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# Oral Cancer and Potentially Malignant Disorders

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## Abstract

Oral Cancer remains a greatly problematic disease with rising distribution globally, particularly the disappointing presentation among younger age groups. Varying common risk factors exist, including but not limited to premalignant disorders such as human papilloma virus (HPV) infection and immunosuppression. Genetical abnormalities and the field of epigenetics remain a new and vital piece of the puzzle in the development of Oral Cancer. Squamous cell carcinoma (SCC) remains the main histological burden with its varying counterparts; however, many types of other Oral Cancers can present in the mouth and are discussed in this chapter. More so, Oral Cancer brings with it the challenging face of diagnosis and treatment as well as effective control of metastasis. We discuss in this chapter, the epidemiology of the disease, Oral Cancer nomenclature, histological advances, clinical presentations, important risk factors, and metastatic disease pathology.

**Keywords:** Oral Cancer, squamous cell carcinoma, epidemiology of squamous cell carcinoma, Oral Cancer nomenclature, risk factors of squamous cell carcinoma, premalignant disorders, genetics of Oral Cancer, histological variants of squamous cell carcinoma, rare cancers of the oral cavity

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## 1. Introduction

This chapter provides a review of Oral Cancer with a highlight of the most recent literature in its many fields. We discuss all types of Oral Cancers, but in particular SCC, the commonest type, occurring in 90–95% of Oral Cancer patients. SCC is now regarded as a neoplastic transformative process where development of malignancy is likely to occur in several stages (usually as a dysplastic lesion that progresses over time). SCC is one of the most destructive diseases in the oral cavity and thought to be the 8th most common neoplasm in the world as well as the 3rd leading cause of mortality in developing populations such as South East Asia, North Africa and Middle East and South America. The development of Oral Cancer occurs

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more so, among low socioeconomic groups, in males and in older populations (although SCC among younger age groups is a worrying trend, owing to HPV infection), as well as certain ethnic groups including but not limited to Africans, Americans and Caucasians who are thought to have the highest Oral Cancer rates; most likely to appear on the tongue. Asian populations tend to develop tumours in the buccal mucosa and palate. The buccal mucosa is one of the poorest prognosis sites and SCC here, is associated with rapid extension into the buccal space, metastasis and local recurrence [1]. The tongue is also an area with rapid local invasion and high recurrence risk. Certain ethnic groups also maintain genetic predispositions to Oral Cancer such as expression of N-acetyl transferase NAT1\*10 genotype among the Japanese, alcohol dehydrogenase type 3 genotypes and families with history of P53 tumour suppressor gene mutations [2].

## 2. Oral Cancer nomenclature

Oral Cancer is often described as early or late stage disease. Early Oral Cancer exists locally, is often unilateral, has not crossed the basement membrane tissue histologically and does not include lymph node involvement. However, local disease may still be quite aggressive and require extensive reconstruction at time of surgery. Locally invasive disease refers to the spread of cells to the cervical lymph nodes. Late stage disease involves widespread or metastatic disease whereby the cancer has spread to other parts of the body. Recurrence (a tumour forming from remaining cancer cells) occurs less than 2 cm away from a previous tumour and within a duration of 3 years since treatment while a second primary disease is in relation to a new Oral Cancer development after which the primary tumour has been completely removed and thus is often more than 2 cm away from original tumour and occurs after a 3-year period [3]. However, there remain difficulties between distinguishing a recurrent lesion from a second primary tumour. Recurrence genetical diagnostics is a new field aiming to compare clones of cancer cells with previous tumour tissue within biopsy and thus the inclusion of field cancerisation concept into clinical review systems that allows better assessment of tumour risk development. Furthermore, nomenclature in regards to metastasis to lymph nodes should also be revised and can be differentiated into isolated tumour cells, micro metastasis, conventional metastasis, occult, overflow pattern, skip metastases, peppering and extracapsular spread [4].

## 3. Histological grading systems of Oral Cancer

TNM refers to the Tumour, Node and Metastasis staging system; a universal grading system used by clinicians worldwide. It is maintained by the Union of International Cancer Control (UICC) and the American Joint Committee on Cancer Staging (AJCC). TNM describes tumour size, spread to lymph nodes and whether there has been metastasis or not. Metastasis may further be specified according to area involved such as bone marrow (MAR), pulmonary (PUL) or osseous (OSS). T or tumour size can be classified as T0 (no primary tumour), Tis

(carcinoma in situ), T1 (tumour equal or less than 2 cm), T2 (tumour equal or less than 4 cm), T3 (tumour greater than 4 cm) and T4 (tumour greater than 4 cm with deep invasion to muscle, bone or deep structures). N or lymph node involvement can be classified as N0 (no nodal involvement), N1 (ipsilateral node less than 3 cm), N2 (ipsilateral node less than 6 cm) and N3 (nodal involvement less than 6 cm or bilateral node involvement). M or Metastasis refers to M0 (no metastasis) or M1 (metastasis noted). Staging is then carried out on the background of the TNM system and aids treatment planning, maintains universal referral information and evaluates treatment. The staging system can be classified as stage 0 (carcinoma in situ), stage 1 (T1, N0, M0), stage 2 (T2, N0, M0), stage 3 (T3, N0, M0) or (T1–3, N1, M0) and stage 4 (T4, N0, M0) or (T1–4, N2, M0) or (T1–4, N1–3, M1). Finally, the grading system refers to microscopical analysis and cell differentiation histologically. This may be classified as Gx (cannot be assessed), G1 (well differentiated or low grade), G2 (moderately differentiated with elongated rete pegs invading lamina propria and keratin pearls), G3 (poorly differentiated or high grade and loss of cellular adhesion) and G4 (Undifferentiated or high grade or sheets of invading epithelium with no resemblance to normal structures). **Table 1** summarises the TNM system, staging and grading system for Oral Cancer.

Recently, it has been well established that other features in early SCC pose their own implications in tumour progression and should be paid attention to in more detail. These include depth of invasion of tumour (vertical height of tumour from level of normal epithelium) and tumour thickness (proliferative component is assessed along with vertical height).

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#### (TNM staging system)

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##### Tumour size

|                        |                         |                                     |                                     |                               |  |
|------------------------|-------------------------|-------------------------------------|-------------------------------------|-------------------------------|--|
| T0 (no primary tumour) | Tis (carcinoma in situ) | T1 (tumour equal or less than 2 cm) | T2 (tumour equal or less than 4 cm) | T3 (tumour greater than 4 cm) | T4 (tumour greater than 4 cm with deep invasion to muscle, bone, or deep structures) |
|------------------------|-------------------------|-------------------------------------|-------------------------------------|-------------------------------|--|

##### Node

|                            |                                      |                                      |  |
|----------------------------|--------------------------------------|--------------------------------------|--|
| N0 (no nodal involvement), | N1 (ipsilateral node less than 3 cm) | N2 (ipsilateral node less than 6 cm) | N3 (nodal involvement less than 6 cm or bilateral node involvement). |
|----------------------------|--------------------------------------|--------------------------------------|--|

##### Metastasis

|                    |    |                       |
|--------------------|----|-----------------------|
| M0 (no metastasis) | OR | M1 (metastasis noted) |
|--------------------|----|-----------------------|

##### The staging system

|                             |                      |                      |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Stage 0 (carcinoma in situ) | Stage 1 (T1, N0, M0) | Stage 2 (T2, N0, M0) | Stage 3 (T3, N0, M0) or (T1–3, N1, M0) | Stage 4 (T4, N0, M0) or (T1–4, N2, M0) or (T1–4, N1–3, M1) |
|-----------------------------|----------------------|----------------------|--|--|

##### Grading system

|                         |                          |                                |                            |                       |
|-------------------------|--------------------------|--------------------------------|----------------------------|-----------------------|
| Gx (cannot be assessed) | G1 (well differentiated) | G2 (moderately differentiated) | G3 (poorly differentiated) | G4 (undifferentiated) |
|-------------------------|--------------------------|--------------------------------|----------------------------|-----------------------|

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**Table 1.** Summary of TNM staging system.

The former is now regarded as an independent factor in the TNM staging system, where the 8th edition has been modified to include: depth of invasion less than 5 cm (T1), 5–10 cm (T2) or greater than 10 cm (T3). Presence of lymphovascular and perineural invasion of tumour is associated with lymph node involvement and local recurrence. Surgical margins greater than 5 mm away from lesion are regarded as excellent, moderate if between 1 and 5 mm and poor were less than 1 mm, where the latter is associated with recurrence and poor survival rate [5]. Other histopathological predictors include sialadenotropism, involvement of underlying skin and the histological variant of the SCC.

Other types of grading systems include the WHO (International agency on Cancer) grading system, based on labelling tumours as well, moderately or poorly differentiated. However, the WHO itself states this system has its limitations on prognosis of Oral Cancer but could be improved when margins are analysed. Broder's classification breaks down tumours into four different grades according to degree of differentiation and keratinisation of tumour cells; Anneroth's grading considers keratinisation, nuclear polymorphism, the number of mitoses, the pattern and stage of invasion and lymphoplasmacytic infiltration within thickness of tumour and Bryne's grading is based on assessing the invasive front excluding mitotic count [6].

The type of invasion front has also been described where 4 patterns may be noted histologically. These include type 1 or tumour with a cohesive advancing front, type 2 or incohesive front with malignant keratinocytes distributed as islands or sheets penetrating at different levels, type 3 or dyscohesion with budded tiny islands of cells at the advancing front and type 4 or super non-cohesion where by malignant keratinocytes invade as individual units [4].

#### **4. Predisposing risk factors for the development of Oral Cancer**

The pathogenesis of Oral Cancer is multifactorial. Genetic damage, microorganisms and carcinogens such as tobacco and alcohol are just some of the major risk factors that predispose to Oral Cancer. Tumour microenvironment such as vascular network proximity to tumour, glucose and lactate concentrations, interstitial fluid pressure, PH extracellularity [7] and interconnections between non-cancer cells and cancer cells all have important associations with Oral Cancer development. Furthermore, hypoxia plays an important role in cancer cell progression, whereby rapid growth of cancer cells leads to a hypoxic environment particularly at the centre of SCC lesions, further increasing their proliferative capacity and malignancy capability. Under these hypoxic conditions, cells undergo the 'Epithelial Mesenchymal Transition (EMT)' where epithelial cells become more fibroblastic in nature and thus more invasive with metastatic potential [6, 8]. The presence of fibroblasts in the environment further leads to growth of epithelial cells with assisted keratinocyte growth factor stimulation. EMT leads to cancer cell movement, ease of invasion and metastasis. Cancer stem cells which are either derived from adult stem cells, the possible fusion of haematogenous stem cells with a differentiated epithelial cell or neosis, have the ability to self-propagate, give rise to different tumour cell populations and allow their differentiation.

It has been postulated that these cancer stem cells have a distinctive phenotype, allowing them to initiate growth of a tumour, control the lineage of tumour growth pattern as well as have lasting power that supports their transformation into malignancy and sustainability through cell mutations. Field cancerisation is a concept implicated in the development of multiple primary tumours, recurrence and second primary tumours. Patients with previous history of SCC in particular or upper aero-digestive tract neoplasms are thought to be at risk up to 35% for the development of another tumour and the prognosis is often poorer for this presenting lesion. Pre-neoplastic alterations, particularly genetic, are thought to lead to field cancerisation. Where cell lines are monoclonal (same mutated lineage of cells), field cancerisation may occur through the process of exportation of cells to adjacent mucosa or through saliva. Where there is polyclonal tumorisation (different mutated lineages of cells), field cancerisation is thought to occur due to the whole cavity being exposed to carcinogens and susceptibility to genetic alterations [3]. Sustainment of angiogenesis is another primary factor in the progression of Oral Cancer where nutrients are provided as well as provision of routes for the development of the tumour away from the primary site and penetration of the circulatory system.

#### 4.1. Potentially malignant disorders

In 2005, the WHO advised to merge both the terms 'potentially malignant lesions' and 'potentially malignant conditions' and classify all these disorders as 'potentially malignant disorders' [9]. Detection of potentially malignant disorders may go unnoticed due to their painless nature. These include White Leukoplakic (Homogenous), Mixed (non-homogenous or speckled) and Red Erythroplakic lesions. Others include actinic cheilitis, lichen planus and submucous fibrosis and systemic/discoid lupus erythematosus as well as rarer conditions that include dyskeratosis congenita (predisposition to leukoplakic lesions), Plummer–Vinson syndrome, Fanconi's anaemia, Epidermolysis bullosa dystrophicans and Xeroderma Pigmentosum. Chronic Immunosuppression is also a risk factor in the development of Oral Cancer.

