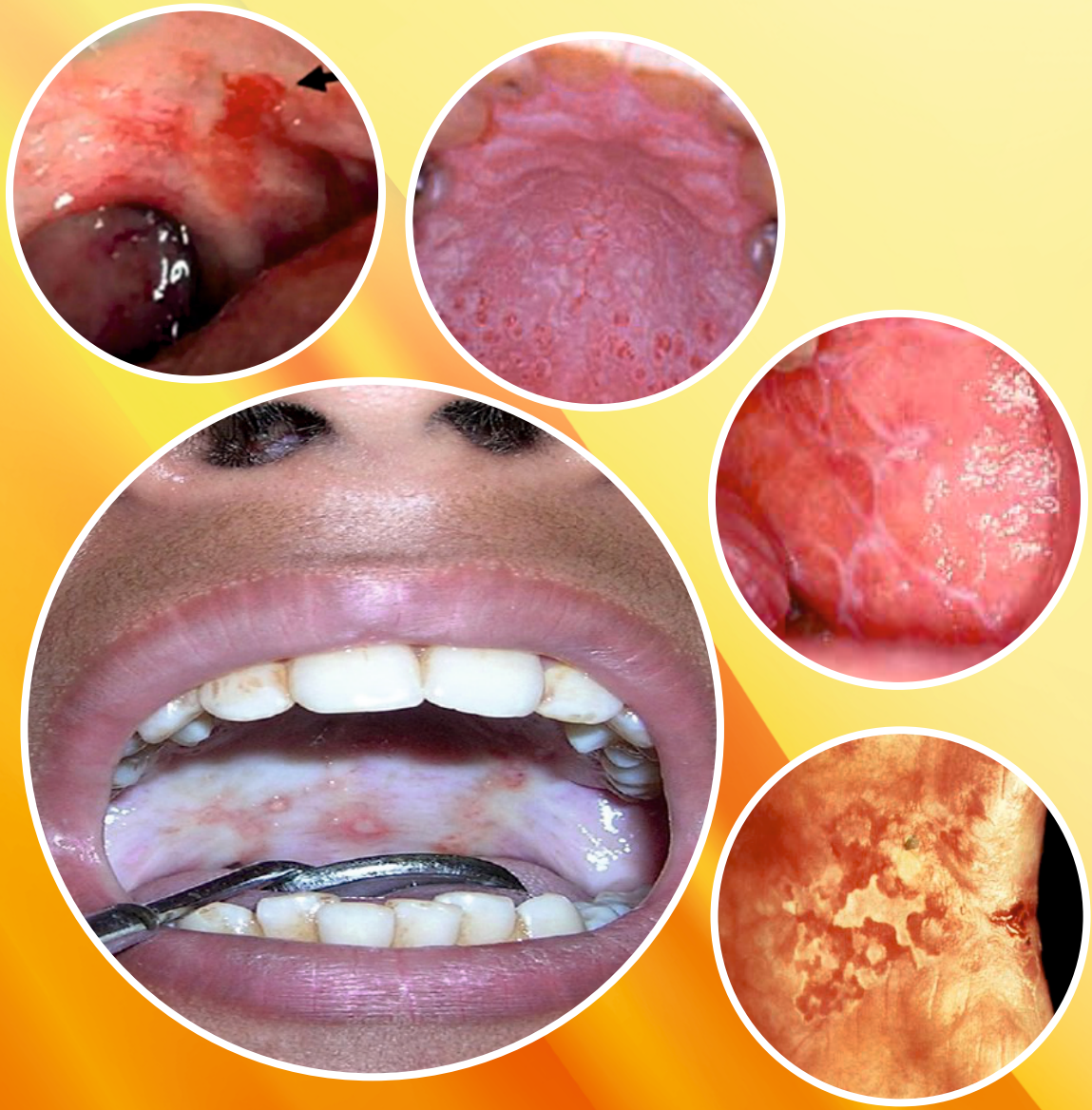
MANUAL OF ORAL CANCERS



STATE INSTITUTE OF HEALTH AND FAMILY WELFARE

UTTAR PRADESH

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FOREWORD

Shri Partha Sarthi Sen Sharma, IAS
Principal Secretary
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Government of Uttar Pradesh

Oral cancer, contributes to substantial morbidity and mortality worldwide, with an estimated 526,481 annual incident cases. As per the Global Burden of Cancer Study 2013, oral cancer ranks second for incident cancer cases among both sexes in India after breast cancer and ranks eighth for deaths occurring as a result of the disease in both sexes.

Seeking cancer treatment in the private sector results in substantial financial burden as the cost of treatment for cancer is high. In public sector, increasing number of oral cancer incidences has put a severe strain on tertiary centres that are providing cancer related treatment and care. Non-medical costs including transportation, accommodation, and other unforeseen expenses add on to this burden.

Above stated facts necessitates the need for specialised training of medical officers in not only treatment of oral cancer but also in early screening and referral to higher centres for treatment. It is evident from several scientific studies that early diagnosis within stages I and II correspond to a vastly improved 5-year survival rate when compared with more advanced stage III and IV lesions and detection of the asymptomatic early stage oral cancer translates in general terms to satisfactory clinical outcome and cure in most patients.

Although surgical management of this disease remains the mainstay of treatment but expose to palliative care and home based care can play an important role in treatment and management of oral cancers.

