Economic and Clinical Features of Patients Recruited in the Study (n=142)

Characteristics	Number of cases	%
Age		
12-21	22/142	15.5
22-32	13/142	9.2
33-42	21/142	14.8
43-52	36/142	25.4
53-62	35/142	24.6
63-72	14/142	9.9
>72	1/142	0.7
Gender		
Female	53/142	37.3
Male	89/142	62.7
Childhood habitat		
Rural	68/141	47.9
Urban	73/141	51.4
Consenginty		
No	132/142	93.0
Yes	10/142	7.0
Family history of cancer		
No	110/142	75.5
Yes	32/142	22.5
Family history of NPC	11/142	7.7
Family history of VADS cancers (NPC exclude)	4/142	3.5
Family history of gastric cancers	5/142	4.2
Family history of lung cancers	4/142	2.8
Family history of genycologic cancers	5/142	3.5
Family history of thyroid cancer cancers	3/142	2.1
Family history of leucemia	3/142	2.1
Family history of prostate cancer cancers	2/142	1.4
Family history of other cancers	2/142	1.4
Degree of family history of cancer		
First-degree family history of cancer	18/142	12.6
Second-degree family history of cancer	15/142	10.5
Third-degree family history of cancer	1/142	0.7
Tabaco consumption		
No	115/142	81.0
Yes	27/142	19.0
Alcohol consumption		
No	123/142	86.6
Yes	19/142	13.4
Histological type		
KSCC	1/142	0.7
NKDC	7/142	4.9
NKUC	131/142	92.3
Others	3/142	2.1
TNM classification		
T1-T2	34/142	23.9
T3-T4	108/142	76.1
TNM classification		
N0-N1	48/142	33.8
N2-N3	94/142	66.2
M0	96/142	67.6
M1	46/142	32.4
Stage of the disease		
I	3/142	2.1
II	14/142	9.9
III	33/142	23.2
IV	92/142	64.8
Symptoms at time of diagnostic		
Neurologic manifestation	39/142	27.4
Otological syndrome	89/142	62.6
Headache	107/142	75.3
Rhinologic symyoms	111/142	78.1
Neck lymph nodes	115/142	80.9

7.7% had at least one family member who treated or is treating NPC. First and second-degree family history of cancer were observed in 12.6% and 10.5% of patients, respectively, while third-degree family history of cancer was reported in one patient (0.7%) (Table 1).

Management timeline

In the present study, the mean duration between diagnosis and initial treatment was 81.1 ± 44.2 days (d) (median of 76.5 d; [20-184 d]). In detail, the mean time between histological diagnosis of NPC and the first oncologic consultation was 29.8 ± 27.9 d (median of 25.0 d; [2-95 d]), and the average delay between the first consultation and the loco-regional extension assessment (MRI and/or CT) was 33.9 ± 33.1 d (median of 22.5 d; [3-173 d]). The delay between the first consultation and the distant extension assessment (TAP-CT and/or PET-CT) was 30.9 ± 24.6 d (median of 21.5 d; [2- 95 d]). The time between the first oncologic consultation and the start of treatment was 62.7 ± 40.9 d (median of 54.0 d [2- 189 d]).

Table 2. Initial Clinical Signs Revealing the Presence of NPC

Initial clinical signs revealing NPC					
	Nombre	%		Nombre	%
Isolated sign	124	87.3	LN*	58	40.8
			R**	38	26.8
			O***	18	12.7
			N****	10	7.0
Associated signs	18	12.6	R+O	6	4.2
			R+LN	5	3.5
			O+LN	3	2.1
			R+N	3	2.1
			O+N	1	0.7

LN*, Neck lymph nodes ; R**, Rhinologic syndrome; O***, Otological syndrome; N****, Neurological syndrome

Table 3: Kaplan-Meier Analysis and Univariate Analyses of Prognostic Factors for OS and LRFFS of Patients with NPC