Dysplasia is described by the WHO as either mild, moderate or severe, and can present in any such form in potentially malignant disorders. New literature also suggests the term 'oral intraepithelial neoplasia' rather than the term 'dysplasia' be used which describes better the histological picture. This includes epithelial proliferation that can be papillary or verrucous, drop-shaped rete ridges, skip areas of normal mucosa where dysplastic epithelium can be found, and hyperorthokeratosis as well as cellular changes including nuclear hyperchromatism, pleomorphism, altered nuclear/cytoplasmic ratio, excess mitotic activity, loss of polarity of cells, loss of differentiation, loss of intercellular adherence and deep cell keratinisation. However, the histological grading of dysplastic lesions is not an accurate method to conclude which lesions are in danger of becoming an SCC as there is a high degree of subjectivity from pathological observers and recent evidence suggests there is little or no correlation between dysplastic grade and progressions to Oral Cancer [10]. Recent studies highlight that variations in length between the apical membrane of basal cells and the basement membrane as well as the disordered arrangement of these cells may be useful in the study of dysplastic lesions [11]. Several biomarkers have been studied to assess the

prognosis of dysplastic lesions, other than histopathological picture and include S100A7, DNA content, DNA ploidy, loss of heterozygosity, p16 methylation, hypermethylation of endothelin receptor type b, kinesin family member 1A [12], the assessment of proliferation marker Ki-67 and cytokeratins 13 and 17 which have all been implicated in the development of SCC from a dysplastic lesion.

#### 4.1.1. *Leukoplakias*

Leukoplakia is defined as 'a white patch or plaque that cannot be scraped off and cannot be clinically or histopathologically determined as any other disease'. Histopathologically, Leukoplakias represent a wide spectrum of non-specific epithelial changes ranging from hyperkeratosis that overlies a thickened acanthotic but ordered mucosa to lesions with marked dysplasia or even carcinoma in situ upon biopsy. The Leukoplakic clinical picture ranges from a thin smooth homogenous white appearance to increased fissuring or a lesion that is verrucous and nodular in nature. The non-homogenous Leukoplakia and Erythroplakia are the most likely to have severe dysplasia or carcinoma in situ, where the latter is of a red appearance due to superficial erosion and an intense inflammatory reaction with vascular dilatation. 'Proliferative Multifocal Leukoplakia (PML)' is a new term to describe verrucous leukoplakia and its concurrent risk for development into verrucous SCC carcinoma, with more accuracy, so that clinicians are aware that in its initial stages even if it is not so verrucous in appearance clinically, there may be frank carcinoma evident histopathologically. PML also has a high rate of Cancerous progression in relation to anatomical location (soft and hard palate, alveolar ridge, buccal and labial mucosa, attached gingivae and gingival sulcus and floor of mouth), gender (more in women) and in those who do not possess risk factors such as smoking and alcohol [13]. It is thought only 1–5% of Leukoplakias progress to cancer; however, there is still no robust method of identifying those lesions that will or will not do so. Subsequently, there is wide variation in the treatment of Leukoplakia among clinicians, whereby some clinicians choose to monitor (except severe dysplasia where excision must occur) and others prefer to remove lesions regardless of histological pattern.

#### 4.1.2. *Lichen planus*

A T-cell mediated disease with tumour necrosis factor-alpha (TNF-alpha) drive, Lichen planus presents clinically as either reticular, annular, plaque-like, atrophic or erosive forms. About 1–5% of lesions of Lichen planus may develop malignant SCC change [14], but the risk is low. Histologically, the term lichenoid dysplasia is a picture of band-like lymphocytic infiltrate underneath dysplastic epithelium that may have an increased risk of malignant change.

#### 4.1.3. *Oral submucous fibrosis*

This premalignant condition is mainly restricted to Asian populations who use betel quid and areca. Progressive irreversible fibrosis and hyalinisation initiates in the lamina propria with progressive destruction of connective tissue, muscle and fat as well as atrophy of overlying

epithelium and change of the normal colour of the mucosa to white/grey. Trismus is a final stage manifestation that may be so severe (due to the formation of fibrous bands in the cheeks, around the lips and fauces) that SCC discovery may be hindered [9].

#### 4.1.4. *Actinic cheilitis*

Ranging histologically from hyperkeratosis to SCC *in situ*, actinic cheilitis is a clinical term for a white, ulcerative crusted lesion to the vermillion border of the lips, which is mainly present in older men due to sun exposure.

### 4.2. Immunological and genetical basis of Oral Cancer

The immune system plays a vital role in either the eradication of malignant cells or their promotion into a neoplasm. Monocytes and macrophages may play a role against tumour progression by releasing proinflammatory cytokines such as IL-2, TNF-alpha and reactive nitrogen particles that exhibit cytotoxic and cytostatic activity as well as promoting dendritic and natural killer cells in the location as a response against cancer cells or on the contrary; the monocyte/macrophage system may be induced to promote neoplastic change by aiding the expression of angiopoietin 2, vascular endothelial growth factor A, chemokine ligand 3 and adhesion molecules that are key in tumour progression [15]. Unlike some genetic disorders which have a distinct development of cancers associated with them such as Multiple Endocrine Neoplasia 2, Fanconi's anaemia, Bloom syndrome, Gorlin Goltz syndrome, Peutz Jeghers syndrome, Li Fraumeni syndrome, Xeroderma pigmentosum and Familial Retinoblastoma [16], Oral Cancer has not been implicated yet with a specific genetic disorder or genetic polymorphism, rather its formation is due to a combination of mutations and progression of damaged cells into cancer sustainability.

Chromosomal alterations and/or epigenetic alterations occur in both premalignant lesions and SCC, and new diagnostic mechanisms as well as therapeutics often target this area. Genomic instability of Oral Cancer involves defects in DNA damage repair, loss of heterozygosity such as that of 9q33 present in nearly 30% of SCC lesions and of 9p21 associated with loss of tumour suppressor activity, defects in chromosomal segregation which are thought to promote resistance against treatment within cancer cells, copy number alterations, loss of telomere stability which leads to prevention of cell destruction and is highly expressed in SCC cells, and regulation of DNA checkpoints. An SCC develops when such genetic changes and others are not counterbalanced, leading to a combination of activation of proto-oncogenes, deactivation of growth inhibitory pathways and loss of function of tumour suppressor genes. Epigenetics deals in particular with defects such as DNA methylation, histone modifications and RNA-mediated silencing. Furthermore, some genetical alterations occur in particular locations of the SCC such as at the invasive front where heterozygosity and microsatellite instability at chromosomal loci TP53 and RPS6 occur more so than in its central or superficial portions [6]. Other genetic defects involved in Oral Cancer include disruption to apoptosis such as CASP8 mutations which inhibit extrinsic apoptotic pathways, immortalisations, and signal transducers, improvement of angiogenesis and gain of growth factor receptors, such as epidermal growth factor receptor (EGFR) [17].

Three distinct regions of deletions have been identified in chromosome 3p associated with development of Oral Cancer [18]. Promoter hypermethylation results in inactivation of the p16 gene, which is an inhibitor of cyclin dependant kinase family of serine/threonine kinases on chromosome 11q13 that activates cell cycle progression and promotes dysplastic cell tissue invasion leading to normal epithelium becoming hyperplastic/hyperkeratotic epithelium. 5-hydroxymethylcytosine, found more in well-differentiated cells, is reduced in dysplastic lesions and SCC and may be associated with the stage of differentiation of malignant cells [19]. The further loss of heterozygosity at 17p with point mutations in the p53 tumour suppression gene leads to cell dysplasia. Genomic alterations to 4q, 6p, 8p, 11q, 13q and 14q have all been implicated in the development of malignant changes.

MicroRNAs (MiRs) are small non-coding RNAs that regulate transcription and may act as either oncogenes (where their overexpression promotes cancerous changes), or as tumour suppressor genes (where their under expression leads to tumorigenesis). MiR7, MiR-21, MiR-24 and MiR-184 when upregulated are implicated in the development of premalignant lesions and the development of SCC while the downregulation of MiR-375 can lead to tumorigenesis via inability to inhibit migration of cancer cells, CAL27 cells. Those lesions with higher expressions of MiR-375 have a protective factor against SCC development [20]. Other downregulated tumour suppressor MiRs includes MiR-133a & b (where their loss un-inhibits the expression of oncogene PKM2), MiR 26a-5p (prevents proliferation of cells, cell cycle progression and induces apoptosis of CAL27 cells) and MiR 34a-5p (its downregulation allows for uncontrolled progression of CAL27 and SCC-15 cells) as well as others such as MiR-29b, MiR-138, MiR-182, MiR-195, MiR-205 and MiR-219, whereby their loss leads to overexpression of oncogenic factors such as G protein alpha inhibiting activity polypeptide 2, Insulin Growth Factor 1 Receptor, Protein Kinase C1 and Survivin [21]. Survivin, an inhibitor of apoptosis, may also be activated by HPV E26 protein when there is reduced expression of p53 and leads to aggressive tumour formation and resistance to treatment, not only in Oral Cancer but also among several other systemic cancers such as breast, thyroid, colorectal, medulloblastoma and glioblastomas [22].

Upregulation of NOTCH 1 expression between cells can act as an oncogene or tumour suppressor gene, stimulating progenitor cells in SCC of the head and neck. The Dachshund homologue 1 is also a tumour suppressor gene where its expression can prevent migration and adhesion of cancer cells and can target cancer cell lines, such as SCC-25 cells, thus functioning as a growth inhibitor [23]. However, its frequent methylation in Oral Cancer leads to its reduced expression and it has been associated with poorly differentiated tumours and lymph node metastasis, in particular SCC affecting the tongue.

EGFR is a proto-oncogene and a tyrosine kinase-based receptor, known to be overexpressed in many systemic cancers such as breast, non-small cell lung cancer and colorectal cancer and leads to uncontrolled cell division. The overexpression of subtype epidermal growth factor (EGF) 4 has been associated with lymph node metastasis in SCC in the oral cavity. Indeed, therapeutics that target subtypes 1 to 4 EGF include cetuximab (reported rarely in treatment of SCC) and trastuzumab, MM-121, AM, G888, TK-A3 and TK-A4 which have been used clinically for other cancer treatments but not for SCC [24]. Argyrophilic nucleolar organising regions (ribosomal DNA) are located on the short arm of chromosome 13, 14, 15, 21 and 22

and when assessed through silver staining techniques, they can be correlated with cellular proliferation of Oral Cancer. Abnormal chromosomal segregation or DNA mono or aneuploidy is also a marker for Cancer formation; however, this remains controversial [25].

#### 4.3. Other markers

Vascular endothelial growth factor C and its receptors such as Flt-4 (class 3 tyrosine receptor kinases) may be released not only by the primary tumour as oncogenes but also by macrophages and surrounding vascular endothelial cells and have a strong role to play in the transmission of metastasis to lymph nodes. Tumour lymphangiogenesis is thought to be promoted by VEGF C expression, particularly in early stages [26, 27]. Transforming growth factor B1 may have tumour suppressor activity in the early stages of Oral Cancer, although it has been widely implicated in the progression of the disease (in particular secondary tumours) by aiding the proliferation of tumour SCC cell lines and their survival, allowing the activation of p63 on chromosome 3 and C-Myc oncogene that leads to cell proliferation and transcription and inhibition of E Cadherin repressors, thus allowing for EMT, an important factor in the progression of SCC [28].

Toll-like receptor (TLR)-4 is expressed by cancer cells, allowing for protection from the immune system and resistance of cancer cells against apoptosis as well as promoting cancer progression, cancer growth, invasion and metastasis. The TLRs further activate protein signalling group NF-kb, in particular nuclear p65, which is important in the progression of malignancy states by inhibiting apoptotic mechanisms. SCC patients with high TLR-4 expression were found to have more aggressive disease and poorer prognosis. Some new therapeutics such as TAK-242 and Eps 7630 working against TLRs specifically and NF kb respectively and some have been trialled in SCC therapy [29].

Proteolysis (degradation of basement membrane by enzymes) occurs in particular by matrix metalloproteinase (MMPS) expression and has an important role to play in the progression of cancer cells. MMP2 has been shown to digest type 3 collagen and disrupt the basement membrane as well as degrading other extracellular matrix proteins [30]. E Cadherins are cell-cell adhesion molecules where their low expression is related to poorly differentiated tumours and metastatic ability. Increased expression of EpCam adhesion molecules further down-regulates Cadherin adhesion and promotes segregation of tumour cells and their metastasis [31].

#### 4.4. Tobacco

Tobacco has been used for centuries and is a well-known carcinogenic material leading to the promotion of all types of bodily cancers; not exclusive to Oral Cancer development alone. Tobacco can come in the form of cigarettes, (both classic and electronic), cigar, pipe, reverse smoking, and as smokeless tobacco. 75% of people with Oral Cancer smoke [32] and the use of smokeless tobacco provides a unique trouble to the oral cavity whereby products are placed directly on oral tissues with increased concentration of nitrosamines absorbed both locally and systemically. Examples of smokeless tobacco products from around the world include Betel quid and Paan in Asia, Shammah in Saudi Arabia, Khat in Yemen and Toombak

in Sudan. Tobacco involves a dose response relationship whereby the level of exposure (increased time, quantity and concentration) determines the risk of developing a tobacco-related dysplasia and tobacco-related Oral Cancer. When cessation arises, the risk of developing Oral Cancer presumes normality after 10–15 years of abstinence. The use of electronic cigarettes is a new area, where the true risk of Oral Cancer development and formation of premalignant lesions in those using electronic cigarettes is yet to be elucidated in Long-term research follow-ups. More younger people are now using electronic cigarettes but their nicotine levels may be higher than what manufacturers advertise. Electronic cigarettes and the heating of E liquids to high temperatures may also release other carcinogenic compounds such as carbonyl compounds (formaldehyde, acetaldehyde and acrolein) that may be SCC associated. Nicotine replacement therapy has also been implicated as a potential factor for SCC development.