This module on Continuing Medical Education (CME) on Oral Cancer for Dental Officers & Medical Officers in Provincial Health & Medical Services in Uttar Pradesh, has been developed with the intent to impart latest knowledge regarding screening, identification and treatment of oral cancer so that the Medical Officers might stay abreast of the rapidly evolving practices in cancer care and management and are equipped with the skills to manage and treat cases of oral cancer at the PHCs/CHCs.

I would take this opportunity to congratulate State Institute of Health & Family Welfare (SIHFW), Uttar Pradesh and other subject matter experts in developing such a comprehensive module. I hope this CME module will prove to be an asset in improving our health services.

(Partha Sarthi Sen Sharma)

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MESSAGE

Dr. Brijesh Rathor
Director General
Medical Health and Family Welfare
Uttar Pradesh

Any uncontrolled growth of cells that invade and cause adjacent tissue impairment is known as cancer. Oral cancer ensues with a small, unfamiliar, unexplained growth or sore in the mouthparts that include lips, cheeks, sinuses, tongue, hard and soft palate, and the base of the mouth extended to the oropharynx. Oral cancer ranks sixth among all types of cancer.India has the largest number of oral cancer cases and one-third of the total burden of oral cancer globally. Oral cancer poses a serious health challenge to nations undergoing economic transition.

In line with the focus on oral neoplasia, this manual on oral cancer for Dental Officres & Medical Officres is being introduced. This manual will guide health professionals in preventing the most common dental problems in the community. It informs on simple, easy-to-adopt, preventive practices like proper and regular tooth brushing, a healthy diet, and the development of mouth rinsing habits after every meal.

Health professionals are often the first point of contact for individuals in the community. With the knowledge acquired upon reading this manual, Dental Officers & Medical Officers will be able to detect common oral cancers early, manage them, and make appropriate referrals. From this manual, they will also learn how to train people to examine their oral health and hygiene.

Considering the above-stated facts, the oral cancer training manual, State Institute of Health & Family Welfare, Uttar Pradesh with the help of subject matter experts has provided a comprehensive, coherent, and insightful module for dental officers.

This manual can potentially create a community that is informed and creates awareness about the importance of and need for oral health services. I wish the team of the State Institute of Health & Family Welfare, Uttar Pradesh, and subject matter experts for such a commendable job.

(Dr. Brijesh Rathor)

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MESSAGE

Dr. Shailesh Kumar Srivastava

Director General (Family Welfare)
Medical Health and Family Welfare
Uttar Pradesh

Oral health is a critical but overlooked component of overall health and well-being among children and adults. Oral health problems such as dental caries, periodontitis, and oral cancers are a global health problem in both industrialized and especially in developing countries. Dental disease restricts activities in school, work, and home and often significantly diminishes the quality of life for many children and adults, especially those who are low-income or uninsured. Huge differences exist in health status including oral health between urban and rural populations in India.

The National Oral Health Programme (NOHP) is an initiative launched in 2014-15 with an overarching aim to provide affordable, accessible, and quality oral healthcare.With less awareness about oral health in our country, people very often suffer from dental problems which, once allowed to progress can be quite expensive to treat and manage.

In line with the focus on the prevention of oral diseases, this manual on oral cancer for Dental Officers & Medical Officers is being introduced. Dental Officres & Medical Officres are often the first point of contact for individuals and it will guide theminpreventing the most common dental problems in the community. With the knowledge acquired upon reading this manual, Dental Officres & Medical Officres will be able to detect common dental diseases early, manage them, and make appropriate referrals. From this manual, theywill also learn how to train people to examine their oral health and hygiene.

Considering the above-stated facts, this module on oral cancer training manual for Dental Officers & Medical Officers in Provincial health and medical services in Uttar Pradesh, State Institute of Health & Family Welfare, Uttar Pradesh with the help of subject matter experts has provided a comprehensive, coherent, and insightful module for dental officers.

I wish the best to the faculties of the State Institute of Health & Family Welfare, Uttar Pradesh, and subject matter experts for such a commendable job.

(Dr. Shailesh Kumar Srivastava)

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MESSAGE

Dr. Narendra Agrawal

Director General-Training
Medical, Health and Family Welfare
Uttar Pradesh

This manual on Oral Cancer for Health professionals is being introduced at a time when a state is dealing with a dual disease burden- tackling both communicable and non-communicable diseases. The best long-term strategy for achieving control of these diseases, all the while ensuring optimal utilization of available resources, is to invest in training our human resources and in disease prevention.

Equipped with the information in this manual, a health professional will be empowered with not just the knowledge of most common oral cancer diseases but also the ability to identify and manage them in their communities. The disease information pertains to people of all age groups; from pregnant women to infants, children and adolescents to adults and geriatrics. This manual will go a long way in achieving this strategy for control of common oral cancer diseases.

Taking that into consideration,the State Institute of Health & Family Welfare, Uttar Pradesh with the help of subject matter experts has developed an extensive and up to date module on continuing medical education on oral cancer for Dental Officers & Medical Officers in Provincial Health and Medical Services in Uttar Pradesh that deals with all the underlying nuances and provides a comprehensive, coherent and insightful module for dental officers.

This manual has the potential to create a community that is informed and creates awareness about the importance of and need for oral health services. I wish the team of the State Institute of Health & Family Welfare, Uttar Pradesh, and subject matter experts for such a commendable job.