	OS				LRFS			
	4-year rate (%)	Mean (months)	Univariate analysis (HR; 95% CI)	p value	4-year rate (%)	Mean (months)	Univariate analysis (HR; 95% CI)	p value
Age								
≤ 30 years	81.6%	45.8	2.40 (1.01-5.69)	0.03	93.1%	50.2	6.30 (1.49-26.65)	0.04
> 30 years	59.8%	36.1			51.1%	38.3		
Gender								
Female	70.3%	40.7	1.48 (0.77-2.83)	0.23	66.0%	39.9	0.77 (0.37-1.63)	0.50
Male	62.4%	37.3			60.6%	42.8		
Tabaco consumption								
No	65.3%	39.1	1.04 (0.48-2.26)	0.90	64.0%	42.2	1.24 (0.50-3.08)	0.63
Yes	68.2%	38.4			57.7%	40.0		
Alcohol consumption								
No	69.6%	40.7	2.22 (1.09-4.51)	0.02	68.4%	42.9	2.36 (0.95-5.88)	0.06
Yes	39.8%	27.1			44.4%	33.5		
Tumor classification								
T1-T2	69.9%	39.7	1.21 (0.51-2.58)	0.66	65.8%	42.5	1.21 (0.51-2.87)	0.66
T3-T4	64.2%	38.4			61.1%	41.5		
Lymph node status								
N0-N1	87.7%	48.8	4.74 (1.86-12.07)	0.001	78.7%	47.3	3.01 (1.20-7.53)	0.01
N2-N3	53.7%	33.4			47.6%	38.1		
Metastasis status								
M0	82.0%	46.2	5.55 (2.94-10.44)	0.000	64.0%	42.8	1.64 (0.71-3.81)	0.24
M1	29.4%	19.6			73.6%	31.1		
Stage of the disease								
I-II	91.7%	49.4	6.28 (0.86-45.67)	0.06	87.5%	50.5	6.02 (0.80-44.97)	0.08
III-IV	62.3%	37.5			57.2%	40.2		

Clinical outcomes

In the present study, and according to the WHO classification of histopathologic variants, NKUC was found in 92.3 % of patients. Imaging results showed that 9.2% of the patients were classified as T1, 14.8% T2, 33.1% T3 and 43.0% as T4. Lymph nodes were not detected in 7.7% of patients (N0); while, 26.1% were classified as N1, 44.4% as N2 and 21.8% as N3. At diagnosis, 32.4% of patients with NPC had distant metastasis (DM), with 52.2% having isolated DM and 43.3% multiple DM. DM affects bone in 52.1%, lymph nodes in 43.4% (mediastinal nodes and others), lung in 32.6%, liver in 17.3% and muscles in 4.3% of patients diagnosed with DM. The number of patients staged as stage I, II, III and IV of NPC were 3 (2.1%), 14 (9.9%), 34 (23.9%) and 91 (64.1%), respectively (Table 1).

Symptoms

Initial clinical presentation consisted of one symptom in 87.3 % of the cases, and two symptoms or more in 12.6 % of patients. The onset of lymphadenopathy (66 patients) was the major symptom leading patients to an initial medical consultation, followed by the appearance of rhinologic syndrome in 52 patients (36.6%), otological syndrome in 28 patients (19.7%) and neurological syndrome in 13 patients (9.1%) (Table 2).

Symptoms characteristics are presented in (Table 1). Out of 142 patients, 115 (81.0%) presented with neck lymph nodes; the lymph node was unilateral in 62 patients (43.7%) and bilateral in 53 patients (37.3%). The second most commonly reported symptom was headache, which found in 107 patients (75.4%). The most common rhinologic symptoms were nasal obstruction observed in 83 patients (58.5%) and epistaxis in 77 patients (54.2%), while rhinorrhea was reported in 35 patients (24.6%). The otological syndrome was observed among our patients, and was manifested by earache in 95 patients (66.9%) and otorrhea in 23 patients (16.2%). Neurologic manifestation was noted in 39 patients (27.5%).