#### 4.5. Alcohol

Ethanol is both a topical and systemic carcinogen and its metabolite acetaldehyde is an even more potent one. Local contact leads to direct irritation of tissues and is thought to promote direct carcinogenic change. The metabolism of ethanol to acetaldehyde is carried out by alcohol dehydrogenase. Acetaldehyde is cytotoxic and leads to production of free radicals as well as activating N Nitrosamines by inducing the CYP1A1 cascade [2]. The use of alcohol and tobacco together leads to a potent synergistic effect (almost a 30 times higher risk of developing SCC when compared to non-users) and is implicated widely in SCC development. Alcohol here, may act as a solvent for carcinogens within tobacco smoke. Finally, the presence of alcohol in mouthwashes, around 20%, and its role in causing Oral Cancer has also been a point of highlight. No strong evidence exists to conclude that the presence of alcohol among these products is significantly responsible for carcinomatous change, as well as the fact that those patients who did develop Oral Cancer while using alcohol mouthwashes also had confounding factors, especially the use of tobacco. However, a large retrospective study on 8981 cases of Head and Neck SCC by the International Head and Neck Cancer Epidemiology Consortium suggested that heavy frequent and long-term users of alcoholic mouthwashes as well as persons with poor oral hygiene or those who replace oral hygiene with use of mouthwash may have a significant connection [33].

#### 4.6. Infections

##### 4.6.1. *Human papilloma viruses (HPVs)*

18–72% of oropharyngeal SCC (tonsils, oropharynx and base of tongue) harbour oncogenic HPV proteins that helps to induce DNA damage, cell cycle dysregulation and keratinocyte dysregulation, but the exact method of how HPV initiates and maintains the development of SCC is still not completely known. The tumour suppressor genes p53 (Arg72pro) and pRb are inactivated by E6 and E7 viral oncoproteins respectively but not all oropharyngeal tumours are E6/E7 positive [34]. The most common HPV infection is HPV 16, but 18, 31, 33, and 35 are also implicated in SCC development. HPV positive SCCs are often non-keratinising with ovoid cells, indistinct cytoplasm and contain other distinct histological features namely mitosid cells or nuclear fragmentation, presence of apoptotic and dyskeratotic cells with

hyperchromatin and cytoplasmic eosinophilia [35]. The role of HPV infection and SCC of the anterior tongue is also a target for further studies. Several HPVs, particularly the recent HPV 56, has also been implicated in SCC of the anterior tongue with poorer outcomes [36].

While it has been generally accepted that patients with positive HPVSCC have an improved prognosis compared to those with negative HPVSCC, this statement is subject to debate. HPV positivity is thought to increase sensitivity to treatments and apoptotic induction as well triggering of the immune response to clear damaged cells. However, some studies have recently suggested a poor prognosis for positive HPVSCC due to HPV positive cells stimulating lymphocyte production and promoting cytokines with an immune profile that promotes HPV infected cancer cell replication. Furthermore, it has been analysed that predictivity of improved outcome is related to other factors such as viral load and transcriptional activity rather than just presence or absence of virus. High viral load with increased E6/E7 expression and transcriptional activity, improves prognosis outcome as these tumours have a distinct phenotype of less chromosomal abnormalities compared to low viral load associated tumours. Vaccines Cervarix and Gardasil are given to adolescent women to protect against cervical cancer but their role in preventing Oral Cancer in both females and males is still under promising research.

#### 4.6.2. Epstein-Barr virus (EBV)

Non-keratinising forms of nasopharyngeal carcinoma are implicated by EBV infection. EBVs are also well known in the association of B-cell lymphomas (in particular Burkitt's Lymphoma), anaplastic carcinoma, salivary gland tumours, but recent literature examines its possible role in the initiation and progression of Oral Cancer SCC. Dysplastic changes among epithelial cells renders them more likely to express CD21, allowing the abundant glycoprotein gp350 of EBV to bind to plasma membrane easily and give it an entry into epithelial cells. An increase in CK19 expression is then observed where the former is a possible stem cell marker and has been associated with premalignant changes and poorly differentiated SCC development. EBV-infected epithelial tissues have been shown to express higher CK19 compared to healthy controls [37]. Furthermore, infection by EBV may allow a growth advantage of mutant cells whereby EBV proteins and transcripts may alter cell behaviour by increasing their proliferation rate. EBV has also been found within keratin pearls and within malignant epithelial cells [38].

#### 4.6.3. Candidiasis

Although controversial, harbouring candida (C) infections has been associated with the development of SCC. However, because these fungi remain a part of normal oral flora, the carcinogenic ability of C infection in some patients remain unclear. Mutagenic C strains, presence of chronic inflammation, production of carcinogens such as nitrosamines by the fungi, their ability to metabolise procarcinogens, and secretion of proteolytic enzymes that damage basement membrane (loss of laminin 332 and E-Cadherins important in keratinocyte adhesion) remain key factors. Recent studies have established SCC development to increased fungi carriage in patients with both dysplasia and SCC compared to healthy controls. *C. albicans* produces a local environment that favours cell proliferation and tumour

cell expansion. Furthermore, patients with chronic C infection have been found to have increased salivary IL-10, associated with poor SCC prognosis. IL-10 although has the beneficial role of balancing the inflammatory environment, leads to neoplastic succession by inactivating the innate immune system [39]. *C. albicans* also induce IL-8 secretion, stimulating the production of TNF-alpha; a potent inflammatory mediator possible aggravating local tissues and thus help drive formation of SCC. NFkb is an important cancer promoter that is induced when *C. albicans* activates TLRs that interact with NFkb and the production of chronic inflammatory mediators all leading to a cancer pro-environment [40].

*C. albicans* genotypes are thought to differ in patients who develop SCC (*C. albicans* genotype A) compared to healthy controls (*C. albicans* genotype B) where these different strains may have increased carcinogenic potential. Also, *C. albicans* converts ethanol to the carcinogenic metabolite acetaldehyde as well as hydroxyethyl radicals, ethoxy radicals and hydroxy radicals which can all potentiate SCC development when alcohol is chronically consumed [41]. Patients with Chronic hyperplastic candidiasis (CHC), for example, are well known to have increased malignant transformation most likely due to the release of the potent carcinogen, N-nitrosobenzylmethylamine formation that leads to keratinocyte cell aggravation. Treatment with triazoles and cessation of smoking may resolve some lesions although this is not definite in all cases. *C. albicans* study from CHC biopsy samples were found to have increased Adh1p mRNA expression, an isoenzyme that majorly catalyses ethanol into acetaldehyde thus potentiating carcinogenesis in these lesions [40].

#### 4.6.4. Bacterial pathogens

Chronic inflammation aids progression of SCC development by increasing malignant cell proliferation, cell survival, stimulation of neoangiogenesis and reducing anti-tumour immunity. Although small, a significant connection between presence of periodontal disease, an important and common type of local chronic inflammation in the oral cavity and development of Oral Cancer may exist. Periodontal disease offers a proinflammatory environment with a display of varying polymorphonuclear cells, presence of proinflammatory local and systemic cytokines (TNF-alpha, IL-6, C-reactive protein), proinflammatory proteins (MMPs) and proangiogenic factors, all aiding neoplastic promotion. Chronic inflammation is further advanced by microbial toxins and bacteria associated with periodontal disease (*Streptococcus sanguis*, *Prevotella melaninogenica*, *S. mitis* others) that may have a role in causing disruption to normal cell growth and prospective tumour formation [42]. Periodontal pathogens have also been associated with promoting EMT in SCC [43], an important factor in progression to metastasis. Furthermore, the periodontal pathogens, *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, may increase SCC invasion and aggressiveness. These bacteria may also contribute to cancer development by activating tumour signalling pathways NFkb and STAT3 leading to production of anti-apoptotic proteins and release of growth factors such as EGF, TNF-alpha and transforming growth factor, and all SCC promoters [44]. HPV E6/E6 mRNA in one study was detected in periodontal pockets and gingival sulcus, a possible risk factor for aiding viral-associated Oral Cancer development.

#### 4.6.5. *Syphilis*

Although syphilitic leukoplakia and its development into SCC is generally a historic finding, an association between tertiary syphilis and development of Oral Cancer, is still being reported. Cases with overriding SCC on syphilitic gumma as well as several reports of syphilitic patients developing Kaposi's sarcoma are present in the current literature. However, direct scientific association has not yet been studied and other risk factors such as these patients also using tobacco and alcohol, being malnourished and being co-infected with HIV, generally confuse the true link between syphilis and development of Oral Cancer. Nevertheless, this relationship cannot be completely neglected and thus should be given some credibility in clinical practice in order to determine those patients with Oral Cancer who do turn out to present with undiagnosed or late-stage syphilitic disease [45, 46].

### 5. Dietary factors

Antioxidants such as Vitamin A, C and E and other trace elements have a protective role against development of SCC and thus when deficient have been associated with SCC in the oral cavity and other organs. Interestingly, people with a high intake of meat and processed meat products are at higher risk of developing Oral Cancer. Iron deficiency is well known to cause epithelial atrophy and patients with post-cricoid web (Plummer Vinson/Patterson-Kelly syndrome) have an increased risk of developing Oral Cancer.

### 6. Radiation

#### 6.1. Ultraviolet

Although skin cancers are more associated with sun exposure, persons whom are highly sensitive to UV exposure such as those who are fair skinned, with solid organ transplantation (particularly an association between kidney transplants and lower lip cancer), as well as with the autosomal recessive condition Xeroderma pigmentosum have an increased predisposition to development of SCC. Women are thought to be better protected from sun-exposed lip cancer due to the use of lipstick. Patients with occupational hazards such as fishermen and farmers and other sun-exposed workers have an increased risk of lower lip cancer. Cases of lower lip cancer in those with renal transplants are unique in particular [47] in that cancer is often preceded by actinic keratosis and dysplasia and worryingly, tumours are often quite subtle in appearance [48] with a short clinical presentation time. It is thought that UV-B radiation enhances immunosuppression locally and impairs antigen presenting Langerhans cells that help eradicate cancer cells.

## 6.2. Therapeutic

Ionising radiation for the treatment of head and neck cancers poses a problematic risk factor for the development of new primary oral malignancies, most commonly aggressive sarcomas and salivary gland tumours. The dose of radiation, exposure time and other factors play a role in the development of such lesions. However, radiation exposure may also have a beneficial effect (see Section 9) in protection against SCC development.

## 7. Immunosuppression

Patients on long-term immunosuppressive medications such as Cyclosporine and Azathioprine as well as other immunosuppressive drugs following transplantations are more at risk of developing Oral Cancer. These drugs are known to lead to DNA mutations, possibly within keratinocytes. Patients with kidney and liver transplants have been shown to develop lip cancer in particular as well as chronic graft versus host disease patients. Patients with Crohns disease who are on long-term azathioprine have also been reported to have an increased risk of developing tongue cancer. Another important factor is the possible HLA incompatibility that arises between host and recipient that triggers the host's immune system and leads to the potentiation of neoplastic progression of cells [49]. HIV infection is another factor where the disease predisposes its patients to increased development of Kaposi's sarcoma and lymphomas (plasmablastic) that may present in the oral cavity; however, the development of Oral Cancer SCC in HIV patients is more likely to be in relation to secondary HPV infection, or Tobacco use.