(Dr. Narendra Agrawal)

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ACKNOWLEDGMENT

Dr. Rajaganapathy R.
I.A.S
Director
State Institute of Health and Family Welfare
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Globally, oral cancer is the sixth most common type of cancer with India contributing to almost one-third of the total burden and the second country having the highest number of oral cancer cases. Oral squamous cell carcinoma (OSCC) dominates all the oral cancer cases with potentially malignant disorders, which is also recognized as a detectable pre-clinical phase of oral cancer.

Tobacco consumption including smokeless tobacco, betel-quid chewing, excessive alcohol consumption, unhygienic oral condition, and sustained viral infections that include the human papillomavirus are some of the risk aspects for the incidence of oral cancer. Lack of knowledge, variations in exposure to the environment, and behavioral risk factors indicate a wide variation in the oral cancer incidences and increase the mortality rate.

Various conventional clinical techniques such as physical and histopathological examination, staining, biopsy, spectroscopic and radiological techniques, etc. are used routinely to detect oral cancer. The diagnosis of cancer in the early stage is a key factor to check further physical, psychological, and financial losses to the patient.

Upon early diagnosis, timely and proper treatment can be initiated that may improve the survival rate up to 90%. With advancements in science and technology, numerous novel techniques are developed that have advantages as compared to the currently practiced conventional diagnostic methodologies.

Taking that into consideration above stated facts, the State Institute of Health & Family Welfare, Uttar Pradesh with the help of subject matter experts has developed an extensive and up to date module on continuing medical education on oral cancer for Dental Officers & Medical Officers in Provincial Health and Medical Services in Uttar Pradesh.

I acknowledge the efforts made by the faculties of State Institute of Health & Family Welfare, Uttar Pradesh and of Dr. (Prof) Ambrish Kaushal, Director- Lakshmi Oral Pathology Lab and Laser Clinic, Lucknow & Member: UPFSL, State Medico-Legal Cell, IAOMP, IDA in developing this enlightening module and congratulate them on a work well done

(Dr. Rajaganapathy R.)

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Chapter 1: Introduction

Dr (Prof) Ambrish Kaushal

Definition of Neoplasia: Robbins and Cotram suggested that ―A neoplasia is a new growth, comprising an abnormal collection of cells the growth of which exceeds and is uncoordinated with that of normal tissue‖.

According to Willis neoplasia is an abnormal mass of tissue the growth of which exceeds and is uncoordinated with that of the normal tissue and persists in the same excessive manner after cessation of the stimuli which evoked the change.

Oral cancer: It includes cancers of the mouth and the back of the throat. Oral cancers develop on the tongue, on the tissue lining the mouth and gums, under the tongue, at the base of the tongue, and the area of the throat at the back of the mouth. It refers to all malignant tumours, including carcinomas arising from the epithelium and sarcomas arising from submucosal regions such as non-epithelial tissues. Carcinomas arise not only from oral mucosa, but also salivary glands and metastatic tumours of other epithelial organs. Malignant lymphoma, nerve-related malignant tumours arising from submucosal regions, are also oral cancer.

Epidemiology of oral cancer

Oral cancer is the sixth most common cancer worldwide, accounting globally for 377,713 new cases and 177,757 deaths in 2020, representing an increase in new cases from 2018. For all regions the incidence of oral cancer for males and females was highest in the central region of India. For males, it was 64.8% and for females it was 37.2% at 70 years of age.

Oral cancer is considered as major problem in Indian subcontinent where it comes under top three types of cancer in the country. Age-adjusted rates of oral cancer in the country is high where 20 per 100,000 persons are suffering from this deadly disease and accounts for over 30% of all cancers. The number of cancer cases in the country has been projected to go up from 14.6 lakhs in 2022 to 15.7 lakhs in 2025 according to ICMR-NCRP. If an age period of 35-70+ years is considered then the probability percentage was found to be 9.94% in males whereas it was 11.6% in females. Taking consideration of these estimates 1 in 10 men and 1 in 8 women in India can expect to develop cancer of any form in their life span after the age of 35 years.

Oral cancer incidence rates are higher for white males than for Hispanic and Black males. However, urbanization, late marriages, late age of pregnancy, obesity, increased alcohol consumption or smoking by females, and sedentary lifestyle have been responsible for increasing the incidence of oral, breast and ovarian cancer in females.

Concept of oral cancer

Oral cancer is a cancer of the upper aerodigestive tract. It includes cancer of the lip, the labial and buccal mucosa, the anterior two thirds of the tongue, the retromolar pad, the floor of the

mouth, the gingiva and the hard palate. It refers to all malignant tumours, including carcinomas arising from the epithelium and sarcomas arising from submucosal regions such as non-epithelial tissues. Carcinomas arise not only from oral mucosa, but also salivary glands and metastatic tumours of other epithelial organs. Malignant lymphoma, nerve-related malignant tumours arising from submucosal regions, are also oral cancer. The oropharynx, nasopharynx and hypopharynx are excluded, as these sites are not easily examined in the dental practice. Sub-sites differ by major risk factor and have variable disease progression.

The curability rate of lip and oral cavity cancers varies depending on stage and specific site. Most patients present with early cancers of the lower lip, whose cure rates reach 90% to 100% through surgery or radiation therapy. Oral potentially malignant disorders (OPMD) often precede squamous cell carcinoma. Early detection of OPMDs can reduce malignant transformation and improve survival rates for oral cancer. Missed opportunities for early diagnosis and treatment, however, result in significant morbidity and mortality worldwide: the five-year survival rate for advanced stage oral and pharyngeal cancer amounts to less than 63%.

