Original Article

Orofacial squamous cell carcinoma: Analysis of histopathological reports of 465 patients in Tanzania

Abstract

Orofacial squamous cell carcinoma (OfSCC) accounts for up to 90% of all malignant lesions in the head and neck region. This study aimed to document the histopathological characteristics of OfSCC in a Tanzanian population concerning the age of presentation, gender, and site of occurrence. This was retrospective study was carried out at the department of Oral and Maxillofacial Surgery, Muhimbili National Hospital. It included histological results of the OfSCC diagnosed between 2016 and 2021. The information gathered included the age and sex of the patient, the location of the tumor, and histological grading. Data analysis was done using Statistical Package for the Social Sciences version 26 computer program. The mean age of patients with which OfSCC was diagnosed was 55.85 (SEM = 0.77) years and the male-to-female ratio was 1.4:1. The 60 years and above age group was predominantly affected (45.2%). Intraoral lesions predominated (87.6%). The frequently affected intraoral location included the tongue (34.5%) and the gingiva/ alveolar ridge (25.6%). Most (68.5%) of extra-oral squamous cell carcinomas occurred in the midfacial region. The majority (72%) of OfSCC were grade I. Males are slightly more affected and a majority of the patients are older adults. The midface is the most affected extra oral location, while intra-orally the tongue, gingiva, and buccal mucosa are frequently affected.

Keywords: *Squamous cell carcinoma, Orofacial, Histopathology, Tanzania*

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Introduction

Malignant conditions in the orofacial region constitute an important group of human diseases with an estimated prevalence of about 5–8% of all malignancies worldwide, and squamous cell carcinoma accounts for up to 90% of all these lesions in the head and neck region.[1-3] Orofacial squamous cell carcinoma (OfSCC) originates from the mucosal epithelium in the aerodigestive tract (oral cavity, pharynx, and sinuses)[4] and keratinocytes in the spinous layer of the epidermis (skin).[5]

Generally, OfSCC tends to affect more males than females by twofold to fourfold, with the median age of diagnosis being around 60 years, though, the incidence of OfSCC in persons under the age of 45 years is increasing.[4, 6] This malignant neoplasm can occur at various orofacial locations, the most frequent being the lips, tongue, and floor of the oral cavity.[7]

Histologically, the lesion undergoes various phases (preneoplastic damage) before the formation of cancer.[7] The progression begins with epithelial cell hyperplasia, followed by dysplasia (mild, moderate, and severe), carcinoma in situ, and, ultimately, invasive carcinoma.[4]

The histopathological diagnosis of OfSCC which is traditionally made using hematoxylin and eosin staining is reported based on the degree of differentiation of the tumor cells.[4, 8, 9] The spectrum of differentiation ranges from a well-differentiated tumor (closely resembles the stratified epithelium, with mature-appearing cells organized into layers with irregular keratinization) to a poorly differentiated tumor (characterized by immature cells with nuclear pleomorphism and atypical mitoses with minimal to no organized stratification of keratinization).[4, 7]

Despite the availability of published data on malignant lesions from Tanzania,[1, 10] the demographic information, and the evaluation of the histopathological pattern of OfSCC are still limited. It is of utmost importance to have documented baseline information regarding different histopathological characteristics of OfSCC

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in Tanzania considering the changing trends of OfSCC seen worldwide. This audit aimed at documenting the histopathological characteristics of OfSCC in a Tanzanian population concerning the age of presentation, gender, and site of occurrence.

Materials and Methods

This was a retrospective study carried out at the Department of Oral and Maxillofacial Surgery (OMFS) of the Muhimbili University of Health and Allied Sciences (MUHAS), Dar es Salaam, Tanzania. All histopathologic reports of biopsied malignant orofacial lesions for 6 years (2nd January 2016 to 31st December 2021) were retrieved from the archive of the department. All reports of patients with histological diagnoses of oral and maxillofacial squamous cell carcinoma met the inclusion criteria and were included in the study. Reports that were inconclusive or without a final diagnosis were excluded.

Data were extracted from histopathology reports using a data collection form that included age, gender, location of the lesion, histological grading, and histological identification number. Histopathological diagnosis was recorded as reported in the biopsy report. In a case where a single patient had more than one result, as one for pre-surgery incisional biopsy and another for post-surgical excision of the lesion, the post-op result was included.