Patients' features and survival

Figure 1 depicts the Kaplan-Meier plots to illustrate the survival of all patients and demonstrate the association between survival and patient characteristics. The mean follow-up period was 28.3 mo [1-54 mo] for surviving patients and 22.7 mo [1-54 mo] for all patients. Our patient's 1-year OS, LRRFS, DMFS and PFS rates were 94.8%, 87.9%, 65.2% and 64.9%, respectively. However, patients' 4-years OS, LRRFS, DMFS and PFS rates were 68.0%, 63.0%, 48.9%, and 39.9%, respectively. In total, 30.2% (43/142) of patients died. Locoregional failure was detected in 19.7% (28/142) of patients, and DM was

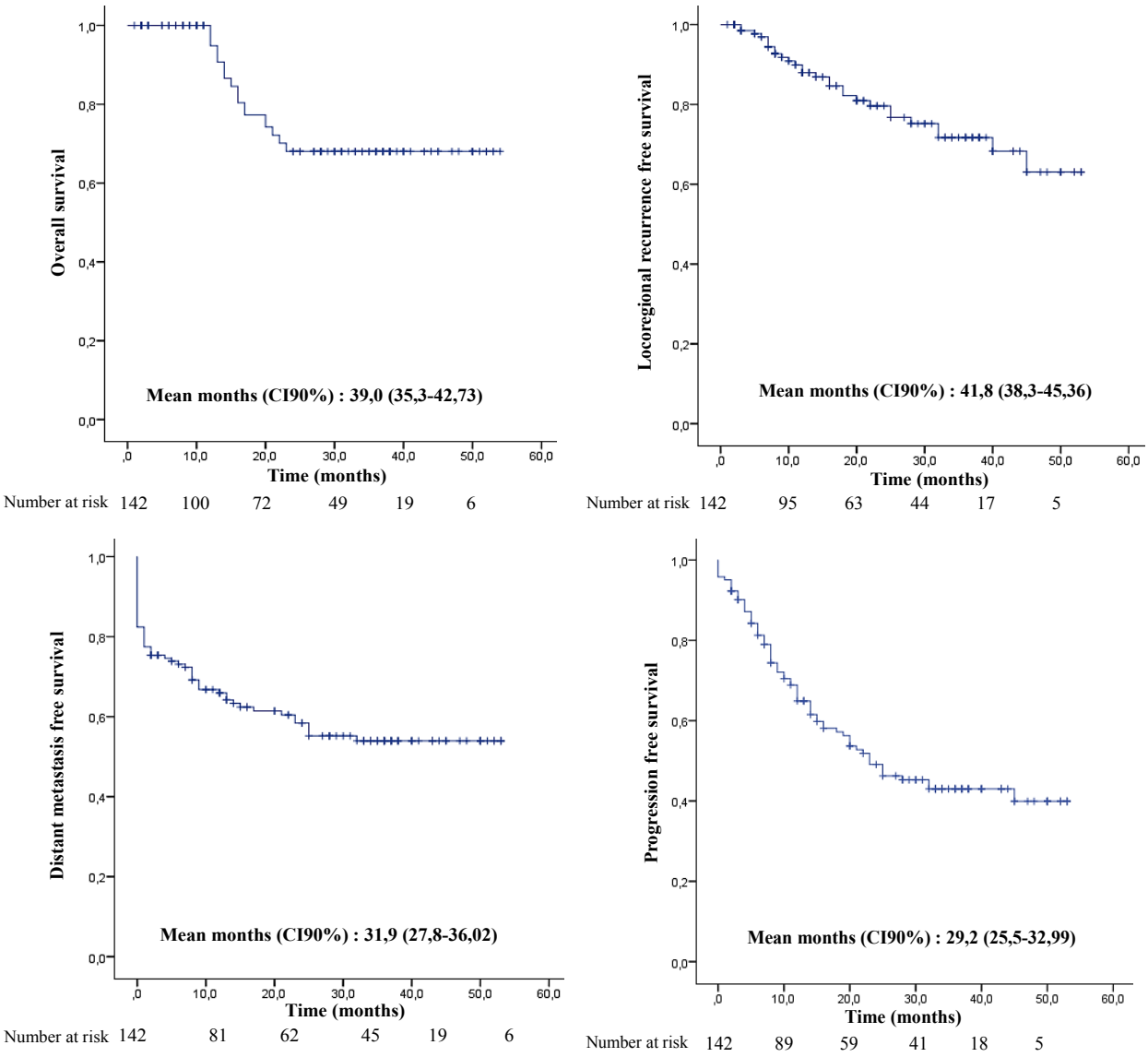

Figure 1. Kaplan-Meier Plots of Different Endpoint of Patients' Survival

observed in 20.6% (20/97) of those initially diagnosed without DM.

