

Prognostic Factors and Survival of Laryngeal Cancer in Cameroon

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Abstract

Background: Laryngeal cancer is a major cause of morbidity and mortality worldwide. It is ranked worldwide as the second ENT cancer with 238,000 new cases and 106,000 deaths each year. In Africa, data on the prognostic factors and the survival of this pathology remain quite limited. **Objective:** To study the prognostic factors of laryngeal cancer and the survival of patients with laryngeal cancer in Yaoundé and Douala. **Methods and Materials:** We performed an analytical, longitudinal (retrospective) study over a period from January 1, 2009 to December 31, 2018 including all patients with histologically proven laryngeal cancer, at the ENT, oncological, anatomopathological, radiotherapy and surgery Department of three reference health structures in the cities of Douala and Yaoundé (Laquintinie Hospital and General Hospital of Douala, General Hospital of Yaounde). The data collected were recorded and analyzed by SPSS version 25 and Excel 2013 statistical computer software. Survival was determined by the Kaplan Meier method and the search for prognostic factors was carried out using the Cox proportional hazards model. The significance level was $p = 0.05$. **Results:** We selected 80 patients whose vital status we knew and who had been followed up after histological evidence. The sex ratio was 5.66. The median age at cancer diagnosis was 62 years old. 60 (75%) were exposed to tobacco, 52 (65%) had alcohol-tobacco poisoning. The Center and Littoral regions were the most represented with 37.5% and 48.8% respectively. Dysphonia was present in 98.8% of patients. The histological type encountered was squamous cell carcinoma in 78 patients; in the majority of cases the cancer was diagnosed at stage IV and the glottis was the most frequent site (86.2%). The median overall survival was 1.41 with 95% CI [1.08 - 1.74]. The overall survival rates at 1 year, 3 years, 5

years and 8 years were 70%, 18%, 3% and 1.5%, respectively. The poor prognosis factor found was: age greater than or equal to 70 years. **Conclusion:** Present study showed that survival in laryngeal cancer in Cameroon is very low with a median overall survival of 1.41 years. The overall survival rates at 1 year, 3 years, 5 years and 8 years are 70%, 18%, 3% and 1.5%, respectively. The age greater than or equal to 70 years is the poor prognosis factor, while receiving surgery in combination with neoadjuvant chemotherapy or surgery in combination with adjuvant radiotherapy is the factor of good prognosis.

Keywords

Laryngeal Cancer, Prognostic Factors, Survival, Cameroon

1. Introduction

Laryngeal cancer is one of the cancers of the upper aero-digestive tract and accounts for 3% of cancers in humans worldwide [1] [2]. In the majority of cases, it affects men with a sex ratio of 8 men to 2 women [2]. It mainly occurs between 45 and 70 years [2]. Worldwide, there are 238,000 new cases each year and 106,000 deaths annually [3]. In North America and the United States in particular, there are approximately 13,000 cases and 3660 deaths each year due to laryngeal cancer [3]. In Europe, the incidence of laryngeal cancer in men in 2012 was 35,981 cases with a mortality of 18,069 of these cases [4]. In French-speaking Africa, its incidence is 0.6 per 100 inhabitants [4]. For a patient with cancer of the larynx, clinical examination, imaging and endoscopy under general anesthesia, and histology are essential to establish the diagnosis, study the tumor and its extensions, look for metastatic lymphadenopathy and synchronous localization [1]. The most frequent histopathological form is squamous cell carcinoma and accounts for 95% of laryngeal cancers [5]. Its treatment depends on the evolutionary stage of the tumor and poses the challenge of laryngeal preservation. This treatment oscillates between very aggressive amputation surgery and still promising chemoradiotherapy, without omitting the role of prevention as a definite therapeutic component [6]. Several factors are associated with the occurrence of these cancers, but tobacco is so far the most incriminated factor with a presence in 98% of patients [7]. The prognosis of laryngeal cancer is linked to several factors. Thus the site of the cancer, the age and sex of the patient, the TNM stage, the association of laryngeal cancer with other non-neoplastic pathologies and anemia have been identified in North America, Europe and Asia, and in some African countries [6] [8] [9]. The overall survival rate of patients worldwide is between 66% - 89.7% all stages combined [6]. In North America, a Canadian study shows that it is 62% at 5 years [10]. In Europe, the net survival in France is 61.6% at 5 years [11]. In Africa, a study done in Morocco on glottal cancer reports a survival rate of 77% [12]. In Cameroon, a few studies have been carried out on laryngeal cancer, namely a study carried out by Mvouni *et al.* in

2006 which found a 3-year survival rate close to 21% [13]. It emerges from the above that few studies have been devoted to laryngeal cancer, hence our interest in studying this pathology and in particular on prognostic factors and patient survival.