Survival rates for oral cancer can be improved through early detection11. It is therefore essential that oral health professionals (OHPs) such as dentists, dental hygienists (DHs), dental therapists (DTs), and oral health therapists (OHTs) understand the importa nce of conducting a thorough oral screening examination for malignant and potentially malignant lesions as part of their routine clinical assessments, even in younger populations considered at lower risk for oral cancer. A recent effectiveness review of oral cancer screening has demonstrated conventional oral examination to be a feasible and satisfactory occasion for opportunistic screening in dental settings, with sensitivity and specificity similar to breast and cervical cancer screening programmes. Several studies have assessed dentists‘ knowledge, attitudes and practices regarding oral cancer. However, few studies include DHs, DTs, and OHTs, meaning that clinical screening practices for oral cancer in the broader dental team remain largely unknown10. FDI World Dental Federation and numerous national dental associations proactively encourage OHPs to incorporate oral mucosal examinations as part of routine assessment.

Etiologic risk factors for oral cancer

Oral cancer is a multifactorial disease. Exposure to one of three broad groups of carcinogenic stimuli, namely, chemical, physical, and viral, is known to induce cancer in genetically and systemically conditioned oral mucosa. Within the oral cavity, it appears that carcinomas are caused predominantly by chemical carcinogens, although evidence implicating viral and physical stimuli in the development of some oral cancers continues to mount. The pathogenesis of oral cancer is equally complex, and exposure to carcinogens does not inevitably result in the development of oral cancer. This is because a number of familial, dietary, hormonal, and sex-related factors are known to modulate neoplastic processes generally. Tobacco and alcohol have emerged as the most important culprits contributing to the etiology of oral cancers. Other factors frequently cited are ultraviolet light, nutritional and dietary factors, precancerous lesions, immunosuppression, genetic, and dental factors.

Diagnosis and management of oral cancer

Early diagnosis of oral cancer has emerged as a priority public health objective whereby oral health professional play leading role. It is presumed that early diagnosis of cancer should lead to less damage from interventional treatment and to a better prognosis. Because most individual are seen more commonly by primary care physicians and general dentists than by specialists, it is imperative for these clinicians to perform screening examinations to identify potential oral and pharyngeal cancers. In addition to the need for improved early detection by clinicians, it is also important that the patient and general public are knowledgeable about the disease. Delays in identification and recognition of suspicious lesions contribute to advanced stage at diagnosis and lower survival statistics.

Patients with invasive oral cancer are best managed by a coordinated, multidisciplinary team of health care professionals, which may include a head and neck surgeon, oral and maxillofacial pathologist, general pathologist, radiation oncologist, neuroradiologist, reconstructive surgeon, medical oncologist, general dentist, oral and maxillofacial surgeon, maxillofacial prosthodontist, dental hygienist, nurse specialist, speech pathologist, nutritionist, and tobacco cessation counsellor. Oropharyngeal cancer may be treated with surgery and/or radiation therapy for early-stage disease. For advanced-stage disease, surgery with adjuvant radiation therapy may be indicated, although recent evidence suggests that the addition of chemotherapy to radiation therapy may provide a survival advantage over radiation therapy alone in this population. It is important to take into account disease status and prevalence of occult disease in the neck when evaluating primary cancers of the lip, oral cavity, and oropharynx (Robbins et al., 2001). Regardless of the treatment modality used, many patients will require consideration of problems related to airway protection, enteral feedings, xerostomia, mucositis, dysphagia, and voice change.

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Chapter 2: Etiology and pathogenesis

Dr (Prof) Ambrish Kaushal

Effect of Oral cancer:

Oral cancer can affect your mouth and your oropharynx. Your oropharynx includes parts of your tongue and the roof of your mouth and the middle part of your throat that‘s visible when your mouth is wide open. Cancer in your oropharynx is called Oropharyngeal cancer. This article focuses on oral cancer in your mouth, or oral cavity.

Causes of Oral cancer

There are numerous risk factors or possible causative agents for oral cancer described. Chemical factors like tobacco and alcohol, biological factors like human papillomavirus (HPV), syphilis, oro-dental factors, dietary deficiencies, chronic candidiasis and viruses have been shown to be significantly associated with Oral Cancer.

Chemical Factors

Tobacco: There are ample evidences suggesting that tobacco in various forms, including smoking, chewing and in betel quid etc., have carcinogenic impact in oral cavity. The commonest form of tobacco use is smoking. The various forms in which tobacco is used as smoke are- cigarettes, cigars, pipe and bidi etc. Hookah or chillum (a clay pipe used to keep the burning tobacco) are other common forms of smoking in some countries of Asia including India. In some part of India like Mizoram, tobacco smoke is dissolved in water (__smoke on the water‘‘) which is another peculiar form of tobacco use.

Tobacco smoke consists of more than 4000 chemical compounds and approximately 60 known carcinogens. Half of these compounds occur naturally in the green tobacco leaf, where the remainder is generated when the tobacco is burned. There are approximately 600 ingredients in cigarettes. When burned, cigarettes create more than 7,000 chemicals. At least 69 of these chemicals are known to cause cancer, and many are toxic.

Many of these chemicals also are found in consumer products, but these products have warning labels—such as rat poison packaging. While the public is warned about the danger of the poisons in these products, there is no such warning for the toxins in tobacco smoke.