## 8. Dental implants

Recent reports highlight a possible link with placement of dental implants and SCC. It is thought that implants may act as a traumatic or irritating factor and SCC has been reported in the peri-implantary tissues in about 1.5% of SCC patients [50]. Peri-implantary inflammation can lead to a persistent promotion of cellular proliferation and cell survival and even the activation of oncogenes and inactivation of tumour suppressor genes. Furthermore, titanium material may not be as inert as originally thought bringing about an allergic reaction and an inflammatory background to tissues. Where there is implant looseness, further activation of inflammation (predisposing factor to SCC) may occur. Implants coated with hydroxyapatite may induce a mucositis with reports of SCC developing 1-year post implantation. Some cases of metastasis (breast, lung and prostate) around implants have also been described in the literature and may be up to 1%. Patients who undergo radiation with implants in place may be subjected to dispersion of the radiation produced, where the dose is increased in front of the implant and decreased posteriorly allowing theoretically for SCC recurrence as well as the possibility of migration of malignant cells through the peri-implantary sulcus to the jaws. Finally, corrosion products such as titanium dioxide may have carcinogenic potential and metallic ions from implants may act as immunodepressants or create a cytotoxic environment [51]. **Table 2** summaries the predisposing risk factors for the development of Oral Cancer.

| Predisposing risk factors for the development of Oral Cancer |   |  |                                      |  |  |  |
|--|---|--|--------------------------------------|--|--|--|
| Local factors  | Potentially malignant disorders         | Genetical abnormalities  | Use of tobacco                       | Infections that may predispose to development of Oral Cancer | Other factors  |  |
| • Vascular network proximity                                 | • White                                 | • Chromosomal alterations (segregation, telomere instability, copy number alterations) | • Cigarette                          | • Human papilloma virus                                      | • Dietary factors (low anti-oxidants, iron deficiency, and malnutrition)                           |  |
| • Low glucose levels   | • Mixed leukoplakic lesions             | • Epigenetic changes (DNA methylation, histone modification, RNA mediated silencing)   | • Electronic Cigar Pipe              | • Epstein Barr virus • Candidiasis                           | -Immunosuppression HIV infection persons on Immunosuppressive medications i.e. transplant patients |  |
| • High lactate concentrations                                | • Actinic cheilitis                     | • DNA damage repair  | • Reverse smoking                    | • Bacterial pathogens  |  |  |
| • High interstitial fluid pressure                           | • Lichen planus                         |  | • Smokeless tobacco                  | • Syphilis   |  |  |
| • Hypoxic environment and                                    | • Submucous fibrosis                    |  |                                      |  |  |  |
| • Development of epithelial mesenchymal transition           | • Systemic/ Discoid Lupus Erythematosus | • Loss of heterozygosity   | Use of alcohol                       |  |  |  |
|  | • Dyskeratosis congenita                | Genetical causations for Oral Cancer   | • Ethanol                            |  |  |  |
|  | • Others                                |  | • Ethanol by-products (acetaldehyde) |  |  |  |
| Local concepts   |   |  | • Nitrosamine contaminants           |  |  |  |
| • Field cancerisation  |   |  | Combined tobacco and alcohol use     |  |  |  |
| • Sustained angiogenesis                                     |   |  | • Synergistic compounded increased   |  |  |  |
| Others   |   |  | Oral Cancer predisposition           |  |  |  |
| • Radiation exposure   |   |  |                                      |  |  |  |
| • Dental Implants  |   |  |                                      |  |  |  |

Table 2. Predisposing factors.

## 9. Factors that may reduce the risk of development of Oral Cancer

Antioxidants are needed for normal growth and differentiation of epithelial tissues where deficiencies can lead to the replacement of metastatic squamous epithelium. Vitamins A, C and E have a protective effect against the induction of tumour formation and their presence and strengthens resistance against tumour formation. A recent study [52] suggests that phenolic compounds such as caffeic and coumaric acids may have a protective role against the development of Oral Cancer. These compounds may prevent oxidative DNA damage. Caffeine has even been proven to reverse cell cycle and have a role in the apoptotic pathway. A meta-analysis on tea consumption highlights a protective effect, particularly from green tea, due to its ability from theaflavins and catechins to induce apoptosis and inhibit cancer cell growth [53]. Radiation therapy has also been shown to have a beneficial effect in reducing the development of second primary tumours, whereby adjacent mucosa that may already have had premalignant changes after irradiation is prevented from further malignant transformation [54, 55].

## 10. Detection of Oral Cancer

Early detection is vital in improving the prognosis of Oral Cancer and can minimise adverse effects of treatment such as surgery reconstruction and help maintain quality of life. Practitioners may have a role to play in the Misdiagnosis, Mistreatment, and Mismanagement of SCC particularly in regards to dysplastic lesions. In general, a lesion that cannot be wiped off and persists for more than 3 weeks should be regarded as highly suspicious unless proven otherwise by trustworthy means. It is important not to forget histological resemblance of well-differentiated squamous cell carcinoma to benign epithelial proliferation, seen adjacent to chronic ulcers and infections, thus Oral Cancer may have several differential diagnoses [56]. As a clinician, one cannot underestimate diligent history taking, visual inspection and digital examination in the early diagnosing of Oral Cancer. When Oral Cancer is detected, all patients must undergo full clinical investigations of the body such as blood pressure, heart, liver and renal function (urea and electrolytes), haematological picture, blood group and calcium levels. Locally, histopathological examination remains the mainstay form of investigation. Early tumours often have no local or distant spread and the 5-year survival for early stage detection is 80% compared to 19% when late finding occurs [57]. Several mainstay and new mechanisms in the detection of Oral Cancer are highlighted below.

### 10.1. Toluidine blue

Toluidine blue is used to optimally select a biopsy site and also aids in the assessment of lesion margins during surgery. The product binds to DNA (mitochondrial, altered and increased DNA) and thus is a vital stain that is not precancer or cancer specific (can also stain traumatic lesions and non-cancerous ulceration) but does have great sensitivity for dysplastic and cancerous lesions. Some studies have shown a positive correlation with toluidine blue and lesions with loss of heterozygosity. The latter information provides further evidence that

toluidine blue may have advantage in detecting seemingly sound lesions that may have pre-cancerous non-visible molecular changes. Strength of stain colour should not be regarded of phenotypical importance as both weak and strong staining of an area suggest suspicious molecular profiles [10, 58].

#### *10.1.1. Iodine solutions*

Iodine solutions such as Lugol's iodine and dental iodine glycerine may be used to detect dysplastic and/or cancerous lesions. Iodine binds to glycogen in the normal epithelium creating a brown/black stain but diseased lesions do not stain effectively. It may be particularly useful in the delineation of lesion margins where they become more sharply defined [59].

#### *10.1.2. Light detection*

Cancer cells are thought to refract and absorb light differently due to their structural and metabolic differences compared to healthy cells calling for the field of light detection-based systems in diagnosing Oral Cancer. These include chemiluminescence or Vizilite (normal epithelium appears blue-white, while abnormal appears distinctly white), Vizilite plus which contains pre-toluidine blue use, tissue fluorescence or Veloscope that aims to detect loss of fluorescence in lesions that are dysplastic or malignant, and tissue fluorescence spectroscopy. These aids are useful adjuncts to diagnosis and therapy, whereby they can obtain safer margins during surgery; however, generally they are not as effective in distinguishing between high-risk and low-risk premalignant lesions [57]. Other weaknesses of these systems include low specificity, high cost and limited sturdy evidence regards their reproducibility and reliability [10].

#### *10.1.3. Laser*

Matrix-assisted laser desorption spectrometry and ionisation of serum may prove beneficial in the detection of proteins by assessing their hydrophobic and hydrophilic anionic and cationic metal-binding properties. These proteins include C terminal fragments of the fibrinogen alpha chain and is highly specific and sensitive for cancer presence [60]. Laser scanning confocal microscopy is a new tool that can detect dysplastic changes after application of a fluorescent cellular contrast (acriflavine hydrochloride) and gives rise to optical sections that are visualised digitally through a live stream image. Cellular structures are highlighted in more precise detail; the multiple cell layers of the oral epithelium (from the surface to basal layer) are analysed for morphological characteristics; polymorphisms in size and shape of cells are much clearer; and dysplastic cell location can be accurately determined. Digital laser technology, thus, is a form of diagnosis that can provide the opportunity for a new histological era... 'the digital histologist' [57].

#### *10.1.4. Exfoliative cytology*

Cells on the surface of dysplasia/carcinoma can be assessed and is termed 'Exfoliative cytology'. This method can be used in screening a wide number of people/populations as well as

serving as an aid in guiding optimum biopsy taking, but may overestimate dysplastic lesions and thus produce false positive results. New research suggests that exfoliated cells may be investigated further for epigenetic changes and other genetic mutations, as well as screening populations with exfoliative cytology-assisted cytomorphology [10].

#### *10.1.5. Brush biopsy*

To improve exfoliative cytology, the technique of brush biopsy may be used. Inadequate or inaccurate, negative or no abnormality, atypical or abnormal and positive or cell atypia/carcinoma are the main results that may be achieved from a sample. Brush biopsy success depends on its correct usage, whereby a sample must penetrate the whole epithelium until basement membrane, effectively leading to 'pinpoint bleeding' on sample taking. Shallow samples are therefore inaccurate and may yield false negative results. Although Brush biopsies have had promising positive predictive values/positive likelihood ratios in predicting dysplasia and/or cancer cells in dysplastic and/or SCC lesions, their false negative results have also been presented in several cases and so wisely, conventional methods (scalpel/punch biopsy) should never be superseded by brush biopsy technique [61]. Recently, advances in brush biopsy include using the assistance of matrix-assisted laser absorption/ionisation time to detect changes between malignant and non-malignant cells by analysing their complete mass spectra [4] to diagnose early cancer cell changes.

#### *10.1.6. Scalpel and punch biopsy*

Although both are surgical techniques, the conventional scalpel biopsy removes all layers of the epithelium and enters connective tissue and can be used to extend the biopsy sample where required. The punch biopsy is a more cleaner form of sampling and should be limited to small lesions, more anterior based or extraoral. Scalpel biopsies may be incisional or excisional and importantly should be carried out before treatment is given and ideally be carried out by the same team, also delivering treatment (healing of biopsy may obscure primary lesion location). It should contain the most suspicious area, be large and deep enough for comfortable histopathological diagnosis, be a representative sample of the disease in progress (multiple biopsies may be required here), is of excellent quality (not crushed) and fixed in formal saline to prevent autolysis. Importantly, where results come back negative and the line of doubt for malignancy still exists, biopsies should be challenged and repeated. Other factors include the informed consent of the patient, the reliability of patient-clinician interrelationship and the management of post-operative complications of biopsy where they occur. A biopsy serves to confirm or change the cancer diagnosis with histopathological clarity and grade stage of disease, indicate cancer type and describe if there is local invasion to bone, nerve and muscle. Incisional biopsies may predispose to seeding particularly in areas such as the salivary glands. Some reports have even highlighted that metastasis to lymph nodes by SCC was predisposed by biopsy, whereby cancer cells have potential to reach peripheral blood after the procedure. However, the importance of this investigation remains vital.

#### *10.1.7. Fine needle aspiration biopsy (FNA)*

Lymph nodes and other superficial areas or lesions may be assessed using FNA, a method using a fine-bore needle to aspirate cells and other materials such as blood, cyst fluid and pus for cytological examination. Ultrasound or CT-guided FNA may be more advantageous in giving accuracy to the location of the sample. When assessing metastasis to a lymph node, other features include size of deposits, anatomical level of involvement, extracapsular spread and presence of embolization/permeation of perinodal lymphatics [62].

#### *10.1.8. Sentinel lymph node biopsy*

Sentinel lymph node biopsy assesses the first lymph node that the primary tumour most likely can drain/spread to and is important in correctly staging Oral Cancer. Techniques for this procedure include applying a radioactive tracer material and using conventional radiography to locate the lymph node in question. Blue dye may be used during surgery and the lymph node is then removed and assessed. Elective neck dissection, however, remains a more strengthened path to treatment as evidence suggests that even with negative sentinel lymph node results, metastasis could occur on nonsentinel lymph nodes and through bilateral drainage in the head and neck, thus predisposing to metastatic development.

#### *10.1.9. Examination under general anaesthesia*

Patients may require more thorough investigation of the mouth, upper aero-digestive tract and areas of the nose pharynx, larynx and oesophagus in obscured, small or untraceable lesions. Lesions that cannot be seen visually or palpated may require this procedure. These also include lesions with an enlarged lymph node where no visible primary neoplasm or margins are ill-defined. Random biopsies may be helpful in areas of nasopharynx, base of tongue and hypopharynx as well as tonsil, fossa of Rosenmuller and ipsilateral tonsillectomy.

#### *10.1.10. Imaging*

Conventional radiography—orthopantomogram, and intra-oral radiographs maybe useful in the initial detection of SCC or other tumours in the oral cavity. Chest X-ray is an important primary investigation to assess pulmonary or airway disease in the lungs, hilar lymph nodes, ribs and vertebrae, as well as the detection of any infectious or metastatic disease of the lungs. Ultrasound can be used in assessing lymph nodes, guiding FNA and helps in diagnosing swellings. Doppler-blood flow studies are important in planning radial free forearm flaps. Nasoendoscopy, Laryngoscopy and Panendoscopy investigations are utilised to visualise upper air passages and the pharynx as well as the latter being used under GA to examine trachea, bronchi and oesophagus. Computerised tomography (CT) and Cone beam computerised tomography (CBCT) are vital in the diagnosis of Oral Cancer and help to delineate the origin, extension and size of lesion as well as degree of bone invasion by tumour and in analysing extent of jaw lesions determining lymph node involvement cervically or distant metastasis. CBCT is advantageous with reduced radiation doses, rapid scan times and unique

oral and maxillofacial display systems. Where there is metastasis in the oral cavity, imaging serves to find the occult primary tumour. Dual energy CT improves tumour margin visibility by providing an image that has a high tissue contrast and image noise reduction (particularly useful for reducing dental filling artefact close to tumour study and improving reconstruction) [63]. Standard magnetic resonance imaging (MRI) is beneficial in soft tissue analysis of neurovascular bundles, and cervical lymph node involvement. MRI serves to delineate specific differences between tissues of neoplasms and inflammation as well as normal tissue. Advanced MRI techniques may also be necessary and include spectroscopy, perfusion imaging and diffusion weighted imaging where the latter can be used to detect tumours, assess their character and analyse metastatic lymph node staging [64]. Additional gadolinium-based intravenous contrast can also aid in assessing tumour extension.