The data obtained from this study were coded and analyzed using Statistical Package for Social Sciences software (SPSS) for Windows (version 26, Armonk, New York: IBM Corp). Data was presented in the form of the median for continuous variables and percentages for categorical variables in the form of tables. The participants' age was grouped into 4 groups: pediatrics (< 18 years), young adults (18 – 39 years), middle-aged adults (40 – 59 years), and elderly (60+ years). The tumor location was grouped as sites: intra-oral sites (tongue, cheeks, palate, gingiva, floor of the mouth) and extra-oral sites (facial skin, maxillary sinus, salivary gland and orbital, scalp, etc). The extra oral sites were further grouped as the upper face (frontal and temporal) mid-face (orbits, nose, paranasal sinuses, upper lip, cheeks, and parotid region), and lower face (lower lip, submandibular and submental regions).

The Shapiro-Wilk test was used to check for normality of the data and the alpha was < 0.05. Where appropriate, One-way Analysis of Variance (ANOVA), and chi-square tests were used to assess the relationship of sociodemographic characteristics with the location, and grade of the lesion. The $\alpha < 0.05$ was selected for statistical significance. Univariate and multivariate linear and logistic regression models were used to assess associations between the socio-demographic characteristic of participants and the location of the lesion.

Results and Discussion

Demographic information

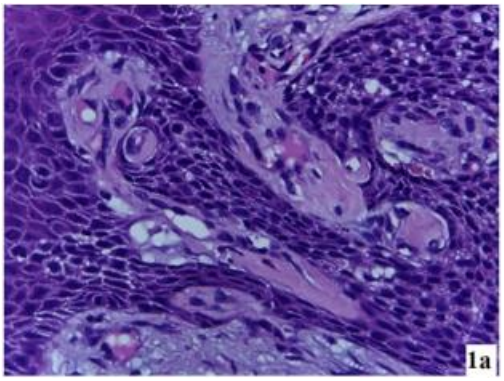
In this retrospective study, histological results of 778 patients with malignant lesions were retrieved and out of these 465 (59.8%) were diagnosed with squamous cell carcinoma of the orofacial region. The patient's age ranged from 5 to 100 years with a mean age of 55.85 (SEM = 0.77) years. The 60 years and above age group were predominantly affected (N=210, 45.2%). There were slightly more (N=268, 57.6%) males, and the male-to-female ratio was 1.4:1 **(Table 1)**. The mean age of the males was 54.16 (SEM = 0.99) years and of the females was 58.16 (SEM = 1.18) years. The difference in the mean age between the sex was statistically significant (p = 0.009).

Table 1. Overall distribution of patients according to age, sex, tumor location, and histological grading

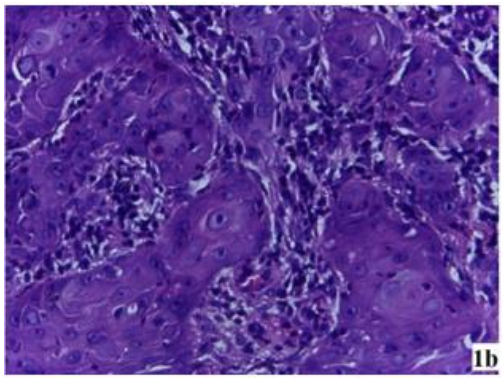
Variables	Frequency (N= 465)
Age Groups (years)	
< 18	9 (1.9%)
18-39	60 (12.9%)
40-59	186 (40.0%)
60+	210 (45.2%)
Sex	
Male	268 (57.6%)
Female	197 (42.4%)
Sites (grouped)	
Not indicated	28 (6.0%)
Intra-oral	383 (82.4%)
Extra-oral	54 (11.6%)
Tumour grade	
Grade I	334 (71.8%)
Grade II	73 (15.7%)
Grade III	23 (4.9%)
Not indicated	35 (7.5%)

The site and histological grade of the lesion

The sites of the lesion were indicated in 437 (94%) reports of the lesion. A majority (N=383, 87.6%) of the lesions were in the intraoral sites. The histological grade of the lesion **(Figures 1a and 1b)** was indicated in 430 (92.5%) reports of which the majority (N=334, 77.7%) were grade I squamous cell carcinoma **(Table 1)**.



a)



b)

Figure 1. Histopathological images (Haematoxylin and eosin stain) of the squamous cell carcinoma: a) Section of tissue showing cells that are pleomorphic, hyperchromatic, and polygonal with abundant eosinophilic cytoplasm. There are intracellular bridge connections, keratin formation, and dyskeratosis. These features are consistent with squamous cell carcinoma grade I (magnification x400). b) Section of tissue showing moderately pleomorphic cells which are hyperchromatic and polygonal with abundant eosinophilic cytoplasm. The nuclei have open chromatin and prominent nucleoli. Intracellular bridges connect the cells and keratin formation is not evident. There are evident abnormal mitoses as well. These features are consistent with squamous cell carcinoma grade II. (magnification x400).