2. Patients and Methods

This was a retrospective cohort study conducted among laryngeal cancers patients at the ENT, oncological, anatomopathological, radiotherapy and surgery-Department of three reference health structures in the cities of Douala and Yaoundé (Laquintinie Hospital and General Hospital of Douala, General Hospital of Yaounde), were retrospectively retrieved from the medical records of those department databases with a 100% rate of accuracy, from January 1, 2009 to December 31, 2018. We carried out non-probability sampling. Records showing complete clinical examination, indicating the presence of malignant tumour in the larynx were included. Patients with other laryngeal conditions and histopathological confirmed non-malignant tumours were excluded. The information was collected on a data collection sheet that we designed, pre-tested and readjusted according to the dysfunctions observed. A trained medical staff took part in this collection. The different sociodemographic, clinical, paraclinical, therapeutical and evolutive data were filled in the questionnaires and the patients or their relatives contacted through phone calls in order to know their vital states and complete all possible lacking information. This information was registered and processed using SPSS version 20 software and Microsoft Excel 2016. We carried out a descriptive analysis of the studied population, the different associations between clinicopathological variables and tumour location was performed using the χ^2 test. or Fisher's exact test. Univariate analysis was performed by performing the survival curves according to the Kaplan-Meier method and the difference in survival was compared statistically by the Log Rank test. Variables statistically significant in univariate analysis were secondarily introduced into the Cox regression model for multivariate analysis. Statistical significance was set at a value of $p < 0.05$.

This work had received an ethical clearance from the Ethics Committee of the University of Douala, who granted us ethical clearance No 2108 CEI-UDo/07/2020/T, to conduct our study in strict compliance with the ethics.

3. Results

We collected data in 111 files of patients with laryngeal cancer whose diagnosis was made between January 1, 2009 and December 31, 2018. Among the 111 files recruited, 31 files were excluded according to the inclusion criteria. Thus, 80 patients were found for our study.

3.1. Survival

We studied the overall survival of our study population, according to socio-de-

mographic variables, lifestyle, clinical, paraclinical and therapeutic characteristics, as presented in **Table 1** and **Table 2**.

The median overall survival in our study was 1.41 years with a confidence interval (95% CI) of (1.08 - 1.74). The overall survival at one year, three years, five years and eight years are at 70%, 18%, 3% and 1.5% respectively (**Figure 1**).

As shown in **Figure 2**, the median progression-free survival is 3.08 years with a confidence interval (95% CI) of (1.17 - 4.14). One-year, three-year, five-year, and eight-year progression-free survival is 83%, 53.5%, 38% and 38% respectively.

Survival with progression shows to us through this curve that one-year, three-year, five-year, and eight-year progression survival were 85%, 30%, 4.8%, and 2.5%, respectively. The median survival with progression was 2.66 years with a confidence interval (95% CI) of (2.11 - 3.21) (**Figure 3**).

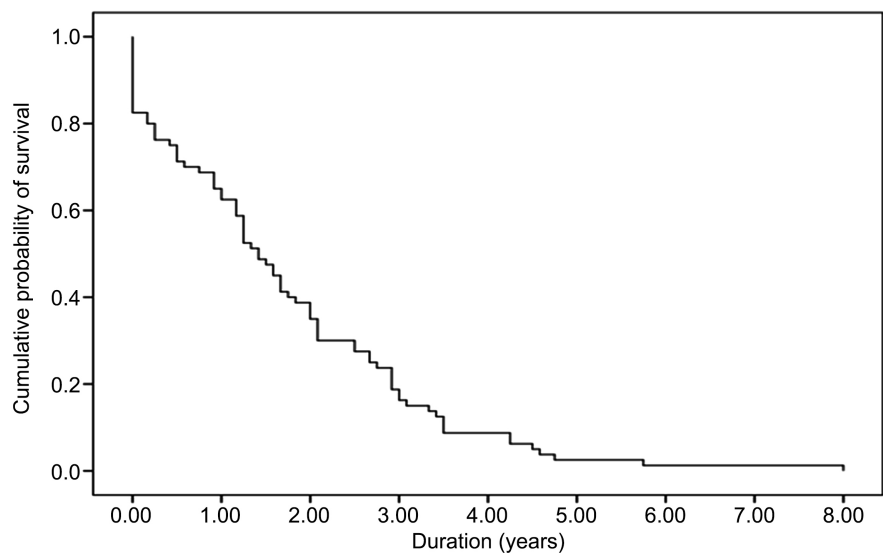


Figure 1. Représentation de la survie globale.

