PREDISPOSING FACTORS AND CLINICO-PATHOLOGICAL PRESENTATION OF MALIGNANT LESIONS OF THE ORO-FACIAL REGION AMONG PATIENTS ATTENDING THE MUHIMBILI NATIONAL HOSPITAL IN DAR-ES-SALAAM, TANZANIA.

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M.Dent Oral Surgery Dissertation

Muhimbili University of Health and Allied Sciences

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By

Dr. Gemma Z. Berege, DDS

A Dissertation Report Submitted in Partial fulfillment of the Requirements for the Degree of Master of Dentistry (Oral Surgery) of the Muhimbili University of Health and Allied Sciences

Muhimbili University of Health and Allied Sciences

October, 2011

CERTIFICATION

The undersigned certify that this is the original work of the investigator and that they have read and hereby recommend for the examination of a dissertation entitled predisposing factors and clinico-pathological presentation of malignant lesions of the oro-facial region among patients attending the Muhimbili National Hospital, Dar es Salaam, in partial fulfillment of the requirements for the degree of Master of Dentistry (Oral Surgery) of the Muhimbili University of Health and Allied Sciences

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Date: ……

DECLARATION AND COPYRIGHT

I, **Dr. Gemma Z. Berege**, declare that this dissertation is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature: …….

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DEDICATION

This dissertation is dedicated to my beloved daughter Blessings who came into existence during the preparation of this work and was born few days after its completion.

ABSTRACT

Background

The oro-facial region is made up of a complex anatomical relationship of structures of which may be a source of development of malignant lesions. Often, patients present at the oral and maxillofacial unit of Muhimbili National Hospital with a variety of malignant lesions in the oro-facial region. Majority of these patients are referred cases from upcountry district/regional hospitals and they present with advanced stages of disease with a wide range of complications. Of recent there has been a dramatic change in the characteristics and demography of some of the common malignant lesions of the oro-facial region. Such changes might be attributed to predisposition or systemic changes following exposure to certain external factors.

Objective

To determine the predisposing factors and clinico-pathological presentation of malignant lesions of the oro-facial region among patients attending the Muhimbili National Hospital.

Study design

Cross sectional descriptive hospital based study.

Setting

Oral and maxillofacial surgery firm, Muhimbili National Hospital.

Methods

All admitted and outpatients with clinically suspected malignant lesions in the oro-facial region who attended at the Muhimbili National Hospital, Oral surgery department from 1st July 2010 to 31st March 2011.

Patients were interviewed using a specially designed questionnaire. Clinical examination was done, followed by fine needle aspiration cytology and/or tissue biopsy. A total of 186 patients with cytologically and/or histologically confirmed malignant lesions were included in the study. Data were entered in a computer, cleaned and analyzed using SPSS for windows version 13.

Results

A total of 186 patients, 104 (56.0%) males and 82 (44.0%) females with a ratio 1.3:1 were involved in the study. The age at the time of diagnosis ranged from 3 to 83 years with a mean age of 48.4 ± 19.2 SD years. Sixty one (32.8%) patients were aged below 40 years. The commonest observed oral and maxillofacial malignant lesion was Squamous cell carcinoma 96 (51.6%) patients followed by Kaposi's sarcoma in 17 (9.1%) patients and carcinoma in 10 (5.4%) patients. Tobacco use was reported by 89 (47.8%) patients, of whom 62 (69.6%) patients had used tobacco for more than 20 years while 96 (51.6%) patients reported alcohol use, of whom 49 (51.0%) reported to have used alcohol more than 20 years. Thirty three (17.7%) patients were HIV positive. All patients with Kaposi's sarcoma were also HIV positive. Malignant eccrine poroma and polymorphous low grade adenocarcinoma are rare tumours in the maxillofacial region that were encountered.

Conclusion

Squamous cell carcinoma was the most common malignant tumour in the oral and maxillofacial region. Use of tobacco and/or alcohol was the predisposing factors for squamous cell carcinoma. There was an increased frequency of malignant tumours in the oral and maxillofacial region among young patients. Patients presented rather late with advanced tumours that many times could only be managed by palliative therapy. All patients with Kaposi's sarcoma were HIV positive.

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Abbreviations

MUHAS=Muhimbili University of Health and Allied Sciences

MNH=Muhimbili National Hospital

MoHSW=Ministry of Health and Social Welfare

NACP=National AIDS control programme

UNAIDS=United Nations programme on HIV/AIDS

WHO=World Health Organization

UICC=International Union Against Cancer

HPV= Human Papilloma Virus

OSCC=Oral Squamous cell carcinoma

HIV=Human Immunodeficiency Virus

AIDS=Acquired Immunodeficiency syndrome

KS=Kaposi's sarcoma

NHL=Non-Hodgkin's lymphoma

EBV=Epstein Barr virus

AJCC= American joint Committee on Cancer

FNAC=Fine needle aspiration cytology

HKSV=Human Kaposi's sarcoma virus

HD=Hodgkin's disease

HL=Hodgkin's lymphoma

OKS=Oral Kaposi's sarcoma

ACC=Adenoid cystic carcinoma

PLGA=Polymorphous low grade adenocarcinoma

BCAC=Basal cell adenocarcinoma

MEP= Malignant eccrine poroma

VDRL=Venereal Disease Research Laboratory

BCC=Basal cell carcinoma

OMM=Oral malignant melanoma

AgNOR= Silver nitrate organizing regions

ACS=American Cancer Society

CDC=Centres for Diseases Control

SPSS= Statistical Package for Social Sciences

1. INTRODUCTION AND LITERATURE REVIEW

The oro-facial region is made up of a complex of anatomical structures that include the lips, floor of the mouth, tongue, mucosa, teeth, gingivae, hard and soft palate, and major and minor salivary glands. Within this complexity of structures are the fundamental tissues found elsewhere in the body like blood vessels, nerves, muscles, bones, mucous membrane and the skin. Any of these structures can undergo various pathological changes, including neoplastic conditions, both benign and malignant, that occur in this region[1,2]. Activities of the oral cavity and the exposed location of the face make this region liable to a wide range of malignant lesions. During eating, for example, oral tissues are exposed to numerous irritants and infective agents that have the potential for predisposing to occurrence of cancers[3]. The close relationship of important structures in this region i.e. the mouth, nose, eyes and ears quite often complicates the disease situation since extension from any of these structures easily affect some or all of the others.

Malignant lesions in the oro-facial region can be primary, that is, arising from local tissues of the oro-facial region or secondary presenting because of metastases from distant sites elsewhere in the body such as the breasts and lungs[4-6].

1.1. EPIDEMIOLOGY

Cancer has become a major cause of human deaths in the last 20 years. According to American Cancer Society, 7.6 million people died of cancer in the year 2007 in the US[7]. Studies have revealed an increase in the number of oro-facial malignant tumors such as squamous cell carcinoma, adenoid cystic carcinoma, lymphomas and sarcomas[8-14]. In Canada, oral cancer was reported to account for 2.0% of all cancer cases while in the United Kingdom they accounted for 5.4% of all oral and maxillofacial specimens [11-13]. A study on oral and perioral cancers in Iran, reported that malignant lesions accounted for 6%[15]. Studies on oro-facial tumors in Indonesia and China found that malignant tumors constituted 45.3% and 50% of the lesions respectively[9,10]. However, the highest prevalence of about ninety percent was reported in Iran[14].

The occurrence of oro-facial malignant lesions in Africa has been seen to vary among different countries with frequencies ranging between 18% and 75%[16-20]. In Nigeria frequencies of oro-facial malignant tumors of as high as 51% have been reported[17]. In Zimbabwe oral malignant tumors constituted 24.8% of all oral biopsies while in Uganda and Tanzania they constituted about 75% and 50% of oro-facial lesions respectively[16,18].

The advent of the human immunodeficiency virus (HIV) infection has influenced changing patterns of occurrence of some disease conditions including malignant lesions. HIV, a retrovirus that infects CD4+ helper T lymphocytes, affects people of all ages but because of the nature of its transmission mostly affects the young section of the population. HIV-infected individuals have a twofold increase in the risk of malignant lesions, higher incidences, widespread clinical dissemination and a more rapidly progressive course of malignant lesions than HIV-negative individuals[21]. Oral malignant lesions associated with HIV infection may manifest as local head and neck diseases or represent systemic malignant diseases.

Oral Kaposi's sarcoma (OKS) has been reported to be the commonest oral malignant lesion among HIV/AIDS patients[21,22]. Malignant lymphoma (ML) mostly sub-classified as non-Hodgkin (NHL) [including Burkitt's lymphoma (BL)] and Hodgkin's lymphoma (HL) are associated with the novel human herpes virus type 8 (HHV-8)/Kaposi's sarcoma-associated herpes virus (KSHV).

In Tanzania and Kenya, KS, NHL, and SCC were the commonest oro-facial malignant lesions found in HIV/AIDS patients[21,22]. Similarly, Chidzonga reported a higher prevalence of KS ad NHL among other oro-facial lesions in Zimbabwean patients[23].

African studies have reported that the majority of oro-facial malignant lesions presented in late stages (III and IV), contrary to studies elsewhere in which the majority presented in early stages (I and II)[23,24]. In Tanzania over 85% of the patients presented in late stages[25].

1.2. ETIOLOGY

Like all malignancies generally in the body, the etiology of oro-facial malignancies is not clearly known although several studies have strongly implicated some predisposing factors in certain types of oral cancers[3,8,26-28]. The oncogenic theory of cancer etiology explains that

one's genotype may also influence the likelihood of developing environmentally induced cancer. The concept of this theory is that genes for cancer are present normally in the body, controlling growth and repair but when activated by an environmental or hereditary factor, they may produce cancer. Oncogenes are the abnormal genes and the mutant version of proto-oncogene (normal gene) result in cancer when abnormal single Deoxyribonucleic acid (DNA) base substitution occurs[29,30].

Age had been frequently named as a risk factor for oral cancer, as historically it occurred in those over the age of 40 years[1]. Age may indicate a time component in the biochemical or biophysical processes of aging cells that allows malignant transformation, or a decrease in immune system competence that occurs with age.

Infection by certain viruses and bacteria has been associated with some malignant conditions, for example HKSV has been strongly associated with KS. HIV infection is associated with KS and oral squamous cell carcinoma (OSCC) in young ages. Epstein Barr virus (EBV) is associated with BL while Syphilis in the oral cavity has for a long time been associated with predisposition to development of OSCC[21,27,31].

Behavioural and environmental factors such as use of tobacco and alcohol consumption, poor oral hygiene, trauma, chronic irritation, nutritional deficiencies, exposure to sunlight, and certain carcinogenic dyes have been seen to have varying degrees of association with certain types of oro-facial malignancies[1-3,32-34]. Alcohol abuse is already the second largest risk factor for the development of oral cancer. Tobacco use in all its forms has been reported as the number one risk factor in individuals over forty years of age. However, the trend has currently changed due to changes in the frequency of occurrence of some risk factors such as some viral infections. For example, it has been reported that in the younger age group, including those who have never used any tobacco products, the cause of OSCC is HPV based[31]. HPV may even be replacing tobacco as the primary causative agent in the initiation of the disease process. It has been proven that people who use both alcohol and tobacco are at an especially high risk of contracting the disease. The dehydrating effect of alcohol on cell walls enhances the ability of tobacco carcinogens to permeate mouth tissues; additionally, nutritional

deficiencies associated with heavy drinking can lower the body's natural ability to use antioxidants to prevent the formation of cancers.

Radiation has also been related to development of sarcomas, but considering the frequency of radiotherapy, radiation-induced soft tissue sarcomas are uncommon. It has been reported that about 0.1% of cancer patients treated with radiation who survive 5 years will develop a sarcoma of either bone or soft tissue[1].

Exposure to some carcinogenic dyes, herbicides or certain metals have been reported to increase the risk to develop sarcomas and salivary gland malignant tumours.

Trauma to the oral soft tissues from sharp edges of grossly carious teeth and/or ill fitting dentures when allowed to persist for a long time may result in changes in the local tissues that make them prone to develop oral cancer. Trauma or past injury has been frequently implicated in the development of sarcomas, with some reported as arising in scar tissue following surgical procedures or thermal or acid burns, in fracture sites, and in the vicinity of plastic or metal implants, usually after a latent period of several years[1,2].

Some studies have proved that a diet low in fruits and vegetables could be a risk factor, and that conversely, one high in these foods may have a protective value against many types of cancer.

Other oral conditions which have been associated with predisposition to oral cancer include chronic oral candidiasis, oral mucosal lesions like erythroplakia, lichen planus, leukoplakia and, oral submucous fibrosis [27,35]. A cumulative damage and/or combination of two or more of these factors have been seen to increase the risk of oral cancers[35].

1.3. CLINICAL FEATURES

1.3.1. Age

Malignant lesions occurring in the oro-facial region affect all age groups with frequencies generally increasing with advanced age[7,36]. However, there are some types of malignancies seen only in specific age zones, for example Lymphomas, particularly BL has been found to be the most common malignancy in children and adolescents in tropical countries, occurring mostly in the first decade of life[36,37]. Recently, studies on oro-facial malignancies demonstrated statistically significant differences in oral cancer rates among population

subgroups, including minorities and various age groups[36,38]. For example, some African studies have reported relatively higher percentages of malignant tumors in the oro-facial region among younger age groups[17,38]. Rising trends of oral cancer in young and middle-aged men, particularly of cancer of the tongue, have also been reported in European countries and the USA[39,40]. Viral infections have been reported to be among factors responsible for oro-facial malignancies at a younger age. However, tobacco use, particularly use of conventional "smokeless" chewing or spit tobacco has also been reported among this age group[41].

Studies in Nigeria, Libya, India and Brazil reported oro-facial malignant lesions with frequencies ranging from 0.25% to 51% among children and adolescents[17,20,36,37,42-44]. Malignant tumors mostly encountered included BL, osteosarcoma and rhabdomyosarcoma. Carcinoma was relatively rare in this age group.

1.3.2. Sex

Oro-facial malignant tumors have been reported to be more common in males than in females, with the male to female ratio rapidly changing from 6:1 to 2:1 over the last few decades. Females, however, have shown to predominate in much older age groups[1,38]. A recent study on cancer profile in India has reported a slightly higher female predominance[8]. This increase has been thought to be due to lifestyle changes, particularly the increased number of women smokers over the last few decades. Higher incidence of viral infections such as HIV among females, and subsequent immune suppression has also been suggested among other reasons. In India, it has been recently found that the majority of the patients from both genders, especially those cases of oral cancers, had a habit of tobacco chewing and use of alcohol[8]. However, some studies have reported slightly higher rates of tobacco use and other associated habits in females than males[45]. Despite a frequently reported male preponderance of oro-facial malignant lesions, a different picture had been encountered in salivary gland lesions among black African populations[15,46]. For example, in a clinico-pathological study of salivary glands tumours in Uganda, about half of male patients were diagnosed with malignant neoplasm against the 43.2% of female patients, however, some lesions had equal frequencies between females and males[46].

1.3.3. Signs and symptoms

Malignant lesions generally grow by progressive infiltration, invasion, destruction, and penetration of the surrounding tissues and may cause pain. They usually grow very fast and have an unlimited growth therefore attaining massive size if no intervention is attempted. The rate at which they grow and/ or invade tissues differ amongst them. While some malignant lesions are very painful from the earliest stages some attain substantial size before they show any symptoms at all[29].

Almost all malignant lesions have the capacity to metastasize although the rates at which they do so differ in different lesions. Metastasis may be through seeding within body cavities, lymphatic spread or hematogenous spread[29]. Apart from lowering the immunity, malignant lesions weaken the patient because of either failure to eat or because of the high metabolic rate associated with their growth.

The characteristics of the lesions to a large extent influence their ultimate management. Because of the wide difference in the behavior and presentation of the different malignant lesions occurring in this region and in order to understand the clinical pathological characteristics of the individual lesions, it is important to look into the details of the specific lesions.

1.4. Epithelial malignant tumours

1.4.1. Squamous cell carcinoma

1.4.1.1. Epidemiology

Oral squamous cell carcinoma (OSCC) is the commonest malignant tumor of the oral cavity worldwide accounting for over 90% of oral cancers[4,19,47]. It constitutes 3-4% of all cancers and caused about 2% of all cancer deaths in the world[8,38]. A study on OSCC in Tanzania, reported that OSCC constituted 0.8% of all biopsies[25]. In Africa, OSCC has been reported to be the commonest oro-facial malignant tumor, accounting for between 10.8% and 64% of oral facial malignant tumors[4,19,38]. In Iran, OSCC constituted 1.7% of all cancers and about 55% of oral malignant lesions[4,15]. In Japan, OSCC constituted 88.7% of oral facial malignant tumors[47].

Although OSCC is the most common cancer in the head and neck region, studies have reported that it has been seen in excess in HIV-infected populations although it is still overshadowed by KS and NHL[48].

1.4.1.2. Etiology

Several environmental factors have been strongly implicated in the development of OSCC. These factors include tobacco, alcohol, sunlight and viruses such as HPV[26,49,50]. Tobacco and alcohol use have been the most strongly associated factors in the causation of OSCC[26]. While a variety of risk factors are important in OSCC, tobacco has been reported to play a central part in the pathogenesis of the disease. Tobacco use and other associated habits such as betel quid, narghile smoking and areca nuts chewing are practices most commonly seen in the Middle and Far East. With the advent of immigration and globalization, the use of tobacco, betel and areca nuts become more widespread[45]. These habits are also associated with occurrence of OSCC[35]. Potentially malignant disorders such as erythroplakia, erythroleukoplakia, oral submucous fibrosis and lichen planus have also been reported as risk factors for OSCC[51]. Syphilis, nutritional deficiencies, immune suppression, poor oral hygiene, trauma and dental irritation have also been associated with OSCC[34].

1.4.1.3. Age

Oral squamous cell carcinoma, like most other malignant tumors affects mostly people above the age of 40 years[1,50]. A change in the demographics of the disease has been recently recognized, whereby it has increasingly been seen in young persons[39,52]. In Iran, the mean age of patients with OSCC was reported to be 56.9 years, with higher frequencies above 60 years of age[4]. However, a unique clinical subgroup of young patients with OSCC has recently been reported in France[52]. Some studies in African countries have found slightly lower mean ages at presentation with peak incidences in the 20 to 29-years and 40 to 49-years age groups[4,38]. A study in Tanzania reported the mean age of 58.6 years, with a peak at 60- 69 years[25].

1.4.1.4. Sex

OSCC affects slightly more men than women. In the U.S, oral carcinoma represents about 3% of all malignancies in men and 2% in women[7]. In Japan and Iran also a male preponderance with male to female ratio of about 1.4:1 has been reported[4,47]. In India, OSCC constituted 17% of all cancers in males and about 10% in females[8]. In Tanzania, the male to female ratio was reported to be 1.3:1 while in other African studies male the ratios ranged from 1.3:1 to

1.7:1[19, 25,38]. However, Otoh and his co-workers reported an equal occurrence of OSCC among males and females[24]. Recently, studies of oral cancer epidemiology demonstrated statistically significant differences in oral cancer rates between genders, with increasing oral cancer rates among females[28].