Kaplan-Meier analysis further revealed that patients younger than 30 years have significantly better OS, LRRFS, DMFS and PFS rates as compared to older patients (81.6% versus 59.8% (p=0.03), 93.1% versus 51.1% (p=0.04), 60.5% versus 46.6% (p=0.02), and 66.1% versus 30.9% (p=0.006), respectively). Of particular interest, sex was significantly associated with DMFS (p=0.03); the estimated 4-years DMFS rates in females were 64.6% versus 47.7% in male patients.

The effect of smoking and alcohol consumption on the different end-points of survival was further assessed. We showed that smoking was not significantly associated with OS, LRRFS, DMFS, and PFS (p>0.05). However, alcohol consumption was significantly associated with OS, DMFS and PFS (p<0.05).

With regard to TNM classification and disease stages, our findings revealed that N, M and the overall stage had a significant impact on patient survival (OS, DMFS and PFS) (p<0.05), while T-category didn't influence any survival end-point (p>0.05). In contrast, the 48 patients with N0-N1 nodal involvement at diagnosis had the highest 4-years OS, DMFS and PFS rates (87.7%, 75.4%, and 66.8%), while patients with N2-N3 had the lowest 4-years OS, DMFS and PFS rates (53.7%, 42.7% and 23.3%). Patients diagnosed with DM had significantly worse 4-years OS, DMFS and PFS than the other subgroups (29.4% vs 82.0% (p=0.000), 13.7% vs 73.4% (p=0,000), and 10.0% vs 55.9% (p=0.000), respectively). The 4-years OS, LRRFS, DMFS and PFS rates of patients at advanced disease stages (III-IV) were 62.3%, 57.2%, 48.8% and 31.6%, respectively, as compared to 91.7%, 87.5%, 91.7% and 91.7%, respectively for patients at early disease stage (I-II) (Table 3 and 4).

Multivariate analysis

In multivariate analysis (Table 5), the 4-years OS was impacted significantly by alcohol consumption (p=0.01), N (p=0.03) and M (p=0.000) category's. Our data further show that better 4-years LRRFS was significantly associated with young age (p=0.01), no

Table 4. Kaplan-Meier Analysis and Univariate Analyses of Prognostic Factors for DMFS and PFS of Patients with NPC

	DMFS				PFS			
	4-year rate (%)	Mean (months)	Univariate analysis (HR; 95% CI)	p value	4-year rate (%)	Mean (months)	Univariate analysis (HR; 95% CI)	p value
Age								
≤ 30 years	60.5%	39.3	2.11 (1.07-4.17)	0.02	66.1%	38.4	2.35 (1.23-4.49)	0.006
> 30 years	46.6%	27.8			30.9%	25.9		
Gender								
Female	64.6%	37.2	1.80 (1.01-3.21)	0.04	49.2%	33.5	1.48 (0.90-2.43)	0.12
Male	47.7%	28.4			34.0%	27.6		
Tabaco consumption								
No	55.5%	32.7	1.30 (0.70-2.40)	0.40	38.9 %	29.4	1.07 (0.59-1.92)	0.81
Yes	46.8%	28.3			38.6 %	27.8		
Alcohol consumption								
No	56.9%	33.6	1.97 (1.04-3.73)	0.03	45.3%	31.0	2.14 (1.19-3.86)	0.01
Yes	34.7%	20.05			39.8%	18.2		
Tumor classification								
T1-T2	67.4%	37.4	1.71 (0.87-3.40)	0.11	53.4%	31.1	1.51 (0.84-2.72)	0.16
T3-T4	49.4%	29.9			39.4%	24.5		
Lymph node status								
N0-N1	75.4%	43.0	3.24 (1.63-6.43)	0.001	66.8%	40.9	3.35 (1.82-6.13)	0.000
N2-N3	42.7%	26.2			23.3%	23.1		
Metastasis status								
M0	73.4%	42.9	9.12 (5.18-16.07)	0.000	55.9%	37.7	5.33 (3.28-8.64)	0.000
M1	13.5%	7.3			10.0%	11.4		
Stage of the disease								
I-II	91.7%	48.9	9.88 (1.36-71.42)	0.02	91.7%	48.9	13.42 (1.85-96.98)	0.01
III-IV	48.8%	29.5			31.6%	26.5		

