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Prognosis and Survival of Nasopharyngeal Cancer in Cameroon

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Abstract

Background: Nasopharyngeal carcinoma (NPC) is an entity belonging to upper aerodigestive tract Cancers. NPC is more widespread in Southern China and South East Asia. In our country, it is the leading cause of head and neck cancers. Its prognosis remains bleak because of the late stage at diagnostic. **Objectives:** The objectives of this study were to determine the prognostic factors and survival rate of patients with nasopharyngeal cancer in six reference hospitals in Cameroon. **Material and Methods:** It was a retrospective analytic study, conducted from January 2009 to December 2018. It was conducted in oncology, surgery and Ear Nose and Throat (ENT) units of six reference hospitals. Data from 114 files meeting the inclusion were collected. We have drawn survival curves and determined the different survival probabilities with the help of Kaplan-Meier Method. The different survival curves were compared using the Log-Rank Test (P < 0.05), variables that were statistically associated with the 5% cut off were introduced into the Cox regression model for multivariate analysis, thus allowing us to bring out the prognostic factors significantly associated with survival. **Results:** The mean age at the time of diagnosis of the 114 patients recruited was 45.30 ± 17.14 years. The predominant histological type was the UCNT (Undifferentiated Carcinoma of the NasoPharynx) representing 84.2%. According to the WHO classification, 2 patients were classified as stage I (1.8%), 33 as stage II (28.9%), 42 as stage III (36.8%), 25 as stage IV A (21.9%) and 12 as stage IV B (10.5%). At the end of the survival assessment period, 34 patients were dead and 73 patients (64%) were still alive. The median overall survival was 44 months. The overall survival rates at one, two, three, and four years were 80%; 74%; 68%; 44%, respectively. The prognostic factors associated with poor survival were: late consultation time of more than 12 months, N3 lymph node involvement, 3 and 4 advanced clinical stages. **Conclusion:** The study showed a low survival,

with a median overall survival of 44 months. The overall survival rates at one, two, three, and four years were 80%; 74%; 68%; 44% respectively. The prognostic factors associated with poor survival were late consultation time of more than 12 months, N3 lymph Node involvement, 3 and 4 advanced clinical stages. In order to improve this survival, it is recommended that special emphasis be placed on early detection.

Keywords

Nasopharyngeal Cancer, Survival, Prognostic Factors, Detection, Cameroon

1. Introduction

Nasopharyngeal cancer (CNP) is a fairly rare entity (<1%) of cancers of the upper aero digestive tract which, for their part, are ranked fifth among cancers in humans, behind prostate cancer, lung cancer, colorectal cancers and kidney and bladder cancers [1]. The very contrasting geographical distribution of this type of cancer is one of the characteristics of the disease. Globally, there are three zones: A very high frequency zone with South China (Guangzhou), where the incidence is 30 to 80/100,000/year, and that of the north, where the incidence is 2 to 3/100,000/year; an intermediate frequency zone (8 to 12/100,000/year) with Taiwan (China), Vietnam, Thailand, Malaysia, The Philippines, The Caribbean, The Mediterranean Basin (Maghreb and Middle East), Alaska and the Greenland; And finally a low frequency zone found in Europe and the United States (0.5 to 2/100,000/year) [2]. The peak is between 40 - 50 years old, with an often bimodal distribution (20 - 30 years and after 50 years) with men more frequently affected than women (sex ratio: 2.5 - 3) [3]. In 2018, 130,000 new cases of nasopharyngeal cancer were diagnosed worldwide with 73,000 reported deaths, or 1% of all cancers [4]. It presents in different histological types, dominated by carcinomas which represent more than 90% of nasopharyngeal cancers [5]. The other types, namely lymphomas of variable grade, adenoid cystic carcinomas and soft tissue tumors such as rhabdomyosarcoma, melanoma or adenocarcinoma are rarer [6]. Clinically, the manifestations of CNP are highly variable, the main warning signs being epistaxis, anosmia, nasal obstruction, serum-mucous otitis media or prevalent lymphadenopathy [7]. Given the good accessibility of the nasopharyngeal mucous space, endoscopy is the first-line exploration as it allows a positive diagnosis by performing biopsies. Magnetic Resonance Imaging (MRI) and CT scan participate in the assessment of the extension of these lesions [8] [9]. Treatment is based on radiotherapy and chemotherapy. Radiotherapy alone, which was the first curative treatment for nasopharyngeal carcinoma, remains the standard treatment for initial stage I, without lymph node involvement, with a 10-year survival rate of 98% [10]. Regarding the prognosis, several clinical, biological and radiological factors affecting local control and survival have been