Here are a few of the chemicals in tobacco smoke and other places they are found:

- **Acetone**—found in nail polish remover
- **Acetic acid**—an ingredient in hair dye
- **Ammonia**—a common household cleaner
- **Arsenic**—used in rat poison
- **Benzene**—found in rubber cement and gasoline
- **Butane**—used in lighter fluid

- **Cadmium**—active component in battery acid
- **Carbon monoxide**—released in car exhaust fumes
- **Formaldehyde**—embalming fluid
- **Hexamine**—found in barbecue lighter fluid
- **Lead**—used in batteries
- **Naphthalene**—an ingredient in mothballs
- **Methanol**—a main component in rocket fuel
- **Nicotine**—used as an insecticide
- **Tar**—material for paving roads
- **Toluene**—used to manufacture paint

Cigars and pipes are often believed to be a less harmful way to smoke tobacco. However, even when not inhaling, cigar and pipe smokers are at increased risk for cancer of the oral cavity, esophagus, voice box, and lungs. Pipe smokers also are at increased risk for lip cancers in areas where the pipestem rests. In addition, cigars take longer to burn and contain more tobacco than cigarettes, increasing the amount of secondhand smoke exposure.

Spit tobacco, also known as chewing tobacco and snuff, are forms of tobacco that are put between the cheek and gum. Chewing tobacco can be in the form of leaf tobacco (which is packaged in pouches), or plug tobacco (which are packaged in "brick" form). Snuff is a powdered form of tobacco, usually sold in cans. The nicotine is released from the tobacco as the user "chews."

Although chewing tobacco and snuff are considered smokeless tobacco products, harmful chemicals including nicotine are ingested. More than 28 cancer-causing chemicals have been found in smokeless tobacco.

Chewing tobacco and snuff can cause cancer in the cheek, gums, and lips. Just as with a pipe, cancer often occurs where the tobacco is held in the mouth. Cancer caused by smokeless tobacco often begins as leukoplakia, with a whitish patch that develops inside the mouth or throat. Or the cancer may erythroplakia. With this condition, a red, raised patch develops inside the mouth. It's also linked to esophageal and pancreatic cancers.

Alcohol: Numerous studies have suggested alcohol to be a major risk factor for oral cancer. There is a certain degree of controversy whether alcohol alone may have carcinogenic impact. This is due to simultaneous tobacco and alcohol intake of study subjects in various epidemiological studies. Studies have shown that individuals consuming more than 170 g of whisky daily have ten times higher risk of oral cancer than the light drinkers. Alcohol may have additive effect and it has been suggested that it facilitates the entry of carcinogens into the exposed cells, altering the metabolism of oral mucosal cells. However, the current evidences do not suggest that pure ethanol alone is carcinogen for the development of oral cancer.

The following reasons have been put forward to explain the association between alcohol and carcinogenesis:

1. Polymorphisms within the ADH and ALDH enzymes vary the amount of ACH and the time it remains presents. For example, ADH-1C1 allele metabolises alcohol two and a half times faster than the ADH-1C2 allele.
2. ACH disrupts DNA synthesis and repair, binding to protein and interfering with enzymes responsible for DNA repair
3. ACH can also bind to DNA creating DNA adducts that can give rise to mutations (these can also be formed by reactive oxygen species [the metabolism of ethanol can give rise to ROS])
4. Reactive oxygen species can lead to lipid peroxidation products which can form DNA adducts
5. ROS can also give rise to up-regulation of vascular endothelial growth factor (VEGF), a mediator of tumour angiogenesis and metastases
6. ROS mediated increases in metalloproteinases (example MMP2) can give rise to breakdown of the extracellular matrix potentially aiding metastasis. The oral microbial oxygenation of ethanol can create ACH levels at much higher levels in saliva than that seen in blood.
7. Ethanol may act as a solvent for other carcinogens acting upon the oral mucosa especially when pooling in the so called non-keratinising sites of floor of mouth/ventral tongue
8. Both ethanol and ACH alter methyl transfer inducing DNA hypomethylation which might alter the expression of oncogenes and tumour suppressor genes
9. Ethanol can decrease levels of retinoic acid due to increased metabolism by the cytochrome P4502E1 system. Retinoids (vitamin A and its derivatives) induce cellular growth, differentiation and apoptosis and hence can potentially protect against carcinogenesis
10. Excess alcohol interferes with retinoid metabolism
11. There is also the possibility of ethanol induced immunodeficiency, which might impede the host response to inhibiting tumour development
12. Alcohol may give rise to a reduction in folate absorption (which may also occur as a result of malnutrition). Although folic acid is necessary for making DNA and RNA its reduction may be associated with cancer. It is possible that ethanol could dissolve the extracellular lipid layer of the oral mucosa that seeks to protect the epithelium. The permeability of the (thinner) so called 'non-keratinised' sites, for example, ventral tongue where oral cancer is more frequent, is much greater than the (thicker) keratinised oral sites, for example, dorsal tongue.
13. It is also possible that chronic alcohol intake, giving rise to sialosis of the parotid gland, could result in decreased saliva flow and therefore decreased efficiency for clearing carcinogens present in the mouth.

14. Systemic effects include alcohol damage to the liver which is then less able to deal with potentially carcinogenic substances.

