Treatment of oral cancer in a poor setting country

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ABSTRACT

Background and Objectives. Treatment of oral cancer (OC) is more challenging in resource-limited settings. The present research aimed to evaluate the treatment challenged of OC in a poor setting area.

Materials and Methods. Retrospective study of 196 patients diagnosed with OC from February 2000 to February 2019 at the Hospital of Kinshasa University was carried out. The treatment approach and factors associated with the outcome were evaluated. Univariate analysis and multivariate analysis were used to identify the factors associated with a suitable outcome. The SPSS 25.0 was used for data analysis and $P < 0.05$ was considered significant.

Results. A total of 196 patients were included in this study. 62% were males and 38% were females. OC was most prevalent in stage IV (44%). The socio-economic low and the advanced stage of the lesion were variables had statistic relevance without the good outcome while the age ≤ 30 years prove to be statistically with a good outcome.

Conclusions. The treatment of oral cancer in a limited resource setting is still challenged.

Keywords: Outcome factors, oral cancer, and limited resource setting

Abbreviations: List all abbreviations & full terms

NOTE: References cited in text are in square brackets **BEFORE** the closing punctuation, e.g. [1,2,3]. Figures/tables are in parenthesis, e.g. (Figure 1) or (Table 1) after the punctuation

INTRODUCTION

Oral cancer (OC) is a malignant neoplasm that squamous cell carcinoma (SCC) represents the most prevalent histological type [1]. It is the sixth most common cancer among head and neck carcinomas in the world and becoming a major health problem [2,3]. The incidence of malignant cancers is increasing every year. The mortality rate reported by the International Agency for Research on Cancer (IARC) was 50% of deaths per year [4]. Several anatomical sites have been

reported in the literature [5]. The floor of the mouth, tongue, and retromolar region were the most prevalent [4]. Smokeless and smoking tobacco, alcohol, and viral infection, especially human papillomavirus are among the greatest risk factors for disease development [6-8].

The treatment of OC is complex and challenging due to several factors including availability of resources (equipment), surgeon training and experience, patient's general medical condition and preferences, etc. The standard of care is primary surgical resection with or without postoperative adjuvant therapy to treat the primary tumor, preserve the function, and possibly limit recurrence [9]. Surgical techniques combined with the routine use of postoperative radiation or chemotherapy generally result in improved survival rates [10].

The outcome treatment of oral cancer remains unfavorable because of the high mortality rates, notwithstanding advances in diagnosis and therapy. Additionally, many of these tumors have an aggressive biological behavior at initial stages with early regional metastases and death. This uncertainty in tumor progression has led researchers to seek possibility that might affect the outcome. Socioeconomic factors, tumor stage, sites, histological grading, treatment methods, access to healthcare services, educational levels, patients' occupations, and cultural factors have been documented as affected the treatment outcome of OC [11,12]. Investigation of these factors aims to learn more about the challenges, so that specific strategies may be applied individually. In the Democratic Republic of the Congo (DRC), no study evaluated the treatment outcome of OC. The purpose of this paper was to evaluate variables related to patient, tumor, and treatment affected OC outcome in the resource-poor setting to plan the protocol for preventing OC in this area.

MATERIALS AND METHODS

Study design and sampling:

Retrospective analysis chart review with a non-probabilistic sampling design of 392 Congolese patients with oral cancer (OC) based on diagnostic criteria outlined in the 2017 World Health Organization classification [13] and treated from February 2000 to February 2019 at the Hospital

of Kinshasa University was carried out. The study was conducted under the supervision of the National Center Research of Dental Sciences in DRC, Ministry of Scientific Research and Technologic Innovation.

A total of 392 patients from January 2004 to February 2019 were reviewed for participation in the study. Of those, 196 cases were excluded from the study for the following reasons: data records were incomplete for review (n=182), and OC was treated initially at other hospitals (n=14). A total of 196 patients were finally retained. The inclusion criteria for the patients were primary OC treated initially with curative surgery at the Hospital of Kinshasa University in that the biological material was biopsied during surgery and stored. However, the incomplete records of the patients, benign tumors, lip carcinomas, and OC treated at another hospital were excluded.