1.4.1.5. Location

Studies have shown that anatomical distribution of OSCC differs geographically and between African and non-Africans, with certain sites found to be more frequently involved than others[38,47]. The tongue was reported to be the commonest affected site in Tanzania[25]. In Nigeria, the mandibular gingivae was the most commonly affected site (31.8%) followed by the maxillary gingiva (23.3%) and the tongue (17.6%)[38]. Other reported sites include the palate, lip and the floor of the mouth[24,38]. In Iran, the tongue was the most commonly affected site (53%), followed by the buccal mucosa (9.5%) and maxillary gingiva (9%)[4]. Different factors such as tobacco habits, occupation and genetical factors have been suggested to explain the variation in anatomical sites and why certain sites are more frequently involved than others[40,49].

1.4.1.6. Gross appearance

OSCC manifests in different clinical presentations depending on the stage of the lesion at diagnosis. Early lesions often present as painless white lumps, nodules, white patches (leukoplakia), red patches (erythroplakia), or mixed red and white patches (erythroleukoplakia)[38]. With time, superficial ulceration of mucosal surface may develop, which in advanced stage, may appear as a discrete ulcer with a raised indurated border or a firm slightly raised plaque. OSCC may appear also as exophytic mass with a fungating or papillary surface. Other lesions have endophytic growth pattern characterized by a depressed, ulcerated surface with a raised, rolled out edges[1].

1.4.1.7. Signs and symptoms

Early OSCC manifests in a variety of ways, depending upon anatomical location but it is typically painless initially. Non healing ulcer, or progressive swelling or enlargement is observed in early presentation[1,2,38]. Other signs and symptoms include sudden tooth-ache or mobility without apparent cause, and unusual oral bleeding. Late presenting signs and

symptoms often include dysphagia, trismus, difficulty in breathing and speech, paresthesia, and dysesthesia of the tongue. Large advanced lesions may present with pain during swallowing, airway obstruction, pain referred to the ear (otalgia) and cervical lymphadenopathy[1].

1.4.1.8. Clinical staging

Like in any other malignancies elsewhere in the body, clinical staging of OSCC is based on the TNM classification. In the scope of this literature, the Tanzanian study reported that 82% of the patients presented with stage IV tumours while no patient presented with stage I tumour[25]. Studies in Nigeria and South America have also reported late presentation of OSCC to hospital with majority of patients reporting with stage III or IV tumours[24,27].

1.4.1.9. Histopathology

Grading of a malignant tumour is based on the microscopic determination of the differentiation of the tumour cells. Well differentiated lesions generally have a less aggressive biological course than poorly differentiated lesions. The microscopic characteristics of OSCC consist of irregular nests, columns and strands of malignant epithelial cells that infiltrate the sub-epithelial connective tissue stroma. The tumor cells may resemble any or all the layers of stratified squamous epithelium. Microscopically, OSCC has been graded as well, moderately, or poorly differentiated. The two main features on which grading is based are cellular proliferation and differentiation. Rapid abnormal proliferation is characterized by hyperchromatism, increased mitotic activity, cellular pleomorphism and nuclear atypia. Differentiation of tissues is assessed by the presence or absence of epithelial bridges and ability to produce keratin. A study in Southern America reported that over half (55.5%) of the patients had moderately-differentiated tumors[27]. In Iran, the well-differentiated type was the most (55.5%) common while the poorly differentiated OSCC was the least (7.5%) common[4]. In Nigeria, poorly differentiated SCC was the most (47.6%) common subtype, followed by well-differentiated (32.6%) and moderately differentiated (19.7%) subtypes[38]. An advanced degree of differentiation, such as closeness to the structural characteristics of the tumor to the parent tissue, is regarded as a feature of favorable prognosis, while lack of differentiation is considered to spell poor prognosis[2]. However, the grading of OSCC, based on differentiation

and maturation of the tumor cell population alone is of limited value as a basis for choice of treatment as well as for prediction of the outcome of the disease.

1.4.1.10. Variants of OSCC

Variants of OSCC include verrucous carcinoma, which is a low-grade malignancy with good prognosis, spindle cell carcinoma also known as carcinosarcoma (sarcomatoid squamous carcinoma), which is aggressive, and is most frequently encountered on the lip, basaloid squamous cell carcinoma and adenoid squamous cell carcinoma[1]. Verrucous carcinoma is characterized by marked hyperkeratosis, acanthosis, parakeratin crypts and large pushing bulbous rete ridges said to resemble elephant foot. Verrucous carcinoma does not have dysplastic histological features and habitually do not metastasize[2].

1.4.1.11. Prognostic factors

Prognosis of patients with OSCC is dependent on both histologic subtype (grade) and clinical extent (tumor stage). However, clinical stage has been reported to be more important. Other factors include age, site or location of the lesion, gender, general health, immune system status, and mental attitude. For most solid tumors, anatomic extent is one of the most important guidelines to treatment and the strongest predictor of the outcome[1,2]. Stages I (T1N0M0) carcinomas are known as early stage tumors since they are relatively small localized lesions without lymph nodes or distant metastases. Stage III (T3N0M0 and /or N1) is an advanced stage with a tumor size of above 4 cm, with or without ipsilateral lymph node involvement but without distant metastasis. Stage IV (T4 with any N/M and/or any T/M, N2/3, or M1 any T/N) is an advanced stage with large tumor, which has involved adjacent tissues and/or metastasized either into regional lymph nodes or distant tissues[53]. Survival rate of these patients depends on regional spread and distant metastasis status. Presence of metastatic lymph nodes drastically reduces the survival rate. The most significant prognostic factor is the presence of regional metastasis in patients with OSCC. The overall 5-year survival rate for OSCC is around 45 to 50%. It is however reported that, if the neoplasm is small and localized, the 5 year cure rate is as high as 60 to 70%, while the survival figures drop to about 25% if cervical metastases were present at the time of diagnosis[2]. The radical neck dissection has been the preferred therapeutic modality to neck metastasis for one

century[51]. Host local immune response and the biological behaviour of the tumor have also been reported among prognostic factors for OSCC. An increased secretion of Tumour necrosis factor (TNF) alpha in the tumours, shows a high invasive potential tha has been reported as one of the facilitating factors for tumor invasion and hence poor prognosis[54]. Location of OSCC has also been reported to be among prognostic factors, with the lower lip reported to have a better prognosis[2].

1.4.1.12. Treatment and prognosis

A variety of accepted modalities of treatment available for treatment of OSCC include surgery, chemotherapy and radiation therapy either alone or in combination[51,54]. The choice of treatment modality depends on the histological grade and the clinical stage of the tumor. The location of the tumor and age of the patient are also important factors in the treatment plan of OSCC. In case of a well differentiated tumor in early stages (I and II) the goal is complete eradication of the tumor. However, in case of a poorly diffetentiated, recurrent tumor, or presence of lymph nodes metastases, palliative treatment is usually considered, if complete eradication is not possible. For localized disease such as stage I and II (T1N0 and T2N0) OSCC which is confined to the oral mucosa such as of lip, floor of mouth, tongue, alveolar ridge, retromolar trigone, hard palate or buccal mucosa, patients are treated with curative intent, usually involving surgery and/or radiation therapy, and both offer an equal chance of cure. However, about 20-40% of these patients have been observed to develop local recurrence of the initial tumor[51,54]. In many centers treatment consist of radiotherapy to the primary site, with or without subsequent neck dissection. Squamous cell carcinoma of the base of the tongue or floor of the mouth frequently metastasize to the submandibular, jugulodigastric, deep cervical lymph nodes and has poorly differentiated histology. Due to anatomical location, the lesion is better treated by radiotherapy.

1.4.2. Basal cell carcinoma (BCC)

Basal cell carcinoma (BCC) is the most prevalent cancer of the skin, and it is the most prevalent cancer of the head and neck arising from basal cells of the skin. The mid-face is the area in which most BCCs are found, most frequently encountered in older patients, with men being more commonly affected than women[55]. The vast majority of BCC occur on sun-

exposed skin, with increased risk among individuals with lighter natural skin pigmentation, long history of chronic sun exposure, and those with one of several predisposing hereditary syndromes, such as the nevoid basal cell carcinoma syndrome. Occasionally xeroderma pigmentosa, burns, tattoos, and pox scars, HPV have also been considered to have an etiologic role[2,55,56].

Clinically, BCC presents as an indurated pearly papule or nodule with telangiectatic vessels coursing over its surface. With time, the centre of the tumour becomes ulcerated and crusted. If untreated, the tumour exhibits a slow but locally destructive nature. Other clinical forms include the pigmented form, presenting with melanin pigmentation in addition, the superficial form presenting as a scaly erythematous lesion with skin surface occasionally appearing as an atrophic scar-like process, and the fibrosing form, which presents as an indurated yellowish plaque that may be slightly depressed or flat, resembling a slow or insidiously enlarging scar in the absence of trauma[2,56].

Histopathologically, three types have been described: polymorphic (frequently reported), solid, and keratinized[56]. Treatment of BCC ranges from surgery and skin grafting to radiotherapy, depending on the size and location of the lesion.

1.4.3. Melanomas

Oral malignant melanoma (OMM) is a rare disease accounting for 0.2% to 11 of all malignant melanomas, with an incidence of 0.07%[2,57]. OMM has been rarely encountered among Africans[58,59]. OMM is regarded as a disease of old age, with the age range of between 40 and 70 years being reported, the average age being 55 years[57]. However, a recent study in Tanzania has reported OMM in a slightly younger age[59]. Although OMM is commonly considered to have a higher preponderance for males compared to females, some studies have found a slight female preponderance[58,59]. The common sites of its occurrence are the palate and gingiva with the maxillary arch being most frequently affected. Other oral sites include the mandibular gingiva, buccal mucosa and floor of the mouth[58,59]. Because of their presence at relatively obscure areas in the oral cavity, most of the malignant melanomas of the oral cavity are diagnosed at a late stage. Predisposing risk factors include a positive family history, light natural pigmentation, and an acute intermittent exposure to sunlight, especially in

childhood. Most melanomas arise *de novo*, although some arise from pre-existing pigmented lesions.

Melanomas are characterized by two growth phases, a horizontal and a vertical phase and are classified into three predominant types according to their clinical features. Superficial spreading melanoma accounting for about 60% of all melanomas, advances across the skin, producing an irregular patch of various colours, and microscopically, neoplastic cells are found in nests at the epidermal-dermal junction and extend laterally from the center of the lesion. While in this prolonged horizontal or radial growth phase, the lesion may be designated as melanoma in situ. Treatment during this phase yields excellent results. Nodular melanomas accounting for about 30%, have only a vertical growth phase, present as dark pigmented papules or nodules that may ulcerate or may exhibit a rapid growth, and exhibit a poorer prognosis. Lentigo maligna melanomas account for 10% of melanomas, occur predominantly in sun exposed skin of the elderly and appear as flat, irregular pigmented patch with ill-defined margins, and have excellent prognosis until the lesion enters a vertical phase.

The AJCC has proposed a clinical classification for malignant melanomas as follows: I-only primary tumor present. II-metastasis present (IIa-adjacent skin involved, IIb-regional lymphnodes involved, flab adjacent skin and regional lymph nodes involved) and III-metastasis beyond regional lymph nodes.

Widespread and unpredictable metastasis to bones (usually the vertebrae), lymph nodes, central nervous system, lungs and liver has been frequently found[58,59]. The primary mode of treatment for malignant melanoma is wide surgical resection with adjuvant radiotherapy[3,59]. However, OMMs have a very poor prognosis. The best indicator of prognosis is the depth of invasion of the tumour, the thinner the neoplasm, the better the prognosis.

1.4.4. Salivary gland tumors

Malignant salivary gland tumours are a diverse group of neoplasms characterized by etiologic and/or biological heterogeneity with varying susceptibility by gender and race[2]. The WHO classification of Salivary gland tumours 2005 is widely accepted[60]. However, little is available in the literature regarding the spectrum of malignant salivary gland tumors in Tanzania in the

basis of clinical and pathological characteristics of these tumours. Malignant salivary gland tumors have been reported to account for about 17% of oral facial malignancies, and 17% to 45% of salivary gland tumours[4,5,18,46,61,62]. Studies among African populations have reported malignant salivary gland tumours to account for about 47% to 61%[46,61,62]. Several African studies have shown that parotid and minor salivary gland tumors are much more likely to be malignant than other tumours of salivary glands[46,61-63]. In Western studies, the submandibular gland has been reported as the main sites of malignancy followed by the palate[64,65]. These studies have shown that there is a nearly equal sex distribution for majority of malignant salivary gland tumors while female predominance has been consistently reported from a number of African studies[61,65-67].

A clinicopathological study of salivary gland tumours in Uganda found that (46.6%) were malignant, with the mean age of patients with malignant lesions being 43.1 years, and the malignant tumors were dominated by adenoid cystic carcinoma (28.8%) followed by mucoepidermoid carcinoma (21.6%)[46]. The same study further concluded that the pattern of distribution of salivary gland tumors in black African population differed from that of Western series in that; females were more affected than males, there was a low proportion of tumors from the parotid gland and high proportion of tumors from the submandibular and minor salivary glands, the parotid (40%) and minor salivary gland tumors (38%) had more probability of being malignant than those tumors from the submandibular gland (22%) and, the newly categorized pathological entities were common[46].

Microscopically, salivary gland tumors are generally divided into high grade, low grade and an intermediate-grade, lying histologically and behaviorally between low and high grade[2]. Malignant and benign salivary gland tumours may resemble each other grossly if seen early in their clinical course. Generally, malignant salivary gland tumours present clinically with a slow growth which may or may not be associated with pain. A painful salivary gland swelling is strongly suggestive of malignancy, although there are no reliable clinical indicators of malignancy. Rapid growth, pain, lymphadenopathy and, in the case of the parotid gland, facial palsy are strongly suggestive and are likely to indicate a poor prognosis[2]. Within the mouth, salivary gland tumours may be firm or rubbery, and may feel lobulated.

Despite the advances in imaging techniques which are in fact useful guidance in planning management, none of them has been reported to be diagnostic. Fine-needle aspiration cytology (FNAC) is diagnostic with a sensitivity of about 80% and specificity of over 95%[71]. Accurate histological diagnosis is dependent on clearly defining the histological cell type and morphological patterns. Low grade tumours are characterized by glandular cells arranged around microcystic structures, with coalescence of small cysts into large cystic spaces. High grade lesions are characterized by neoplastic cell clusters that are more solid with fewer cystic spaces and glandular cells. Low grade tumours follow a benign clinical course (although several metastases have been reported) and higher 5 year survival rates after surgical excision of the primary tumour. High grade tumours have been reported to be aggressive and management should in addition include radical neck dissection and adjuvant radiotherapy[2].

1.4.4.1. Mucoepidermoid carcinoma

Mucoepidermoid carcinomas form 1.5% of parotid tumors, nearly 9% of minor salivary gland tumors, and are virtually never found in sublingual glands. In a Ugandan study, mucoepidermoid carcinoma accounted for about 20% of salivary gland tumours[46]. Almost any age can be affected, but the peak incidence is in the fifth decade. Mucoepidermoid carcinoma has been reported to occur twice as much in males than in females[72].

Clinically, most mucoepidermoid carcinomas are usually indistinguishable from benign tumors and rarely cause facial weakness or pain. Intra oral mucoepidermoid carcinomas may appear more vascular and may grow faster than benign tumors.

Histopathologically, mucoepidermoid carcinomas are often well circumscribed, although the lesion typically demonstrates infiltrataion of adjacent tissues[46]. Mainly two distinct but contiguous cell types are seen. These are epidermoid (squamous) cells and large, pale, faintly granular mucous cells. Microcysts formation is common and can occasionally consist of large monolocular cyst with tumor forming only mural thickening. Most low-grade mucoepidermoid carcinomas are composed of mucus-secreting cells arranged around microcystic structures, often with an intermingling of intermediate or epidermoid cellular cells. High-grade (and intermediate-grade) malignancies are characterized by neoplastic cell

clusters that are more solid with fewer cystic spaces and mucous cells. Larger numbers of epidermoid cells and intermediate cells are seen at the expense of more differentiated mucous cells.

Short history, production of symptoms and location in the tongue or floor of the mouth in association with microscopic criteria of malignancy (a small intracystic invasion, necrosis and anaplasia) are indicative of poor prognosis. Low-grade mucoepidermoid carcinomas characteristically follow a benign course, however, in several instances low-grade lesions have metastasized widely. Studies among white populations have reported a 5-year survival of 95% or greater associated with low-grade lesions and survival rates of as low as 40% for high-grade lesions[64,65]. African studies have reported lower survival[72].

Treatment of mucoepidermoid carcinoma is essentially surgical. High-grade malignancies are usually managed with surgery plus postoperative radiotherapy to the primary site. Radical neck dissection is usually required in high-grade lesions and is rarely performed in small lesions of low-grade malignancy. Central mucoepidermoid carcinomas are usually of low grade behavior. Most tumor recurrences in mucoepidermoid carcinomas occur within 1 year of treatment, with low local recurrence rates in low-grade neoplasms and about 80% in high-grade neoplasms[72].

1.4.4.2. Adenoid cystic carcinoma

Adenoid cystic carcinoma (ACC) is a high grade malignant tumour which is thought to arise from the intercalated duct reserve cell or terminal tubule complex. Differentiation is believed to be along the intercalated duct cell line[2]. This lesion accounts for about 23% of all salivary gland carcinomas with over 50% reported in minor salivary glands[70,71]. The parotid gland has been reported to be the most commonly affected major salivary gland[2,71]. Although it presents a widespread age distribution, peak incidence occurs between the 5th and 6th decades of life, with a nearly equal occurrence in males and females[70].

ACC is characterized by an indolent growth rate, relatively low probability of regional lymph node metastases, and a high likelihood of haematogenous dissemination[70,71]. In the major salivary glands, the clinical appearance is usually that of a unilocular mass that is firm on palpation, occasionally with some pain or tenderness. Intraoral lesions particularly those

arising on the palate frequently present with ulceration of the overlying mucosa. Bone invasion occurs frequently, initially without radiographic changes because of infiltration through marrow spaces.

The most common site of distant metastasis is the lung[72].

Facial nerve weakness or paralysis may occasionally be the initial presenting symptom, especially in late-stage lesions. Invasion of perineural spaces, with the neoplasm often found well beyond the site of clinical disease is characteristic to the tumor[72].

Microscopically, ACC presents a cribriform of cylindromatous pattern, a tubular pattern, a solid basaloid pattern of growth, or a combination of these. Studies have shown that the solid basaloid pattern is associated with the worst prognosis[72,73]. Areas of central necrosis within solid clusters of cells may indicate a more aggressive form of disease. More important factors regarding prediction of behavior include size of the primary lesion, anatomic location, presence or absence of metastatic disease at time of diagnosis, and facial nerve involvement.

Regardless of the site of the primary tumor, surgery is regarded as the treatment of choice for adenoidcystic carcinomas[73].

Loco-regional control rates for ACCs treated by surgery along with postoperative radiation range from 64–95% five years post surgery[74,75]. Survival rate at 5 years approximates 70% while at 15 years the rate is only 10%, with tumours of the major salivary glands being associated with longer survival rate[76].

1.4.4.3. Acinic cell carcinoma

Acinic cell carcinoma is a distinctive neoplasm of salivary gland origin believed to originate from the intercalated duct reserve cell. It accounts for 14% of all parotid gland tumors and 9% of the total salivary gland carcinomas of all sites[2]. Major salivary glands, especially parotid are mostly affected, while fewer cases have been reported within the submandibular and intraoral minor salivary glands, with most cases occurring in the palate and buccal mucosa. The acinic cell carcinoma may be found in all age groups, including children, with the peak incidence noted within the fifth and sixth decades of life. There appears to be no gender predilection. Acinic cell carcinomas usually present as slow-growing lesions. Rarely there is pain and facial nerve paralysis.