Squamous cell carcinoma - Extra-oral sites

Among the 54 (12.4%) reports of the patients with extra-oral squamous cell carcinoma, males were 30 (55.6%) with a male to female ratio of 1.25: 1. The patients' age ranged from 5 to 86 years with a mean age of 45.54 (SEM = 2.41) years. The 40-59 years age group was most affected (N=23, 42.6%). The mean age of males was 46.1 (SEM = 3.71) years and of females was 44.83 (SEM = 2.89) years, however, the difference in the mean age between the sex was not statistically significant (p = 0.797).

The majority (N=37, 68.5%) of extra-oral squamous cell carcinomas **(Figure 2a)** occurred in the midfacial region, followed by the upper face (N=9, 16.7%) and the lower face (N=8, 14.8%). The histological grade of the extra-oral lesions was indicated in 41 (75.9%) reports of which the majority (N=28, 68.3%) were squamous cell carcinoma-grade I **(Table 2)**.

a)

b)

c)

Figure 2. Clinical pictures of orofacial squamous cell carcinoma, a) an ulcerative lesion in the extra oral site (temporo-zygomatic region) in a patient with albinism, b) an ulcerative lesion on the lateral border of the tongue, c) an ulcerative lesion on the gingiva around the region of lower right molars.

Table 2. Distribution of patients according to age, sex, and histological grade of the lesion with respect to extra-oral and

Variables	Extra-oral site (N= 54)	Intra-oral site (N= 383)	P-value
Age Groups (years)			
< 40	15 (27.8%)	42 (11.0%)	0.001
40+	39 (72.2%)	341 (89.0%)	
Sex			
Male	30 (55.6%)	226 (59.0%)	0.630
Female	24 (44.4%)	157(41.0%)	
Location			
Upper-face	9 (16.7%)	*N/A*	N/A
Mid-face	37 (68.5%)	*N/A*	
Lower-face	8 (14.8%)	*N/A*	
Labial mucosa	*N/A*	34 (8.9%)	
Tongue	*N/A*	132 (34.5%)	
Buccal mucosa	*N/A*	59 (15.4%)	
Gingiva/ alveolar ridge	*N/A*	98 (25.6%)	
The floor of the mouth	*N/A*	23 (6.0)	

Retromolar trigone	*N/A*	5 (1.3%)	
Hard palate	*N/A*	32 (8.4%)	
Tumour grade			
Grade I	28 (51.9%)	289 (75.4%)	0.239
Grade II	11 (20.4%)	60 (15.7%)	
Grade III	2 (3.7%)	20 (5.2%)	
Not indicated	13 (24.1%)	14 (3.7%)	

NB: In eight reports neither the location nor the tumor grading was indicated.

Squamous cell carcinoma - Intra-oral sites

Among the 383 reports of the patients with intra-oral squamous cell carcinoma, males were 226 (59%) with a male to female ratio of 1.44: 1. The patients' age ranged from 8 to 100 years with a mean age of 57.31 (SEM = 0.814) years. Nearly half (N=187, 48.8%) of the patients with intra-oral squamous cell carcinoma belonged to the 60 years and above age group. The mean age of the males was 54.84 (SEM = 1.03) years and of the females was 60.86 (SEM = 1.28) years and the difference in the mean age was statistically significant ($p < 0.000$).

The frequently affected intraoral location **(Figures 2b and 2c)** included the tongue (N=132, 34.5%), the gingiva/ alveolar ridge (N=98, 25.6%), and buccal mucosa (N=59, 15.4%). The histological grade of the lesions was indicated in 368 (96.1%) whereby the majority (N=289, 75.5%) were squamous cell carcinoma-grade I **(Table 2)**.

Site versus sex and age groups

The site of the lesion (extra-oral vs intra-oral) was not significantly associated with the sex of the patient, however, the association between the site of the lesion and the age group of the patients was statistically significant ($p = 0.001$). The odds of patients aged < 40 years old having squamous cell carcinoma in the extra-oral site were 3 folds higher than those aged 40 years and above (OR= 3.1, 95% CI 1.59 -6.14).

For the case of intra-oral sites, patients aged 40 years and above were three times more likely to have squamous cell carcinoma in intraoral sites compared to those aged below 40 years (OR= 2.8, 95% CI 1.41 -5.79).