studied; among these we note: age and sex, type and stage of tumor, EBV serology. The dose of radiotherapy and the treatment schedule have been studied primarily as a local disease control factor [11]. The prognosis of CNP remains relatively unfavorable (survival rate of around 50% at 5 years) apart from cancers classified T1 - T2 N0, due to local recurrences and metastatic relapses [12].

Concerning Cameroon, although epidemiological work carried out by Yeme N in 1986 showed that it is located in a low-risk zone, CNP ranks first among cancers of the ENT sphere [13] [14]. In fact, 720 cases of caval cancer had been counted over the past five years, according to GLOBOCAN 2018 data. Very little research has been carried out on this subject to our knowledge. The case of a study by Mouelle *et al.*, on the evolutionary aspect of patients with caval cancer in 1996, found a mediocre overall survival rate of 56% at 1 year and 29%, at 5 years, and a recurrence-free survival rate of 44% at 1 year [15]. Also, faced with the scarcity of local data on this condition and the frequency of which is becoming worrying in Cameroon, we see a need to contribute to the knowledge of this pathological entity, particularly in terms of prognostic factors associated with survival.

2. Patients and Methods

This was a retrospective analytical study, conducted from January 2009 to December 2018, in the ENT and oncology departments of six first and second category hospitals of the Cameroon health pyramid (Douala General Hospital, Douala Laquintine Hospital; Yaounde General hospital, Yaounde Central Hospital, Yaounde University Health Center, Yaounde National Social Insurance Fund Hospital Center). Histologically proven nasopharyngeal cancer patient records were included and followed during this period in these structures. Patients with other large nasopharyngeal conditions and histopathological confirmed non-malignant tumours were excluded. The various socio-demographic, clinical, paraclinical, therapeutic and evolutionary data were taken from the registers of the oncology, surgery and Ear Nose and Throat (ENT) departments of these hospitals. Patients were contacted during their follow-up visits to the hospital and those who could not report for review in the hospital were contacted via telephone. Deaths of subjects were confirmed via contact with their families and relatives. These variables were recorded and processed using SPPS version 20 software. The different associations between the variables were studied using the χ2 test or Fisher's exact test. We plotted the survival curves and determined the probabilities of survival using the Kaplan-Meier method. The comparison of the different survival curves was made using the Log-Rank test ($p < 0.05$). Variables that were statistically associated with the 5% cut-off were introduced into the Cox regression model for multivariate analysis, allowing us to identify prognostic factors associated with survival.

This work had received an ethical clearance from the Ethics Committee of the University of Douala, who granted us ethical clearance No 2116 CEI-Udo/01/

2020/T, to conduct our study in strict compliance with the ethics.

3. Results

3.1. General Characteristics of the Study Population

3.1.1. Epidemiological Characteristics and Medical History

We collected a total of 114 patients. The mean age at tumor diagnosis was 45.30 ± 17.14 years, with extremes ranging from 12 to 82 years, for a median of 45.50 years. A male predominance at 66.7% (76 cases) was noted, for a sex ratio of 2.0 M/1F. The majority of patients were married (81 cases, 71.1%).

The mean time to consultation was 10 months ± 7.25, with extremes ranging from 3 weeks to 27 months, for a median of 9 months. A total of 36.8% of patients (42 cases) had already had an ENT infection, the nature of which was not specified. The patients in our series shared a diet based on smoking and curing in 86% of cases (98 patients). The family history of nasopharyngeal cancer was noted in 1.8% of cases (2 patients) (Table 1).

3.1.2. Clinical Signs

As is shown in Table 2, the clinical picture was dominated by the appearance of a tumor syndrome found in 82.5% of patients (94 cases). Our patients could also present in an isolated or associated way rhinological, otological or neurological signs.