Microscopically, a marked cystic growth pattern can be noted. Large lobules or nests of tumor cells can be noted. Large lobules or nests of tumor cells with little intervening stroma are characteristic. The solid pattern of growth is the most common, followed closely by a trabecular pattern. Other variations include microcystic, papillary cystic and follicular forms. The predominant cell type is the well-differentiated acinar cell containing cytoplasmic granules[2]. ACC is a moderately malignant tumour.

Surgery has been reported to be the most preferred treatment. Metastasis is rare but the tumour has a strong tendency to recur even many tears after surgery.

1.4.4.4. Carcinoma Ex-mixed tumor

Carcinoma ex-mixed tumor represents an epithelial malignancy arising in a preexisting mixed tumor where such remnants may be identified. It usually arises from an untreated benign mixed tumor known to be present for several years or from a benign mixed tumor that has had many recurrences over many years. Malignancy occurring within a previously benign tumor is heralded by rapid growth after an extremely long period of minimally perceptible increase. When metastatic disease occurs, only the malignant component metastasizes[2]. Over 60% of carcinoma ex-mixed tumors are found in the parotid gland, and about 20% are found in the minor intraoral salivary glands. The average age when malignancy becomes evident is 60 years, approximately 20 years beyond the age noted for benign mixed tumours[77]. Suspicious signs of malignancy include fixation of the mass to surrounding tissues, ulceration and regional lymphadenopathy.

Microscopically, the margins of carcinoma ex-mixed tumor are generally well defined, although infiltrative areas are likely to be present. Necrosis and hemorrhage with areas of dystrophic mineralization are frequently noted. Most areas of malignancy appear as adenoid cystic carcinoma, undifferentiated carcinoma, or a combination of both.

Treatment of carcinoma ex-mixed tumor is almost exclusively surgical excision, with radical neck dissection in patients with evidence of cervical lymph node involvement. Local recurrence has been reported in nearly half of the patients[77]. Distant metastases are not uncommon and they are usually to the lungs and bones[2].

1.4.4.5. Epimyoepithelial carcinoma

Epithelia-myoepithelial carcinoma (EMC) is a distinctive tumor that is relatively rare and accounts for only 1–2% of all primary salivary tumors, with the parotid gland reported to be mostly affected[2,71].

The pathognomonic microscopic feature of EMC is the typical biphasic pattern of inner epithelial cells forming small ducts some of which may contain eosinophilic material, and the outer layer of myoepithelial cells that forms circumferential clear cell collars around the ducts. The stroma is usually hyalinized with basement like bands that imparts nodularity of the tumor. Foci of necrosis and perineural and vascular invasion are occasionally viewed, mitoses are rare[2].

Treatment of EMC is essentially surgical. When it occurs in the parotid gland, superficial parotidectomy is the treatment of choice[2]. Neck dissection is reserved for patients demonstrating lymphadenopathy. The overall recurrence and metastasis rates, however, are low, with this lesion best regarded as low-grade malignancy[2].

1.4.4.6. Polymorphous low grade adenocarcinoma

Polymorphous low grade adenocarcinoma (PLGA) is a low grade malignancy largely restricted in minor salivary glands, but cases from major salivary glands and seromucous glands of the nasopharynx have been reported[2,71]. The neoplasm occurs in the fifth through eighth decades of life, with a mean age of 59 years. There is no gender predilection. The lesion occurs almost exclusively in minor salivary glands with the palate being the most frequently reported site[78].

PLGA typically presents as firm, elevated, non-ulcerated, nodular swellings that are usually non-tender. Neurologic symptoms are usually not reported in association with this tumor.

Microscopically, it consists of variable morphologic patterns in the same tumor namely, lobular, papillary, cystic, cribriform, and trabecular. Also, solid, tubular/trabecular and cribriform patterns exist. Fascicular areas, papillary structures and indian file alignment of tumor cells are characteristic to PLGA. In addition to that, uniform cells with vesicular nuclei and eosinophilic cytoplasm characterize PLGA. Pleomorphism is rarely seen, whereas mitoses can be identified. Malignant epithelial cells in PLGA have cytologic uniformity,

diverse morphology and an infiltrative growth pattern with low metastatic capability. It has the propensity to attack nerves and blood vessels and sometimes can metastasize to distant sites.

The indolent nature of this tumor mandates conservative surgical excision. In the rare cases in which cervical lymph node involvement is noted, appropriate surgical dissection is indicated.

The prognosis of this low-grade malignancy is generally good, although long-term follow up should be part of patient management. Perineural invasion by this malignancy does not appear to affect prognosis[60,78].

1.4.4.7. Salivary duct carcinoma

Salivary duct carcinoma is a high-grade malignancy of major salivary glands, characterized clinically by a distinctive predominance in the parotid gland. Nearly 80% of cases have been reported in males, and the overall peak incidence is in the seventh decade. The lesion arises as a firm, painless mass. Microscopically, resemblance to ductal carcinomas originating in the breast is noted, with architectural features that include papillary cribriform and solid growth patterns along with a desmoplastic stroma and necrosis. Most tumors have infiltrative margins, with neural invasion[2]. The lesion is treated by surgical excision with concomitant neck dissection or postoperative irradiation or both. Pulmonary and osseous metastases are frequently noted.

1.4.4.8. Squamous cell carcinoma of salivary glands

This is a rare tumor arising within the salivary glands. The submandibular gland is most commonly involved, followed by the parotid. Obstructive sialadenitis has been thought to be a predisposing condition. Most patients tend to be in the seventh decade of life or beyond. They are generally well to moderately well differentiated with no evidence of mucin production. Local recurrences and regional lymph node metastasis are common events, and distant metastasis is unusual. Surgery is the treatment of choice[2].

1.4.4.9. Basal cell adenocarcinoma (BCAC)

This is a slow-growing, rare tumor of major salivary glands believed to be the malignant counterpart of basal cell adenoma. It appears microscopically similar to basal cell adenoma,

except that it exhibits infiltrative growth pattern and has the ability to metastasize. About 90% occur in the parotid gland followed by the submandibular and minor salivary glands[2,46]. These tumors are composed of nests, cords, and solid zones of basaloid cells.

The 2005 WHO classification categorizes BCAC as a low-grade tumour with a favourable prognosis[60]. Treatment options include wide local excision with radiotherapy reserved for close surgical margins or for local recurrence.

1.5. Mesenchymal malignant tumours

1.5.1. Soft tissue mesenchymal malignant tumours

1.5.1.1. Malignant fibrous histiocytoma

Malignant fibrous histiocytoma is an infrequently reported lesion in the head and neck although it is the most common adult soft tissue sarcoma in the rest of the body[1,2]. It may also occur in bones, where it follows a more aggressive course than in soft tissues. It has significant recurrence and metastatic potential that is dependent on anatomical site, superficial or deep location and size.

Malignant fibrous hystiocytomas have been reported to occur late in life and rarely in children[81]. Males are affected more frequently than females. Signs and symptoms include pain, facial paralysis, epistaxis, rhinorrhea, hemoptysis and dysphagia.

Malignant fibrous hystiocytomas cause radiolucencies with poorly defined margins which may have a moth-eaten appearance. Cortical expansion may be seen, and a pathologic fracture may occur with larger lesions. Microscopically, proliferation of fibroblasts, macrophages and giant cells is the commonest feature. Radical excision is the treatment of choice, sometimes with adjuvant radiotherapy

1.5.1.2. Rhabdomyosarcoma

Rhabdomyosarcoma is a malignant soft tissue neoplasm consisting of cells derived from the primitive mesenchyme, exhibiting a profound tendency to myogenesis, with varying degrees of striated muscle cell differentiation and a relative predilection for the head and neck region[1]. About 35% of rhabdomyosarcomas arise in the head and neck. According to their anatomical location and propensity for invasion of the central nervous system, these Rhabdomyosarcoma

are divided in orbital, parameningeal and non-orbital non-parameningeal forms. Parameningeal tumors carry the worst prognosis. Oral Rhabdomyosarcomas are classified within the non-parameningeal group of tumors, which present a better prognosis and tend not to invade the central nervous system[2]. The oral sites most frequently reported include the floor of mouth, soft palate, tongue and buccal mucosa. The mean age of patients is about 50 years and the age range extends from children to older adults. Rhabdomyosarcoma of the head and neck has been reported primarily in children, usually presenting as a rapidly growing submucosal mass, which if there is jaw involvement, may cause pain or paresthesia[2,43,44].

Two microscopic variants of rhabdomyosarcoma have been recognized: the adult type, in which the neoplastic cells closely mimic their normal counterpart and the fetal type, the neoplastic cells are elongated and less differentiated and exhibit fewer cross striations. Four broad subtypes of Rhabdomyosarcomas have been established: (a) botryoid and spindle cell rhabdomyosarcoma (both less common variants of rhabdomyosarcoma); (b) embryonal rhabdomyosarcoma, consisting of primitive round cells in which striations are rarely found and generally having a superior prognosis (c) alveolar (including the solid-alveolar variant) rhabdomyosarcoma composed of round cells but in a compartmentalized pattern and generally having a poorer prognosis and (d) Pleomorphic rhabdomyosarcoma which is the most well differentiated, consisting of strap or spindle cells that often exhibit cross-striations. Finally, a category of sarcoma nor otherwise specified was created for tumors that could not be classified into a specific subtype[82]. A combination of surgery, radiation and chemotherapy has been shown to produce far better clinical results, with survival rates as high as 85%[44].

1.5.1.3. Fibrosarcoma

Fibrosarcoma is a very rare type of bone malignancy of the head and neck. Soft tissues may also be affected. This tumour affects most commonly young adults[2]. Secondary ulceration occurs as the lesion enlarges. It is an infiltrative neoplasm that is more of a locally destructive problem than a metastatic problem.

Microscopically, fibrosarcoma exhibits malignant-appearing fibroblasts, typically in a herringbone or interlacing fascicular pattern. Collagen may be sparse and mitotic figures

frequent [2]. Because of difficulty in controlling local growth, wide surgical excision has been generally advocated for fibrosarcoma. Recurrences are uncommon. Metastases are more likely via the bloodstream.

1.5.1.4.Kaposi's sarcoma

Kaposi's sarcoma is a proliferation of endothelial cell origin, although dermal/submucosal dendrocytes, macrophages and probably mast cells may have a role in the genesis of these lesions. The various etiologic factors cited as possibly having significance include genetic predisposition, infection (especially viral), environmental influences of various geographic regions, and immune dysregulation, such as reduced immune surveillance. Human Herpes Virus 8 (HHV8) or Kaposi's sarcoma human virus (KSHV) has been identified in all forms of KS lesions, as well as AIDS-associated body cavity lymphomas[21,83]. This virus is believed to have a significant role in the induction and/or maintenance of KS through perturbation of focally released cytokines and growth factors. It is generally regarded as a neoplasm, although much evidence suggests that it is inflammatory in nature, especially in early stages. Three different clinical patterns of KS have emerged since it was first reported by Kaposi in 1872.

The classic type of KS was initially seen in older men living in the Mediterranean basin. It appears as multifocal reddish-brown nodules primarily in the skin of the lower extremities, although any organ may be affected. Oral lesions are rare in this type. The classic form has a rather indolent course and only a fair prognosis.

The Endemic type of KS was identified in Africa, where it is now considered to be endemic. It is seen typically in the extremities of blacks. The most commonly affected organ is the skin. Oral lesions are rarely seen. The clinical course is prolonged, and the overall prognosis is also only fair.

The immunodeficiency type of KS has been seen in patients with immunodeficiency states, or organ transplants, and especially HIV/AIDS. Skin lesions are not limited to the extremities and may be multifocal. Visceral organs may also be involved. A younger age group is affected. Oral and lymph node lesions are relatively common. The clinical course is relatively rapid and aggressive, and the prognosis is correspondingly poor. Over 80% of the AIDS patients with KS have been found to develop oral lesions, which may be the initial site of

involvement or the only site [21,83]. It has been described in most oral regions, although the palate, gingival, and tongue seem to be the most commonly affected sites. OKS ranges from a rather trivial appearing, flat lesion to a rather ominous, nodular, exophytic lesion. It may be single or multifocal. The colour is usually red to blue. AIDS affected patients with OKS may have other oral problems concomitantly, such as candidiasis, hairy leukoplakia, advancing periodontal disease, and xerostomia.

Microscopically, early lesions of KS may be composed of hypercellular foci containing bland-appearing spindle cells, ill-defined vascular channels, and extravasated red blood cells. Later, hemosiderin and inflammatory cells may be seen in addition.

Surgery, low-dose radiation and intra-lesional chemotherapy have been reported to be useful treatments for localized lesions. For larger and multifocal lesions, systemic chemotherapeutic regimens are being used [2]. A decrease in the incidence of HIV-KS and regression of some established HIV-KS lesions has been evident after the introduction of highly active anti-retroviral treatment (HAART)[2,83].

1.5.2. Malignant bone tumors

Malignant bone tumors can be categorized into primary, that is, begin in bone tissue and secondary bone tumors. Malignant bone tumors destroy normal bone tissues.

1.5.2.1. Osteosarcoma

Osteosarcomas are primary malignant non odontogenic bone tumors in which mesenchymal cells produce osteoid[2]. They are generally the most common malignant bone neoplasm, although lesions of the jaw are uncommon. The mean age of occurrence is 34 years, with a nearly equal involvement of the maxilla and mandible reported[79,80].

The main clinical findings are swelling and localized pain. Other symptoms reported include redness, loosening and displacement of teeth, paresthesia, epistaxis, nasal obstruction and eye problems. The average duration of symptoms has been reported to vary from three to four months before diagnosis[2].

Microscopic examination shows areas of osteoid and chondroid formation surrounded by a cellular stroma. Osteosarcoma of jaws present variable histologic patterns, namely

osteoblastic, chondroblastic (the most common variant), fibroblastic, telangiectatic and low-grade intra-osseous osteosarcoma[84].

Survival rates of between 25% and 60% have been reported for jaw osteosarcomas[79,80]. Osteosarcomas are best treated by radical mandibulectomy or maxillectomy, with radiotherapy and chemotherapy for recurrences, soft tissue extension, or metastatic disease[79]. Recurences have been frequently reported with osteosarcomas of the jaws, with metastasis commonly to lungs and brain and rarely regional lymph nodes[80].

1.5.2.2. Chondrosarcoma

Chondrosarcoma is the second most common type of malignant bone tumors. This type of tumor originates from the cartilage cells. It is most commonly found in people over 40 years of age. It mostly affects the bones of hips and pelvis. Chondrosarcoma arising in the mandible and maxilla are extremely rare and account for approximately 1% of chondrosarcomas of the entire body[85].

In the oral facial region, chrondrosarcomas more frequently involve the maxilla than the mandible. Lesions arising in the maxilla usually involve the anterior region (lateral incisor-canine region) and the palate. Mandibular chondrosarcomas occur more frequently in the premolar and molar regions, symphysis, coronoid process and occasionally the condylar process[85]. No distinct gender predilection has been reported. The mean age of occurrence of 60 years has been reported although almost half the cases have been reported to arise during the third and fourth decades of life[85].

The commonly reported signs include a painless swelling and expansion of the affected bones, with subsequent loosening of teeth or ill-fitting dentures. Pain, visual disturbances, nasal signs and headache may result from extension of the tumour from the jaw bones to contiguous structures[84,85].

Radiographic appearance of chondrosarcomas varies from moth-eaten radioluscencies that are solitary or multilocular to diffusely opaque lesions.

The histologic appearance of chondrosarcomas is variable, usually showing recognizable cartilage and a lobular growth pattern, but cellular evidence of malignancy was often subtle, with most of the tumors being well differentiated. The prognostic significance of the

pathologic grading of chondrosarcomas has been well reported[85]. Chondrosarcomas are considered to be radioresistant, and therefore wide local or radical surgical excisions have been reported to be the treatment of choice[85]. Metastasis, more common with high- grade chondrosarcomas, is generally to lungs or bones. The 5 year survival for chondrosarcomas of the jaws and craniofacial bones has been reported to be about 80%[85].

1.5.2.3. Ewing's sarcoma

Ewing's sarcoma is the most aggressive round cell type of bone tumor, occuring mostly in younger people between 4-15 years of age. It mostly affects the middle of the long bones of arms and legs. It is related to peripheral primitive neuroectodermal tumor (PNET), sharing a common karyotype translocation t(11;12), (11;22), (q24;q12) in approximately 90% of these tumors. It accounts for approximately 6% of all malignant bone tumors, with 4 % arising in the bones of the head and neck, out of which 1% occurring in the jaws. The ramus of the mandible is the commonest site in the jaw bones, with few cases reported in the maxilla[86].

Ewing's sarcoma occurs between the ages of 5 and 30 years, with 60% occurring in males[2,87]. The mean age of occurrence for primary tumors involving the bones of the head and neck is 10.9 years. Pain and swelling are the most common presenting symptoms. Other symptoms include facial deformity, destruction of alveolar bone with loosening of teeth, and mucosal ulcers.

Radiographic findings may simulate an infection as well as a malignant process. Metastasis of Ewing's sarcoma to other bones has been reported. Chemotherapy followed by radical resection and radiotherapy have been reported to offer favourable results[87].

1.5.2.4. Malignant odontogenic tumours

Malignant odontogenic tumours are extremely rare, aggressive lesions which may appear *de novo* or originate from pre-existing odontogenic epithelium, tumours, or cysts[2]. They occur in a younger age group (thirties) and two thirds arise from the mandible while one third arise from the maxilla. Males are reported to be more affected than females[90]. Included in this group are Ameloblastic carcinoma and Primary intraosseous carcinoma. A four year study on

odontogenic tumours in Tanzania, encountered one case (0.9%) of malignant odontogenic tumours[91].

The most common symptom is a rapidly progressing painful swelling. Microscopically, less differentiation, cytologic atypia and mitotic figures are seen. Keratin formation and peripheral palisading of epithelial nests may also be seen. Local control is difficult due to metastasis, which appears usually in the lung, regional lymph nodes, skull, liver, spleen, kidney, and skin. Wide surgical excision with or without radiotherapy is the most common treatment modality. Prognosis has been reported to be poor, with a 5 year survival rate reported at 40% [2].

1.5.2.5. Secondary Bone malignancies

Secondary bone malignancies are rare in the jaws and facial bones. They are caused by metastasis. Malignant tumours that have metastasized to the oral and maxillofacial region from distant sites account for only 1% of all malignancies of the jaw and may be the source of definitive diagnosis of malignancy[8]. These metastatic tumours have been reported most often in the mandible, and the majority of these in the molar region[1,2,92]. The exact location of the primary tumour, however, is often difficult, sometimes impossible, to identify. In adults, metastases to the jaws most commonly originate from primary carcinomas of the breast in women and lung in men. In children, bone malignancies are common in the second decade of life. Other common primary sites are the kidney, colon and rectum, prostate and thyroid gland [2,92]. The older age groups are more likely to be affected by metastatic carcinoma to the jaws, mostly in the fifth to seventh decades of life, with an average age of 45 years[92].

The mechanisms of spread to the jaws are usually hematogenous from the primary visceral neoplasm or from lungs[1,2].