Biological Factors

Viruses: Role of oncogenic viruses in human cancer is an emerging area of research. Viruses are capable of hijacking host cellular apparatus and modifying DNA and the chromosomal structures and inducing proliferative changes in the cells. HPV and Herpes simplex virus have been established in recent years as causative agents of oral cancer. HPV has been identified in approximately 23.5% of oral cancer cases. The most commonly detected HPV in head and neck squamous cell carcinoma (HNSCC) is HPV-16, which has been demonstrated in 90–95% of all HPV positive HNSCC cases, followed by HPV-18, HPV-31, and HPV33. The prognostic significance of HPV in pre-cancerous oral lesion is not clear. However, few studies have found improved disease-specific survival and better prognosis for HPV positive oral cancer.

HPV is part of an ancient family of pathogens known to infect epithelial tissues of amphibians, reptiles, birds, and mammals. This group of DNA viruses forms a separate Papovaviridae family, which includes Papillomaviridae and polyomaviruses. HPV can be phylogenetically classified into genera, species, and types. Genera classification includes alpha, beta, gamma, mu, and nu. More than 150 types of HPV are currently known, and approximately 120 types are fully sequenced. The classification of HPV types is based mainly on sequence analyses of the L1 gene, which is the most conserved gene in all known papilloma viruses. HPV types can be differentiated by less than 10% homology in the L1 ORF, subtypes by less than 2% to 10% homology, and variants by less than 2% homology (2% in coding regions and 5% in non-coding regions). Approximately 80% to 90% of similarities in the same species share biological properties such as tissue tropism, disease manifestation, and pathogenicity.

HPV is also classified according to cutaneous or mucosal tropism characteristics. The cutaneous types are associated with skin lesions; HPV 1, 2, and 4 are most prevalent in plantar warts, and HPV 5, 8, 9, 12, 14, 15, 17, 19-25, 36, 46, and 47 are frequently found in epidermodysplasia verruciforme. HPV 5 and 8 are also related to skin carcinomas. In contrast, mucosal types infect the anogenital tract and upper aerodigestive tract and include HNSCC, OPSCC, and oral cancer. Mucosal types can be subdivided into low-risk and high-risk types based on oncogenic potential. The most relevant low-risk types are HPV 6 and 11, and HPV 40, 42, 43, 44, 54, 61, 70, and 72 can be observed in benign genital mucosal lesions. HPV 31, 33, 35, 52, 58, and 67 are known to be moderate to high-risk, and among the high-risk types, HPV 16 and 18 are most common, and type 16 can be found in various cancers such as cervical cancer, OPSCC, and penile carcinoma.

Until recently, approximately 20% of oral cancers and 60% to 80% of OPC were thought to be attributable to HPV infection. The International Agency of Research of Cancer (IARC) declared that there was sufficient evidence to associate a subtype of HPV 16 with oral cancers. Additionally, these HPV-related oral cancers differ from HPV-negative tumors or cancers in their clinical response and overall survival rates. In the oral cavity, 24 types of HPV, 1, 2, 3, 4,

6, 7, 10, 11, 13, 16, 18, 30, 31, 32, 33, 35, 45, 52, 55, 57, 59, 69, 72, and 73, have been associated with benign lesions, and 12 types, 2, 3, 6, 11, 13, 16, 18, 31, 33, 35, 52, and 57, with malignant lesions. A total of 99% of HPV infections in HNSCC are related to high-risk types 16, 18, 31, or 33, with HPV 16 as the most common subtype and HPV 33 accounting for up to 10% of cases.

Epidemiologically, HPV-positive HNSCC occurs more frequently in younger patients (younger than 50 years), which differs from the typical age of HNSCC patients. A direct correlation between HPV-positive patients and sexual behavior has also been shown in HNSCC. High-risk HPV16 is correlated with vaginal or oral sex and frequent sexual encounters without barrier usage. Current changes in sexual practices, including first sexual experience at an earlier age, high number of sexual partners, and high probability of oral sex, may be associated with the increasing prevalence of HPV infection. Clinically, HPV-associated tumors can appear as a strawberry-like exophytic lesion, frequently at the base of the tongue or in the tonsil area. Most show poorly differentiated pathologic findings and cystic changes in the metastatic neck lymph nodes. As described, the transformation of normal oral mucosa in OSCC could be related to precancerous lesions, such as oral leukoplakia (OL), oral erythroplakia (OE), oral lichen planus (OLP), nicotine stomatitis, tobacco pouch keratosis, and oral submucous fibrosis. The role of HPV in malignant transformation of precancerous lesions has not been confirmed, but OL has been reported as the most frequent potentially malignant lesion, OE can be associated with severe epithelial dysplasia combined with carcinoma in situ or invasive carcinoma, the chronic mucocutaneous type of OLP is susceptible to HPV infection, and p16 with INK4a protein is a reliable precancerous marker in smokeless tobacco keratosis.

Gene expression profiles also differ in HPV-positive oral cancers based on evidence from different pathways, such as the p53 and pRb pathways involved in cell cycling, the EGFR pathway, which is an important therapeutical target (especially in breast and lung cancers), the TGFβ pathway, the PI3K-PTEN-AKT pathway, and angiogenesis and hypoxia pathways. The wide variation in HPV prevalence might result from different detection techniques, small sample numbers, epidemiologic characteristics of populations, and sampling techniques. Sampling techniques for HPV include microscopy, ELISA, Southern blot, dot blot, hybrid capture, DNA microarray, and ligase chain reaction for probe amplification. Although a standard procedure has not yet been generally accepted, both polymerase chain reaction and in situ hybridization assays are well validated, and gene expression by DNA microarray has recently gained acceptance as a high throughput method.