Among the 92.1% (105 cases) who presented cervical lymphadenopathy, it was objectified that they were, in 48.6% (51 cases), of a size between 3 and 6 cm, their site was mainly jugulocarotid in 57.1% (60 cases), and in 71.4% of cases (70 patients), they were of bilateral topography.

The auditory examination carried out by otoscopy mainly revealed serum-mucous otitis in 87% of the patients (87 cases) in our series.

Exploration of the rhinological system was done with a nasofibroscope and revealed an ulcerative budding lesion in 80% of cases (80 patients).

3.1.3. Histolopathological and Treatment Characteristics

UCNT (Undifferentiated Carcinoma of the NasoPharynx) was the predominant histologic type in 84.2% of patients (80 cases), while Non-Hodgkin's Malignant Lymphomas (NHLM) were the least represented histologic type with 3.5% of patients (4 cases) (Table 3). Patients were classified according to the TNM classification adopted by the AJCC Cancer Staging Manual 8th edition (2017). We found, for clinical tumor size, a predominance of patients classified T2 and T3, respectively 49.1% and 29.8% of cases (56 cases and 34 cases). N2 lymph node invasion was predominantly observed, and 21.9% of patients (25 cases) developed metastases. In our series, 69.2% of patients (79 cases) were diagnosed in stages III and IV, on the other hand only 1.8% (2 cases) were grouped together in stage I (Table 3).

The main therapeutic modalities found were concomitant radio chemotherapy and exclusive radiotherapy administered respectively in 47.4% and 31.5% of cases (54 and 36 patients).

Table 1. General characteristics and medical history of patients.

Variable	N	%
Age		
10 - 19	16	13.9
20 - 29	9	7.9
30 - 39	15	13.0
40 - 49	26	22.6
50 - 59	23	20.0
≥60	25	21.7
Gender		
Male	76	66.7
Female	38	33.3
Consultation delay		
<1	9	7.9
2 - 6	30	26.3
7 - 12	30	26.3
>12	45	39.5
Comorbidities		
ENT infection	42	36.8
AHT	15	13.2
Diabetes	9	7.9
HIV	3	2.6
Epigastralgia	2	1.8
Hepatitis B	2	0.9
Chronic sinusitis	1	0.9
Tuberculosis	1	0.9
Surgical history		
Cervical adenectomy	1	0.9
Toxicological history		
Alcoholic intake	15	13.2
Smoking history	8	7.0
Diet		
Smoked fish/meat	98	86.0
Spicy food	71	62.3
Very salty meat fish	1	0.9
Family history		
Cavum cancer	2	1.8
Breast cancer	1	0.9
Cervical cancer	1	0.9
Thyroid cancer	1	0.9

Table 2. Symptoms and physical signs of the study population.

Symptoms/Signs	N	%
Cervical swelling	94	82.5
Rhinological Syndrome		
Nasal obstruction	53	46.5
Epistaxis	46	40.4
Otologic syndrome		
Hearing loss	50	43.9
Tinnitus	19	16.7
Otalgia	18	15.8
Neurological syndrome		
Headache	50	34.8
Facial neuralgia	4	3.5
Trismus	2	1.6
Cervical lymphadenopathy	51	48.6
Nasofibroscopy		
Budding ulcerative lesion	80	84.2
Infiltrating	13	13.7
Polypoid	2	2.1

Table 3. Histopathological and treatment characteristics.

Variable	N	%
Histological types		
WHO type III (UCNT)	80	84.2
WHO type I	12	10.5
WHO type II	9	7.9
LMNH	4	3.5
Stages		
I	2	1.8
II	33	28.9
III	42	36.8
IVA	25	21.9
IVB	12	10.5
Treatment		
Concomitant radiochemotherapy	54	47.4
Exclusive radiotherapy	36	31.5
Palliative chemotherapy	13	11.4
1st chemotherapy + concomitant radiochemotherapy	5	4.4
1st chemotherapy + Locking radiotherapy	6	5.3

3.2. Survival

As shown in Figure 1, the median overall survival was 44 months with a confidence interval (95% CI) of (37.56 - 50.43). The overall survival rates at one, two, three and four years were 80%, respectively; 74%; 68%; 44%.