Study variables

The study variables were gender, age, education, socio-economic level (sociodemographic variables), site of involved OC, treatment methods, risk factors, clinical stages, and levels of differentiation were recorded and assessed. The socioeconomic level of the patient was defined according to the index of possession of certain assets by the household from the demographic survey and Health of the Democratic Republic of the Congo, 2013-2014. It was determined according by 3 categories: high status when using drinking water in the household, electricity, internal toilet, radio, television, refrigerator, and car; (2) middle status when using both drinking and no drinking water, toilet, electricity, and using radio, television, refrigerator and car of less quality than those defined by the high-level status; and (3) low-status when using non-drinking water, no toilet, no electricity, no radio, television, refrigerator, and no car. The primary outcome variables were the poor outcome (presence of recurrence) or suitable outcome (no recurrence) during the study period.

Data collection and measurements

Data were collected from medical records of patients at the mentioned Hospital, Department of Oral and Maxillofacial Surgery. The additional information was obtained from the patient's medical records in the Pathology Department of the same institution and from the computed tomography scan. The microscopic slides of the patients were reviewed by a panel of two pathologists to confirm the diagnosis of OC and to evaluate the histopathological characteristics.

Management Treatment

After clinical or histopathologic confirmation of the OC diagnosis, the patients were treated. The treatment methods performed included surgery alone, surgery followed by chemotherapy using only Fluorouracil, chemotherapy alone, and abstention therapy. The patients had undergone

surgical removal of the primary lesions with curative intent as well as chemotherapy alone. The abstention therapy was defined as an approach of supportive care and pain management either due to lack of money treatment or the lack of oncologists in oral maxillofacial and neck Surgery in the country. Recurrence was evaluated by the presence of OC on clinical examinations, and radiographs, and reconfirmed by histopathologic examination. The outcome treatment of OC in post-operative was categorized as poor (presence of recurrence), and suitable (without recurrence) during the study period.

Statistical Analysis

Descriptive statistics were used to report the data as frequency distributions, graphic representations, and the mean ± standard deviation. The difference in the clinical characteristic and predictor variable was analyzed using the Chi-square test. Univariate and multivariate analyses were performed to measure the association between any variables of interest and the outcome variable using the Pearson x2 test. Statistical significance was set at 5%.

Ethical aspects

It was a retrospective study conducted according to the tenets outlined of the Declaration of Helsinki and to the STROBE guidelines. All patients and/or their parents had provided written informed consent for the agreed interventions.

RESULTS

The frequency distribution for each variable according to the baseline data of patients is shown in Table 1. The mean age was 43.4 ± 4 (SD) years and the majority of patients were males (62%). Sixty-two percent of patients had a university education level, sixty patients had a middle economic situation. Smoking and alcohol consumption were almost equal risk factors for OC with 37.8% and 36.7% respectively. The surgery was performed in 50% of patients, of which 30% received surgery or chemotherapy alone, and 20% received surgery followed by postoperative chemotherapy. The remaining patients received abstention therapy mostly because of the lack of oral maxillofacial and neck Surgeon oncologists in the country. The features of OC are detailed in

Table 2. Bilateral lymph nodes were observed in 45% of cases, and stage IV was clinically most prevalent (44%). Well-differentiated OC was the most prevalent (53.1%) compared to poorly differentiated OC and no differentiated OC. The 3 main sites of involved area were the floor of the mouth (32.7%), retromolar (24.5%), and the palate (20.4%). Table 3 demonstrates an analysis of factors affecting OC outcome. Low and medium economic level [45 (5.44; 371.91)], [13.5 (2.00; 90.69)], bilateral lymph nodes [18.6 (3.09; 112.43)] and advanced stage [19.4 (3.23; 122.52)] where statistically associated with the outcome treatment of OC. After adjustment, medium economic level and bilateral lymph nodes did not prove to be statistically significant. Only the low socioeconomic standard of living and the advanced stage of OC were significantly related to the recurrence (Table 4). Additionally, the age $\leq$ 30 years was associated with a suitable outcome.