#### *10.1.11. Nuclear medicine*

Positron emission tomography (PET) scan is utilised to provide 3d imaging in the investigation for accurate tumour localisation, discovery of metastatic disease and occult lymph node involvement where a radioactive drug is injected such as 18-fluorodeoxyglucose that is taken up by cells with increased metabolic activity (cancer cells). PET fusion scans are also beneficial in the evaluation of a patient with metastatic lymph nodes particularly where the primary tumour cannot be found. The use of PET/CT combination serves to stage head and neck malignancies, lymphadenopathies and to exclude malignancy in lesions that are not fully determined by CT [57]. Bone scans show any abnormal areas of bone, where a radioactive substance is injected into a vein and hot spots are revealed such as Technetium 99 bone scans that are useful in determining bone metabolic activity and active growth or infection.

#### *10.1.12. Saliva*

The role of saliva analysis in diagnosing Oral Cancer is a new field, and a unique one due to the contact relationship between Oral Cancer and saliva composition. Indeed, many changes have been found in saliva composition among Oral Cancer patients compared to healthy controls. Such compositional changes include increase in total sugar, free and protein-bound sialic acid, sodium, calcium and calcium-binding protein, albumin and lactate dehydrogenase. Immunological alterations within saliva have also been detected and include presence of Immunoglobulin C and increased insulin-like growth factor, matrix metalloproteinases and Interleukin 8 and 1B. Epithelial tumours markers such as CYFRA 21-1 and genetic alterations such as presence of HA3 oncogene, Micro RNAs 125a and 200a, and DUSP1, a regulator of cell proliferation, have all been noted within saliva of Oral Cancer patients compared to controls thus allowing saliva to become a future examination in the detection of Oral Cancer.

#### *10.1.13. Blood*

Blood samples may become new aids in the diagnosis of Oral Cancer. Mineral levels of iron and selenium (low in Oral Cancer patients) and copper (high in Oral Cancer patients) may be useful adjuncts. Serological parameters include squamous cell carcinoma-associated antigen, carcinoembryonic antigen, inhibitor of apoptosis fragments and cytokeratin fragments as well

as Annexin A1 [19]. Recently, it has been proposed that the combination of Serum IL-6 mRNA and Salivary IL-8 mRNA has almost complete sensitivity and specificity in the detection of Oral Cancer [10].

#### 10.1.14. Micro RNAs

MiR-21, MiR-125b and MiR-203, for example, have all been highlighted as potentially new diagnostic aids not only in diagnosing SCC but also in the differentiation of tumour subtypes. Tumours from different locations in the oral cavity (base of tongue and tonsil) were shown to express different Micro RNAs thus, where tumour location is unknown or primary origin of nodal metastasis is unclear, the study of Mi-RNAs may become a promising field. MiR-21 and MiR-375, in particular, have been detected in cytological samples in people with early tongue SCC compared to controls and thus may have a role in the accurate detection of this disease while MiR-139-5p was found to be reduced in saliva patients of tongue SCC compared to controls. MiR-184 in plasma was elevated in patients with tongue SCC compared to controls and returned to normal upon removal of tumour [21].

#### 10.1.15. Others

The analysis of cellular proliferation and DNA ploidy with flow cytometry may be a promising new field as detection of aneuploid DNA content within cancer cells is an important biological characteristic. The use of 5-bromodeoxyuridine to detect cellular proliferation particularly in poorly differentiated SCC may be a new method of investigation as well as differentiating tumours with increased lymph node involvement [65]. Biomarkers are also a new and important field in the detection of Oral Cancer. Along with TNM staging, the depiction of Oral Cancer using specific and unique features to determine prognosis are all important non-negligible addition to Oral Cancer diagnosis.

## 11. Clinical features of SCC

SCC often appears as a raised, firm swelling with rolled margins and a granular floor, or as a plaque-like lesion with irregular, roughened or verrucous areas of mucosal thickening. As they continue to enlarge, they may become ulcerated and protruded masses that have irregular and indurated borders with necrosis centrally. Pain may arise as lesion gets more infiltrative and nerves become involved. SCC development often includes the lower lip due to sunlight exposure and the lateral margins of the tongue and the floor of the mouth (non-keratinised areas) are often preceded by an Erythroplakic lesion. Other areas include the posterolateral margin of the tongue which is often termed the 'coffin corner', usually detected as late-stage disease with metastatic involvement and the alveolus and gingivae are often affected in the mandibular premolar and molar regions. The buccal mucosa unfortunately presents with one of the most aggressive clinical courses of SCC and occurs in the areas of the buccal commissures and retromolar areas. Finally, carcinomas in the palate may affect both the soft and hard region and may be of minor salivary gland origin or extending from the maxillary antrum [56].

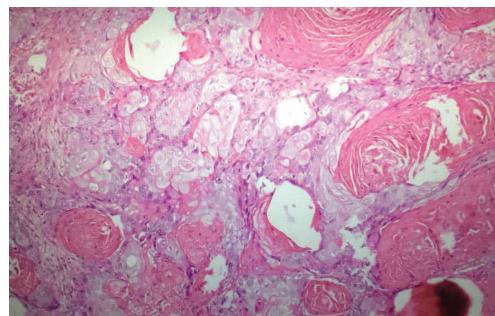
Spread of SCC depends on location and is related to anatomical features of that area. Cancers of the lip, for example, invade adjacent skin, orbicular muscle and when increased in size, the buccal mucosa, mandible and mental nerve. Those tumours of the tongue usually arise on lateral and posterior surfaces and eventually invade the floor of the mouth, root of tongue and causes fixation. Floor of the mouth SCC further extends into the sublingual gland, mid-line muscle and extends towards the gingivae and mandible. Tumours of the buccal mucosa rapidly invade underlying muscles and may even penetrate skin. Other areas include the hard palate where the maxillary antrum may become involved. The retromolar region often involves the adjacent buccal mucosa, anterior tonsillar pillars, maxilla, pterygomandibular space, medial pterygoid muscle and buccinator. The mandible often is affected in the body and then spreads to the ramus.

## 12. Associated signs and symptoms of Oral Cancer development

These include but are not limited to the development of premalignant lesions, non-healing oral ulceration, non-healing extraction sockets, swellings of the mouth and neck, firm and fixed lesions, loosening of one or more teeth, altered dental occlusion, jaw pain, ear pain (ear pain in relation to SCC of the tongue in particular), neck stiffness, regional or cervical lymphadenopathy (30–80% of patients may present with lymph node enlargement as initial presentation), difficulty in mastication, swallowing and speech, paraesthesia, voice hoarseness and temporomandibular joint (TMJ) disorder symptoms. Indeed, pain is an important factor that is associated with the Oral Cancer directly and in metastatic lesions to the oral cavity that can affect nerves. Nasopharyngeal tumours often present with TMJ disorder-like symptoms such as trismus, deviation of the jaw and headaches. Paraneoplastic phenomena may be also be evident in cases of SCC and include the presentation of hypercalcemia and melanosis. Oral paraneoplastic melanosis is a newly described entity that may present with SCC, direct or adjacent to tumour where there is melanin pigmentation that is not histologically associated with tumour histology, rather a distinct entity of unknown aetiology with its presence being a possible diagnostic aid in SCC [66].

## 13. Histological variants of SCC

SCC can vary widely in histological pattern and other microscopic features. Some SCCs are infiltrated with eosinophils, and melanocytes and some may resemble other tumours such as large cell malignant lymphoma. Immunohistochemistry also varies for SCCs where most are invariably positive for keratin. CK 5, 6, 8, 13, 18 and 19 are all variably expressed within lesions where CK13, for example, is associated with metastasis. Desmosome-related proteins and involucrin expression (a marker of terminal differentiation of squamous epithelial cells and keratinisation) are also important immunohistochemical findings (**Figure 1**).



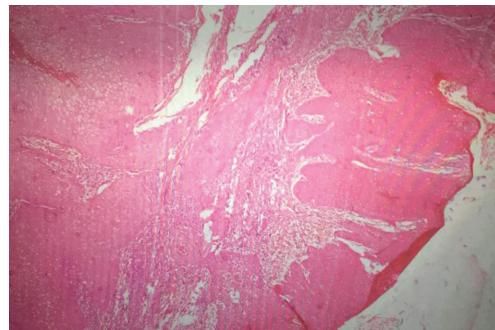
**Figure 1.** Keratin pearls and nests of well-differentiated invasive (keratinising) squamous cell carcinoma (40 $\times$ ).

### 13.1. Verrucous SCC or Ackerman's tumour

Verrucous SCC or Ackerman's tumour does not usually metastasise (although can invade bone and nerves) and is often seen on the alveolar ridge, mandibular sulci or buccal mucosa in patients who use smokeless tobacco. Clinically, it resembles an exophytic lesions with papillary growth that can become infected. Histologically, there are bulbous rete ridges that are swollen and increased in volume with smooth rounded outlines, blunt invasion from a wide advancing front and minimal cytological atypia (**Figure 2**).

### 13.2. Papillary SCC

Papillary SCC is another variant that shows paraorthokeratosis or orthokeratosis, significant cellular atypia and micro abscesses at the tips of bulbous rete ridges. The tumour may resemble verrucous carcinoma in its blunt invasion or may be single celled or island cell invasion however often contains HPV infection and is more present in the oropharynx in elderly patients.



**Figure 2.** Verrucous squamous cell carcinoma showing pushing borders (4 $\times$ ).

### **13.3. Adenoid squamous cell carcinoma, acantholytic or pseudoglandular SCC**

Adenoid squamous cell carcinoma, acantholytic or pseudoglandular SCC commonly arises on the lower lip (probably due to UV radiation) with an aggressive pattern compared to its skin counterpart. There is proliferation of malignant squamous cells and acantholysis with pseudoglandular structures. This SCC may be misdiagnosed as an adenocarcinoma, adenosquamous cell carcinoma or mucoepidermoid carcinoma.

### **13.4. Adenosquamous cell carcinoma**

Adenosquamous cell carcinoma is mainly found in the posterior tongue with poor prognosis (65% risk of metastasis). This variant is a proliferation of squamous cells with formation of duct-like structures containing mucous cells and basaloid epithelial cells.

### **13.5. Basaloid SCC**

Basaloid SCC is an aggressive variant with presence of solid tumour islands, peripheral palisading, thick basement membrane as well as basal lamina material. Cystic spaces are often present and such may resemble adenoid cystic carcinoma or ameloblastoma.

### **13.6. Squamous proliferation with neoplastic goblet cells**

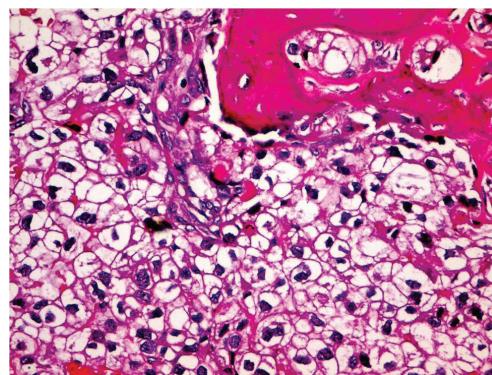
Squamous proliferation with neoplastic goblet cells should also not be confused with clear cell carcinoma [4]. Small cell carcinoma may be pure or has a squamous component with aggressive nature (similar to lung presentation). NUT midline carcinoma is a newly recognised type of carcinoma with molecular changes to NUT gene on chromosome 15 affecting midline structures of the head and neck. Histologically, there are islands of undifferentiated carcinoma with keratinisation with positivity for CK8/18 and CK5/6 respectively.

### **13.7. Clear cell SCC**

Clear cell SCC is a rare histological entity where epithelial malignant cells exhibit this appearance due to degeneration and accumulation of intracellular fluid and contain glycogen. Histologically, these tumours are Periodic acid Schiff (PAS), mucicarmine and S100 negative, CK8 and CK18 positive with squamous differentiation with absence of vasculature or haemorrhaging (**Figure 3**).

### **13.8. Lymphoepithelioma-like carcinoma**

Lymphoepithelioma-like carcinoma is a poorly differentiated or undifferentiated SCC with prominent reactive lymphoplasmacytic infiltrate resembling its non-keratinising nasopharyngeal counterpart and rarely can affect the oral tissues such as the tongue. Malignant cells contain vascular nuclei, prominent nucleoli, pale chromatin and ill-defined cell borders. Pseudovascular SCC may be misdiagnosed as angiosarcoma or giant-cell carcinoma and immunohistochemistry for cytokeratins or endothelial markers should differentiate these.



**Figure 3.** Clear cell SCC. Sheets of cells with dark nuclei, small nucleoli and abundant clear cytoplasm. There are scattered mitoses. The tumour is infiltrating bone at the top right of the figure (40x). Courtesy of Prof. Elhassan and Prof. Elimairi.