3.3. Pronostic Factors

3.3.1. Univariate Analysis

In univariate analysis, some factors were found to be significant; in particular, young age (10 - 20 years), and advanced age (over 60 years), consultation time of less than one month and those over 7 and 12 months, locally advanced tumor size (T3 and T4), lymph node invasion (N2 and N3), presence of metastases, WHO stages 3 and 4, palliative chemotherapy, conformational radiotherapy, dosimetry ≥65 Gy, spreading over 6 weeks of radiotherapy (Table 4).

3.3.2. Multivariate Analysis

After multivariate analysis by calculating the Hazard Ratio of each factor using the Cox model, it emerges that the factors associated with death were: The late consultation period of more than 12 months, N3 lymph node invasion, Stages 3 and 4 cancer (Table 5).
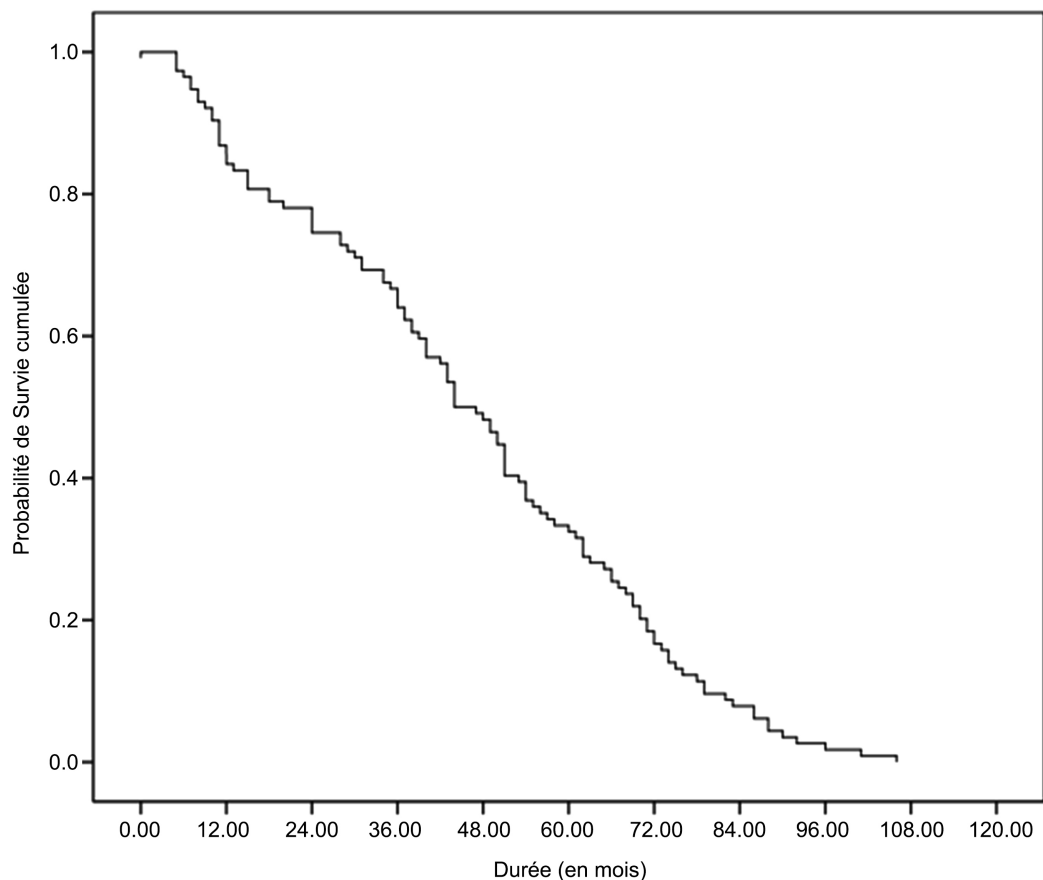

Figure 1. Overall survival curve of the study population.

Table 4. Univariate analysis of prognostic factors.