1.6. Lymphoid malignancies

Lymphomas are solid tumours of any type of lymphocyte, and they are all malignant. They comprise of Hodgkin's lymphoma (HL) and non- Hodgkin's lymphoma (NHL). The etiology of lymphomas is unknown, but they have been reported frequently in immunosuppressive treatment, cytotoxic chemotherapy, autoimmune diseases, AIDS and irradiation[21,22]. Infection by certain viruses, climate, vegetation, geographical location,low socio-economic status,

exposure to certain chemicals (such as asbestos) and certain pesticides and plant species, have also been reported to be associated with an increased incidence of oral lymphomas[1,2,93,94]. Lymphomas, particularly HL are rare tumours in the mouths of otherwise healthy persons, though they relatively frequently involve the cervical lymph nodes. The majority of oro-facial lymphomas affect four regions: Waldeyer's ring, nasal and paranasal sinus, oral cavity and salivary glands particularly the parotids.

1.6.1. Hodgkin's lymphoma

Hodgkin's lymphoma (HL) rarely involves the oral cavity although there are rare cases which appear in the soft tissues as well as the jaws. On occasion, in some cases oral manifestations may represent the primary site of involvement while in other cases, associated cervical lymphadenopathy or more widespread Hodgkin's disease (HD) may be noted concurrently.

Clinically, HD is characterized by painless enlargement of lymph nodes or extra nodal lymphoid tissue. Within the oral cavity, tonsillar enlargement, usually unilateral, may be seen in the early phase. When extranodal sites are involved, submucosal swellings may be seen, sometimes with mucosal ulceration or erosion of underlying bone.

Microscopically, Reed-Sternberg cells; large- sized cells with bilobed nuclei and large nucleoli are characteristic. Four histological subtypes of HD have been developed, and they reflect prognosis. These are: (i) lymphocyte predominant type in which a small mature lymphocyte is the most prevalent cell, but it is mixed with scattered macrophages (ii) nodular sclerosis type characterized by bands of collagen that originate from the periphery and penetrate into the lymph node, subdividing it into islands of tumour that contain Reed-Sternberg (RS) cells. This type has also been reported to be the most frequent form of the disease (iii) mixed cellularity type containing a combination of lymphocytes, eosinophils, neutrophils, plasma cells, macrophages, and many RS cells (iv) lymphocyte depletion type (abundant pleomorphic RS cells and relatively few lymphocytes. The lymphocyte predominant type has the most favourable prognosis and, the lymphocyte depleted type has the least favourable prognosis[95].

External radiation therapy and/or multiple-agent chemotherapy have been reported to be the treatment modalities for HD. Clinical staging and histologic classification of HD are critical

in determining management and prognosis. However, clinical stage has a greater influence on overall prognosis than does histologic subtype[2].

1.6.2. Non-Hodgkin's lymphoma

NHLs are relatively common lesions and often occur in extranodal head and neck sites, especially in HIV/AIDS patients[1,2,21,96]. With the emergence of HIV infection, oral HIV-associated lymphomas are now encountered with increased frequency and have been accompanied by a distinct shift to predominantly high-grade tumours and appositive correlation with EBV in the lesion. In the year 1985 the Center for Diseases Control (CDC) included NHL as an AIDS-defining diagnosis[97]. NHL is the second most common malignancy affecting people with HIV infection in Western countries.

Middle-aged and elderly individuals are commonly affected by NHL, except for BL, which can be encountered in children. Studies show that males have a slight preponderance over females. Gradual asymptomatic enlargement is characteristic of nodal disease. Oral NHLs may appear in mucosa-associated lymphoid tissue (Waldeyer's ring), or may develop as infiltrates in nonlymphoid tissues and are characterized by an absence of symptoms and by tumescence, often with overlying ulceration. After the tonsil, the palate is the second most common site. If bone is the primary site, alveolar bone loss and teeth mobility are often the presenting signs. Swelling, pain, numbness of the lip, and pathologic fracture may also occur. Staging of NHL is done after the diagnosis of lymphoma has been established.

In general, two basic morphologic groups of lymphomas have been recognized; nodular and diffuse. The diffuse form has a significantly poor prognosis[1,2]. Nodular lymphomas show malignant cells arranged in a pattern characterized by regular nodules distributed throughout a lymph node or extra nodal site. Nodular lymphomas may be subdivided into three subtypes: poorly differentiated lymphocytic, which presents with generalized disease but a relatively favourable prognosis, mixed lymphocytic-histiocytic, and histiocytic or large cell subtype which is associated with the least favourable prognosis. In diffuse lymphomas, abnormal cells are distributed uniformly throughout the involved tissue. In either case, the normal architecture of the lymphoid tissue is destroyed. Numerous classification schemes for NHL

have been reported; however, the working formulation for NHL integrates microscopic features along with clinical behavior that is low grade, intermediate grade or high grade

Local radiation therapy is generally used for stage I disease. Treatment of other stages of lymphoma may be irradiation only or a combination of irradiation and multiple agent chemotherapy[1,2].

Five -year survival rates in stage I NHL treated with primary radiation have ranged from 50 to 90%. Survival rates ranging between 30 and 60% have been reported in patients with more advanced disease (stages II, III, and IV). AIDS-associated lymphomas, which are usually high grade lesions have been associated with a poor prognosis[96,98].

1.6.2.1.Burkitt's lymphoma

Burkitt's lymphoma (BL) is a high grade NHL comprising of undifferentiated uniformly primitive lymphoreticular cells. Evidence for a causal relationship between EBV and BL in the endemic form is fairly strong with frequency of association varying between different patient groups and different parts of the world. EBV may play a role in the pathogenesis of BL by deregulation of the oncogene c-MYC by chromosomal translocation. The emergence of HIV and a distinct subtype of BL in HIV infected individuals has brought a new dimension to the disease particularly in areas where both HIV and BL are endemic[21-23,96,98]. The role of other possible risk factors such as low socio-economical status, exposure to a plant specie common in Africa called Euphorbiaceae, exposure to certain pesticides and to other infections such as schistosomiasis and arbovirus (an RNA virus transmitted by insect vectors) remain to be elucidated. Two forms of BL have been reported, the African type (endemic) and the American type (sporadic), which are histologically and immunophenotypically identical but clinically different. Endemic BL is markedly affected by climate, vegetation and geographical location[1,2,93].

In Africa, BL accounts for over 50% of all childhood malignancies, with a peak incidence between 3 and 8 years of age and a 2 to 1 male predominance while the American form affects a slightly older age group, with a mean age of 11 years, and has no gender predilection[12,93,94].

African BL typically involves the mandible, maxilla and abdomen, with extra nodal involvement of retroperitoneum, kidneys, liver, ovaries, and endocrine glands while involvement of jaws is relatively uncommon in the American form of the disease[12,93-95,98]. The incidence of jaw tumours in African BL is related to the age of the patient, with 88% of those younger than 3 years and only 25% of those older than 15 years showing jaw involvement[12].

Clinical features of BL involving the jaws include an expanding intraoral mass, severely mobile teeth, displaced teeth and generalized lymphadenopathy (submandibular, cervical, axillary and inguinal). Pain and paresthesia are occasionally present. In addition to a facial mass, in the American population, toothache is the common complaint as well as paresthesia of the lip. BL has also been noted to invade the dental pulp, especially in the developing teeth[2].

Radiographically, a moth-eaten, poorly marginated destruction of bone is observed. The cortex may be expanded, eroded, or perforated, with soft tissue involvement[2]. Studies in Africa have reported that majority of the patients presented with an advanced disease[12,93,94,98].

Microscopically, BL is a neoplastic B cell proliferation that contains cell-surface B- lineage differentiation antigens and monoclonal surface antigens immunoglobins. Although the lymphoma may be nodular, most often it is a diffuse proliferation of small transformed or non-cleaved follicular centre cell lymphocytes that are considered undifferentiated. Throughout the lymphoid proliferation are numerous scattered macrophages containing pyknotic debris, contributing to the so-called starry- sky appearance[1,2]. Combined chemotherapy has proved to be extremely sensitive to and, therefore potentially curable for BL[12,93].

The aim of this study therefore, is to determine the predisposing factors and clinico-pathological presentation of malignant lesions of the oro-facial region among patients attending the Muhimbili National Hospital.

2. PROBLEM STATEMENT

Often, patients present at the oral and maxillofacial unit of MNH with a variety of malignant lesions in the oro-facial region. Majority of these patients are referred cases from upcountry district/regional hospitals. They present with advanced stages of disease with a wide range of complications such as pain, bleeding, infection, facial disfigurement, tooth mobility and loss of function e.g difficulty in chewing, trismus and difficulty in breathing. Majority of the patients are rural dwellers whose health-seeking behavior is influenced by socio-economic and cultural backgrounds inherent within their tribes or communities. Reaction to disease differs among societies, however, traditional and faith-based healers still play a big role in the Tanzanian society. Patients, therefore, report to the health care facilities after a considerable delay due to, among other reasons, consulting these alternatives.

The Tanzanian health care system starts with the village health post with a non-trained person, the dispensary with junior medical personnel (Assistant Clinical Officer), a health centre run by a clinical officer, and a district hospital with qualified medical officer or assistant medical officer. None of these facilities has histopathological diagnostic capability due to non-availability of equipment and personnel. Furthermore, only few regional or zonal centers can perform histopathological examinations. Since none of the district hospitals can diagnose and treat malignancies, all such cases have to be referred to regional or zonal centers, where they are ultimately referred to MNH. Due to the fast rate of growth of most of the malignant lesions and their potential to cause gross destruction, the long process the patient undergoes before arriving at MNH results in patients presenting with incapacitating conditions. Since there are no histopathological services in majority of the regional hospitals, on arrival at MNH the patient has to undergo investigations that include biopsy taking, the results of which take several weeks or a month to come out. This gives time for further advancement of the disease and further incapacitation of the patient both of which complicate the management. Except for KS, which has been associated with HIV/AIDS and some studies that have associated OSCC with tobacco use, there exists no scientific information on other oro-facial malignancies and associated factors in Tanzania. Many of the studies on malignant lesions in the oro-facial region were done for individual tumours, therefore comparison among different tumours was

not possible. Furthermore, the presenting features of most of the diseases that patients present with are rather unique to this part of the developing world. They are therefore rarely seen in the available literature which is largely Western based.

3. RATIONALE OF THE STUDY

The results of this study shall provide useful information regarding the association of particular predisposing factors and specific malignant conditions of the oro-facial region in the Tanzanian population. The clinical and pathological data shall provide a useful guide on the characteristics of different malignant lesions that occur in the oro-facial region. Although it is beyond the scope of this study, the immediate treatment outcome of these conditions and the impact of the treatment offered on the quality of life of the patient shall to a certain extent be known.

This is important since most information we rely on currently is from foreign sources, mostly European or American in origin which do not necessarily represent the local reality. The results of this study will form a valuable source of information for clinicians and researchers regarding malignant lesions of the oro-facial region in Tanzanian patients.

Furthermore, th information gained from this study shall be submitted to the MoHSW for use in planning community-based preventive programmes and provision of manpower, medicines, materials, and equipment nationwide for patients suffering from such conditions.

4. GOALS AND OBJECTIVES

4.1.Broad Objective

To determine the predisposing factors and clinico-pathological presentation of malignant lesions of the oro-facial region among patients attending the Muhimbili National Hospital.

4.2.Specific Objectives

1. To determine the frequency of occurrence of oro-facial malignant lesions.
2. To determine the socio-demographic characteristics of patients with oro-facial malignant lesions.
3. To determine factors which predispose to oro-facial malignant lesions.
4. To determine the clinical features of oro-facial malignant lesions.
5. To determine pathological characteristics of oro-facial malignant lesions

5. MATERIAL AND METHODS

5.1. Study settings

This study was conducted at the Muhimbili National Hospital (MNH) in Dar es Salaam, Tanzania. MNH is a teaching hospital and a referral centre that houses the largest dental clinic in the country, the only one offering oral and maxillofacial treatment. It provides services to residents of Dar es Salaam and all other regions in Tanzania. The study included out patients and in patients.

5.2. Study design

This was a descriptive prospective cross-sectional study.

5.3. Study duration

The study was conducted for the duration of 8 months, from 1st July 2010 to February 2011 inclusive.

5.4. Study population

The study population included all admitted and outpatient oral surgical patients attending MNH with clinically suspected oro-facial malignancies during the duration of the study.

5.5. Inclusion criteria and exclusion criteria

5.5.1. Inclusion criteria

All patients who presented at the Oral and Maxillofacial Surgery department with clinically suspected malignant lesions in the oro-facial region and confirmed cytologically/histologically to be malignant and who consented were included in the study.

5.5.2. Exclusion criteria

Patients who did not give consent.

Patients with clinically suspected malignancy in the oral facial region but cytology/histology could not be done or could not prove malignancy.

Patients with oral facial lesions which histology proved to be benign.

5.6. Sample size

A total of 186 patients participated in the study over a period of 9 months since July 2010 to March 2011.

Sample size calculation

$$n = z^2 \frac{P(1-P)}{e^2}$$

where n = sample size

P = prevalence of malignant tumours in the oral and maxillofacial region=50.53% (Kamulegeya et al.2008)

e = maximum error = 0.05

z = 95% confidence interval = 1.96

$$n = \frac{1.96^2 \times 0.51(1-0.51)}{0.05^2}$$

n= 383

5.7. Sampling procedures

All patients meeting the inclusion criteria were enrolled into the study.

5.8. Data collection

After getting informed consent from the patients (Appendix I or II), each patient was interviewed using a specially designed questionnaire. A thorough patient examination was then conducted, and clinical staging was done. This was followed by cytology and/or histology.

5.8.1. Patient interview

Patient interview was done using a questionnaire (Appendix III or IV) which consisted of socio-demographic data and predisposing factors. Apart from sociodemographic data such as serial number, date of interview, hospital registration number, address and category. It also consisted of questions regarding predisposing factors and, patient's main complaint.

5.8.1.1. Predisposing factors

This part composed of questions enquiring on tobacco, alcohol and betel/areca use and, occupation. Predisposing factors were considered regardless of whether previous or current.

The questionnaire enquired on the type or form tobacco used (dipping, chewing, snuffing and smoking), frequency of tobacco use per day and, duration of tobacco use in years.

On alcohol consumption, the questionnaire enquired on the type of alcohol used (beer, local brew, spirits or local spirits), frequency and, duration of alcohol use in years.

5.8.1.2. Patient's main complaint and duration

This enquired on the patients'problems which made them seek for medical attention, for example ulcer, pain, swelling, bleeding, difficulty in chewing, difficulty in opening the mouth, nasal congestion, tooth/teeth mobility, numbness/paresthesia, difficulty in breathing and others.

The duration of the main complaint was also enquired.

5.8.1.3. Initial presentation and Symptoms

This enquired on the initial presentation of the problem (ulcer, pain, swelling, bleeding, difficulty in chewing, difficulty in opening the mouth, nasal congestion, tooth/teeth mobility, numbness/paresthesia, difficulty in breathing, etc) and various symptoms that the patients had experienced since the beginning of the problems.

5.8.2. Clinical examination

A thorough clinical examination was carried out with the patients seated on the dental chair using artificial light. Details of examination findings were recorded in special clinical forms (Apendix V) which included: appearance of the lesion (whether swelling, induration, ulcer, discolouration or, a combination of these), location of the lesion in the oro-facial region, size of the primary tumor at the greatest diameter measured in centimeter, involvement and/or destruction of local tissues and lymph node status (size, consistence and, whether fixed or not).

To ensure consistence, all examinations were done by the same examiner (investigator).

5.8.3. Assessment of metastases

Metastasis to regional lymphnodes was assessed by palpation of the regional lymph nodes.

Distant metastasis was assessed using anterior-posterior plain x-ray of the chest. For some patients with lymphomas, abdominal ultra sound was used in addition.

5.8.4. Clinical staging

After thorough clinical examination and radiological investigations, clinical staging of the tumors was done.

Carcinomas were staged according to the TNM classification system of head and neck malignant tumors as recommended by the International Union against Cancer (UICC1997). TNM is a numeric system for the clinical staging of malignant tumours where T represents size of the tumor, N is an estimation of the regional lymph nodes metastases, and M indicates the absence or presence of distant metastasis. T1 stands for tumour less than 2 cm in diameter, T2 stands for tumour 2 to 4 cm in diameter, T3 represents tumour greater than 4 cm in diameter and T4 stands for a tumor which has invaded adjacent tissues. T1 indicates small tumor with good prognosis, whereas T4 indicates a poor prognosis. N0 indicates no palpable nodes, N1 represents ipsilateral palpable nodes, N2 contralateral or bilateral nodes and N3 represents fixed palpable nodes. Regarding distant metastasis, M0 stands for absence of distant metastasis whereas M1 represents clinical or radiographic evidence of metastasis. Four stages of OSCC are known. The addition of numbers to these three components (TNM) indicates the extent of the tumor, thus: T0, T1, T3, T4, N0, N1, N2, N3, and M0, M1. TNM deals with the anatomical extent of tumor before treatment.

5.8.5. Investigations

Each patient underwent a series of routine investigations as well as specific investigations depending on the clinical examination findings as per MNH protocol of patient management. These included laboratory, radiological and histopathological investigations. In addition, all patients were counseled for HIV testing (HIV serology). For patients who consented for HIV testing, blood was drawn by the investigator and sent to the laboratory for testing according to the MoHSW HIV testing algorithm. All patients were also tested for syphilis infection using the Venereal Disease Research Laboratory (VDRL) test.

Routine investigations included all investigations which any surgical patient with a suspected malignant lesion should undergo, such as Full Blood Count (FBC), erythrocytes sedimentation rate (ESR), urine analysis, stool examination and, an anterior-posterior view chest radiograph (CXR).

Depending on the provisional diagnosis, anatomical site and size of the lesion as well as general medical condition, the patient underwent specific investigations, which included abdominal ultra sound (USS), comprehensive chemistry panel (CCP), FNAC and/or tissue biopsy. Useful adjuncts included conventional skull radiographs, orthopantomograph (OPG) and intraoral radiographs. Diagnostic imaging evaluation either by computed tomography (CT) or magnetic resonance imaging (MRI) were also used in some cases with indication to assess the extent of local and regional tumor spread, the depth of invasion, and the extent of lymphadenopathyamong patients who could afford to pay for them.

All investigations were done by the patients according to the cost sharing Government policy.

5.8.5.1. Haematological/Immunological investigations

These included HIV serology for HIV and VDRL serology for syphilis (Appendix VI).

In HIV serology, pre-test counseling of patients for HIV testing was done for every patient. For those who consented, blood specimen was taken by the investigator and sent to the CPL for investigations. After the results were ready, post-test counseling was done and those who tested positive were referred to the Muhimbili National Hospital Care and Treatment Centre (CTC). Those who tested negative in the baseline test were adviced to repeat the test after three months.

In VDRL serology, all patients were tested for syphilis infection, whereby patients who tested positive were treated according to the MoHSW guidelines for treatment of syphilis. VDRL test was used because it is relatively cheap and easily accessible at the MNH as a test for syphilis.

5.8.5.2. Radiological investigations

These included conventional chest x- rays, skull x-rays and intraoral dental x-rays depending on the location of the lesion (Appendix VII).

5.8.5.3. Histopathological investigation

This was the major means of confirming the diagnosis of oro-facial malignant lesions, whereby the histopathological diagnosis and the grade/subtype of the lesion was reported (Appendix VIII). It involved cytological or histological analysis of cells or tissue specimens respectively, depending on the location and the clinical diagnosis of the lesion. Specimens for

cytological analysis, such as lesions clinically diagnosed as either lymphomas or tumors of major salivary glands were obtained through fine needle aspiration (FNA) which was done by a pathologist at the Central Pathology Laboratory (CPL) in the Histopathology unit at MNH.