DISCUSSION

The treatment of oral cancer (OC) is complex and generally associated with a poor outcome. This study aimed to evaluate the challenges affecting the outcome treatment of OC in the resource-poor setting to plan a protocol preventing those lesions. The findings showed that 70.4% of the patients had an advanced-stage OC. Low socio-economic level and advanced stage of OC negatively affected the outcome, while age $\leq$ 30 years was associated with a suitable outcome.

The present results confirm that in developing countries, OC is still diagnosed at advanced stages, unlike in developed countries in which the most prevalent stages are I and II [14]. Socio-economic factors, ignorance of the patients, and misdiagnosis decrease the survival rates among patients in developing countries [15]. The primary location of most tumors was the floor of the mouth as was found by Bhurgri et al [16], while other studies observed the tongue as the primary site [17]. These anatomical regions are recognized as more difficult to control, even though the tumor site has no significant effect on the outcome treatment of OC.

In the literature, several treatment regimens for OC have been discussed and these are taken either alone or in combination. However, the most effective treatment modality has not yet been established. Surgery is the first-line treatment indicated for stage I and II tumors, and combined

with radiotherapy or chemotherapy for advanced-stage lesions (III and IV) [18]. Patients who were frail or intolerant to the toxicities induced by surgery and radiotherapy, the combination of chemotherapy drug and radiotherapy proved to be an alternative treatment. Concomitant standard treatment of platinum-based chemotherapy associated with radiotherapy improves patient survival and quality of life compared to radiotherapy alone [19]. The management of OC in this study when compared to other studies was vastly different [20,21]. The therapeutic abstention of the patient has been usually observed in this cohort. Mean that, the management of OC is challenging and largely attributed to the lack or limited number of surgeon training and the poor economic situation of patients. Oncologist surgeon requires in-depth knowledge in the field with adequate experience. A small number of specialists in oral and maxillofacial surgery, and the lacking of the trained surgeons in head and neck oncology up to 2019 may explain the above outcome. Additionally, the international guidelines for the management of OC assumed the availability of cytology, imaging, high levels of surgical expertise, and postoperative chemo/radiation therapy [13]. However, chemotherapy, surgery and radiotherapy as standard cancer treatment modalities are not all available in the present resource-poor setting and in the patients with low economic situation. This also might lead to inappropriate investigations and treatment challenges that consequently affected the outcome. Costs for medical treatment and housing abroad are not at the expense of the government. Additionally in the present research, nothing is known whether the patients had undergone surgical removal with safety margins of the primary lesions, whether elective neck dissection was done in T2 to T4-staged patients with no neck metastases or not. Accordingly, a protocol preventing oral cancer and the policy of revising and updating the current OC educational curriculum in dental schools, and the creation and establishment of a National Cancer Control Plan are of utmost need in the RDC.

In the present study, the low social standard of living and the advanced clinical stage of the lesions has affected the outcome of OC. Some authors consider OC as a disease associated with low economic and educational status [22,23]. The older age seemed to be a high-risk factor for

poorer outcome [24]. Advanced age, especially among those older than 69 years, was a significant risk factor for mortality due to poor tolerance to treatment and lower performance status.

OC prevention predominantly relies on dentists to raise awareness amongst oral healthcare workers regarding OC signs [25]. The knowledge level of dentists about common clinical features of OC, associated risk factors of OC and the most frequent stage of diagnosis in DRC has been evaluated and concluded to be very low [26]. The earlier oral cancer is detected, the more effective the treatment is. However, the failed opportunities for early diagnosis and treatment are responsible for significant morbidity and mortality. There is clear evidence in the literature that OC screening as part of a screening program is a low-cost and effective method to improve the survival rates in low-resource countries. Those with limited access to healthcare facilities with poor socioeconomic status must benefit from such screening campaigns.

In the DRC, the advantages of early OC detection remain undervalued by the political authority, physicians, and health professionals. Based on the current findings and previous studies [26,27], a plan for the treatment regime in a resource-poor setting is suggested as follows: Firstly, the prevention and early detection of OC like a key component of an overall cancer control plan that is one of the four key drivers to impact cancer mortality [28]. Consequently, the proposed screening and management protocol for OC prevention in a resource-poor setting are summarized in 7 steps as follows:

Step 1: Training team of dentist's oral health professionals, and physicians to identify and advise on promoting oral cancer screening activities in the community and development of the materials to raise awareness.