alcohol consumption (p=0.04), and early N category (p=0.02), whereas, better 4-years DMFS was significantly associated with young age, no alcohol consumption (p=0.01), early N category (p=0.04) and absence of DM at diagnosis (p=0.04). Our data further showed that older age (p=0.01), alcohol consumption (p=0.02), advanced N category (p=0.02), DM (p=0.00) and advanced overall stage (p=0.03) were significantly associated with very worse 4-years PFS.

Discussion

The present study showed that most NPC patients were males with a M:F sex ratio of 1.6. This finding is in agreement with widely reported data showing that independent of race and ethnicity, NPC is more incident in males than females (Xie et al., 2013). The reasons behind this is still unclear; although it has been suggested that this

Table 5. Multivariate Analyses of Prognostic Factors for OS, LRRFS, DMFS and PFS of Patients with NPC

	OS		LRRFS		DMFS		PFS	
	Multivariate analysis (HR; 95% CI)	pvalue	Multivariate analysis (HR; 95% CI)	pvalue	Multivariate analysis (HR; 95% CI)	pvalue	Multivariate analysis (HR; 95% CI)	pvalue
Age	1.59 (0.69-3.65)	0.27	6.58 (1.54-28.12)	0.01	2.11 (0.99-4.50)	0.05	1.98 (1.04-3.76)	0.03
Gendre	-	-	-	-	1.29 (0.72-2.32)	0.37	1.00 (0.60-1.66)	0.98
Tabaco consumption	-	-	-	-	-	-	-	-
Alcohol consumption	1.90 (0.90-3.99)	0.09	2.75 (1.01-7.52)	0.04	1.82 (0.94-3.51)	0.07	1.94 (1.05-3.59)	0.03
T	-	-	-	-	1.21 (0.58-2.50)	0.60	0.82 (0.44-1.55)	0.55
N	2.94 (1.06-8.15)	0.03	1.78 (0.65-4.90)	0.25	2.04 (0.97-4.28)	0.000	1.98 (1.04-3.78)	0.03
M	4.02 (2.07-7.79)	0.000	-	-	7.93 (4.32-14.48)	0.05	4.20 (2.54-6.96)	0.000
Stage of the disease	1.90 (0.19-18.46)	0.57	7.80 (0.74-83.74)	0.08	2.63 (0.29-23.52)	0.38	6.95 (0.82-85.71)	0.07

can be partially due to differential exposure between sex to environmental risk factors (Yuan et al., 2000; Zou et al., 2000). Recently, several studies reported a significant change in the percentage of female patients between young and adult NPC cases (Andejani et al., 2004; Xie et al., 2013). Accordingly, we observed juvenile cases for whom the M:F sex ratio was near equilibrium (1.2) while in cases above 30, there was an imbalance with a M:F sex ratio of 1.8.