For the rest of the patients, tissue biopsy was done by the investigator either at the outpatient clinic under local anesthesia with the patient seated on the dental chair or in the main operating theater under general anesthesia. Tissue biopsy was either incisional: by taking a wedge shaped specimen from each lesion or excisional where the lesion was entirely excised or debulked.

Immediately after obtaining the tissues, they were put into a special container, clearly pre-labeled with patients' identifications (patient's name, hospital registration number, age, sex and the name of clinic or ward number) and filled with 10% formalin of volume at least ten times the tissue volume. The fixed tissue specimens were then transferred to the laboratory together with histological laboratory investigation request forms containing patient's particulars (similar to those on a container), details of clinical examination, clinical diagnosis, clinical stage of the tumor and radiological report. At the laboratory the tissue specimens were registered, counter-checked for the particulars on the containers and investigation forms and were then assigned identification numbers for laboratory identification and records. The tissues were then macroscopically inspected and sampled ready for processing. Secondary fixation of the tissue specimens were then done, first with formalin then dehydrated in alcohol in ascending concentration of 70%, 90% then 100%. Tissues were then washed with xylene to remove alcohol. Embedding was thereafter done whereby tissues were embedded in paraffin wax to prepare blocks. Cutting of slices was done using a microtome machine at 3-5 microns and the slices were then mounted on the microscope glass slides labeled with the identification numbers. The sections were then deparafinized with xylene then washed with alcohol, followed by de-ionized water. Staining was done using haematoxylin and eosin followed by coating and placing cover slip for protection.

For lesions where aspiration cytology was done, the aspirated materials were suspended in 70% alcohol for 20-40 minutes then mounted on slides and stained with the Papanicolaou stain.

The slides (of both tissues and fine needle aspiration biopsy) were then examined under a light microscope at magnifications of 4x10, 10x10, and then 40x10. The histological/cytological examination and reporting was done by experienced pathologists.

After establishing the histological/cytological diagnosis, tumours were graded/subtyped. The grading of malignancy was determined by a combined assessment of several histological features: 1. Degree of cellularity 2. Cellular pleomorphism or anaplasia, 3. Mitotic activity (frequency and abnormality of mitotic figures), 4. Degree of necrosis, and 5. Expansive or infiltrative and invasive growth. Additional factors included the amount of matrix formation, and the presence or absence of hemorrhage, calcification, and inflammatory infiltrate. The amount of matrix formation, such as collagen or mucoid material, is usually inversely proportional to cellularity and degree of differentiation. The histological type and subtype may be used as a short cut to establish the tumour grade.

SCC was sub-typed into 1. Well differentiated 2. Moderately differentiated 3. Poorly differentiated.

Since immunohistochemistry is not routinely done at the MNH histopathology laboratory, a detailed histological review of mesenchymal and lymphoid tumours could not be done.

Malignant lesions of salivary glands origin were graded into three grades: 1. Low grade, 2. Intermediate grade and 3. High grade.

5.8.6. Reproducibility

To reduce variation of the histopathologic assessments, all the slides were reviewed by one of the supervisors who is the consultant pathologist in the Department of Pathology and Morbid Anatomy, MUHAS.

Skull x-rays, occlusal views and OPGs were reviewed by a supervisor who is a specialist in oral radiology. CXRs and other imagings were reviewed by a specialist in general radiology.

5.9. Data handling and analysis

Data were entered and managed in a personal computer on the same day of collection. Data management included: daily data quality checks for inconsistencies and wrong entries, etc. The data were analyzed using SPSS software for Windows version 13.0. A biostatistician was

consulted regarding data analysis and interpretation. Statistical significance testing was done using the chi-square test; p-value of less than 0.05 was considered statistically significant.

5.10. Ethical consideration

The investigator introduced herself to each individual patient and gave explanation on what the study was about before asking the patient to participate in the study. Only patients who gave consent were enrolled for the study. Patient interview was conducted in a private room with only the investigator and the patient. Clinical examination and biopsy taking was conducted at the Oral Surgery department, with the patient seated on a dental chair. All the examinations, tests and investigation methods were procedural, that is the ones usually done for any patient with suspected malignancy. Therefore, they were all safe. There were no special tests. The investigator was supervised by specialists in the field who were available to guide and assist in case of any problem. The patients' information and results were handled confidentially. Patients who were found to have oro-facial malignancies were managed per existing Muhimbili National Hospital and Ministry of Health and Social Welfare protocols.

5.10.1. Ethical clearance

The proposal was presented in the department of Oral Surgery and Oral Pathology of the Muhimbili University of Health and Allied Sciences. Ethical clearance was thereafter obtained from the Research and Publication committee of the Muhimbili University of Health and Allied Sciences.

5.11. Research personnel

The personnel comprised of the *investigator* (Dr. Gemma Z. Berege) and two *supervisors* (Dr. Elison N.M. Simon and Dr. Edda Vuhahula).

6. RESULTS

Between July 2010 and March 2011 a total of 10,288 biopsies were submitted to the Department of Histopathology at Muhimbili National Hospital (MNH). Among these, 200 had histological diagnosis of various malignant tumors of the oral maxillofacial region. Out of 200 patients diagnosed, 186 (93%) were recruited in this study, whereas 14 (7%) were excluded due to insufficient information.

Demographic features

The study group consisted of 104 (56%) males and 82 (44%) females, with a male to female ratio of 1.3:1. The age at the time of diagnosis ranged from 3 to 83 years with mean age of 48.4 years ± 19.2 SD years. Peak age was at 50-59 years (19.9%), followed by 30-39 (16.1%) (Table1). Patients aged below 40 years accounted for about 33%.

Majority 116 (62.4%) patients had a maximum of primary level education; whereas 46 (24.7%) patients had no formal education. Only 24 (13%) patients had secondary education and above.

Majority, 114 (61.3%) patients were married, with males being 76 (40.9%) and females 38 (20.4%).

Ninety three (50.0%) patients were peasants or pastoralists while 30 (16.1%) patients were petty traders. Only 28 (15.1%) patients were employed (Figure 1).

Frequency of occurrence of oral maxillofacial malignant tumors

Out of the 186 patients, 96 (51.6%) patients had squamous cell carcinoma followed by 17 (9.1%) patients with Kaposi's sarcoma. Ten (5.4%) patients had carcinoma which could not be specified and 7 (3.8%) patients had adenoidcystic carcinoma. Burkitt's lymphoma, adenocarcinoma, and mucoepidemoid carcinoma comprised of 5 (2.7%) patients each, while osteosarcoma and basal cell carcinoma comprised of 4 (2.2%) patients each. Basal cell adenocarcinoma, diffuse large cells lymphoma, acinic cell carcinoma and, Hodgkin's lymphoma comprised of 3 (1.6%) patients each. Malignant melanoma, diffuse lymphocytic lymphoma, PLGA, nasopharyngeal carcinoma, and verrucous carcinoma comprised of 2 (1.1%) patients each. The rest of tumors like malignant eccrine poroma, leiyomyosarcoma, liposarcoma, angiosarcoma, synovial sarcoma, soft tissue sarcoma, fibrosarcoma,

rhabdomyosarcoma, round cell tumour and small cell lymphocytic lymphoma and others, comprised of 1 (0.5%) case each.

Predisposing factors

Tobacco use was reported by 89 (47.8%) patients among whom 69 (37.1%) were males and 20 (10.8%) females. Ninety six (51.6%) patients comprised of 67 (36.0%) males and 29 (15.6%) females reported alcohol use. Among tobacco users, 62 (69.6%) patients reported to have used tobacco for more than 20 years while among alcohol users 49 (51.0%) reported to have used it for more than 20 years. Only 1 (0.5%) male patient reported use of betel/areca. Statistically, tobacco and alcohol use was significantly more in males than females (p=0.000 and p=0.000 respectively).

Among the 96 patients with squamous cell carcinoma, 62 (64.6%) used tobacco of one form or another and 60 (62.5%) used alcohol, with males significantly more than females (p=0.001 and p=0.005 respectively). The use of both tobacco and alcohol was reported by 49 (51.0%) SCC patients (Table 6). Forty four (71.0%) of tobacco users were smokers while 7 (11.3%) were tobacco dippers, 3 (4.8%) snuffers and 2 (3.2%) tobacco chewers (Table 7).

Clinical features

Duration of lesion

Generally, 133 (71.4%) patients reported duration of between 2 and12 months, among these 58.6% were males and 41.4% were females (p=0.47). Only 9 (4.8%) patients reported a duration of ≤1 month while 24 (13%) reported duration of >24 months.

Signs and symptoms

In all types of lesions, pain was the major complaint. Eighty six (86.5%) of patients who had SCC presented with ulcerated lesions. Majority of ulcers were easily bleeding and had characteristic indurated margins with everted edges. Centrally, the ulcers were covered with necrotic tissue and necrosis. In all cases, a big proportion of patients presented with swellings. Other symptoms included pain during mouth opening, difficult mouth opening and, teethache. Most patients reported that the lesions had been interfering with aesthetics and function. All patients agreed that the lesions had been causing discomfort.

Anatomical location of tumors

Twenty six (27.1%) squamous cell carcinoma lesions were located on the tongue followed by 18 (18.8%) on the gingivae, 12 (12.5%) on the skin and 8 (8.3%) on the oropharynx and floor of mouth each (Table 4).

The most commonly involved site by Kaposi's sarcoma was the palatal mucosa as was found in 5 (29.4%) patients, followed by the oropharynx 4(23.5%) patients and tongue 3 (17.6%) patients while the gingivae and skin were locations in 2 (11.8%) patients each (Table 4).

Verrucous carcinoma was located on the mandibular gingivae in one patient while in the other was on the palatal mucosa. Malignant melanoma was exclusively located on the palate (Table 4).

Salivary gland tumors were mainly (32.0%) located on the palate followed by the parotid glands (24.0%), buccal vestibule (16.0%) (Table 8). In adenoid cystic carcinoma, the palate and parotid glands were the commonest locations (2 cases in each), while the parotid glands were the commonest locations for adenocarcinoma (3 cases). Mucoepidermoid carcinoma was mainly located on the palate (2 cases). Both cases of PLGA were located on the palate while the skin was the commonest location for basal cell adenocarcinoma (2 cases).

In osteosarcoma, the mandible was the commonest (75%) location while 25% of the tumours were locted on the maxilla.

Distant metastasis

One HIV positive patient with CD4+ count of 53 cells/µl and who did not use any form of tobacco or alcohol, with a well differentiated squamous cell carcinoma of the tongue had distant metastasis to the lungs. The tongue lesion had a duration of between 12 and 18 months.

Clinical stage of the tumor

Ninety (93.8%) patients, 58(60.4%) males and 32 (33.3%) females with squamous cell carcinoma, had stage IV tumour (p=0.154). Only 7 (7.4%) patients had stage II and III tumours. No patient had stag I tumour.

Clinical staging of SCC in relation to age

Among patients with stage IV SCC, majority 56 (58.9%) of them were aged between 50 and 79 years followed by 19 (21.1%) patients aged below 40 years and only 4 (4.5%) patients aged 80 years or above. There was no statistical significance between tumour stage and age (p=0.700).

Clinical staging of SCC in relation to tumor duration

Seventy five (78.2%) of stage IV tumors had a duration of between 2 and 18 months while only 3.4% had duration of 1 month and below. Statistically there was relationship between tumour stage and duration (p=0.026).

Histological features

One hundred and forty two (76.3%) patients had tumours of epithelial origin, 29 (15.6%) patients had mesenchymal tumours and 15 (8.1%) had tumours of lymphoid origin.

Tumour category in relation to age and sex

Epithelial tumours were the most common, found in 142 (67.6%) patients, 84 (59.2%) males and 58 (40.8%) females, with male to female ratio of 1.4:1 (p=0.020). The age at the time of diagnosis ranged from 6 to 83 years with mean age of 53.3 ±17.2 SD years. Majority 121 (86%) patients with epithelial tumours were aged between 30 and 79 years while only 13 (9.2%) patients were below 30 years. Sixty eight (67.6 %) of epithelial tumours were SCC.

Twenty five (13.4%) patients constisting of 8 (32.0%) males and 17 (68.0%) females, with male to female ratio of 1:2.1 were found to have various types of soft tissue mesenchymal tumours in this study. The age at the time of diagnosis ranged from 16 to 75 years with mean age of 35.2 ±14.2 SD years. Majority, 14 (56.0%) patients with soft tissue tumours were aged between 20 and 39 years. Only 1 patient was aged above 59 years. Kaposi's sarcoma was the commonest, 17 (68.0%) soft tissue mesenchymal tumour.

Hard tissue mesenchymal tumours were found in 5 (3.3%) patients, 3 (60.0%) males and 2 (40.0%) females in this study (p=0.261). The age at diagnosis ranged from 9 to 59 years, with majority (75%) of patients aged below 40 years. The mean age was 30.8±18.7 SD years. Osteosarcoma was the commonest hard tissue mesenchymal tumour found in 4 (2.2%) patients in this study.

Lymphoid tumours were encountered in 15 (8.1%) patients in this study, comprised of 9 (60.0%) males and 6 (40.0%) females. The age at diagnosis ranged from 3 to 68 years, with mean 28.9±20.2SD years. Majority, 12 (80.0%) patients were aged below 40 years. Burkitt's lymphoma was the predominant lymphoid tumour encountered in 5 (33.3%) patients.

Histological diagnosis in relation to age and sex

Among patients with squamous cell carcinoma, 59 (61.4%) patients were aged between 50 and 79 years. Twenty one (21.9%) patients were aged below 40 years. The age at the time of diagnosis ranged from 6 to 83 years, with mean 54.1±17.4SD and a male to female ratio of 1.7:1.

Fifteen (88.2%) patients with Kaposi's sarcoma were aged between 20 and 49 years. No patient of less than 20 years of age was diagnosed with Kaposi's sarcoma. The age at the time of diagnosis ranged between 22-52 years, mean 35.9±9.5SD with the male to female to ratio was 1:3.3.

Patients with carcinoma were aged between 31 and 70 years with mean age of 48.0±14.8SD years and a male to female ratio of 4:1.

Regarding salivary gland tumours, the age at the time of diagnosis ranged from 13 to 81 years with mean age of 49.2 years ± 18.8 SD years. Peak age was at 40-49 years (32.0%). Only 2 (8%) patients were aged below 19 years while only 1 (4.0%) patient was aged above 79 years. Adenoidcystic carcinoma was the commonest malignant salivary gland tumour encountered in 7(28.0%) patients, followed by adenocarcinoma and mucoepidermoid carcinoma 5 (20.0%) patients each (Table 8). Patients with adenoidcystic carcinoma were aged between 20 and 59 years with a male to female ratio of 1:1.3 while those with acinic cell carcinoma were aged between 60 and 79 years with a female to male ratio of 1.3:1. Adenocarcinoma and mucoepidermoid carcinoma had male to female ratio of 2:1 and 1:1.5 respectively. Acinic cell carcinoma and PLGA were found exclusively in females while basal cell adenocarcinoma was predominant among females.

All patients with Burkitt's lymphoma were aged below 20 years, with a male to female ratio of 1.5:1. Patients with diffuse large cells lymphoma (3 patients) were aged between 30 and 59 years. Hodgkin's lymphoma was found in 3 patients aged between 10 and 29 years.

One case of malignant eccrine poroma was diagnosed in a 48 years old male peasant who had no history of tobacco or betel/areca use but had a history of alcohol use for more than twenty years.

Histological grade of SCC

Histological review of SCC revealed that 53 (55.2%) lesions were well differentiated (G_1), 32 (33.3%) were moderately differentiated (G_2), and 11 (11.5%) lesions were poorly differentiated (G_3).

Histological grade of SCC in relation to age

Well differentiated tumours were found in 75 (52%) SCC patients aged 40 years and above. However, there was no statistical significance between histological grade of SCC and age (p=0.299).

Relationship between histological grade of SCC and tumor duration

Majority of patients presented with tumour between 2 and 18 months. There was no significant difference in differentiation of tumours according to tumour duration. (p=0.394).

Histological grade of SCC in different anatomical locations

Majority of tumours located on the tongue (69.2%), skin (50.0%), maxillary sinus (83.3%) and oropharynx (62.5%) were well differentiated (G_1). All tumours located on the lip were well differentiated (G_1) while all tumours located on the nasopharynx were poorly diffentiated (G_3). No tumours on the buccal vestibule, palate, maxillary sinus and, floor of mouth was poorly differentiated (G_3). The relationship between histological grade of SCC and anatomical location was statistically significant (p=0.002).

Histological grade of SCC in relation to clinical stage of SCC

Ninety four (94.3%) of well differentiated SCC were clinical stage IV while no poorly differentiated tumour was in clinical stage II. However, no statistical significance was established between this relationship (p=0.885)

General features.

About 80% of the patients presented with different levels of anaemia (i.e. Haemoglobin levels <10g/dl). Regarding HIV serology, 33(17.7%) patients tested positive, 152 (81.7%) negative, and 1 (0.5%) refused to be tested. Majority (81.8%) of HIV positive patients were aged between 20 and 49 years, out of which 77.2% were females.

All 17 (100%) patients with Kaposi's sarcoma tested positive for HIV while all patients with BL were HIV negative. Two (66.7%) patients with diffuse large cells lymphoma were HIV positive.