Step 2: Prevention team of risk factors of OC to promote

- Conducting self-examination of the mouth,

- Reduce the use of tobacco products and avoid excessive alcohol consumption,

- Consuming a well-balanced meal with fruits and vegetables,

- Avoid unprotected sun exposure;

- Limit the number of sexual partners to reduce the risk of HPV infection;

- Consult a dental surgeon for an oral examination every 6 months.

Step 3: Target population identification which should include:

- Being of an age ≥ 30 years

- Using tobacco in its different forms

- Having a history of alcoholism (old or active)

- Having sex with multiple partners or associated with cervical cancer

- Frequently exposed to different forms of radiation or photo-exposition

Step 4: Proper Screening with 3 methods that will be used:

1. Questionnaire to identify the history or risk factors associated with,

2. An oral examination that will help to observe any facial abnormality and help examination of the lips, buccal mucosa, gingiva, dorsal and ventral surfaces of the tongue, retromolar trigon, the floor of the mouth, and palatal mucous membrane.

3. Supplemental utilization of other techniques included light-based techniques, histopathology, etc.

Step 5: Patient-referral pathways:

- Patients could be referred directly to the department of oral medicine or histopathology analysis, the Oral and maxillofacial department after taking a biopsy as the standard technique to confirm oral cancer.

Step 6: Cancer Management: need a formation of the dentist, the medical oncologist and oncologist surgeon and all staff members in the management of OC

- Excision of tumors along with performing neck dissections as well as reconstruction of post-ablative surgery.

- Chemotherapy or radiotherapy depending on the case.

Step 7: Post-screening follow-up for suspected cases or post-operative cases treated

-        In the absence of lesion or suspected oral cancer, the patient will be monitored and evaluated every 2 months up to one year;

-        The operated case will be reviewed every 3 months in the first two years, 2 times a year in the 3-5 years and once a year after 6 years.

To proceed and help with the above protocol for screening, Figure 1 should be strictly used as a guideline review of screening OC. This protocol was elaborated under the supervision of the National Center Laboratory of Oral Biomedicine Ministry of Research Innovation and Technology, the Democratic Republic of the Congo, in collaboration with the Director of the World Health Organization (WHO African Office region) and WHO DRC Office), the Director of the National Dental Health Program and, the independent expert of the WHO who is the Director of a Non-Profit Organization "Espoir le la Nation Congolese".

Given the retrospective nature of the present study, there are some limits. The study included only patients who had undergone primary surgery. The scarcity of available data on the surgical treatment of OC, and study design variability have made comparisons with other studies difficult. However, the study design was implemented with high standard scientific rigor, and these weaknesses should not affect the reliability of the results to a great extent.

CONCLUSION

The poor resource setting, the advanced stage of OC, and the low socio-economic status of the patients were the identifiable variables negatively affecting the outcome. Early diagnosis, formation of all members staff in the management of OR cancer is utmost need in the RDC

CONFLICT OF INTEREST

None declared.

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None declared

AUTHOR'S CONTRIBUTIONS

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FIGURES AND TABLES AND

TABLES

Table 1. Sociodemographic parameters

Variables	Number of patients	Percentage
Sex		
Male	122	62.2
Female	74	37.8
Age (Year)		
≤ 30	14	7.1
31-40	36	18.4
41-50	38	19.4
51-60	76	38.8
61-70	20	10.2
≥ 71	12	6.1
Education level		
Primary School	18	9.2
High School	52	26.5
University	122	62.2
No education level	4	2.0
Economic level		
Low	48	24.5
Middle	118	60.2
High	30	15.3
Risks Factors		
Smoking	14	7.1
Alcohol	36	18.4
Smoking & Alcohol	72	36.7
Niether smoking or alcohol	74	37.8
Duration of the lesion (months)		
≤ 3	60	30.6
4 - 6	70	35.7
7 – 9	42	21.4
> 10	24	12.2
Treatment		
Surgery	58	29.6
Surgery and Chemotherapy	40	20.4
Chemotherapy	58	29.6
Abstention	40	20.4