Published data report that the age incidence of NPC differs between populations. In high and low-risk ares for NPC, the incidence increases monotonically with age; the incidence peaks are currently around ages 45 to 59 years and declines thereafter, with limited cases of juvenile cases (Liu et al., 2014; Zhang et al., 2015). For intermediate risk populations, the age incidence curve for NPC shows a bimodal distribution with a significant peak between 10 and 25 and a second peak around ages 50 to 59 years old (Daoud et al., 2003; Spano et al., 2003). A similar bimodal age distribution of NPC was observed in our cohort, with a high proportion of young individuals (≤30 years old), suggesting the involvement of exposure to oncogenic agents early in life, and the potential impact of genetic susceptibility. In the present study, 19.0% of NPC patients were smokers and 14.1% were alcohol consumers. The impact of tabacco smoking and NPC development is controversial. Some authors reported that, in contrast to the other head and neck cancers, tobacco smoking and alcohol consumption are less involved in the development of NPC (Jethwa and Khariwala, 2017; Goffinet et al., 2019), whereas others suggested that cigarette smoking can promote carcinogenesis in the normal nasopharyngeal epithelium and is associated with higher NPC mortality (OuYang et al., 2013; Lin et al., 2015). Results of a large meta-analysis provided robust evidence that tobacco smoking is one of the most important risk factors for NPC (Xue et al., 2013).

Reported data showed that alcohol drinking is a useful predictor of prognosis in male NPC patients; drinkers, especially heavy drinkers, have poorer prognosis (Chen et al., 2016). In the present study, multivariate analysis revealed an association between alcohol consumption and worse LRRFS, DMFS and PFS.

Family history of NPC has consistently been associated with an increased risk of developing NPC in high risk populations for NPC (Bei et al., 2012; Xie et al., 2015). Unfortunately, there are few data regarding family history of NPC in Morocco. Recent studies have reported a relationship between family history of cancer and tumor progression (Rehioui et al., 2019) and circulating EBV DNA load (Gihbid et al., 2021). In the present study, family history of cancer was found within 22.5% of patients, among them 8.4% had at least one family member who treated or is currently treating NPC. These results are in agreement with data from high risk populations for NPC, reporting close rates of positive family history of NPC (3.64% to 11.7%) within NPC patients (Ouyang et al., 2013; Wang et al., 2017).

Worldwide, diagnosis of NPC at advanced stages is the main problem that oncologists face in NPC management, which has a considerable impact on therapeutic success and patient survivals (Abdullah et al., 2009). Assessment of disease stage reported that most patients were diagnosed at an advanced stage (III, 23.9% and IV, 64.1%); while only few patients diagnosed at an early stage of the disease (I, 2.1% and II, 9.9%). Furthermore, a high rate of DM was detected among our patients (32.4%) which was comparable to that observed in high endemic areas for NPC (Wei and Sham, 2005) (Chang and Adami, 2006).

Currently, limited data regarding the prognosis of NPC from intermediate risk-population are available. Thus, we assessed 4-years patient survival and influencing prognostic factors in the Moroccan context, where this malignancy occurs at an intermediate risk. The overall prognosis of recruited patients was poor, with very low rates of DMFS and PFS (53.9% and 39.9% at 4 years). These results go beyond previous reports from other studies, highlighting that NPC is a particular tumor with a high rate of regional recurrence and DM (Li et al., 2015; Marnouche et al., 2017). The prognostic impact of gender in NPC is still controversial. Some studies highlighted that being female was a favorable factor, and female NPC patients were less exposed to have DM and exhibited superior OS and PFS rates compared to male patients (Lu et al., 2013; Xiao et al., 2013). Whereas other studies reported no significant difference in survival between the two sexes (Lee et al., 2005; Yunsheng et al., 2008). In the present study, we showed that females with NPC tend to have better OS, DMFS and PFS rates than males, although the difference was not statistically significant.

Previous reports studying the prognostic impact of age in NPC showed that disease-related survival, local control and DM were significantly affected by age (Liu et al. 2008; Yunsheng et al., 2008; Xiao et al., 2013). Similarly, multivariate analysis indicated that advanced age was an independent predictor factor for poor LRRFS, DMFS and PFS (p=0.03). The increased NPC related deaths and disease progression observed in older patients can be related to the poor performance status and/or the presence of comorbidity in this patients group (Sarfati et al., 2016).