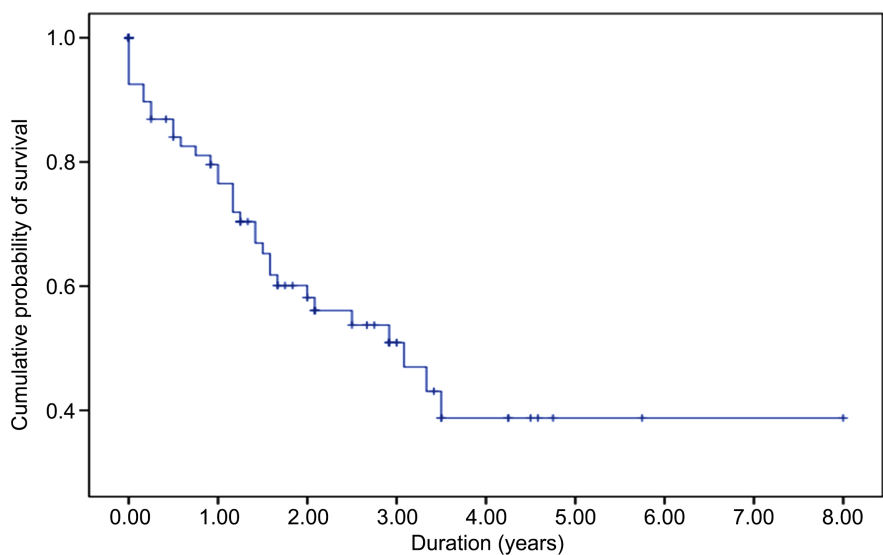


Figure 2. Progression-free survival curve.

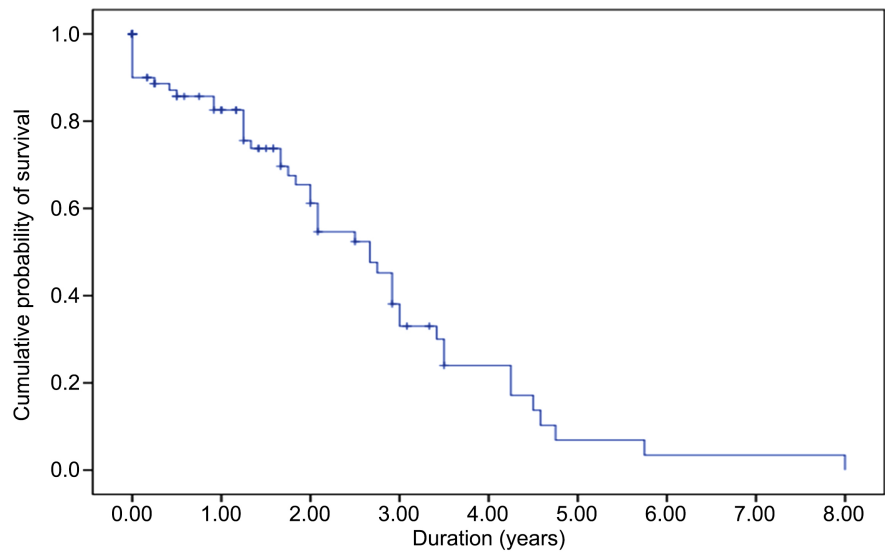


Figure 3. Survival curve with progression.

Table 1. Association of socio-demographic and lifestyle characteristics with survival using log rank test.

Variable	Frequency (n. %)	Median OS (95% CI) (months)	p-value
Age (Years)			
<40	2 (2.5%)	4 (2.79 - 5.5)	0.001*
40 - 49	11 (13.8%)	2.91 (2.48 - 3.35)	
50 - 59	14 (17.5%)	2.91 (2.61 - 3.22)	
60 - 69	37 (46.3%)	1.41 (1.16 - 1.66)	
70+	16 (20.0%)	0.25 (0.03 - 0.46)	
Sex			
Women	12 (15.0%)	1.66 (0.44 - 2.89)	0.932
Men	68 (85.0 %)	1.25 (0.87 - 1.62)	
Smoking			
No	20 (25.0%)	1.42 (0.68 - 2.14)	0.484
Yes	60 (75.0%)	1.25 (0.69 - 1.80)	
Alcoholism			
No	17 (21.2.0%)	1.04 (1.2 - 5.01)	0.105
Yes	63 (78.8%)	2.02 (0.87 - 10.4)	
BMI			
Underweight	26 (32.5%)	2.83 (1.01 - 7.9)	0.218
Normal weight	40 (50.0%)	4.33 (1.53 - 11.6)	
overweight	14 (17.5%)	0.12 (0.01 - 1.01)	

Table 2. Association of clinical, pathological and therapeutic parameters with survival using log rank test.