Table 2. Distribution of oral cancers according to clinical variables

	Number of patients (196)	Frequency (100)
Lymph nodes		
Unilateral	38	19,4
Bilateral	88	44,9
None	70	35,7
Stage of lesions		
Stage I	20	10,2
Stage II	38	19,4
Stage III	52	26,5
Stage IV	86	43,8
Differentiation		
Well-differentiated	104	53,1
Poorly differentiated	62	31,6
Non-differentiated	30	15,3
Clinical forms		
Exophytic	16	8,2
Nodular	28	14,3
Ulcerative	98	50
Mixed	54	27,6
Tumor sites		
Tongue	24	12.2
Floor of the mouth	64	32.7
Retromolar	48	24.5
Palate	40	20.4
Vestibula	14	7.1
Lips	6	3.1

Table 3. Univariate Analysis of outcome factors

Variables	Pronostic N(%)		
	Good n=30(12,2)	**Bad** n=68 (33,7)	**OR** (IC 95%)
Socio demographic Factors			
Sex			
Male	16(53,3)	42 (61,8)	0,7 (0,21;2,42)
Female	14(46,7)	46 (38,2)	1
Age (years)			
18-30	10(41,7)	4(5,9)	0,1 (0,01;0,06)
31-50	12 (33,3)	24(15,2)	0,4 (0,09;1,71)
51 and greater	8 (16,7)	40 (21,2)	1
Socio-economic Level			
Low	4(13,3)	40(58,8)	45 (5,44; 371,91)
Medium	8(26,7)	24 (35,3)	13,5 (2,00; 90,69)
High	18(60)	4 (5,9)	1
Clinical Aspects			
Duration of the lesion (months)			
≤ 3	20(66,7)	6(8,8)	0,01 (0,001;0,13)
4 - 6	8(26,7)	12 (17,6)	0,06 (0,002;0,631)
> 7	2(6,6)	50 (73,5)	1
Sites			
Tongue	2(6,7)	8 (11,8)	0,3 (0,01;5,66)
Rétromolar	2(6,7)	22(33,4)	0,8 (0,04;14,03)
Buccal mucosa	8(26,7)	2(2,9)	0,02 (0,001;0,354)
Lip	6 (20)	2(2,9)	0,02 (0,001;0,498)
Palate	10 (33,3)	6 (8,8)	0,04 (0,004; 0,513)
Floor of the mouth	2(6,7)	28 (41,2)	1
Lymph nodes			
Unilateral	8(26,7)	20(29,4)	6,7 (1,14;38,83)
Bilateral	6(20)	42(61,8)	18,6 (3,09; 112,43)
None	16(53,3)	6(8,8)	1
Clinical Stage			
Stage I	14(46,7)	2(3)	0,3 (0,02;4,24)
Stage II	8(26,7)	4 (6)	0,04 (0,002; 0,544)
Stage III	2(6,7)	12 (17,6)	19,4 (3,23; 122,52)
Stage IV	6(20)	50 (73.4)	1
Pathological finding			
Well diffrenciated	16 (53,3)	24(35,3)	0,33 (0,06;1,97)
Poor differenciated	10(33,3)	26(38,2)	0,6 (0,1; 3,7)
None	4 (13,3)	18(26,5)	1
Clinical Forms			
Exophytic	8(26,7)	8(11,8)	0,3 (0,04;1,80)
Nodular	10(33,3)	8(11,8)	0,2 (0,03; 1,36)
Ulcerative	6(20)	30(44,1)	1,4 (0,23; 8,08)
Mixed	6(20)	22(32,4)	1

Table 4. Factors associated with outcomes

Covariables	ORa (IC 95%)
Age	**5.8 (1.4 ; 12.2)**
Low economic level	**3.5 (1.6 ; 13.1)**
Duration of the lesion	0.7 (0. 1 ; 2.4)
Sites	1.5 (0.4 ; 6.3)
Lymph nodes	1.1 (0. 2 ; 3.3)
Stage	**4.1 (1,2 ; 24.3)**

FIGURES

Figure 1. Screening review of early detection of oral cancer signs and symptoms