Table 1. Distribution of patients with oro-facial malignant lesions by age and sex

Age group	Sex				Total	
	Male		Female			
	n	%	n	%	N	%
0-9	3	1.6	2	1.1	5	2.7
10-19	3	1.6	9	4.8	12	6.5
20-29	6	3.2	8	4.3	14	7.5
30-39	17	9.1	13	7.0	30	16.1
40-49	15	8.1	13	7.0	28	15.1
50-59	19	10.2	18	9.7	37	19.9
60-69	20	10.8	9	4.8	29	15.6
70-79	14	7.5	10	5.4	24	12.9
80+	7	3.8	0	0.00	7	3.8
	104	**55.9**	**82**	**44.1**	**186**	**100.0**

Table 2. Distribution of patients with oro-facial malignant lesions by level of education and sex

Education level	Sex				Total	
	Male		Female			
	n	%	n	%	N	%
No formal education	22	11.8	24	12.9	46	24.7
Primary education	66	35.5	50	26.9	116	62.4
Secondary education	14	7.5	6	3.2	20	10.8
Tertiary education	2	1.1	2	1.1	4	2.2
Total	**104**	**55.9**	**82**	**44.1**	**186**	**100,0**

Table 3. Distribution of patients with oro-facial malignant lesions by marital status and sex

Marital status	Gender				Total	
	Male		Female			
	n	%	n	%	N	%
Single	15	8.1	16	8.6	31	16.7
Married	76	40.9	38	20.4	114	61.3
Widow	0	0.0	19	10.2	19	10.2
Widower	9	4.8	0	0.0	9	4.8
Divorced	4	2.2	9	4.8	13	7.0
Total	**104**	**56**	**82**	**44**	**186**	**100.0**

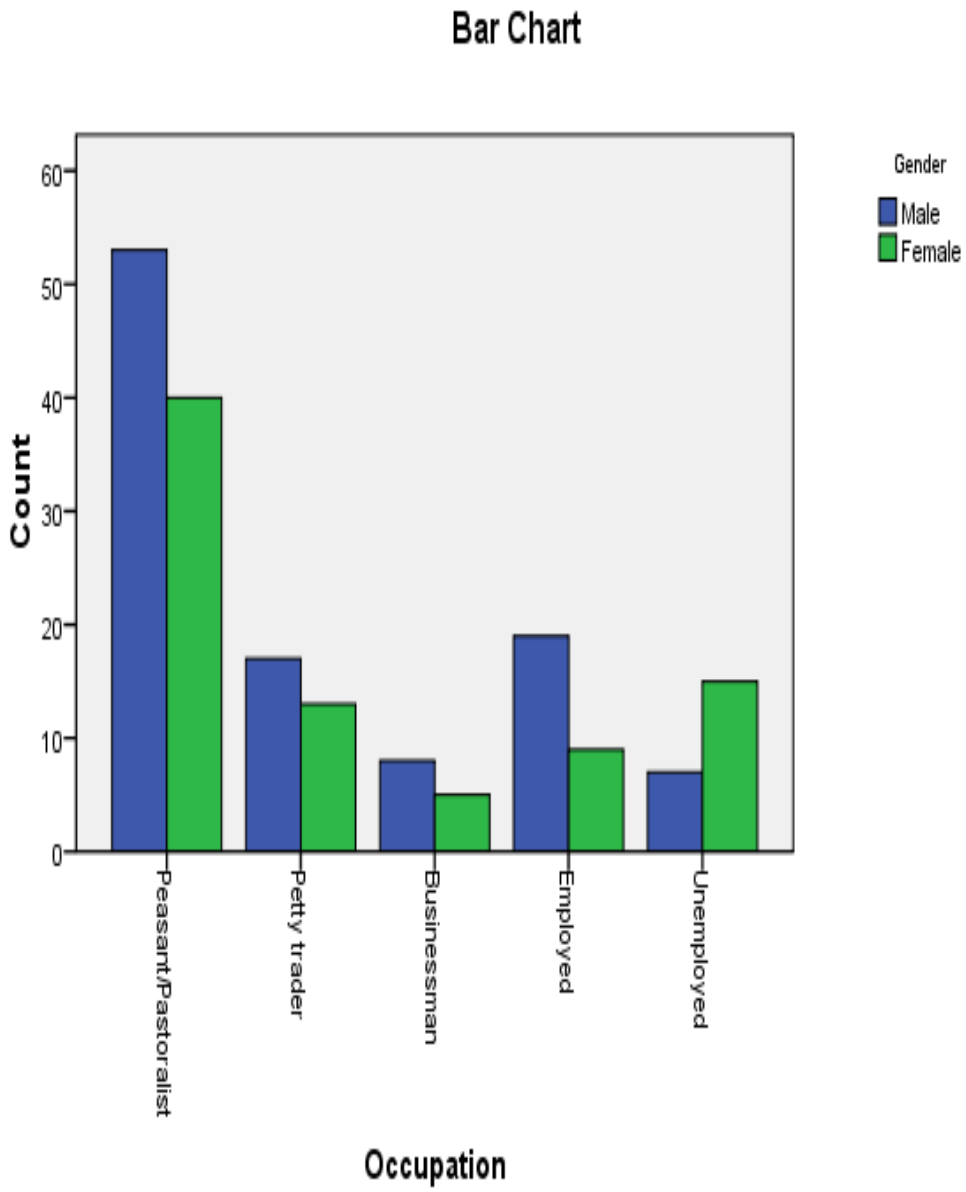

Figure 1. Distribution of patients with oro-facial malignant lesions by occupation and sex

Table 4. Histological diagnosis of oro-facial malignant lesions by site

See file: Table 4

Table 5. Distribution of patients with oro-facial malignant tumours by histological diagnosis, age and sex

See file: Table 5

Table 6. Distribution of patients with squamous cell carcinoma by sex and predisposing factors

Habit of using		Sex						X^2 value
		Male		Female		Total		
		n	%	n	%	n	%	
Tobacco	Yes	46	47.9	16	16.7	62	64.6	0.001
	No	14	14.6	20	20.8	34	35.4	
Alcohol	Yes	44	45.8	16	16.7	60	62.5	0.005
	No	16	16.7	20	20.8	36	37.5	
Betel/areca	Yes	1	1.0	0	0	1	1.0	0.436
	No	59	61.5	36	37.5	95	99.0	
Tobacco and alcohol	Yes	39	40.6	10	10.4	49	51.0	0.004
	No	21	21.9	26	27.1	47	49.0	

Table 7. Different uses of tobacco among squamous cell carcinoma patients

Type of tobacco	Sex						X^2 value
	Male		Female		Total		
	n	%	n	%	n	%	
Smoking	40	64.5	4	6.5	44	71.0	0.000
Dipping	1	1.6	6	9.7	7	11.3	0.000
Snuffing	0	0.0	3	4.8	3	4.8	0.000
Chewing	0	0.0	2	3.2	2	3.2	0.000
A combination of any of the above	5	8.1	1	1.6	6	9.7	0.000
Total	**46**	**74.2**	**16**	**25.8**	**62**	**100**	

Table 8. Distribution of salivary gland tuours by site

Site	Salivary gland tumour					
	Adenoidcystic carcinoma	Adenocarcinoma	Mucoepidemoid carcinoma	PLGA	Basal cell adenocarcinoma	Acinic carcino
Skin	0	0	0	0	2	0
Lip	0	0	1	0	0	0
Floor of mouth	0	0	1	0	0	0
Gingivae	0	0	0	0	0	1
Maxillary sinus	1	0	0	0	0	0
Palate	2	1	2	2	0	1
Parotid	2	3	1	0	0	0
Buccal vestibule	1	1	0	0	1	1
Submandibular	1	0	0	0	0	0
Total	**7**	**5**	**5**	**2**	**3**	**3**

7. **DISCUSSION**

7.1. Sociodemogrphic characteristics

In this study over 60% of the patients were above 40 years of age and the majority were aged between 50 and 59 years (Table 5). This is in concurrence with several other African studies which also showed that malignant lesions of the oral and maxillofacial region occurred more commonly among patients above 40 years[16,17,25]. There was one six years old patient who was found with SCC of the right infraorbital region that also involved the lower eyelid. This patient also suffered from xeroderma pigmentosum, a condition which is sometimes associated with causation of skin cancer[99]. A slight male preponderance encountered in this study is in agreement with what has been reported in available African studies[5,16]. Males tend to have a higher exposure to the commonly known predisposing factors to malignancies.

Peasants, unemployed people and petty traders made up 77.9% of all the patients with malignant tumours (Fig.1). It is more likely that people belonging to the low socio-economic class were more inclined to indulge in excessive alcohol and tobacco use since these are considered as means of refreshment or recreation (Table 6).Nevertheless, people of low socio-economic satatus are more likel;y to be exposed to carcinogens during agricultural and other socio-econimic activities.

7.2. Frequency of occurrence

The study showed that squamous cell carcinoma (51.6%) was the most commonly seen malignant tumour in the oral and maxillofacial region with the peak incidence in the 6th decade of life (Table 5). This is in concurrence with available literature from Africa and elsewhere[4,16,17,42,100].

The frequency of occurrence of lymphomas was seen to be low compared to a previous Tanzanian study as well as other studies in Africa and Europe[16-18,42,101]. This might be attributable to the fact that most patients with Burkitt's lymphoma, which is one of the most common lymphomas, are either treated upcountry in the regional, district or religious organisantions' hospitals or are referred directly to the ORCI for management.

A remarkable fact from this study is the presence of some malignant tumours which are rarely reported in the oral and maxillofacial region. A case of malignant eccrine poroma was

encountered in a 48 years old HIV negative male peasant who presented with a painful swelling on the right cheek for 2 years. The patient had no history of tobacco or betel use but had been using about 5 liters of local brew per week for almost 25 years. The patient had no history of any type of cancer in his family. The lesion presented as a firm, tender ulcerated swelling on the right infra orbital region, measuring 5x6 cms. The overlying skin was fixed to the tumour and the swelling was fixed to underlying structures. It also involved the right upper buccal sulcus. Clinically, no palpable lymph nodes were found. CT scan imaging revealed involvement of the lateral wall of the right maxillary sinus. The patient underwent wide surgical excision followed by adjuvant radiotherapy. Malignant eccrine poroma (eccrine porocarcinoma, EPC) is an extremely rare type of skin cancer arising from the intraepidermal portion of eccrine sweat glands or acrosyringium, being a primary tumor or, even more common, a malignant transformation of an eccrine poroma (EP), representing 0.005-0.01% of all cutaneous tumors[102]. Little is available in both African and European literature regarding malignant eccrine poroma in the head and neck region[103,104].

Another rare finding was a 60 years old HIV negative male, diagnosed to have Castleman's disease which progressed into non-Hodgkin's lymphoma. He had neither history of tobacco nor alcohol use. This patient complained of two non painful, non ulcerated swellings on the right side of the floor of mouth for six months. Submandibular, cervical, axillary and inguinal lymphnodes were enlarged bilaterally. The patient did not have any other medical problem. Histological diagnosis revealed multicentric Castleman's disease. However, a repeat biopsy revealed NHL. Castleman's disease is a nonclonal lymphoproliferative disorder that can affect a single lymph node station or can be generalized. Castleman's disease has been reported to progress into either KS or NHL in HIV positive patients[105]. KSHV; also known as HHV8 is the causative agent of multicentric Castleman's disease (MCD) in HIV patients. Since this patient was HIV negative this might mean that there are other factors that are associated with this condition. Nevertheless this must be interpreted with caution because this was only a single case.

7.3. Predisposing factors

Tobacco (47.8%) and alcohol (51.6%) use was high among males (over 70%). This conforms to a report from elsewhere[16,49]. This is in agreement with the fact that head and neck cancers are commoner among men than women. Direct contact with tissues is an important factor in tobacco carcinogenesis in the mouth[49]. The habit of using both tobacco and alcohol as was encountered in this group reflects that our society is at risk of developing malignant lesions. The use of both alcohol and tobacco increases the possibility of developing cancer than using either of them[106,107]. Tobacco and alcohol use have been shown to contribute to the high rates of oral and pharyngeal cancers with increased risks in sites that are in direct contact with tobacco and/or alcohol compared to those with little or no contact[3,26].

Betel use was reported by only one (1%) patient. This is very low compared to studies among Asians and some migrant communities in Africa, Europe, and North American countries[108-111]. The difference could be attributable to social cultural differences whereby, areca (betel) nut is mostly used by people with Asian originality. While areca nut chewing may cause oral submucous fibrosis, its use along with tobacco can cause leukoplakia, which is also a premalignant lesion. Studies in Asia have proved that betel quid chewers are heavy smokers and that there was an independent risk from betel quid chewing per se on oral cancer, over and above the risk from smoking[108,111].

Although one tenth of the patients in this study reported to have one or more family member/relative who had suffered from some type of malignancy, the effect of genetics on cancers in the oral and maxillofacial region has to be further investigated. Unlike breast cancer, there is no available literature regarding family history and risk of oral and maxillofacial cancers.

As it was found in this study, majority (71.0%) of squamous cell carcinoma patients who were tobacco users were smokers (Table 7). Tobacco smoking was ten-fold greater among males than females. This is in agreement with other African and Asian studies where tobacco smoking is a common practice among males[16,49,112]. On the other hand, dipping, snuffing and chewing together were nineteen-fold greater among females than males. This is reflected in the finding of the sites of occurrence of SCC in the oral cavity whereby in females, the

location was mostly on the gingivae. Usually, in tobacco dipping, the tobacco is put in contact with the gingivae in the buccal or labial sulcus for long periods which allows constant irritation and hence mucosal transformation.

In Sudan and India tobacco dipping was commoner among males than it was for females [49,112]. A combination of different types of tobacco use was encountered among 10% of tobacco users in this group.

7.4. Clinical characteristics

Most (23.5%) of Kaposi's sarcoma lesions in this study occurred on the palatal mucosa and oropharynx, followed by the tongue and gingivae (17.6%) (Table 4). Little information is available in the current literature regarding locations of oral Kaposi's sarcoma, however, a case report from India reported that palatal lesions were common[59]. Location of KS on the oropharynx has many challenges especially as it increases in size it may compromise eating and/or obstruct the airway. KS lesions located on the gingival and/or palate are exposed to trauma from the teeth during chewing (Figure 2). If there is ulceration because of trauma or any other reason secondary infection can set in accompanied by severe pain.

In this study, late presentation was a feature in majority of the patients. Pain, swelling, ulceration and aesthetics were the main reasons for reporting for medical care. While benign tumours mostly did not present any symptoms, malignant tumours presented with a variety of features where pain was present in almost every patient. Toothache and difficulty/painful mouth opening interfered with feeding leading to debilitation and problems with esthetics. This might have resulted in psychological effects to the patient leading to loss of self esteem (Figure 3).

7.5. Histological features

The microscopic appearance of SCC showed irregular nests, columns and strands of malignant epithelial cells that infiltrated the sub-epithelial connective tissue stroma. The tumor cells resembled the layers of stratified squamous epithelium. Majority (55.2%) of SCC lesions were well differentiated. Two main features on which grading was based were cellular proliferation and differentiation. Rapid abnormal proliferation was characterized by hyperchromatism, increased mitotic activity, cellular pleomorphism and nuclear atypia.

Differentiation of tissues was assessed by the presence or absence of epithelial bridges and ability to produce keratin. Ten (5.4%) tumours were diagnosed as carcinoma which could not be specified.

KS composed of hypercellular foci containing bland-appearing spindle cells, ill-defined vascular channels, and extravasated red blood cells. Occassionally, hemosiderin and inflammatory cells were seen.Majority (70.6%) of KS lesions were nodular type.

Histologically, sarcomas presented with macrophages, giant cells and cross striations. Osteoid and chondroid formation surrounded by a cellular stroma characterized osteosarcoma.However, some soft tissue mesenchymal tumours could not be graded or subtyped due to lack of immunohistochemical investigation. As a result, some sarcomas were just diagnosed as soft tissue sarcoma.

Lymphocytes, eosinophils, neutrophils, plasma cells, macrophages and large- sized cells with bilobed nuclei and large nucleoli (RS cells) characterized lymphoma. Bands of collagen were occasionally seen. BL addionally comprised of undifferentiated uniformly primitive lymphoreticular cells.

7.5.1. Squamous cell carcinoma

This study revealed that majority (64.2%) of patients with squamous cell carcinoma were aged between 50 and 79 years. This is in agreement with available information from other studies which indicate that squamous cell carcinoma was commonly seen in the 6^{th} and 7^{th} decades of life[25,42,100,113-115].

Behaviours are usually acquired during teenage and in early twenties, usually following peer influence or as a result of meeting strange situations in life, among other reasons[41]. It has been proved that, healthy oral mucosa exposed to smoking, alcohol, and other irritants undergo epithelial atypical changes[3,32,33]. Moreover, the fact that cells change with age increases chances of older cells to transform into malignant cells. Together, progressive and prolonged contact of cells to irritants and age of the individual increases the chances of development of malignancy and are reasons why it is usually seen in adulthood or oldage. A higher frequency (18.9%) of young people with SCC was reported in this study compared to previous studies done in Tanzania[18,25]. This concurs with other recent African as well as Western

studies[17,39,42,52]. In contrast, a study in India reported slightly lower frequencies of SCC among young adults[114]. Such increasing frequencies of SCC among young adults could be attributable to several emerging risk factors such as viral infections especially HIV and HPV, family history of cancer, and dietary factors. Human Papilloma Virus (HPV) is an emerging risk factor associated with oral cancer, with high-risk strains like HPV 16/18 implicated with high malignant potential[31]. However, tobacco and alcohol use cannot be excluded as among predisposing factors for SCC in young ages. The role of all these known and emerging risk factors for SCC in young aged patient has to be further established. It is however, most likely that most cases of SCC in the youngs involve a combination of two or more of these factors. Similar to other studies in the African continent there were significantly more males with SCC compared to females[4,16,18,19,28,49]. This conforms well to the fact that in this group of patients there were more males than females who indulged in the risk behaviours of tobacco and alcohol use. However, deeper analysis on the associated risk factors was beyond the scope of this study.

The most commonly affected sites for SCC in this study was the tongue (Table 4) which is also in concurrence with studies done within and outside the country[4,25,100,115]. Nevertheless, there was some variation from findings from Nigeria, Zimbabwe and India where the maxillary antrum, the mandibular gingivae an the buccal mucosa were reported to be the commonest sites[16,42,112]. In one Indian study, the tongue was reported to be the commonest site for SCC in the younger age group while the buccal mucosa was the commonest in the older age group[114]. Variation of anatomical sites has been postulated to be associated with aetiological factors involved in the geographical location[1,49]. Other sites in this study were gingivae, skin, oropharynx, maxillary antrum, lips, and floor of mouth. The tongue has been reported to be among the sites with unfavourable prognosis as compared to other sites in the oral cavity proper[39]. In this study, majority of ulcers were easily bleeding and had characteristic indurated margins with everted edges. Centrally, the ulcers were covered with necrotic tissue and necrosis (Figure 4).

Clinical stage of SCC is the most prognostic marker used in the treatment plan of patients and in predicting the outcome of the disease. Early stages of SCC (I and II) are associated with

good prognosis as compared with advanced stages (III and IV). In this study, majority (98%) of tumours were in advanced stages (III and IV). Similar results have been reported by other studies in the African continent and elsewhere[19,27,39,114]. Studies among Africans and black Americans reported that majority of tumours were diagnosed at an advanced stage therefore increasing mortality rate of SCC patients. In this study therefore, the prognosis of majority of SCC patients was predictably poor.

Late reporting was shown by the duration of the lesions as majority (81.2%) of patients presented between 2 and 18 months. This concurs with other studies showing late reporting of SCC patients[24,25,56]. Ignorance of patients, poverty and to a certain extent problems inherent in the country's cumbersome referral system are most likely among reasons for patients' late reporting Other reasons are lack of facilities for definitive diagnosis at primary centres (districts and regional hospitals) leads to patients receiving non-curative symptomatic treatment only.

Histological grading is one of the prognostic parameters of SCC[1]. It is considered that well differentiated tumours do better than poorly differentiated ones, therefore, any staging procedure should logically take histological grading of SCC into account. In this study 53 (55.2%) out of all SCC tumours were well differentiated. This finding is in agreement with other studies[16,25]. In contrast, reports from South America and Nigeria showed that majority of lesions were moderately and poorly differentiated respectively[27,38]. However, in this study, 94.3% of well differentiated tumours were in stage IV. Nevertheless, all eleven poorly differentiated tumours were in advanced stages (stage III and IV). This may be attributable to the histological grading of SCC which is not specific in assessing biological aggressiveness of tumours. This therefore calls for routine use of supplementary indicators to provide objective prognostic parameter to predict clinical behavior of SCC as well as other neoplasms. Determination of silver nitrate organizing regions (AgNOR) for example, could save the purpose as proved by the previous studies[25]. Majority (69.2%) of well differentiated SCC were located on the tongue contrary to the mandibular gingivae as was reported in Zimbabwe and India[16,114].

7.5.2. Verrucous carcinoma

Verrucous carcinoma was encountered in 2 (1.1%) patients both of whom were males, one with the mandibular gingivae and the other palatal mucosa lesions. The frequency of verrucous carcinoma in this study was higher compared to previous studies in Tanzania and Uganda[18,25]. Even higher frequencies were reported in Iran[15]. Verrucous carcinoma when discovered early and treated early is curable. Nevertheless, delay as it was the case with most of our patients could lead to transformation to invasive carcinoma.