HSV-1 or ‘‘oral herpes’’ is commonly associated with sores around the mouth and lip and has been suggested to be a causative agent of oral cancer. Epidemiological studies show that higher level of IgG and IgM antibodies to oral cancer patients compared to control subjects. It has also been reported that oncogenic relationship between HSV-1 and oral squamous cell carcinoma (OSCC). A population-based study showed HSV-1 to enhance development of OSCC in HPV infected patients and individuals with history of cigarette smoking. Risk of oral cavity and pharyngeal cancer is two-fold higher among human immunodeficiency virus (HIV) patients indicating a link between HIV and OSCC. Epstein Barr Virus (EBV), human herpesvirus-8

(HHV-8) and cytomegalovirus have also been reported as risk factors of OSCC in different studies.

Herpes Simplex Virus (HSV) is a common human pathogen found worldwide, and produces a wide variety of diseases. Transmission of virus can result from direct contact with infected secretions from a symptomatic or an asymptomatic host, with infections ranging in severity from subclinical to life threatening conditions. When primary HSV-1 infection is symptomatic, it is most often characterized by infection of the gums, mouth, tongue, lip, face and/or pharynx (Herpetic Gingivostomatitis). Following primary infection HSV establishes life-long latency in nerve cells in the brain or spinal cord and is present for life. Recurrence of lesions thus reflects reactivation of the latent virus, rather than re-infection and manifesting as _cold sores' or _fever blisters' or _ocular herpes' in the form of herpes labialis. The presence of HSV antigens and RNA complementary to HSV- DNA in tumor tissue of oral carcinoma but not from normal mucosa from the same patients is the strongest evidence for an involvement of HSV with oral carcinoma. Evidence has also supported that HSV may act oncogenically by a ―Hit and Run Mutagenic Effect‖ and the oncogenic potential of HSV has been reaffirmed by representing that HSV-1 can act synergistically with tobacco products to produce oral carcinoma. It was found that there is an increased cell-mediated immune response to HSV-1 in patients having oral leukoplakia with epithelial atypia as compared with patients having oral leukoplakia without atypia or control subjects (without any adverse habit).

Oral squamous cell carcinomas (OSCC) usually originate from the non-keratinizing stratified mucosal epithelium and show morphological similarity to squamous cell carcinomas of other body regions, like those of cervix, anus, or bronchi. It is generally agreed that tobacco, betel quid, and alcohol consumption are the major environmental risk factors for developing OSCC. However, some patients develop OSCC without exposure to these risk factors. This element suggests that additional causes, such as genetic predisposition, diet, or oncogenic viruses, may also help cells to override or escape the physiological mechanisms of proliferation control.

Incidence and prevalence of OSCC is significantly higher in subjects exposed to the putative virus than in those not exposed. Evidence of exposure to the putative virus is more common in subjects with the cancer than in those without. Temporarily, the onset of the cancer follows exposure to the putative virus, and a spectrum of signs and symptoms follows such exposure. A measurable host response, such as antibody response and/or a cell-mediated immune response, follows exposure to the putative virus. Experimental reproduction of the cancer follows deliberate exposure of animals or humans to the putative virus but non-exposed control subjects remain disease free. Elimination of the putative virus and/or its vector decreases the incidence of the cancer. Prevention or modification of infection via immunization or drugs reduces the incidence of the cancer and, finally, the whole concept should follow biological and epidemiological reasoning.

Syphilis: The data on causal association between syphilis and oral cancer is weak. There are reports of 19 and 6% serological positivity for syphilis among tongue cancer patients. Syphilis is caused by the spirochete *Treponema pallidum* and may present with a wide variety of

symptoms depending on stage, earning it the title ―Great Imitator‖ amongst clinicians. Importantly, syphilis has several manifestations in the head and neck region, specifically the oral and oropharyngeal cavities, which are frequently misdiagnosed as alternative pathologies, ranging from benign ulcers to head and neck cancer. Otolaryngologists are frequently consulted for suspected carcinoma of the head and neck, especially with rising rates of HPV-associated oropharyngeal squamous cell carcinoma.

Although oral manifestations of syphilis are most likely to be observed during secondary disease, all stages of the disease can give rise to oral lesions. Significant oral lesions such as gumma-associated bony destruction and a possible predisposition to oral squamous cell carcinoma are associated with tertiary disease. Since the prevalence of infective syphilis in heterosexuals has been increasing, there has now been a gradual rise in the number of children born with congenital syphilis. Consequently, the congenital disease gives rise to dental anomalies as well as bone, skin, and neurological anomalies of the face.

PRIMARY SYPHILIS

The mouth, perhaps surprisingly, is rarely the site of primary syphilis, and because of its transient nature, the oral ulceration of primary syphilis often goes unnoticed by the patient or by any unsuspicious clinician. In addition, albeit rarely, the lesions of primary disease may be confused with other pre-existing mucocutaneous disease. A chancre develops within 1 to 3 weeks of acquisition. Primary syphilis is usually the consequence of orogenital or oroanal contact with an infectious lesion. Kissing may, very rarely, cause transmission; indeed, it has been suggested that intrafamilial oral acquisition of syphilis in a child may have occurred via this route, although more usually oral syphilis in a child is indicative of sexual abuse.
Primary syphilis of the mouth manifests as a solitary ulcer usually of the lip or, more rarely, the tongue. The upper lip is more commonly affected than the lower in males, while the opposite occurs in females—probably reflecting the anatomy involved with fellatio and cunninlingus. The pharynx or tonsils may rarely be affected. The ulceration is usually deep, with a red, purple, or brown base and an irregular raised border. There is usually an accompanying cervical lymphadenopathy. The ulceration of primary syphilis may be confused with other solitary ulcerative disorders, most notably traumatic ulceration, squamous cell carcinoma, and non-Hodgkin's lymphoma.