## 14. Metastasis, recurrence and survival

SCC of the oral cavity invades locally before metastasising to regional lymph nodes and distant sites. Features that aid metastasis of SCC include its location (high risk posterior tongue, oropharynx, floor of mouth), microscopic differentiation (poorly differentiated), depth of invasion or tumour thickness (more than 9 mm) and presence of inflammatory component. SCC often proliferates as single cells locally or as islands and cords. Those tumours with bulbous rete ridges often invade slowly with less metastasis. Once there is lymphovascular, perineural or bone invasion, local and distant metastasis may be present with recurrence high and possibly poor survival. The submental and submandibular lymph nodes are often the first to be affected and tumours of the posterior tongue often drain to the jugulodigastric or tonsillar lymph nodes and may be bilateral. Distant metastasis includes the mediastinal lymph nodes, lungs, breast and kidneys with bone and liver being affected less commonly. Cervical lymph node metastasis by oral SCC can sometimes exhibit peculiar histological changes such as cystic degeneration that can thus resemble branchial cyst with malignant changes and foreign body giant cell reaction around keratin without presence of tumour cells.

## 15. Metastasis of distant cancers to the oral cavity

Metastasis from infrabodily regions to the oral cavity affects the hard and soft tissues and carries with it its own sequelae and important signs and symptoms. Metastatic cancer cells, most often carcinomas but may also be sarcomas, enter the circulatory system by a process of intravasation and leave by extravasation, adhere to vessels and arrest due to their large size. Colonisation of tissues then quickly occurs by metastatic cells as well as their adaptability to

the local environment with buildup of neovascularity. The bone, i.e., jaw and in particular the mandible, is the most common location affected by metastatic cancer in the head and neck due to chemoattraction and release of cytokines released by it that attracts metastatic cell growth but soft tissues are affected as well. Indeed, osteolytic lesions such as breast and myeloma and osteoblastic lesions such as prostate, commonly can present in the mandible or maxillary regions. Other metastatic possibilities include the kidney, thyroid, lung, cervix, bladder, liver, colon and stomach. Batsons vertebral venous plexus may be a route for cancers to reach the jaws without affecting the lungs. Metastasis to the soft tissues is mainly to the attached gingivae and the tongue and often resembles a benign exophytic or polypoid lesion with high vascularity.

Signs and symptoms of metastatic to the jaws include pain, increasing tooth mobility, swellings, paraesthesia (numb chin syndrome) and other features such as delayed healing of extraction socket, progressive trismus and other symptoms that mimic TMJ dysfunction. Radiographic features include lytic radiolucent lesions, moth-eaten appearance of bone, resorption of teeth and mimicry of periodontal disease. These, however, are often late presenting signs of metastasis and earlier disease may require other investigations such as bone scintigraphy. Soft tissues signs and symptoms include swellings with haemorrhagic tendency, ulceration and necrosis. Finally, the salivary glands should also be noted where metastatic cancers of the salivary glands represent about 8% of all tumours to the gland, the parotid being the main one affected. Commonly, metastasis to the glands is from the head and neck region itself mainly SCC and melanoma. Other tumours include renal, lungs, breast and prostate cancer. Signs and symptoms include swellings, paraesthesia and facial weakness. For a metastatic tumour to be diagnosed, criteria must be reached that includes finding a primary tumour that is histologically accurate to the metastatic sample and that the neoplasm does not involve histopathological appearance of oral tumours [7].

## 16. Other types of Oral Cancer

### 16.1. Odontogenic malignancies

Odontogenic tumours are often benign and local, however although rare, odontogenic malignancies can also occur and are discussed in this paragraph. Peripheral intraosseous SCCs (solid or cystic form) are thought to arise from either odontogenic epithelium or incisive canal epithelium and thus initiate in the jaws with exclusion of secondary spread or metastasis to site. Other intraosseous odontogenic carcinomas include mucoepidermoid carcinoma presenting at the angle of the mandible with histological display of squamous differentiation, mucous cells and mucicarmine positivity.

Ameloblastomas, a common and usually benign odontogenic tumour, can however metastasise, tracking to the lungs (through spill into lymphatic/blood vessels or possibly suggested aspiration of tumour fragments during surgery) leading to multifocal deposits. Through dedifferentiation of cells, ameloblastic carcinomas may also develop either out of

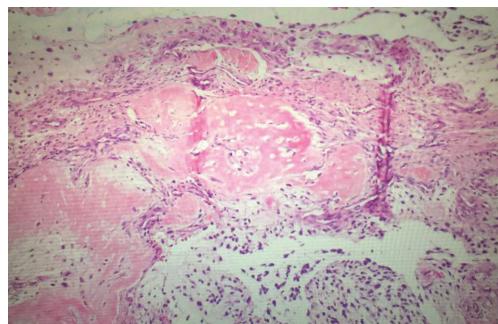
an ameloblastoma or occur as de novo displaying an aggressive neoplasm overgrowing the ameloblastic component with great cytological atypia, mitotic activity with basilar hyperplasia as well as perineural invasion. Low grade spindle ameloblastic carcinoma is another form displaying cellular stroma and fibroblastic cells. Ghost cell odontogenic carcinomas are often locally invasive but can metastasise to the orbit, cranium or lungs, and are a form of ameloblastic carcinomatous differentiation with histological positivity for enamel matrix protein amelogenin and display of ameloblastic columnar cell pattern at periphery. Other findings include sheets of basaloid cells and stratified squamous epithelium with ghost cell keratinisation (enlarged epithelial cell with eosinophilic cytoplasm). Clear cell odontogenic carcinoma may also show peripheral palisaded ameloblastic columnar cells and show budded cords, islands of malignant epithelial cells as well as clear cells (cells with abundant pale cytoplasm with distinct cell borders). Clear cell odontogenic carcinoma should be differentially diagnosed from calcifying epithelial odontogenic tumour, metastatic renal carcinoma, clear cell variant of mucoepidermoid carcinoma and clear cell squamous cell carcinoma. Ameloblastic fibrocarcoma usually occurs de novo but can arise from ameloblastic fibroma, presenting in young age groups in the mandible with extraosseous soft tissue extension and present radiologically as an expansile radiolucency. Histologically, there is benign odontogenic epithelium with malignant connective tissue cells. Even more so, dentine and/or enamel differentiation may also occur leading to the term ameloblastic dentinosarcoma and/or ameloblastic odontosarcoma. The keratocyst and dentigerous cyst are the commonest odontogenic cysts that can develop malignancy where the former often is present in older age groups as an asymptomatic or otherwise painful pericoronal lesion associated with an unerupted mandibular wisdom tooth as well as canines and the latter may arise within lesion or after surgeries [67].

## 16.2. Osteosarcomas

Osteosarcomas are primary bone tumours of mesenchymal origin and are rare in the head and neck region however when do present, are often in the jaws around the 4th decade of life (compared to infrabody osteosarcoma which occurs around the 2nd decade and associated growth spurts), and are aggressive lesions (although jaw osteosarcoma has better prognosis compared to other locations due to less haematogenous spread and better histological differentiation). Possible aetiopathological factors exist such as genetical pleomorphisms (inactivation of the retinoblastoma gene), bone dysplasias and previous radiation therapy. Radiographically, bone undergoes a typical sunray appearance and widening of periodontal ligament space (Grittman's sign). Histologically, malignant spindle cells are found producing osteoid and immature bone with possible cartilaginous differentiation (**Figure 4**).

## 16.3. Lymphomas (B, T and NK cell)

Where cases of non-Hodgkin's Lymphoma (NHL) do occur in the oral cavity, 70% of them present in Waldeyer's ring (tonsil, adenoid, tongue base, nasopharynx) lack in ulceration and are present with dysphagia, airway obstruction, Eustachian tube blockage and neck



**Figure 4.** Osteosarcoma: sheets of malignant cells with adjoining osteoid and new bone (4 $\times$ ).

involvement. Those that do occur in the oral soft tissues are usually to the buccal vestibule, gingivae and hard palate as well as centrally within the jaws, presenting as a rapidly growing tumour with ulceration and necrosis sometimes accompanied with an erythematous purplish appearance. The different types of NHL that can affect the oral cavity are summarised below.

#### 16.3.1. *Diffuse large B-cell lymphoma (DLBCL)*

DLBCL often presents in elder age groups (6th and 7th decade) as a painless mass. Histologically, centroblastic, anaplastic, and immunoblastic and T cell/histiocyte rich subtypes exist. Plasmablastic B cell lymphoma is a DLBCL variant most commonly in HIV affected persons and usually affects the buccal-gingival mucosa. Histologically they are CD20- and CD138+ lack of cancerous plasma cells but existence of plasmablastic morphology.

#### 16.3.2. *Burkett's lymphoma*

This is an aggressive, highly proliferative tumour (nearly 100% Ki-67 proliferation fraction) occurring as either endemic (Africa, 1st, 2nd decade in life, 95% EBV + associated), sporadic (no geographical or age predilection, <30% EBV + associated) or HIV-related cases (25–40% EBV + associated) and almost uniquely presenting in the jaws. Classical histology includes a starry sky appearance (scattered macrophages) with round medium-sized blastic lymphoid cells that contain coarse chromatin and multiple nucleoli with CD10, 19, 20, and 22 positivity. Genetically, Burkett's lymphoma is known to be associated with c-myc translocation and 100% Bcl-6 hypermutation, as well as being BCL2 (anti-apoptotic) negative.

#### 16.3.3. *Mantle cell lymphoma*

Rare cases have been reported in particular palatally masked by prosthetic appliances in elderly patients. Histologically, these lymphomas contain small lymphoid cells with hyperchromatism and CD-19, 20 and cyclin D1 positivity. These tumours are also CD5, CD10 and CD23 negative and BCL-2 positive.

#### 16.3.4. Follicular lymphoma

Often in salivary glands, malignant lymphocytes are in follicular patterns with progressive destruction of salivary gland structure. Follicular lymphoma is also highly positive for the anti-apoptotic protein BCL-2 positive as well as CD-20.

#### 16.3.5. Mucosal associated lymphoid tissue (MALT) lymphoma

Another associated salivary gland lymphoma is MALT lymphoma usually associated with Sjogrens syndrome patients and thus has a female predominance. This tumour contains T cells, B cells as well as plasma cells and macrophages often with a slow course.

#### 16.3.6. Mycosis fungoides

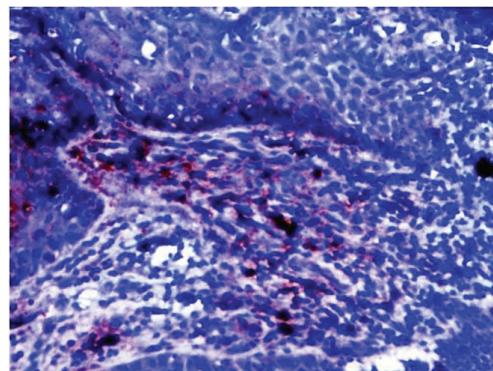
Also known as cutaneous T cell lymphoma, only a handful of oral cases have been reported in the literature and often occur after skin lesions. The tongue is a favourable site where ulceration, indurated leukoplakic-like lesions and erosions occur. Malignant proliferation of helper (CD-4) T lymphocytes and suppressor T lymphocytes occurs with histological dense infiltrate of pleomorphic lymphocytes and Pautrier's microabscesses.

#### 16.3.7. Peripheral T cell lymphoma

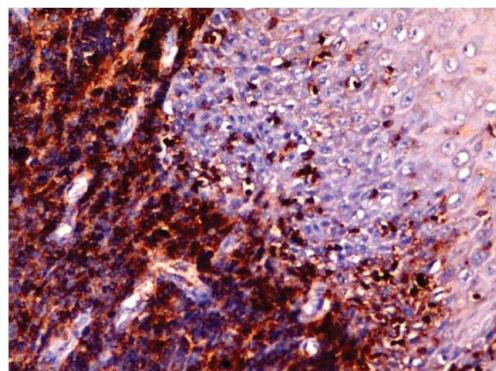
While these may simulate NK/T cell lymphoma, they are a rare type of T cell lymphoma and even rarer to occur in the oral cavity. These often occur at elder age and immunohistochemistry distinguishes them by their CD56 and CD20 negativity and CD3 positivity (**Figures 5 and 6**).

#### 16.3.8. Lethal midline granuloma/natural killer T cell lymphoma

As its name, this tumour often has an extremely rapid course with terrible prognosis. Typically originating in the nasal cavity, perforation intraorally to the palate as well as extension to



**Figure 5.** Peripheral T cell lymphoma. Immunohistochemistry: cells negative for CD56.



**Figure 6.** Peripheral T cell lymphoma. Cells positive for CD3. Courtesy of Prof. Elhassan and Prof. Elimairi.

midface region occurs often in young males with an unclear aetiology. Initially, non-specific rhinitis and/or sinusitis as well as epistaxis confuses the initial clinical picture; however, progressive facial swelling and deep necrotic ulceration in the midline of the face ensues, leading to oronasal destruction and systemic manifestations. Histologically, there are bizarre lymphocytes with large and hyperchromatic nuclei.