Variable	Frequency (n, %)	Median OS (95% CI) (months)	p-value
Consultation delay (Months)			
<3	6 (7.5%)	3 (0.29 - 5.70)	0.005*
[3 - 6]	5 (6.3%)	2.91 (2.39 - 3.13)	
[6 - 12]	3 (3.8%)	2.91 (0 - 7.58)	
>12	66 (82.5%)	1.25 (0.94 - 1.55)	
Diagnosis time (Months)			
<1	18 (22.5%)	0.5 (0.03 - 7.99)	0.101
[1 - 2]	39 (48.75%)	1.0 (0.05 - 18.92)	
[2 - 4]	22 (27.5%)	1.67 (0.29 - 9.76)	
>4	1 (1.25%)	-	
Depth of Tumour Invasion			
T1	3 (7.1%)	0.25 (0.11 - 0.38)	0.096
T2	22 (27.8%)	1.16 (0.85 - 1.47)	
T3	29 (36.7%)	1.66 (0 - 4.57)	
T4	25 (32%)	1.58 (0.73 - 4.3)	
Lymph node involvement			
N1	11 (25%)	0.5 (0 - 1.10)	0.125
N2	28 (63.6%)	1.16 (0.73 - 1.59)	
N3	3 (6.81%)	4.25 (0 - 9.85)	
Distant Metastasis			
M0	44 (55.8%)	1.58 (0.68 - 2.48)	0.002*
M1	30 (38.2%)	1.16 (0.73 - 1.53)	
Metastasis location			
Absence	30 (37.4%)	1.58 (0.68 - 2.48)	0.002*
Lung	18 (22.5%)	0.25 (0 - 1.13)	
Lung. vertebra	5 (6.2%)	-	
Spine (cervical)	1 (1.2%)	2.08 - NC	
TNM tumour stage			
Stage 1	8 (10.0%)	2.66 (2.08 - 3.24)	0.001*
Stage 2	27 (33.8%)	1.66 (1.10 - 2.23)	
Stage 3	26 (32.5%)	1.33 (1.12 - 1.54)	
Stage 4	19 (23.8%)	0.58 (0 - 1.53)	

Continued

Histological type			
Squamous cell carcinoma	78 (97.5%)	1.41 (1.05 - 1.77)	0.742
Verrucous carcinoma	1 (1.2%)	-	
Adenocarcinoma	1 (1.2%)	-	
Surgical resection margin			
Healthy	45 (68.1%)	2.08 (1.07 - 3.08)	0.007*
Invaded	21 (31.9%)	1.25 (0.62 - 1.87)	
Treatment			
Chemiotherapy + radiotherapy	13 (16.3%)	1 (0.37 - 1.62)	0.008*
Surgery + chemotherapy	6 (7.5)	0.19 (0.01 - 3.95)	
Surgery + Radiotherapy	34 (42.5%)	1.3 (0.61 - 2.04)	
Surgery + Chemotherapy + Radiotherapy	21 (26.3%)	1.75 (1.36 - 2.13)	
Exclusive surgery	6 (7.5%)	0.41 (0.15 - 0.68).	

3.2. Pronostic Factors**3.2.1. Log Rank Test**

Table 1 shows that the only socio-demographic and lifestyle characteristic which was statistically significant association with survival was age ($p = 0.001$); Patients who 60 - 69 years old or more than 70 years, had low median survival time (60 - 69 years = 1.41 months, 70 + = 0.25 months) compared to more young people. There was no significant association between survival and other variables.

As shown in **Table 2**, treatment modality was significantly associated with survival ($p = 0.008$). Surgical resection margin was also associated with survival ($p = 0.007$). The median survival time of patient who healthy surgical resection margin was higher (2.08 months) compared to those with invaded (1.25 months). TNM stage was also significantly associated with survival ($p = 0.001$) with patient in stage 4 having the least median survival time (0.58 months). There was significant difference concerning delay ($p = 0.005$); patients who consulted very late (after 12 months) had low median survival (1.25 months) compared to early consultation (3 months). The presence of distance metastasis was also significantly associated with survival ($p = 0.002$). Other parameters were not significantly associated with survival.