Location versus sex and age groups

The location of the lesion for both intra-oral sites and extra-oral sites had no significant relationship with the sex of the patients ($p \geq 0.05$). The age group of the patient was not associated with the location of the lesion for all intra-oral sites ($p \geq 0.05$), however, for extra-oral sites, the age group was associated significantly with only the mid-face location ($p = 0.004$). The odds of patients aged < 40 years old having squamous cell carcinoma in the midface location were 3 folds higher than those aged 40 years and above (OR= 3.2, 95% CI 1.51 – 7.02).

Mean age of occurrence and histological grading of squamous cell carcinoma according to the location

The mean age of patients and the histological grading of the lesion concerning the location where the squamous cell carcinoma occurred is summarized in **Table 3**.

Table 3. Mean age and histological grading of the squamous cell carcinoma according to the location of occurrence

Location of the lesion	Mean age (years) ± Standard error of the mean	Histological grading of the lesion		
		Grade I	Grade II	Grade III
Extra-oral site				
Upper-face	33.00 ± 6.08	7 (77.8%)	2 (22.2%)	-
Mid-face	45.84 ± 2.60	19 (73.1%)	5 (19.2%)	2 (7.7%)
Lower-face	58.25 ± 6.33	2 (33.3%)	4 (66.7%)	-
Intra-oral site				
Labial mucosa	55.74 ± 3.50	29 (85.3%)	3 (8.8%)	2 (5.9%)
Tongue	54.90 ± 1.12	101 (80.8%)	18 (14.1%)	6 (4.8%)
Buccal mucosa	59.46 ± 2.21	47 (82.5%)	8 (14%)	2 (3.5%)
Gingiva/ alveolar ridge	58.74 ± 1.85	68 (73.1%)	22 (23.7%)	3 (3.2%)
The floor of the mouth	55.52 ± 3.09	16 (69.6%)	3 (13.0%)	4 (17.4%)
Retromolar trigone	59.00 ± 1.92	4 (80.0%)	1 (20.0%)	-
Hard palate	59.44 ± 13.84	24 (75.0%)	5 (15.6%)	3 (9.4%)

NB: There were 27 cases in which the histological grading was not indicated. The percentage displayed on the table did not account for the missing data.

Orofacial malignancies include malignant neoplasms of the oral cavity and adjacent structures such as the paranasal sinuses and salivary glands.[11] The majority of these lesions (50% to 90%) are squamous cell carcinoma.[1-3, 10, 11] The preponderance of OfSCC in the current study was nearly 60%, which is similar to the results of previous studies from Tanzania[1, 10] and elsewhere.[11-13] The high prevalence of OfSCC may be attributed to the fact that it arises from the epithelial cells which are among the most abundant cells in the body. These cells line up the surface of the orofacial region which is exposed to a multitude of carcinogens that pass through in large quantities through various complex routes (ear, mouth, and nose) hence making the region prone to malignancy specifically squamous cell carcinoma.[1]

Most worldwide studies about OfSCC have reported that males are affected more than females, with male to female ratio ranging between 1:3:1 and 20.3:1.[2, 12, 14-17] Similarly, in the current study a slight male predominance was observed. It is widely recognized that there is a strong association between orofacial cancer and risky behaviors like smoking and alcohol consumption, which males tend to display more.[18] However, the slim male predominance cannot be simply explained by the

patterns of exposure to carcinogens via risky behaviors alone but rather by a multitude of factors including infections (e.g HPV) and their biological and genetic makeup.

In this study, the mean age of patients at diagnosis was 56 years, similar to the findings of studies from Kenya,[2] Iran,[16] and Taiwan[17] but lower than the reported mean age of Romanians.[8] Cancer is widely considered an age-related disease due to its increased incidence with the advancement of age.[19, 20] The increased incidence of malignant conditions in advanced age may be explained by the multistage modal of carcinogenesis which hypothesizes that individual cells become cancerous after accumulating a series of genetic changes and that these changes are primarily the result of somatic mutation.[21] Likewise, some of the same biologic mechanisms that regulate aging also may be involved in the pathogenesis of cancer.[19] OfSCC is rarely seen in pediatric patients.[2, 16] Similarly, the findings in the present study depicted less than 2% of patients were aged below 18 years. The majority of these pediatric patients had underlying conditions like albinism or xeroderma pigmentosum.

Similar to findings in a study from Germany,[18] the mean age at which the diagnosis of OfSCC was made in males was lower than that of females by approximately four years in this study. This may be explained by the fact males tend to engage in risky behavior earlier in life than females. Yet still, it may be worthwhile to question the role of biological differences between males and females in developing cancers. Preston *et al*.[22] proposed that extremely high rates of cell division and proliferation in males may enhance the likelihood of predisposition to the development of cancer.