#### **16.4. Plasmacytomas (intramedullary, extramedullary or multiple myeloma)**

In the oral cavity, malignant plasma cells can rarely give rise to solitary proliferations that are present either in the bone (intramedullary), in soft tissues (extramedullary) or as part of multifocal disseminated disease known as multiple myeloma [68]. The latter is characterised by other systemic features such as M proteins, bone lytic lesions, kidney failure, hepatomegaly and splenomegaly with progressive hypercalcaemia and hyperviscosity, as well as aplastic anaemia with concurrent infections. Oral lesions can develop in up to 30% of patients with multiple myeloma and can be present as jaw pain, pathological fractures, swelling, paraesthesia and tooth complications such as mobility and resorption. Radiologically, bone loss and osteolytic lesions in the jaws may be evident giving a punched out appearance. Painless soft tissue ulceration and swelling may be evident. A not uncommon feature is amyloidosis relating to the disease and can present as macroglossia, papules, nodules and plaque-like lesions in the soft tissues as well as rarely in the salivary glands [69]. Histologically, clusters, nodules or sheets of malignant plasma cells in an interstitial, focal or diffuse manner in a hypercellular marrow are evident with osteoclastic activity and CD138 positivity. Plasma cells with Russell bodies (intracytoplasmic hyaline inclusions) may also be seen and are termed Mott cells as well as other histological features including Dutcher bodies.

#### **16.5. Kaposi's sarcoma**

Kaposi's sarcoma, a low grade tumour of endothelial vascular cell arises as either classic or sporadic (Mediterranean and Eastern Europe), endemic (Africa), epidemic (HIV associated)

or immunosuppression forms (transplant, immunosuppressive therapy such as Rituximab or Corticosteroid) [70]. Kaposi's sarcoma develops in the skin, lymphatics, mucous membranes and viscera such as the lungs, stomach and liver. A combination of aetiopathological factors exists, most importantly of which is HHV-8 seroconversion that is thought to lead to the Warburg effect among cells, promotes release of pro-inflammatory cytokines and allows immune breakdown. Immunosuppression plays a strong role in development of Kaposi's sarcoma as well as chronic inflammation. Up to 70% of HIV patients can develop Kaposi's sarcoma in the oral cavity and 20% of any associated pattern of Kaposi's sarcoma will manifest in the mouth.

Orally, Kaposi's sarcoma lesions, which are commonly due to the epidemic and immunosuppression forms, are often round, single or multiple swellings that are flat, papuled or nodular, most likely to appear on the palate and gingivae (sometimes mimicking gingival hyperplasia), but rarely can present in the lips, tongue and buccal mucosa. It is often purple, red, brown or blue colour and may be associated with secondary bleeding, ulceration and necrosis if long standing. Bone involvement and tooth mobility may also arise. Histologically, Kaposi's sarcoma lesions contain spindle-shaped malignant cells, abnormal vessels (stellate or ecstatic patterns), vascular slit-like spaces, extravasated erythrocytes, haemosiderin laden macrophages, hyaline globules and chronic inflammatory infiltrate with plasma cells and lymphocytes. Anaplastic, pyogenic granuloma-like and lymphangioma-like histological variants exist. Endothelial cell markers CD31 and CD34 are positive as well as presence of vascular endothelial growth factor 3 relates to lymphatic differentiation within Kaposi's sarcoma. MMPs and IL6 presence are associated with angiogenesis; however, no chromosomal abnormalities are known [71].

### 16.6. Ewing's sarcoma

Unfortunately, not an uncommon aggressive tumour present in childhood or adolescence (more commonly among Caucasians), Ewing's sarcoma carries a poor prognosis with likely metastasis upon clinical presentation. Most likely derived from neuroectodermal cells, Ewing's sarcoma may also have a reticular and mesenchymal cell origin. Genetically, the translocation t (11.22) (q24:12) is present in over 90% of cases leading to fusion of the Ewing's sarcoma/Friend leukaemia integration 1 transcription factor that gives rise to a strong oncogene. Other genetic alterations include P16 activation and p53 suppression. Histologically, Ewing's sarcoma consists of small round cell tumours that are CD99 positive and neural marker negative and exhibits intracellular glycogen granules and abundant intermediate filaments. Head and Neck Ewing's sarcoma accounts for 3% of cases but 10% of all bone malignancies of mandible. Patients present with a hard or elastic soft bone swelling are most likely in posterior mandible but can occur in maxilla and maxillary sinus, gingival swelling, pain or toothache, dental abscess, paraesthesia as well as dental disturbances that include destruction of dental follicles, premature exfoliation, tooth mobility and resorption. Overlying mucosal may appear normal but can show erythema or ulceration. Radiographically, the tumour is radiotransparent with irregular margins and no sclerotic reaction [72].

### 16.7. Malignant melanoma

Arising from primary malignant transformation of melanocytes in the basal layer (and less commonly from immature melanocytes in lamina propria), malignant melanoma represents a rare entity (0.5% of Oral Cancer) in the oral cavity with very poor prognosis. Melanoma may arise in a background of benign oral pigmentation such as nevus but can occur de novo with absence of any existing pigmented lesion and often presents in the hard palate, gingivae, buccal mucosa or retromolar region as either a macule, papule or exophytic lesion. Rarely, it may secondarily metastasise from skin melanoma to the oral cavity. Tumours are often painless, irregular and represent mottled pigmentation that is of a brown to black nature with lesional bleeding. Invasion to deeper structures, satellite tumours and metastasis to local and distant lymph nodes occurs rapidly. The aggressiveness of this tumour is both in relation to its melanotic progenitor cells, when replicate provides new melanotic amplified cells with an extremely high proliferative rate, but also to its histopathological growth pattern which allows malignant cells to invade along the whole of the basal cell layer of epithelium, followed by vertical growth of malignant cells into the lamina propria thus spreading widely undisturbed before being clinically visible. Genetically, melanocortin receptor 1 polymorphisms (associated with less DNA repair and apoptosis of damaged melanocytes), CKit proto-oncogene overexpression and altered cadherin cell adhesion molecules (increased N cadherin expression promotes cell proliferation, migration and invasive potential) are implicated in the development of this tumour. Interestingly, a cancer promoting cycle occurs during melanin biosynthesis whereby melanin degradation leads to the release of reactive oxygen species, formation of quinines and other products that are mutagenic and produce melanocyte instability. Histologically, melanoma cells are highly mitotic with eosinophilic nuclei in either solid or loose arrangement with variable melanin expression. Melanin expression can also be detected within macrophages and extracellularly, sometimes so much as to hide cancer cell morphology. Absence of pigment in melanoma cells reveals another variant that is amelanotic melanoma with an even poorer prognosis than its counterpart, owing to its delayed diagnosis [73].

### 16.8. Collision, bimorphic and hybrid tumours

Two or more primary tumours may rarely grow alongside one another with no or limited histological intersection, termed; collision tumours. Often these consist of carcinomas and sarcomas, sarcomas and lymphomas or two types of carcinomas. Cases in the literature including SCC growth include alongside ameloblastomas, pleomorphic adenomas, salivary duct carcinomas, thyroid carcinomas and melanomas have been reported. A bimorphic tumour consists of two types of tissues or cells, one of malignant cell origin and one form often considered non-cancer proliferation such as the stromal background (thought to be a reaction to presence of epithelial carcinoma cells) seen within spindle cell SCC or pseudosarcoma. However, the latter tumour also delivers other histological concepts, such as tumour cell polyclonal originality, where both epithelial and spindle cells are originated from different stem cell lines and monoclonal originality whereby mutagenic changes at some point lead to spindle cell formation within the tumour or just dedifferentiation of original tumour cells. Neuroectodermal tumour of infancy is another example of a biphasic tumour consisting of both neuroblastic cells and large melanin containing epithelial cells. Hybrid tumours consists of two or more tumour tissue in a single

neoplasm and arises within the same topography of lesion such as sarcomatous change within a carcinoma (carcinosarcoma) [74]. It may be of note that infections and synchronous SCC growth have also been reported such as tuberculosis and SCC growth within one anatomical space and Paracoccidioidomycosis alongside an oesophageal carcinoma.

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## References

- [1] Niu LX et al. Prognostic factors of squamous cell carcinoma of the buccal mucosa: A retrospective study of 168 cases in Journal of Oral Maxillofacial Surgery. American Association of Oral and Maxillofacial Surgeons. 2014;**72**(11):2344-2350. DOI: 10.1016/j.joms.2014.05.021
- [2] Scully C, Bedi R. Ethnicity and oral cancer. Lancet Oncology. 2000 Sep;1(1):37-42
- [3] Tabatabaeifar S et al. Investigating a case of possible field cancerization in oral squamous cell carcinoma by the use of next-generation sequencing. Oral Oncology. 2017;**68**:74-80. DOI: 10.1016/j.oraloncology.2017.03.018
- [4] Weinstock YE, Iii IA, Dierks EJ. Pitfalls in determining head and neck surgical margins. Oral and Maxillofacial Surgery Clinics of NA. 2014;**26**(2):151-162. DOI: 10.1016/j.coms.2014.01.003
- [5] Subramaniam N, Balasubramanian D. Adverse pathologic features in early oral squamous cell carcinoma and the role of postoperative radiotherapy d a review. Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology. 2017;**124**(1):24-31. DOI: 10.1016/j.oooo.2017.03.002
- [6] Wagner VP, Webber P, Curra M. 'Bryne' s grading system predicts poor disease-specific survival of oral squamous cell carcinoma: A comparative study among different histologic grading systems. Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology. 2017;**123**(6):688-696. DOI: 10.1016/j.oooo.2017.02.012
- [7] Vega LG, Dipasquale J. Head and neck manifestations of distant carcinomas. Oral and Maxillofacial Surgery Clinics of NA. 2008;**20**(4):609-623. DOI: 10.1016/j.coms.2008.06.003
- [8] Kaneko T, Dehari H, Sasaki T. Hypoxia induced epithelial-mesenchymal transition is regulated by phosphorylation of GSK3-b via PI3 K/Akt signalling in oral squamous cell carcinoma. Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology. 2016;**122**(6):719-730. DOI: 10.1016/j.oooo.2016.06.008

- [9] Van Der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. *Oral Oncology*. 2009; **45**(4-5):317-323. DOI: 10.1016/j.oraloncology.2008.05.016
- [10] Kalmar JR. Advances in the detection and diagnosis of oral precancerous and cancerous lesions. *Oral and Maxillofacial Surgery Clinics of North America*. 2006; **18**:465-482. DOI: 10.1016/j.coms.2006.06.013
- [11] Okamura T et al. Disordered arrangements of basal cells as a prognostic factor for oral epithelial dysplasia: A morphometric study of 96 cases. *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology*. 2016; **122**(3):355-361. DOI: 10.1016/j.oooo.2016.05.005
- [12] Hwang JTK et al. Individualized five-year risk assessment for oral premalignant lesion progression to cancer. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*. 2017 Mar; **123**(3):374-381. DOI: 10.1016/j.oooo.2016.11.004
- [13] Sciubba JJ, Helman JI. Current management strategies for verucous hyperkeratosis and verrucous carcinoma. *Oral and Maxillofacial Surgery Clinics of North America*. 2013 Feb; **25**(1):77-82, vi. DOI: 10.1016/j.coms.2012.11.008
- [14] Na B et al. Oral cancer development in patients with oral lichen planus. *Journal of Oral Pathology & Medicine* 1993 Oct; **22**(9):421-424
- [15] Grimm M et al. Analysis of circulating CD14 D/CD16 D monocyte-derived macrophages (MDMs) in the peripheral blood of patients with oral squamous cell carcinoma. *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology*. 2016; **121**(3):301-306. DOI: 10.1016/j.oooo.2015.10.024
- [16] Warnakulasuriya S. Causes of oral cancer—An appraisal of controversies. *BDJ*. 2009; **207**(10):471-475. DOI: 10.1038/sj.bdj.2009.1009.
- [17] Ali J et al. Genetic etiology of oral cancer. *Oral Oncology*. 2017; **70**:23-28. DOI: 10.1016/j.oraloncology.2017.05.004
- [18] Ko L et al. Advances in brief allelic imbalance on chromosome 3p in oral dysplastic lesions: An early event in oral Carcinogenesis. *Cancer Research*. 1996; **56**:1228-1232
- [19] Woo S et al. Biological significance of 5-hydroxymethylcytosine in oral epithelial dysplasia and oral squamous cell carcinoma. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*. 2018 Jan; **125**(1):59-73.e2. DOI: 10.1016/j.oooo.2017.06.006. Epub 2017 Jun 16
- [20] Harrandah AM et al. MicroRNA-375 as a biomarker for malignant transformation in oral lesions. *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology*. 2016; **122**(6):743-752.e1. DOI: 10.1016/j.oooo.2016.07.022
- [21] Karatas OF et al. MicroRNAs in human tongue squamous cell carcinoma: From pathogenesis to therapeutic implications. *Oral Oncology*. 2017; **67**:124-130. DOI: 10.1016/j.oraloncology.2017.02.015
- [22] Mishra R et al. High expression of survivin and its splice variants survivin D Ex3 and survivin 2 B in oral cancers. *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology*. 2015; **120**(4):497-507. DOI: 10.1016/j.oooo.2015.06.027