In our study, we didn't evaluate the prognosis impact of the histological type of NPC, due to the large predominance of the NKUC type (92.3%). However, several studies demonstrated that NPC related mortality significantly differed between histological subtypes (Wang et al., 2016; Wu et al., 2019). Wu and all showed that patients with KSCC had poorer NPC-specific survival (SS) than UNKC (HR 2.323, 95% CI: 1.636–3.297, P<0.001), while NPC-SS was comparable between DNKC and UNKC (HR 1.435, 95% CI: 0.945–2.111, p=0.067) (Wu et al., 2019).

Scientific evidence showed that the treatment of any cancer involves staging; an accurate staging will help in guiding planned treatment and will also allow clinicians to predict the prognosis. In the present study, multivariate analysis showed that T size was not an independent prognostic factor and highlighted that N status is a powerful independent prognostic factor for NPC. In fact, advanced nodal status was associated significantly with all survival endpoints [(OS: HR= 0.34 (CI: 0.12-0.94), p=0.03), (LRRFS: HR=0.32 (CI: 0.12-0.83), p=0.02, (DMFS: HR= 0.32 (CI: 0.16-0.64), p=0.001), (PFS: HR=

0.45 (CI: 0.24-0.86), p=0.01)]. In line with these results, previous studies demonstrated that the N involvement is more important than the T size in prognosis prediction (Han et al., 2010; Mak et al., 2015; Li et al., 2018; Xu et al., 2019).

Currently, it's widely accepted that DM is one of the main causes of death and the key obstacle to treatment (Ong et al., 2003; Qu et al., 2020); accordingly, our results showed that the presence of DM at diagnosis predict significantly worse OS and PFS in NPC patients (p<0.000). In multivariate analysis, disease stage was not significantly associated with NPC patient's survival. However, Kaplan-Meier showed that as the disease stage increased, the 4-years DMFS and PFS rates decrease significantly; they were at 100% for patients with stage I, 88.9% and 88.9% for patients with stage II, 78.3% and 50.5% for patients with stage III and 38.5% and 28.6% for patients with stage IV, respectively. These results were in line with those reported in previous studies (Mak et al., 2015; Li et al., 2018).

Data of our study are very informative and provides an overview of NPC patients' features and highlights the urgent need for an effective diagnostic, therapeutic and follow-up strategy for Moroccan patients with NPC. In endemic areas for NPC, screening programs are generally based on naso-endoscopy, EBV IgA serology tests, and EBV DNA levels (Tay et al., 2016). Given that survival rates are better among patients diagnosed at an early clinical stage, specifically those with non-nodal involvement; the implementation of NPC new biomarkers' into routine managment in intermediate incidence areas for NPC could be helpful to control this disease, prevent death and improve patient outcomes. In this field, it's of particular interest to assess the usefulness of recent and non-invasive tools such as EBV DNA load (Gihbid et al. 2023), high sensitive imaging (PET-MRI) for initial diagnostic and recurrence detection (Gihbid et al. 2022) and to extend personalized treatment for optimum management of these patients.

In conclusion, our study carried out in a Moroccan population shows that NPC affects young adults and it's often diagnosed at advanced stages of the disease impacting negatively the survival of patients; which was in line with the data from endemic areas. Thus, the use of novel biomarkers that could help in early diagnosis and prognoses prediction, as well as incorporating the recent treatment modality are the key factors for an efficient management of NPC in Morocco.

Author Contribution Statement

AG: participated in the project design, patients recrutement and follow-up, statistical analysis and drafted the manuscript; NT and NB: participated in the project design and review of the final manuscript; ZB and SS: participated in patient's recruitment and data collection; KB: participated in the statistical analysis: AB: participated in patient's recruitment and data collection; JI and AG: participated in patient's recruitment and data collection; RC: participated in the design of the project and review of the final manuscript; MEM: participated in the design of the project and review of the final manuscript; MK: participated in the design and coordination of the project and review of the final manuscript..

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Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee on human experimentation and with the Helsinki declaration of 1975, as revised in 1983. Protocol of the present study was approved by the Ethics Committee of Ibn Rochd Hospital of Casablanca, Morocco. A written informed consent was obtained from each patient.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Conflict of interest statement

The authors declare that they have no competing interests.

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