Variable	Median OS (95% CI) (months)	p-value
Age (years)		
≥60	18 (5.47 - 30.52)	<0.0001*
Consultation delay (months)		
7 - 12	49 (42.73 - 55.26)	0.032*
>12	30 (20.79 - 39.20)	<0.0001*
Tumor size		
T3	35 (50.00 - 73.99)	0.006*
T4	18 (9.39 - 26.60)	<0.0001*
Lymph node metastasis (N)		
N2	50 (47.31 - 52.68)	<0.0001*
N3	24 (14.65 - 33.93)	<0.0001*
Distant Metastasis (M)		
yes	30 (17.12 - 42.85)	0.041*
Stage		
III	50 (47.24 - 52.75)	0.002*
IV	20 (10.70 - 29.29)	<0.0001*
Treatment		
Palliative chemotherapy	24 (15.31 - 32.68)	<0.001*
Type of radiotherapy		
Conformational	44 (38.13 - 49.86).	<0.001*
Radiation therapy dose		
≥65 Gy	51 (45.05 - 56.94)	<0.001*
Staggered radiotherapy		
≥6 weeks	51 (45.42 - 56.57)	<0.001*
Chemotherapy protocol		
CDDP + Doxoribucin	88 (15.0 - 161)	0.027*

Table 5. Multivariate analysis.

Variable	HR (IC 95%)	p-value
Consultation delay (months)		
≥12	10.03 (1.64 - 21.18)	0.012*
Lymph node involvement (N)		
N3	3.83 (0.88 - 16.62)	0.018*
Stage		
IV	24.38 (7.72 - 76.99)	<0.001*

4. Discussion

In our study, the overall survival rates at one, two, three, and four years were 80%, 74%; 68%; 44% respectively. Our results at one year are similar to those found by Soundouss Raissouni in 2009 in Morocco, Kwong *et al.* in Hong Kong in 2006, Tham *et al.* in Singapourg in 2009, which had respectively values of 81%, 86.5% and 88% [16] [17] [18]. Our overall 4-year survival rate of 44% is comparable to those found by Soundouss Raissouni in 2009 in Morocco, Haddaoui *et al.* in Tunisia in 2013, which had respective values of 38% [16] and 50% [19]. However, it was lower than those found by Sultanem *et al.* In the United States in 2000; Kwong *et al.* In Hong Kong in 2006; Tao *et al.* in China in 2013, with their respective values of 82%, 78%, 80.6% [17] [20] [21]. This difference could be explained by the fact that, in our context, the diagnosis of nasopaharyngeal cancer are more often made at an advanced stage (III and IV in 69.2% of our cases), thus compromising the patient's prognosis. Apart from the anatomical reasons mentioned above in our context, this late diagnosis can be explain, by the negative effect of the ignorance and the poverty of the patients, by their sometimes impossibility of having access to specialized hospitals which are concentrated in the main cities, by the insufficient number of doctors and cancer specialists and by diagnostic errors following numerous consultations with traditional practitioners, houses of prayer and self-medication. Moreover, it was better than those found by Yomi *et al.* in Cameroon in 1995; Mouelle *et al.* in Cameroon in 1996; Hind C in Senegal in 2013; Mamadou G in Senegal in 2017, who found respective values of 34%, 36%, 0% and 26% [15] [22] [23] [24]. This could be explained by the fact that, despite the late diagnosis in our context, progress has been made in recent years in the management of caval cancer, in particular by the adoption of new therapeutic strategies in terms of radiotherapy (use of higher doses with more suitable irradiation of the cervical lymph node areas) but also chemotherapy (neoadjuvant chemotherapy and new protocols).

After running the Cox regression model, and calculating the adjusted Hazard Ratio of death for each factor identified by univariate analysis and comparison of survival curves using the Log-Rank test, the relevant prognostic factors that remained associated with the survival with bad prognosis were the late consultation period of more than 12 months, N3 lymph node invasion and stages 3 and 4 of cancer. Our results are comparable to those of Haldum *et al.* in Turkey in 2001, they showed in a series of 357 patients with caval cancer including 272 of WHO type 3 that lymph node involvement was a major prognostic factor in terms of disease-free survival and overall survival [25]. Chua *et al.* have also shown in a study including 290 patients in China in 1997 where they calculated lymph node volume as an important factor affecting remote control and disease-free survival [26]. Mu-Tai Liu in China in 2003 had also shown that lymph node status was an important prognostic factor for overall survival [27]. Likewise, Earnest A. *et al.* in a meta-analysis in 2012 in Singapore demonstrate that lymph node involvement is by far the determining prognostic factor for survival,

in both adults and children [28].