7.5.3. Basal cell carcinoma

The frequency of basal cell carcinoma was higher compared to a previous study by Kamulegeya in Tanzania and Razavi in Iran[15,18]. Contrary to sex predilection reported by some studies, basal cell carcinoma was equally distributed among men and women in this study[18,55]. All lesions in this study were located on the midface. Several other studies have reported the midface as the commonest location[55,56]. Although lighter natural skin pigmentation has been reported to be among predisposing factors for basal cell carcinoma, to the contrary in this study no patient with BCC had a naturally lighter pigmented skin[1,2,55,56].

7.5.4. Malignant melanoma

The frequency of malignant melanoma in this study was higher compared to a previous study in Tanzania as well as other African studies[15,18]. Contrary to reports on melanoma in Zimbabwe and Tanzania whereby a female predominance was reported, this study encountered an equal distribution among genders[58,59]. Malignant melanoma lesions were exclusively located on the maxillary gingivae while other studies reported lesions on the mandibular gingivae, buccal mucosa and floor of mouth[57-59]. The widespread and unpredictable metastasis of malignant melanoma was encountered in this study whereby a 48 years old female patient, apart from a huge, soft, easily bleeding, black pigmented palatal lesion, she also presented with bilateral fixed cervical and supraclavicular lymphnodes > 6 cm greatest diameter, which were histologically proven to be metastatic melanoma. In this patient the maxillary alveolus and the hard palate were grossly eroded.

7.5.5. Salivary gland tumours

Salivary gland tumours accounted for 13.4%. This is in agreement with African literature[4,5,15]. In this study, the age at diagnosis of malignant salivary gland tumours was a decade older than that in a Ugandan study[46]. Children accounted for only 8% of patients with malignant salivary gland tumours in this group.

Distribution of salivary gland malignant tumours among genders has shown to vary among different African populations. The female predominance encountered among patients with salivary gland tumours in this study was also reported by some studies in Africa[46,66]. However, there are some African studies which reported male predominance[62,63]. The Western literature has been showing an equal distribution of malignant salivary gland tumours among genders[64,71]. In this study, male predominance was only found in adenocarcinoma. Like the variation of distribution of malignant salivary gland tumours among genders, the frequencies of various types of these tumours has been reported to vary among geographical locations in Africa. As was found in a previous study in Tanzania, adenoidcystic carcinoma was the commonest malignant salivary gland tumour, accounting for 28.0% of malignant salivary gland tumours[116]. Similar findings were reported in Uganda and Nigeria, while in Iran and Libya, mucoepidemoid carcinoma was reported to be the commonest tumour followed by adenoidcystic carcinoma[5,15,46,63]. In the European literature, adenoidcystic carcinoma was reported as the commonest salivary gland malignancy[117,118]. Rare malignant salivary gland tumours such as PLGA and basal cell adenocarcinoma were also encountered in this study albeit in very low frequencies, 2 (8%) each as was reported in Uganda[46].

The palate was the commonest location (32.0%) followed by the parotid glands (24.0%). Similar findings have been reported in Nigeria and Iran[15,63]. However, the submandibular glands have been reported to be the commonest location in the Western literature[64,65]. Intraoral minor salivary glands were involved in 18 (72.0%) patients, with the palate (50%) being the commonest. Similar to other African studies, the parotid gland was the most commonly affected major salivary gland followed by the submandibular glands[15,46,66,116].

Adenoid cystic carcinoma was commonly found from the 3rd to 6th decades of life with a slight female predominance. In minor salivary glands this tumour was found to occur almost

equally among males and females contrary to some African and European reports[46,118]. Mucoepidermoid carcinoma accounted for 20% of malignant salivary gland tumours, with the palate being the commonest site. A female predominance in this study is different from other reports[18,69].

PLGA was encountered in 2 female patients aged 54 and 45 years, located on the palate. This concurs with the scant literature available regarding this lesion[15]. However, Vuhahula reported cases of PGLA with locations in submanndibular, parotid glands as well as minor salivary glands[46]. PLGA is a low grade malignancy largely restricted in minor salivary glands, but cases from major salivary glands and seromucous glands of the nasopharynx have been reported.

Basal cell adenocarcinoma was found in 3 (12.0%) patients with malignant salivary gland tumours with a male to female ratio of 1:2. Two lesions were located on the skin while the other was on the buccal vestibule. Vuhahula found 3 lesions of basal cell adenocarcinoma exclusively in the parotid glands[46]. These two rarely reported tumours (PLGA and BCAC) were not reported by previous studies in Tanzania[18,116]. This could be due to the fact that these reports were published prior to the present WHO classification of salivary gland tumours[60]. Neoplastic lesions such as PLGA, BCAC, epithelialmyoepithelial carcinoma (EMC) and malignant myoepithelioma with myxomatous or chondroid differentiation can simply be diagnosed as benign tumors due to absence of obvious microscopic malignant features. Acinic cell carcinoma was found exclusively in females in this study, and in very low frequency compared to the Ugandan report[46]. All patients who were found to have malignant salivary gland tumours presented with swellings.

7.5.6. Kaposi's sarcoma

Kaposi's sarcoma was the second most common malignancy as was found among 17 (9.1%) patients in this study. This concurs with the previous study in Tanzania[18]. In contrast, in Uganda KS was reported as the commonest oral and maxillofacial malignant tumour[18]. In several other African studies KS was not reported as a rarer tumour[5,16,17] and in Iran among oral malignancies KS did not feature at all[15]. Remarkably, all patients with Kaposi's sarcoma were HIV positive at the time of diagnosis. This is different from another Tanzanian report

where 32.5% of KS patients were HIV negative[119]. KS is promoted during HIV infection by various angiogenic and pro-inflammatory factors including HIV-Tat[29].

The age range of patients with KS sarcoma was 20 to 59 years, majority (88.2%) of whom, were between 20 and 49 years and none was aged below 20 years. Several studies in the Sub-Sahara have reported that this age group is the commonest HIV infected[22,120]. However, the findings of this study is contrary to what was reported in a study in HIV positive patients in Tanzania where oral Kaposi's sarcoma was reported in several patients aged below 18 years[120]. A study on oral tumours among children in Tanzania, reported some cases of oral KS[121]. This could be due to the fact that children accounted for a small proportion in the current study.

The male to female ratio in Kaposi's sarcoma in this study was 1:3.3. This is in agreement with other studies in Tanzania and elsewhere[22,120]. However, this is contrary to the report by Mwakigonja and his colleagues where a male to female ratio of 2.75:1 was reported for KS patients[119].The low male to female ratio could be due to the fact that females form the major group among HIV infected patients as they are more prone to be infected with HIV compared to males**.**

Of 17 patients with KS, 15 (88.2%) patients presented with both oral and skin (including facial skin) lesions while only 2 (11.8%) patients presented with exclusively skin lesions. In South Africa, oral KS lesions were reported to be more frequent than skin lesions among HIV patients[122]. KS lesions presented as bluish-red, easily bleeding nodules, patches or plaque (Figure 2).

The 4 (23.5%) patients who had lesions in the oral pharynx and palate apart from the discomfort also faced difficulties with swallowing. Location of KS in the oropharynx posed an additional danger of obstructing the airway. Intra-oral lesions of KS often bleed after minor trauma during the process of eating so it entailed great care during biopsy taking. Studies in Kenya and India, have reported that the palate was the commonest site for KS among HIV positive patients[22,59]. This could be due to the fact that HHV-8 has been reported to infect B cells in the tonsillar regions.

7.5.7. Osteosarcoma

Osteosarcoma was seen at a younger age in this study compared to other studies[78,79]. Predilection to the mandible was a feature in this study contrary to other studies where a nearly equal involvement of the mandible and maxilla was reported[78,79]. Jaw swelling, mucosal ulceration, teeth mobility and displacement were presented by all patients with osteosarcoma (Figure 5).

7.5.8. Lymphomas

The frequency of lymphomas in this study (8.6%) is lower compared to other studies in Africa and worldwide[17,98]. However, some studies in Iran have reported lower frequencies compared to this study[4,15]. Contrary to other studies in East Africa where BL was the commonest NHL, this study found that BL occurred at nearly the same frequency as other NHLs[96,98]. This could be attributable to a smaller sample size in this study. A quarter (25%) of patients who were found to have lymphomas in this study were also HIV positive.

Frequency of BL in this study has been found to be lower compared to previous studies in Tanzania[18]. The fact that some cases of BL are managed in district, religious based and regional hospitals or are sometimes referred directly to ORCI for management may have contributed to the low number of patients with BL in this study. Several other African studies reported higher frequencies of BL[4,16,17]. Larger sample sizes compared to the current study could be among the reasons. The fact that majority of patients who were found to have BL were below 10 years and that no case of BL was encountered in adults in this group concurs with other African studies that African BL occurs almost exclusively in children and mainly in the first decade of life [17,18,94,121]. Contrary to other studies, no patient with BL was found to be HIV positive[98,101]. Teeth mobility and displacement and expanding intraoral mass were the common clinical presentations of patients who were found to have BL.

8. CONCLUSION

1. Squamous cell carcinoma was the most common malignant tumour in the oral and maxillofacial region.
2. Use of tobacco and/or alcohol was a predisposing factor for SCC.
3. A rather young group of patients were found to have malignant lesions in the oral and maxillofacial region.
4. Patients presented rather late with advanced tumours that many times could only be managed by palliative therapy.
5. HIV infection is the predisposing factor for Kaposi's sarcoma in the oral and maxillofacial region.

9. RECOMMENDATIONS

1. There is a need to educate the community on the possible predisposing factors and the importance of taking precautionary measures.
2. Raising awareness of the community on the importance of early reporting whenever they see development of suspicious signs.
3. Continuing education to non-dental health professionals on the importance of early detection and referral of suspected or diagnosed cases since they are the first to see the majority of the cases.
4. Strenghen the capacity of regional and district hospitals equipping them so that they can have the capacity to carry out histological diagnosis.
5. Conduct further studies on malignant lesions in the oral and maxillofacial region inorder to address other predisposing factors.

10. STUDY LIMITATIONS

1. This was a hospital based study therefore some patients with malignant conditions might not have reported to the hospital at all or somewhere referred but could not report due to socio-economical and other reasons.
2. Some patients were too sick to undergo any surgical intervention and were therefore excluded from the study.
3. Patients with tumours which required advanced histological investigations such as immunohistochemistry could not be histologically diagnosed and were excluded from the study.

11. DISPOSAL OF PATIENTS

Treatment depended on the histological diagnosis, clinical stage and location of the tumour. The general condition was also an important factor in determining the management. Patients who required radiotherapy or chemotherapy were sent to ORCI for management. Palliative therapy was the main treatment for patients who were found to have malignancies. Surgery with adjuvant radio/chemo therapy was done for some patients who presented with stage II and III tumours. All patients with osteosarcoma were treated by surgery and adjuvant chemotherapy and/or radiotherapy.All patients with lymphomas and those with KS were reffered to ORCI for chemotherapy and/or radiotherapy. Twelve patients, 7 males and 5 females absconded or refused treatment for different reasons including fear of radiotherapy and for some fear of surgery. Five patients died before treatment majority of them due to pulmonary complications.

12. DISSEMINATION OF RESULTS

The findings of this study will be reported as part of the fulfillment of the Master of Dentistry in Oral Surgery (Mdent. Oral surgery) degree course of MUHAS. Findings of this study will also be presented in scientific sessions and later published in scientific journals.

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14. APPENDICES

14.1. APPENDIX I: CONSENT FORM- ENGLISH VERSION

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

DIRECTORATE OF RESEARCH AND PUBLICATIONS, MUHAS

INFORMED CONSENT FORM

ID-NO. ☐☐☐

Consent to Participate in a Study

Greetings! My name is Dr. Gemma Berege; I am working on this research with the objective of determining the predisposing factors and clinico-pathologic presentation of malignant lesions of the oro facial region.

Purpose of the study

The study is conducted in partial fulfillment of the requirements for the degree of Master of Dentistry in Oral Surgery of MUHAS. This study is aiming to determine the predisposing factors and clinico-pathologic presentation of malignant lesions of the oral facial region. You are being asked to participate in this study because you have particular knowledge and experiences that may be important to the study. Kindly please be honest and true for betterment of the results that could lead to better intervention and recommendations for future.

What Participation Involves

If you agree to join the study, you will be interviewed in order to answer a series of questions in the questionnaire prepared for the study. You will also undergo clinical examination inorder to know the clinical presentation of your problem. Thereafter, you will undergo a series of investigations including blood tests for HIV, Syphylis,full blood count; X- rays and an investigation which will involve taking part or the whole of the swelling or ulcer for investigations under the microscope.

Confidentiality

I assure you that all the information collected from you will be kept confidential. Your name will not be written on any questionnaire or in any report/documents that might let someone identify you. Your name will not be linked with the research information in any way. All information collected on forms will be entered into computers with only the study identification number. Confidentiality will be observed.

Risks

We do not expect that any harm will happen to you because of participating in this study. Some questions could potentially make you feel uncomfortable. You may refuse to answer any particular question and may stop the interview at anytime.

Right to Withdraw and Alternatives

Taking part in this study is completely voluntary. You can stop participating in this study at any time, even if you have already given your consent. Refusal to participate or withdrawal from the study will not involve penalty.

Benefits

The information gathered from you will ascertain the predisposing factors and clinic-pathologic presentation of malignant lesions of the oral facial region and will therefore aid in the management of patients with malignant lesions.

Who to Contact

If you ever have questions about this study, you should contact the Principal Investigator, Dr Gemma Z. Berege of Muhimbili University of Health and Allied Sciences, P. O. Box 65001, Dar es Salaam.

If you ever have questions about your rights as a participant, you may contact the Chairperson of the Senate Research and Publications Committee, P. O. Box 65001, Telephone : 255 22 2152489 Dar es Salaam or Dr E. N. M. Simon and Dr Edda Vuhahula who are supervisors.Do you agree?

Participant agrees ……..Participant does NOT agree ……...

I ……have read the contents in this form. My questions have been answered. I agree to participate in this study.

Signature of participant ……..…Signature of Investigator ……

Date of signed consent …….

14.2. APPENDIX II: CONSENT FORM- SWAHILI VERSION

CHUO KIKUU CHA SAYANSI ZA AFYA MUHIMBILI

KURUGENZI YA TAFITI NA UCHAPISHAJI

FOMU YA RIDHAA

Namba ya utambulisho ☐☐☐

Ridhaa ya kushiriki kwenye utafiti

Hujambo! Ninaitwa Dr Gemma Z. Berege, nashughulika kwenye utafiti huu wenye lengo la kutathmini sababu/vitu mbalimbali vinavyosababisha saratani katika kinywa na uso, na tabia za muonekano wa kipatholojia wa saratani hizo. Utafiiti huu unafanyika katika kutimiza sehemu ya matakwa ya shahada ya uzamili ya Upasuaji kinywa na meno ya Chuo Kikuu cha Afya na Sayansi ya Tiba Muhimbili. Utafiti unalenga kuchunguza sababu au vitu mbalimbali vinavyosababisha saratani mbalimbali katika maeneo ya kinywa na uso. Utafiti huu pia unalenga kuangalia na kutambua tabia na muonekano wa kipatholojia wa saratani hizo. Unaombwa kushiriki katika utafiti huu kutokana na upeo na ufahamu ulio nao ambavyo ni muhimu kwa utafiti huu. Tafadhali kuwa mkweli na muwazi kwa vile matokeo ya utafiti huu yanaweza yakatoa maamuzi na mapendekezo ya baadaye.

Jinsi ya kushiriki

Ukikubali kushiriki katika utafiti huu, utasailiwa ili kuweza kujibu maswali toka kwenye dodoso lililoandaliwa kwa ajili ya utafiti huu na kisha utafanyiwa uchunguzi ambao utahusisha kuangalia muonekano mzima wa tatizo ulilonalo. Pia utafanyiwa vipimo mbalimbali kama vile vipimo vya damu (virusi vya UKIMWI, kaswende na kuangalia wingi na seli mbalimbali za damu), X- ray na kisha kipimo ambacho kitahusisha kuchukua sehemu ya uvimbe au kidonda na kisha kwenda kukiangalia kwa darubini katika maabara ili kujua ni uvimbe/kidonda cha aina gani.

Usiri

Taarifa zote zitakazokusanywa zitaingizwa kwenye ngamizi kwa kutumia namba za utambulisho.Kutakuwa na usiri na hakuna mtu yeyote asiyehusika atakayepata taarifa zilizokusanywa.

Hatari

Hatutegemei madhara yoyote kukutokea kwa kushiriki kwako kwenye utafiti huu.

Faida

Kama utakubali kushiriki kwenye utafiti huu taarifa utakazotoa zitatuwezesha kujua kiwango au ukubwa wa tatizo ambao ni muhimu katika uamuzi wa kuzuia au kupunguza tatizo.

Athari na kukitokea madhara

Hutegemewi kupata madhara yoyote kutokana na ushiriki wako katika utafiti huu. Baadhi ya maswali yanaweza yasikupendeze, unaweza kukataa kujibu swali lolote la aina hiyo na unaweza kuamua kusimamisha udahili wakati wowote.

Uhuru wa kushiriki na haki ya kujitoa

Kushiriki kwenye utafiti huu ni hiari. Unaweza kujitoa kwenye utafiti huu wakati wowote hata kama umeshajaza fomu ya ridhaa ya kushiriki utafiti huu. Kukataa kushiriki au kujitoa kwenye utafiti huu hakutaambatana na masharti yoyote.

Nani wa kuwasiliana naye

Kama una maswali kuhusiana na utafiti huu, wasiliana na Mtafiti mkuu wa utafiti huu, Dr. Gemma Z. Berege wa Chuo Kikuu cha Afya na Sayansi ya Tiba Muhimbili, S. L. P. 65001, Dar es Salaam. Kama una swali kuhusu stahili zako kama mshiriki unaweza kuwasiliana na Mwenyekiti wa kamati ya Utafiti na Uchapishaji, S.L.P 65001, Simu: 255 22 2152489 Dar es Salaam au wasimamizi wa utafiti huu Dr E. N. M. Simon au Dr Edda Vuhahula.

Je umekubali?

Mshiriki amekubali ……..... Mshiriki hajakubali …….....

Mimi .....nimesoma maelezo ya fomu hii. Maswali yangu yamejibiwa.Nakubali kushiriki katika utafiti huu.