- [23] Zhang L et al. Effects of human dachshund homolog 1 on the proliferation, migration, and adhesion of squamous cell carcinoma of the tongue. *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology*. 2016;**121**(1):58-66. DOI: 10.1016/j.oooo.2015.08.021
- [24] Ohashi Y, Kumagai K, Miyata Y. Overexpression of ErbB4 is an independent marker for lymph node metastasis in Japanese patients with oral squamous cell carcinoma. *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology*. 2016;**122**(3):313-321. DOI: 10.1016/j.oooo.2016.04.017
- [25] Takes RP. Staging of the neck in patients with head and neck squamous cell cancer: Imaging techniques and biomarkers. *Oral Oncology*. 2004 Aug;**40**(7):656-667. DOI: 10.1016/j.oraloncology.2003.11.001
- [26] Matsui T, Shigeta T, Umeda M. Vascular endothelial growth factor C (VEGF-C) expression predicts metastasis in tongue cancer. *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology*. 2015;**120**(4):436-442. DOI: 10.1016/j.oooo.2015.06.002
- [27] Moriyama M et al. Immunohistochemical study of tumour angiogenesis in oral squamous cell carcinoma. *Oral Oncology*. 1997 Sep;**33**(5):369-374
- [28] Hu L et al. Transforming growth factor- $\beta$  1 activates D Np63/c-Myc to promote oral squamous cell carcinoma. *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology*. 2016;**122**(4):460-482.e4. DOI: 10.1016/j.oooo.2016.05.018
- [29] Yang J et al. Prognostic value of toll-like receptor 4 and nuclear factor- $\kappa$  Bp65 in oral squamous cell carcinoma patients. *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology*. 2016;**122**(6):753-764.e1. DOI: 10.1016/j.oooo.2016.08.002
- [30] Sakamoto T et al. Critical roles of Wnt5a – Ror2 signalling in aggressiveness of tongue squamous cell carcinoma and production of matrix metalloproteinase-2 via D Np63 b-mediated epithelial–mesenchymal transition. *Oral Oncology*. 2017;**69**:15-25. DOI: 10.1016/j.oraloncology.2017.03.019
- [31] Takes RP. Staging of the neck in patients with head and neck squamous cell cancer: Imaging techniques and biomarkers. *Oral Oncology*. 2004 Aug;**40**(7):656-67. DOI: 10.1016/j.oraloncology.2003.11.001
- [32] Scully C, Porter S. Oral Cancer Toolbox. *BMJ*. 2000;**321**:97-100
- [33] Olshan A et al. Mouthwash use and cancer of the head and neck: A pooled analysis from the International Head and Neck Cancer Epidemiology Consortium (INHANCE). *European Journal of Cancer Prevention*. 2016 Jul;**25**(4):344-348. DOI: 10.1097/CEJ.0000000000000179
- [34] Mirghani H et al. Human papilloma virus testing in oropharyngeal squamous cell carcinoma: What the clinician should know. *Oral Oncology*. 2014 Jan;**50**(1):1-9. DOI: 10.1016/j.oraloncology.2013.10.008. Epub 2013 Oct 26
- [35] Khanal S et al. Histologic variation in high grade oral epithelial dysplasia when associated with high-risk human papillomavirus. *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology*. 2017;**123**(5):566-585. DOI: 10.1016/j.oooo.2017.01.008

- [36] Garcia de A et al. Human papillomavirus in carcinomas of the tongue: Clinical and prognostic implications. International Journal of Oral & Maxillofacial Surgery. 2014 Mar;43(3):274-280
- [37] Jiang R et al. Oral dysplasia and squamous cell carcinoma: Correlation between increased expression of CD21, Epstein-Barr virus and CK19. Oral Oncology. 2012 Sep;48(9):836-841. DOI: 10.1016/j.oraloncology.2012.03.017. Epub 2012 Apr 16
- [38] Shamaa AA et al. The significance of Epstein Barr Virus (EBV) & DNA Topoisomerase II alpha (DNA-Topo II alpha) immunoreactivity in normal oral mucosa, Oral Epithelial Dysplasia (OED) and Oral Squamous Cell Carcinoma (OSCC). Diagnostic Pathology. 2008;3:45. <https://doi.org/10.1186/1746-1596-3-45>
- [39] Berkovits C et al. Analysis of oral yeast microflora in patients with oral squamous cell carcinoma. Springer Plus. 2016. DOI: 10.1186/s40064-016-2926-6
- [40] Bakri MM et al. Revisiting the association between candidal infection and carcinoma, particularly oral squamous cell carcinoma Journal of Oral Microbiology. 2010;2. DOI: 10.3402/jom.v2i0.5780
- [41] Alnuaimi AD et al. Oral Candida colonization in oral cancer patients and its relationship with traditional risk factors of oral cancer: A matched case-control study. Oral Oncology. 2015;51(2):139-145. DOI: 10.1016/j.oraloncology.2014.11.008
- [42] Javed F, Warnakulasuriya S. Is there a relationship between periodontal disease and oral cancer? A systematic review of currently available evidence. Critical Reviews in Oncology/Haematology. 2015;1-9. DOI: 10.1016/j.critrevonc.2015.08.018
- [43] Abdulkareem AA et al. Periodontal pathogens promote epithelial-mesenchymal transition in oral squamous carcinoma cells in vitro. Cell Adhesion & Migration. 2017 Sep;5: 1-11. DOI: 10.1080/19336918.2017.1322253
- [44] Gallimidi AB et al. Nucleatum promote tumour progression in an oral-specific chemical carcinogenesis model. Oncotarget. 2015 Sep 8;6(26):22613-22623
- [45] Carneiro J, Alcino L, Porter SR. Review oral manifestations of syphilis. Clinics (Sao Paulo). 2006 Apr;61(2):161-166. Epub 2006 Apr 25
- [46] Dickenson AJ, Currie WJR, Avery BS. Screening for syphilis in patients with carcinoma of the tongue. British Journal of Oral and Maxillofacial Surgery. Oct 1995;(5):319-320
- [47] Visscher D et al. Squamous cell carcinoma of the lower lip in renal transplant recipients: Report of 6 cases. International Journal of Oral and Maxillofacial Surgery. 1997;26:120
- [48] Gaston NK et al. Increased prevalence of dysplastic and malignant lip lesions in renal transplant recipients. New England Journal of Medicine. 1995;1052-1057
- [49] Thomas DW et al. Systemic immunosuppression and oral malignancy: A report of a case and review of the literature. British Journal of Oral and Maxillofacial Surgery. 1993 Dec;31(6):391-393. [https://doi.org/10.1016/0266-4356\(93\)90197-5](https://doi.org/10.1016/0266-4356(93)90197-5)

- [50] Kaplan I et al. Clinicopathologic evaluation of malignancy adjacent to dental implants. *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology*. 2017;**123**(1):103-112. DOI: 10.1016/j.oooo.2016.08.023
- [51] Salgado-Peralvo AO et al. Is there an association between dental implants and squamous cell carcinoma? *British Dental Journal*. 2016;**221**(10):645-649. DOI: 10.1038/sj.bdj.2016.863
- [52] Li Y, Peng J, Li L. Coffee consumption associated with reduced risk of oral cancer: A meta-analysis. *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology*. 2016; **121**(4):381-389.e1. DOI: 10.1016/j.oooo.2015.12.006
- [53] Wang W, Zhang W, Wu W. Association of tea consumption and the risk of oral cancer: A meta-analysis. *Oral Oncology*. 2014;**50**(4):276-281. DOI: 10.1016/j.oraloncology.2013.12.014
- [54] Rennemo E et al. Reduced risk of head and neck second primary tumours after radiotherapy. *Radiotherapy and Oncology*. 2009;**93**(3):559-562. DOI: 10.1016/j.radonc.2009.08.005
- [55] Tae S et al. Chronic, reactive conditions of the oral cavity simulating mucosal carcinomas B CT and MR imaging findings with pathologic correlation in five patients. *Clinical Imaging*. 2005 Nov-Dec; **29**(6):406-611. DOI: 10.1016/j.clinimag.2005.06.026
- [56] Kalavrezos N, Scully C. Mouth cancer for clinicians part 7: Cancer diagnosis and pre-treatment preparation. *Dental Update*. 2016 Jan-Feb; **43**(1):50-54, 57-60, 63-65
- [57] Lestón JS, Dios PD. Diagnostic clinical aids in oral cancer. *Oral Oncology*. 2010;**46**(6):418-422. DOI: 10.1016/j.oraloncology.2010.03.006
- [58] Hiroshi Kurita KK. Vital staining with iodine solution in delineating the border of oral dysplastic lesions. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontontology*. 1996 Mar; **81**(3):275-280
- [59] Awan KH, Morgan PR, Warnakulasuriya S. Evaluation of an autofluorescence based imaging system (VELscope™) in the detection of oral potentially malignant disorders and benign keratoses. *Oral Oncology*. 2011;**47**(4):274-277. DOI: 10.1016/j.oraloncology.2011.02.001
- [60] El Hallani S et al. Ex vivo confocal imaging with contrast agents for the detection of oral potentially malignant lesions. *Oral Oncology*. 2013;**49**(6):582-590. DOI: 10.1016/j.oraloncology.2013.01.009
- [61] Maurer K et al. Oral brush biopsy analysis by MALDI-ToF mass spectrometry for early cancer diagnosis. *Oral Oncology*. 2013;**49**(2):152-156. DOI: 10.1016/j.oraloncology.2012.08.012
- [62] Toepker M et al. Can dual-energy CT improve the assessment of tumour margins in oral cancer? *Oral Oncology*. 2014;**50**(3):221-227. DOI: 10.1016/j.oraloncology.2013.12.001
- [63] Payne KFB et al. The role of diffusion-weighted magnetic resonance imaging in the diagnosis, lymph node staging and assessment of treatment response of head and neck cancer. *International Journal of Oral & Maxillofacial Surgery. International Association of Oral and Maxillofacial Surgery*. 2015;**44**(1):1-7. DOI: 10.1016/j.ijom.2014.09.008

- [64] Ouyang T, Iv BFB. Advances in head and neck imaging. *Oral and Maxillofacial Surgery Clinics of NA.* 2010;22(1):107-115. DOI: 10.1016/j.coms.2009.10.002
- [65] Hass HG et al. DNA ploidy, proliferative capacity and intratumoral heterogeneity in primary and recurrent head and neck squamous cell carcinomas (HNSCC)—Potential implications for clinical management and treatment decisions. *Oral Oncology.* 2008 Jan;44(1):78-85. Epub 2007 Mar 9. DOI: 10.1016/j.oraloncology.2006.12.013
- [66] Elimairi I et al. Oral paraneoplastic melanosis (OPM) as a rare presentation of neoplastic and non-neoplastic disease. *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology.* 2017;124(3):e198. DOI: 10.1016/j.oooo.2017.05.501
- [67] Slater LJ. Odontogenic malignancies. *Oral and Maxillofacial Surgery Clinics of North America.* 2004;16(3):409-424
- [68] Kamal M, Kaur P, Gupta R, Gupta S, Singh S. Mandibular plasmacytoma of jaw—A case report. *Journal of Clinical and Diagnostic Research.* 2014;8(8):20-21
- [69] Shah A, Latoo S, Ahmad I. In: Gupta A. editor. *Multiple Myeloma and Dentistry, Multiple Myeloma—An Overview.* InTech; 2012. ISBN: 978-953-307-768-0. Available from: <http://www.intechopen.com/books/multiple-myeloma-an-overview/multiple-myeloma-and-dentistry>
- [70] Berenice F, Gil D. Oral Kaposi's sarcoma in immunosuppressed patients—Report of cases. *The South Brazilian Dentistry Journal RSBO (Online).* 2013;10(1):89-95
- [71] Douglas JL, Gustin JK, Moses AV, Dezube BJ, Pantanowitz L. Kaposi sarcoma pathogenesis: A triad of viral infection, oncogenesis and chronic inflammation. *Translational Biomedicine.* 2010;1(2). pii: 172
- [72] Margáix-muñoz M, Bagán J, Poveda-roda R. Ewing sarcoma of the oral cavity. A review. *2017;9(2)*
- [73] Feller L, Khammissa RAG, Lemmer J. A review of the Aetiopathogenesis and clinical and Histopathological features of oral mucosal melanoma. *Scientific World Journal.* 2017;2017:1-7
- [74] Arvind Babu RS, Ramana Reddy BV, Anuradha CH. Histogenetic concepts, terminology and categorization of biphasic tumours of the oral and maxillofacial region. *Journal of Clinical and Diagnostic Research.* 2014;8(2):266-270