Chen Cheng *et al.* in China found that stage was an important prognostic factor in terms of relapse-free survival [29].

In Jouin Bortolotti's series in 2016 in France, the delay in diagnosis appears to be the only risk factor affecting overall survival [30]. In fact, in our series, 65.8% of cases (75 patients) consulted after a period of 7 months, which explains the diagnostic delay and the advanced stages of our series. In addition, we found in our series that patients without lymphatic involvement, or whose involvement was limited to stage 1, had better survival than those with lymph node invasion stage 3. Moreover, Patients diagnosed with WHO stage 1 had better survival, compared to those diagnosed at stages 3 and 4.

In our study, age did not appear as a prognostic factor affecting overall survival; which is similar to the findings of Soundouss Raissinou in Morocco in 2009 and Mamadou G in Senegal in 2017. On the other hand, in the study of Haldun *et al.* it was established that adolescents and young adults had a better prognosis than the elderly [25]. This difference could be explained by the fact that the age group under 20 represents only 13.9% of our study population.

Concomitant radiochemotherapy was not a prognostic factor associated with survival in our study; unlike those of Yeh *et al.*; Zeng *et al.*, who showed that local control of the tumor was dependent on the action of radiotherapy combined with chemotherapy [31] [32]. We did not find any benefit in doing concomitant radiochemotherapy over radiotherapy in our series. This is probably due to the bias of the retrospective study and to the unbalance of the two treatment arms: the number of patients and the characteristics of the patients (given that 51.8% of the patients in the concomitant radiochemotherapy group were of III and IVA). This unperceived benefit can also be explained by the fact that the decision to combine radiotherapy with chemotherapy is taken late.

The dose of radiotherapy to the cavum has been studied extensively, especially as a local controlling factor. This factor would be all the more important as the tumor is more developed locally. Bedwineck *et al.* did not report a change in the local control rate of tumors classified T1 and T2 if the irradiation dose delivered was greater than 60 Gy. However, they showed that, for tumors classified T3 and T4, there was a linear increase in local control from 55 Gy to 75 Gy [33].

Fang *et al.* observed in their study an increase in local control rates at three years for tumors classified as T3 and T4, with an increase in the dose delivered. For these, the rates were 46% and 63%, respectively, with irradiation doses less than and greater than 75.6 Gy (p = 0.02) [29]. For Lee *et al.* the risk of relapse was 1.16 for patients who received an irradiation dose between 60 and 63 Gy and 1.86 for those who received a dose between 55 and 59 Gy, compared to patients who had a dose greater than 64 Gy (p = 0.008) [34] [35]. For the same authors, the risk of local relapse decreased by 9% per additional Gy in the tumor from a dose of 45 Gy. In our series, the radiation dose was not a prognostic factor affecting the overall survival of patients.

5. Limitations of the Study

The main limitation of our study comes from its retrospective nature and the biases associated with this type of methodology. Indeed, we encountered difficulties in the use of files linked to insufficient data, in particular with regard to biological data such as EBV serology, which is a major prognostic factor because it is associated with nasopharyngeal cancer in Literature. Or radiological data such as tumor volume obtained from CT images by calculating the sum of the different diameters, which constitutes a prognostic factor affecting local control of the disease. The second difficulty was linked to a follow-up bias due to the fact that there are only two radiotherapy centers in Cameroon: The Douala General Hospital and the Bekoko center were not included in our sites. As a result of the closed up of the Yaounde radiotherapy center since 2012, patients diagnosed in a structure other than the Douala General Hospital were systematically referred to one of the two centers for further treatment, giving a problem of file traceability. This significantly affected our data collection. Despite these limitations, this study made it possible to assess the prognostic factors of cavum cancer in six referral hospitals in the cities of Douala and Yaoundé.

6. Conclusion

Nasopaharyngeal cancer (NPC) is diagnosed at a relatively young age. Survival was poor, with a median overall survival of 44 months; the overall survival rates at one, two, three, four years were 80%, respectively; 74%; 68%; 44%. Poor prognosis factors identified were time of consultation of more than 12 months, N3 lymph node invasion, stages 3 and 4 of cancer. In order to improve survival, it is recommended to place particular emphasis on early detection as well as the use of new therapies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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