In the current study, we found that young individuals (< 40 years) were more likely to develop extra oral OfSCC than older ones (40 years and above). This may be because a majority of young individuals are active and tend to spend more time under the sun looking for daily bread thus getting exposed to ultraviolet radiation. In addition, individuals with skin disorders like albinism and xeroderma pigmentosum are prone to develop OfSCC at considerable early stages of life, especially in our locality. On the other hand, for the intraoral sites, older individuals had higher odds of suffering from OfSCC, and this may be because of the cumulative effect of carcinogenic substances one has been exposed to over time.

In the extra-oral sites, the majority of the lesions occurred in the midfacial region, followed by the upper face. Such findings could be explained by the mere presence of structure on this site. The midface region is the area where paranasal sinuses, nasal cavities, and parotid glands are located. These structures are prone to squamous cell carcinoma. In the upper face, lesions were mostly located in the frontal region, especially among patients who had albinism. The forehead is directly exposed to sunlight hence the ultraviolet light. Considering that individuals with albinism lack cutaneous melanin, they tend to be less protected against sunlight which causes oxidative stress-induced DNA damage that leads to OfSCC.[23]

OfSCC can occur in any intra-oral site. The findings of the current study revealed that the frequently affected intra-oral location included the tongue, the gingiva/ alveolar ridge, and buccal mucosa. Several studies throughout the world[12, 14, 17, 18, 24] have reported the tongue and the gingiva/alveolar ridge to be the most frequently affected intra-oral locations. Other commonly affected sites have been either the buccal mucosa or the floor of the mouth.[12, 14, 17, 18, 24] The tongue is the most common site of oral cancer and it is believed to be a multifactorial condition, with not only tobacco and alcohol playing a part but also chronic trauma and infection having a role.[25] It has been documented that the ventral surface of the tongue and the floor of the mouth are commonly affected locations because they are lined by thin non-keratinized epithelium, thus carcinogens readily penetrate this thin epithelium to reach the progenitor cell compartment.[6] The buccal mucosa, gingiva, and floor of the mouth may be a common location for OfSCC among those with habits of areca nut- and tobacco chewing.[26] Constant accumulation of the carcinogens and chronic inflammation caused by tobacco/ betel nuts in the floor of the mouth or buccal vestibule leads to OfSCC in these sites. [6]

The purpose of a grading system is to give exact prognostic and predictive information about the patient's disease course and potential response to treatment schemes.[27] The grade of histological differentiation of OfSCC reflects the aggressive capacity of the tumor.[6, 9, 27] In this study, regardless of the location of the OfSCC, the majority of the lesions were grade I. Grade I lesions are well-differentiated and they spread to regional lymph nodes only after invading connective tissue, muscle, or bone. Unlike grade III, which are poorly differentiated and tend to be more aggressive thereby spreading to regional lymph nodes early in the course of the disease.[6] Though it may be expected that lower graded OfSCC means a better prognosis for our patients, the reality may not be so. This is because the grading system adopted by WHO is based on Broders criteria and many studies indicate it has minor or no prognostic value.[9]

The strength of this study lies in the fact that it was carried out at one of the well-established oral and maxillofacial surgery centers in Tanzania. A substantially large population of patients from all over the country suffering from neoplastic conditions in the orofacial region are referred and managed in this center. Therefore, this study provides an almost realistic overview of the disease situation in the country.

This study had a few limitations. One is that we might have missed some histological reports of patients who had attended our institute for treatment due to loss of results or any other reason. Another was missing information regarding the location and grading of the OfSCC in some of the histological reports. This sort of deficiency in the quality of pathology reports has been documented and the suggestion of developing and implementing a standardized reporting template that contains all variables of prognostic significance.[28] Despite these limitations, the study gives an insight into the trend of OfSCC in Tanzania, thus equipping health professionals with

necessary information regarding squamous cell carcinoma of the orofacial region. This may allow dentists and general practitioners to have a high degree of caution when they notice non-healing ulcerative and indurated lesions in young individuals as well.[14]

Conclusion

Squamous cell carcinoma is the most predominant type of malignant condition in the orofacial region. Males are slightly more affected and a majority of the patients are older adults. The midface is the most affected extra oral location, while intra-orally the tongue, gingiva, and buccal mucosa are frequently affected. The majority of the OfSCC are well differentiated (grade I).

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Conflict of interest
None.

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None.

Ethics statement
Ethical clearance was sought from the MUHAS research and ethics committee (DA.25/111/01B/208), and permission to conduct the study was obtained from the appropriate authorities of the department of OMFS-MUHAS.

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