Sahihi ya mshiriki…… Sahihi ya mtafiti ……

Tarehe ya kutia sahihi ya idhini ya kushiriki……

14.3. APPENDIX III QUESTIONNAIRE- ENGLISH VERSION

I. Sociodemographic data

1. Serial No._ _ _2. Date _ _/_ _/_ _ _ _ 3. Hosp. Reg. No. _ _ _ _ _ _ _ _

4. Address 1. Ward/Division _ _ _ _ _ _ 2. District _ _ _ _ _ 3. Region _ _ _

Tel. No. _ _ _ _ _ _ _ _ _ _ or _ _ _ _ _ _ _ _ _ _ _or _ _ _ _ _ _ _ _ _ _

5. Category 1. Out patient
2. In patient

6. Age (in years)

7. Sex 1. Male 2. Female

8. Residence
1. Dar- urban
2. Dar peri-urban
3. Upcountry urban
4. Upcountry rural

9. Education level
1. No formal education
2. Primary education
3. Secondary education
4. Tertiary education

10. Marital status
1. Single
2. Married
3. Widow
4. Widower
5. Divorced
6. Cohabiting

11. Occupation
1. Peasant
2. Petty trader
3. Businessman

4. Employed (State the nature of the job …….)

5. Unemployed

II. Predisposing factors

Tobacco use

12. Have you ever used tobacco? 1. Yes 2. No ☐

If YES:

13. What type of tobacco do you use? ☐

1. Smoking
2. Dipping
3. Snuffing
4. Chewing
5. A combination of any of the above

If smoking,

14. What type of tobacco smoking? ☐

1. Pipe smoking
2. Cigarette smoking

15. How many cigarettes do you smoke per day? ☐

1. 1- 5 cigarretes
2. 5- 10 cigarretes
3. 10-20 cigarretes
4. >20 cigarretes

If dipping,

16. How many times do you dip tobacco per day? ☐

1. 1- 5 times
2. 5- 10 times
3. 10-20 times
4. >20 times

17. Where (in which part of your mouth) do you dip tobacco? ☐

1. Floor of mouth

2. Labial sulcus mandibular

3. Labial sulcus maxillary

4. A combination of any of the above-mentioned sites

If snuffing

18. How many times do you snuff per day?

1. 1- 5 times ☐
2. 5- 10 times
3. 10-20 times
4. >20 times

If chewing,

19. How many times do you chew tobacco per day?

1. 1- 5 times ☐
2. 5- 10 times
3. 10-20 times
4. >20 times

20. Do you use any kind of additives such as lemon, salt, etc in tobacco?

1. Yes (Mention…….) ☐
2. No

21. Are you currently still using tobacco? 1. Yes 2. No ☐

If NO:

22. When did you stop using tobacco? ☐

1. <1 year
2. 1- 5 years
3. 6-10 years
4. >10 years

23. For how long did you use tobacco?

1. 1-5 years ☐
2. 6-10 years
3. 11-20 years

4. > 20 years

24. Do you use betel/areca nuts 1. Yes 2. No ☐

If YES:

25. How many times do you use betel/areca nuts per day?

1. 1- 5 times ☐
2. 5- 10 times
3. 10-20 times
4. >20 times

Alcohol drinking

26. Have you ever drunk alcohol? 1. Yes 2. No ☐

If YES,

27. What type of alcohol?

1. Local brew ☐
2. Beer/lager/factory-made beer
3. Factory-made spirits
4. Locall-made spirits spirits
5. A combination of any of the above
6. Others (Mention……..)

28. How frequent do you drink alcohol per week?

1. < one day ☐
2. 1-3 days
3. 4-6 days
4. 7 days

29. On average, how much beer do you drink per week?

1. < 2 litres ☐
2. 2-5 litres
3. 5-8 litres

4. > 8 litres

30. For how long have you been drinking alcohol?

1. 1-5 years
2. 6-10 years
3. 11-20 years
4. > 20 years

31. Are you still drinking alcohol? 1. Yes 2.No

If NO,

32. When did you stop drinking alcohol?

1. < 2 years ago
2. 2-4 years ago
3. ≥ 5 years ago

33. What made you stop drinking alcohol?

1. After getting sick
2. Decided to quit
3. Medical advice
4. Economic reasons
5. Religious reasons
6. Other reasons (Mention……)

34. Have you ever used artificial teeth or any other type of dental prosthesis?

1. Yes 2. No

35. Do you have any family member or relative who has suffered from any type of cancer?

1. Yes 2. No

What is the main complaint that has brought you to the hospital?

36. Swelling 1. Yes 2. No ☐

37. Ulcer 1. Yes 2. No ☐

38. Pain 1. Yes 2. No ☐

39. Difficulty in opening the mouth 1. Yes 2. No ☐

40. Painful mouth opening 1. Yes 2. No ☐

41. Painful tooth/teeth 1. Yes 2. No ☐

42, Mobile tooth/ teeth 1. Yes 2. No ☐

43. Discomfort 1. Yes 2. No ☐

44. Numbness/Paraesthesia 1. Yes 2. No ☐

45. Bleeding 1. Yes 2. No ☐

46. Interference with function (e.g Speech, Chewing, Swallowing, Breathing)
1. Yes 2. No ☐

47. Discolouration 1. Yes 2. No ☐

48. Esthetics 1. Yes 2. No ☐

49. Others (State…….)

50. When did the problem begin?

1. ≤1month
2. 2-4 months
3. 4-6 months
4. 6 to 12 months
5. 12 to 18 months
6. 18 to 24 months
7. >24 months

51. How did the problem initially present?

1. Ulcer
2. Swelling
3. Mobile tooth/teeth
4. Painful tooth/teeth
5. Discolouration
6. Numbness
7. Others (Mention……..)

52. How did the problem progress?

1. Fast growing
2. Slow growing
3. Bleeding
4. Others (Mention……..)

53. Did you seek alternative treatment (traditional, faith-based, etc) for your problem before visiting the hospital?

1. Yes 2. No

14.4. APPENDIX IV: QUESTIONNAIRE- SWAHILI VERSION

1. Namba _ _ _ 2. Tarehe _ _/_ _/_ _ _ _ 3. Na.ya Hosp. _ _ _ _ _ _ _ _

4. Anuani 1. Kitongoji/Kijiji _ _ _ _ 2. Wilaya _ _ _ _ __ 3. Mkoa _ _ _ _

4. Na.ya simu. _ _ _ _ _ _ _ _ _ _ au _ _ _ _ _ _ _ _ _ _ _au _ _ _

5. Aina ya mgonjwa 1. Wa kliniki ya nje ☐
2. Wa wodini

6. Umri (miaka) ☐☐

☐

7. Jinsia 1. Mme 2. Mke

8. Makazi 1. Dar- es-Salaam mjini ☐
2. Dar-es-Salaam nje ya mji
3. Mkoani mjini
4. Mkoani vijijini

9. Kiwango cha elimu 1. Hukupata elimu kabisa ☐
2. Msingi
3. Sekondari
4. Zaidi ya Sekondari

10. Hali ya ndoa 1. Hujaoa/hujaolewa
2. Umeoa/umeolewa ☐
3. Mjane
4. Mkane
5. Mtaliki/mtalika
6. Huna ndoa ila unaishi na mwenza

11. Kazi 1. Mkulima
2.Mfanyabiashara ndogondogo ☐

3. Mfanyabiashara

4. Muajiriwa (Eleza kazi unayofanya …….)

5. Huna kazi

II. Predisposing factors

Matumizi ya tumbaku

12. Je, umewahi kutumia tumbaku? 1. Ndiyo 2. Hapana ☐

Kama NDIYO:

13. Ni njia gani ya matumizi ya tumbaku?

1. Kuvuta ☐
2. Kuweka mdomoni
3. Kunusa
4. Kutafuna
5. Mchanganyiko wa zilizotajwa hapo juu

Kama KUVUTA:

14. Unavuta tumbaku kwa njia gani? ☐

1. Kiko
2. Sigara

15. Je, unavuta sigara ngapi katika siku moja?

1. 1- 5 ☐
2. 5- 10
3. 10-20
4. >20

Kama KUWEKA MDOMONI:

16. Unaweka tumbaku mdomoni mara ngapi kwa siku moja?

1. 1- 5 ☐
2. 5- 10
3. 10-20
4. >20

17. Unaweka tumbaku katika sehemu gani ndani ya mdomo?

1. Chini ya ulimi
2. Kati ya meno ya chini nje na mdomo
3. Kati ya meno ya juu nje na mdomo
4. Sehemu zaidi ya moja katika zilizotajwa hapo juu

Kama KUNUSA

18. Je, unanusa tumbaku mara ngapi katika siku moja?

1. 1- 5
2. 5- 10
3. 10-20
4. >20

Kama KUTAFUNA:

19. Je unatafuna tumbaku mara ngapi katika siku moja?

1. 1- 5
2. 5- 10
3. 10-20
4. >20

20. Je unaongeza kitu chochote kama vile ndimu, limau, chumvi, n.k katika tumbaku unayotumia?

1. Ndiyo (Taja…….)
2. Hapana

21. Je, bado unatumia tumbaku? 1. Ndiyo2. Hapana

Kama HAPANA:

22. Ni miaka mingapi imepita tangu ulipoacha kutumia tumbaku?

1. <1
2. 1- 5
3. 6-10
4. >10

23. Umekuwa ukitumia tumbaku kwa miaka mingapi?

1. 1-5
2. 6-10
3. 11-20
4. > 20

24. Je, unatumai beteli/areka/kubeli? 1. Ndiyo2. No

Kama NDIYO:

25. Je, unatumia beteli/areka/kubeli mara ngapi katika siku moja?

1. 1- 5
2. 5- 10
3. 10-20
4. >20

Matumizi ya pombe

26. Je, umewahi kunywa pombe? 1. Ndiyo2. Hapana

Kama NDIYO:

27. Ni aina gani ya pombe?

1. Ya nafaka iliyotengenezwa kienyeji
2. Ya nafaka iliyotengenezwa kiwandani
3. Pombe kali iliiyotengenezwa kiwandani
4. Pombe kali iliiyotengenezwa kienyeji
5. Mchanganyiko wa kati ya zilizotajwa hapo juu
6. Nyinginezo (Taja……..)

28. Je, unakunywa pombe mara ngapi katika wiki moja?

1. < siku moja
2. siku 1-3
3. siku 4-6
4. siku 7

29. Kwa wastani, unakunywa pombe kiasi gani katika wiki moja?

1. lita < 2
2. lita 2-5

3. lita 5-8
4. lita > 8

30. Umekunywa pombe kwa miaka mingapi?

1. 1-5
2. 6-10
3. 11-20
4. > 20

31. Je, bado unakunywa pombe? 1. Ndiyo 2.Hapana

Kama HAPANA:

32. Ni miaka mingapi imepita sasa tangu ulipoacha kunywa pombe?

1. miaka < 2
2. miaka 2-4
3. miaka ≥ 5

33. Ni kwa sababu gani umeacha kunywa pombe?

1. Baada ya kuugua
2. Uliamua tu kuacha
3. Ushauri wa kitaalamu
4. Uchumi binafsi kuporomoka
5. imani/dini
6. Sababu nyinginezo (Taja……)

34. Je, umewahi kutumia meno ya bandia au kifaa chocho cha kuvaa mdomoni?

1. Ndiyo 2. Hapana

35. Je, kuna mtu yoyote katika familia/ukoo amewahi kuugua saratani?

1. Ndiyo 2. Hapana

Je, ni kwa sababu gani umekuja hospitali?

36. Uvimbe 1. Ndiyo2. Hapana

37. Kidonda 1. Ndiyo 2. Hapana ☐

38. Maumivu 1. Ndiyo 2. Hapana ☐

39. Kushindwa kufungua mdomo 1. Ndiyo 2. Hapana ☐

40. Maumivu wakati wa kufungua mdomo 1. Ndiyo 2. Hapana ☐

41. Maumivu ya jino/meno 1. Ndiyo 2. Hapana ☐

42. Jino/Meno kulegea 1. Ndiyo 2. Hapana ☐

43. Usumbufu 1. Ndiyo 2. Hapana ☐

44. Ganzi 1. Ndiyo 2. Hapana ☐

45. Kutoka damu 1. Ndiyo 2. Hapana ☐

46. Kupata shida katika kuongea, kutafuna, kumeza, kupumua, n.k.
1. Ndiyo 2. Hapana ☐

47. Kubadilika rangi 1. Ndiyo 2. Hapana ☐

48. Muonekano mbaya wa uso 1. Ndiyo 2. Hapana ☐

49. Sababu nyinginezo (Elezea…….)

50. Je, tatizo hili lililokuleta leo, lilianza lini? ☐

1. Mwezi ≤1
2. Miezi 2-4
3. Miezi 4-6
4. Miezi 6 to 12
5. Miezi 12 to 18
6. Miezi 18 to 24

7. Miezi >24

51. Je, ni namna gani tatizo hili lilianza?

1. Kidonda
2. Uvimbe
3. Jino/Meno kulegea
4. Maumivu ya Jino/Meno
5. Kubadilika rangi
6. Ganzi
7. Namna nyinginezo (Taja……..)

52. Je, tatizo hili liliendeleaje?

1. Kwa kasi
2. Polepole
3. Kutoka damu
4. Mengineyo (Taja……..)

53. Je, ulihudhuria tiba mbadala kama vile tiba za ki imani, tiba za jadi, n.k kwa ajili ya tatizo hili kabla ya kuhudhuria hospitalini?

1. Ndiyo 2. Hapana

14.5. APPENDIX V: CLINICAL EXAMINATION FORM

Location of the malignant lesion in the oro-facial region

54. Tongue

1. Tip
2. Lateral border right
3. Lateral border left
4. Dorsal surface anterior 2/3 Rt
5. Ventral surface anterior 2/3 Lt
6. Posterior 1/3 Rt
7. Posterior 1/3 Lt
8. Ventral tongue Rt
9. Ventral tongue Lt
10. More than one sites of the tongue
11. Involving nearby structures (e.g Floor of mouth, Gingivae)

55. Floor of the mouth

1. Right
2. Left
3. Anterior

56. Palate

1. Soft palate 2. Hard palate 3. Hard and soft palate

57. Oropharynx

1. Yes 2. No

58. Maxillary sinus

1. Left Maxillary sinus
2. Right Maxillary sinus
3. Right and Left maxillary sinus

59. Lip

1. Lower lip outer part of vermilion border
2. Lower lip inner part of vermilion border
3. Lower lip inner and outer part
4. Upper lip outer part of vermillion border
5. Upper lip inner part of vermilion border
6. Upper lip inner and outer part
7. Upper and lower lip

60. Mucobuccal sulcus

1. Labial sulcus
2. Buccal sulcus maxillary Rt
3. Buccal sulcus maxillary Lt
4. Buccal sulcus mandibular Rt
5. Buccal sulcus mandibular Lt.
6. Buccal and labial sulcus
7. Others (Mention……..)

61. Retromolar region

1. Right
2. Left

62. Gingiva

1. Maxillary
2. Mandibular
3. Others (Mention……..)

63. Parotid gland

1. Left
2. Right
3. Left and right

64. Submandibular gland

1. Left
2. Right
3. Left and right

65. Sublingual glands 1. Yes 2. No

66. Mandible

1. Anterior
2. Posterior Rt.
3. Posterior Lt.
4. Anterior and posterior

67. Maxilla

1. Anterior
2. Posterior Rt.
3. Posterior Lt.
4. Anterior and posterior

68. Other bones (Mention……)

69. Other sites in the oro-facial region (Mention……).

70. Clinical stage 1. I 2. II 3. III 4. IV

14.6. APPENDIX VI: RADIOLOGY FORM

71. Chest X-ray 1. Metastasis 2. No metastasis ☐

72. Lateral view skull 1. Bone involvement 2. No bone involvement ☐

(Mention bones(s) involved ……)

73. Postero-anterior view skull 1. Bone involvement 2. No bone involvement ☐

(Mention bone(s) involved ……..…)

74. Occipitomental view skull 1. Bone involvement 2. No bone involvement ☐

(Mention bone(s) involved ……..)

75. Occlusal view skull 1. Bone involvement 2. No bone involvement ☐

(Mention bone(s) involved ……)

76. OPG 1. Bone involvement 2. No bone involvement ☐

(Mention bone(s) involved ……...)

77. Abdominal ultra sound 1. Metastases 2. No metastases ☐

(Mention organ(s) involved ……)

78. Other radiological findings

(State…….)

14.7. APPENDIX VII: HAEMATOLOGY/IMMUNOLOGY FORM

79. HIV 1. Positive 2. Negative

80. VDRL 1. Positive 2. Negative

FBP with ESR

81. Anaemia 1. Yes 2. No

82. ESR 1. Normal 2. High

14.8. APPENDIX VIII: HISTOPATHOLOGY FORM

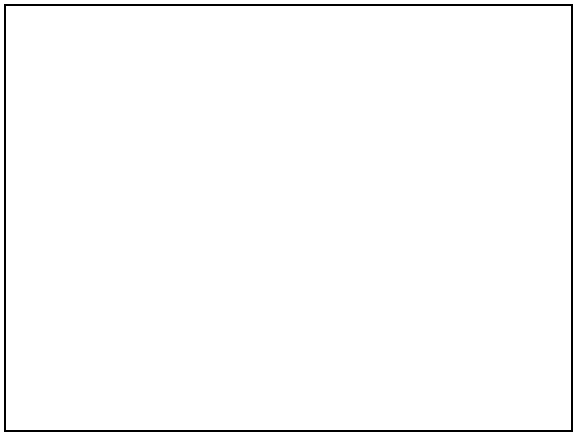
HP No. _ _ _ _ _ _ _ _ or HC No. _ _ _ _ _ _

83. Histological diagnosis…….

84. Grade/subtype…….

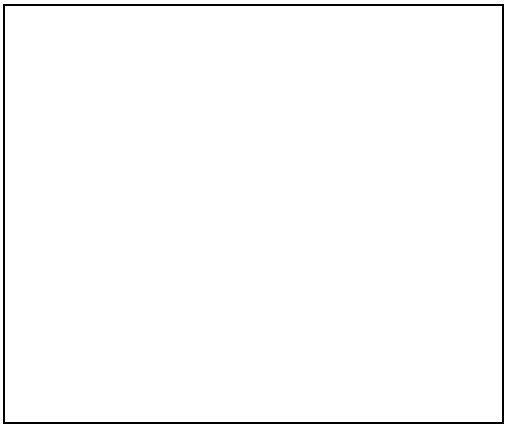
14.9. APPENDIX IX: ILLUSTRATIONS

Figure 2



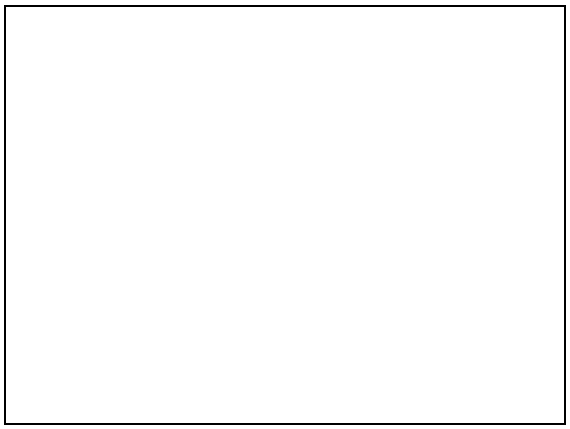
A young woman with KS lesions on the skin and the palate

Figure 3



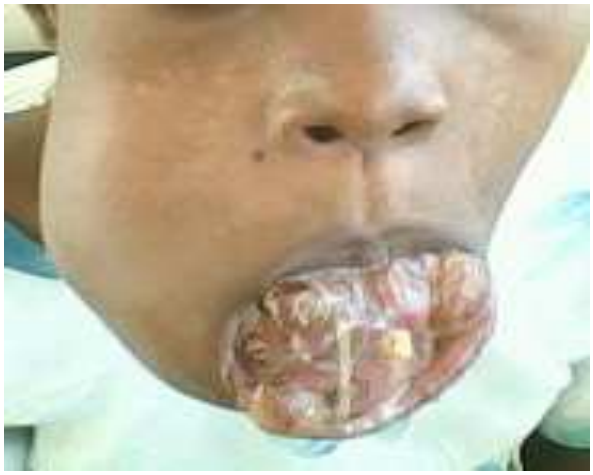
A 31 years old male with a massive round cell tumour of the upper jaw

Figure 4



Squamous cell carcinoma of the dorsum of the tongue showing raised edges and indurated areas

Figure 5



Osteosarcoma of the lower jaw in an 8 years old girl