3.2.2. Multivariate Analysis (Cox regression)

According to the cox regression analysis, age ≥ 70 years (HR = 19.52, $p = 0.027$), surgical treatment combined with neoadjuvant chemotherapy (HR = 0.42, $p = 0.039$) and surgical treatment combined with radiotherapy (HR = 0.45, $p = 0.019$) were variable that were significantly associated with survival. But, it is important to notice that, age ≥ 70 was a factor of poor prognosis; while age < 40 were the factors of good prognosis (**Table 3**).

Table 3. Association of different characteristics with survival using Cox regression analysis.

Variable	HR (IC 95%)	p-value
Age (Years)		
<40	Réf	1
40 - 49	2.08 (0.22 - 19.68)	0.521
50 - 59	2.44 (0.21 - 27.51)	0.47
60 - 69	8.81 (0.73 - 106.20)	0.087
≥70	19.52 (1.40 - 270.58)	0.027*
Distant metastasis		
M0	Réf	1
M1	2.37 (0.67 - 14.07)	0.097
Metastasis location		
Absence	Réf	1
Poumons	0.78 (0.30 - 2.01)	0.609
Poumons, Os	1.37 (0.12 - 15.60)	0.799
Vertèbre cervicale	0.73 (0.06 - 8.22)	0.802
TNM tumour stage		
Stage 1	Réf	1
Stage 2	2.04 (0.66 - 6.27)	0.212
Stage 3	1.22 (0.38 - 3.91)	0.731
Stage 4	3.32 (0.71 - 15.55)	0.127
Consultation delay (Months)		
<3	Réf	1
[3 - 6]	2.97 (0.57 - 15.26)	0.192
[6 - 12]	3.16 (0.50 - 19.71)	0.216
≥12	2.24 (0.48 - 10.33)	0.298
Limits of surgical excision		
Healthy	Réf	1
Invaded	1.11 (0.49 - 2.48)	0.792
Surgery		
No sugery	Réf	1
With chemotherapy	0.42 (0.11 - 0.68)	0.039*
With radiotherapy	0.45 (0.35 - 0.77)	0.019*
With chemotherapy + radiotherapy	2.26 (0.73 - 7.00)	0.156
Exclusive	5.41 (0.98 - 29.92)	0.053

4. Discussion

In our study, the one-year, three-year, five-year, and eight-year overall survival rates are 70%, 18%, 3%, and 1.5%, respectively. Our overall one-year survival is similar to that found by Daneshi *et al.* in Iran for whom, the patients' 1-, 3-, 5-, and 10-year survival rates were 81%, 62%, 53%, and 38%, respectively; in USA, the 5-year relative survival rate was 46% for Supraglottis location, 76% for Glottis and 52% for subglottis [14] [15]. But these results are lower than those of Zhang *et al.* in China with 99% and 100% respectively [16]. Our lower survival rate than that in the literature could be explained by the advanced stages consultation of our patients during the disease.

Our overall three-year survival is 18%, it was higher than the overall survival rate in Brazzaville, which was estimated at 15% [17]. But, our result is lower than those found by Balakrishna (45.7%), Santos (61.4%), Daneshi (62%), even Zhang *et al.* in China in 2013 [with a rate of 81.5%, [14] [16] [18] [19]. In another study, the 3-year survival rate for advanced stage was 61% [20]. This discrepancy between our series and the results of the literature could be explained by the non-compliance of patients, the non-compliance with medical monitoring for various reasons and the late diagnosis of the disease.

The overall five-year survival in our series is 3%. Pezier *et al.* reported a 35.6% survival rate among American patients after 5 years of diagnosis, another study in the USA reported the 5-year survival rate of the patients as 53%, [21] [22]. Daneshi reported about 53% which is far below the data found in the literature [14]. The discrepancy between our series and the literature could be explained by the small size of our sample, the advanced stage during the diagnosis in our patients and the late diagnosis in the latter.

After analysis of the survival curves by the Log-Rank test, the factors that influenced survival in our study were: age, stage (TNM), presence of metastasis, surgical resection margin, type of treatment and consultation delay. These results agree with those of Boffeta *et al.* in Italy who found lymph node involvement, TNM stage, age, smoking and the location of the tumor [23]. Daneshi discovered significant relationship between patients' survival and age at diagnosis, disease stage, tumor grade, positive L. node, and type of treatment [14]. Brandstorp-Boesen *et al.* by studying Impact of stage, management and recurrence on survival rates in laryngeal cancer, revealed that, concerning the glottic cancer, surgical treatment improved overall survival, whereas old age, alcohol, T3-T4 status, positive N-status and no treatment were associated with worse survival. In supraglottic, age, alcohol, and positive N-status had a significant impact on overall survival by multivariate analysis [24]. Zhang *et al.* also discovered that the surgical resection margin, clinical stage, and comorbidity were independent factors affecting the laryngeal cancer prognosis [16].

A study by Gourin *et al.* on patients with stage 4 of LC suggested that those with a higher N stage were at a greater risk of death. Accordingly, the risk of death in people at N2 and N3 stages was 2.29 and 2.96 times more than those at

a N0 stage

The factors found above, influencing survival in our series, were re-analyzed according to the Cox model in order to estimate the Hazard Ratio. The resulting prognostic factors are: age: ≥ 70 (HR = 19.52, $p = 0.027$) as a factor of poor prognosis; Surgical treatment associated with neoadjuvant chemotherapy (HR = 0.42, $p = 0.039$) and Surgical treatment associated with neo-adjuvant radiotherapy (HR = 0.45, $p = 0.019$) as a factor of good prognosis. In most studies on the survival of patients with LC, age was considered as an important risk factor. Dameshi *et al.* illustrated that the risk of death in patients aged between 50 and 70 and patients over 70 was, respectively, 1.77 and 3.69 times more than those under 50 [14]. In a series of 1030 head and neck cancer patients, Lacy *et al.* found that younger patients had a significantly better five year survival rate than middle aged or old patients [25]. Brandstorp-Boesen *et al.* in the study of supraglottic LSCC revealed that older age (>60 years) was a significant negative prognostic factor [24]. Boffeta *et al.* in Italy concluded that patients in older age groups experienced significantly worse survival than younger patients, the difference being particularly relevant between patients aged < 70 years at diagnosis and those aged > 70 years at diagnosis [23]. Some other authors found no significant relationship between age and the risks of death [21] [26]. The advanced age would be a factor of poor prognosis could be justified first of all by the fact that the patients drag this pathology for a long time and thus arrive at advanced stages and should be noted that the more the patients age the lesser the support of side effects of different treatments

According to Bradford *et al.*, Surgery and radiotherapy, either alone or in combination, are the conventional modalities for the management of squamous cell carcinoma of the larynx; in squamous cell carcinoma, chemotherapy in conjunction with radiotherapy is an alternative to laryngectomy in patients with advanced larynx cancer [9]. Wolf *et al.* found that good survival rates were achieved in patients selected for primary surgery, and both neoadjuvant chemotherapy and primary surgery had better survival rates than with concurrent chemoradiotherapy. Although the optimal individualized treatment approach for patients with advanced laryngeal cancer has not yet been defined, and likely does include surgery [27]. In the series of Iseh and Kufreh in 2011 in Nigeria, the combination of surgery and radiotherapy was a good prognostic factor as in our series [28]. The combination of surgery-radiotherapy, surgery-chemotherapy will have an advantage of limiting and controlling the evolution of the tumor, increasing the chances of completing remission and reducing recurrence and metastasis.

Limitations of Study

Our study concerned patients with laryngeal cancer in Cameroon, particularly in the cities of Yaoundé and Douala, and at the end of our recruitment we retained 80 patients out of the 101 files found between 10 years. During this study, we

were stuck with problems such as the absence and/or insufficiency of key information for our study: patient history, clinical examination data, anatomopathological, biological and morphological examination results. Notwithstanding these limiting parameters of our study, we nevertheless succeeded in identifying the prognostic factors and the survival of patients with laryngeal cancer in the Yaounde General Hospitals, Douala General Hospital and Douala Laquintinie Hospital.

5. Conclusion

Present study showed that survival in laryngeal cancer in Cameroon is very low with a median overall survival of 1.41 years. The overall survival rates at 1 year, 3 years, 5 years and 8 years are 70%, 18%, 3% and 1.5%, respectively. The age greater than or equal to 70 years is the poor prognosis factor, while receiving surgery in combination with neoadjuvant chemotherapy or surgery in combination with adjuvant radiotherapy is the factor of good prognosis.

Conflicts of Interest

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

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