SECONDARY SYPHILIS

The features of secondary syphilis reflect the hematogenous spread of *T. pallidum,* and similarly to its other mucocutaneous features, the oral manifestations of secondary syphilis can be more extensive and/or variable than those of the primary disease. Oral lesions arise in at least 30% of patients with secondary syphilis, although very rarely oral ulceration may be the only manifestation of infection. The 2 principal oral features of secondary syphilis are mucous patches and maculopapular lesions, although nodular lesions may rarely arise.

MACULOPAPULAR LESIONS

- *Macular syphilides*: Macular lesions tend to arise on the hard palate and manifest as flat-to-slightly raised, firm, red lesions.
- *Papularsyphilides*: These are rare. They manifest as red, raised, firm round nodules with a grey center that may ulcerate. The papules usually arise on the buccal mucosa or commissures.
- *Mucous patches*: A variety of descriptions of mucous patches have been reported, but in general these manifest as oval-to-crescenteric erosions or shallow ulcers of about 1 cm diameter, covered by a grey mucoid exudate and with an erythematous border.[16] The patches usually arise bilaterally on the mobile surfaces of the mouth,[18] although the pharynx, gingivae, tonsils, and very rarely the hard palate can be affected.[19] At the commissures, the mucous patches may appear as split papules, while on the distal and lateral aspects of the tongue, they tend to ulcerate or manifest as irregular fissures. The mucous patches may coalesce to give rise to, or arise *de novo* as, serpiginous lesions, sometimes termed snail track ulcers.

ULCERONODULAR DISEASE (LUES MALIGNA)

Ulceronodular disease is an explosive generalized form of secondary syphilis characterized by fever, headache, and myalgia, followed by a papulopustular eruption that rapidly transforms into necrotic, sharply demarcated ulcers with hemorrhagic brown crusts, organized in rupioid layers commonly on the face and scalp. The mucosa is involved in about one third of affected patients. Lues maligna gives rise to crateriform or shallow ulcers on the gingivae, palate or buccal mucosa, with multiple erosions on the hard and soft palates, tongue and lower lip.

NODULAR DISEASE

Rarely, secondary syphilis can manifest as nodules alone. This nodular eruption of syphilis has a predilection for the face, mucous membranes, palms of the hands and soles of the feet. Lesions may occur on the vermillion, mimicking squamous cell carcinoma or keratoacanthoma.

TERTIARY SYPHILIS

Clinical disease arises in about one third of patients with untreated secondary syphilis. The oral complications of tertiary syphilis center upon gumma formation, and much more rarely, syphilitic leukoplakia (and risk of oral squamous cell carcinoma) and neurosyphilis.

GUMMA FORMATION

Gummas tend to arise on the hard palate and tongue, although very rarely they may occur on the soft palate, lower alveolus, and parotid gland. A gumma manifests initially as 1 or more painless swelling. When multiple, they tend to coalesce, giving rise to serpigninous lesions. The swellings eventually develop into areas of ulceration, with areas of breakdown and healing.

There may be eventual bone destruction, palatal perforation, and oro-nasal fistula formation. Rarely, a gumma may erode into blood vessels—eg, the inferior alveolar artery. Gumma manifests radiologically as ill-defined radiolucencies that may resemble malignancy. The areas of ulceration eventually heal, although the resultant scarring can, at least on the tongue, cause fissuring.

SYPHILITIC LEUKOPLAKIA AND RISK OF SQUAMOUS CELL CARCINOMA

Syphilitic leukoplakia would appear to be a homogenous white patch affecting large areas of the dorsum of the tongue. There are few good descriptions of syphilitic leukoplakia, and it is unclear whether this lesion truly reflects syphilis, or more likely a tobacco smoking habit—indeed this was observed by Hutchinson in the 19th century.

An association between tertiary syphilis and oral squamous cell carcinoma—particularly of the tongue—has been suggested for many years. Both clinically- and serologically-based studies have suggested an increased prevalence of syphilis in patient groups with squamous cell carcinoma of the tongue (up to 60% in one study), the association being stronger in males than females. However, it remains unclear whether any risk of oral squamous cell carcinoma in syphilis is a direct consequence of infection (which seems unlikely) or is the effect of recognized causative factors for oral malignancy, i.e., tobacco, alcohol, and malnourishment.

Candida: Candida has been suggested to play a role in initiation of oral cancer. Clinical studies have reported that nodular leukoplakia infected with Candida has a tendency for higher rate of dysplasia and malignant transformation. It has also been shown that epithelium of the chick embryo, when infected with Candida albicans show squamous metaplasia and higher proliferative phenotype. The causal association of Candida infection and oral cancer is still controversial and demands further proof.

The presence of Candida albicans (as the normal flora) is able to contribute to the development of oral cancer. Among the other species of Candida, Candida albicans has the highest prevalence found in OSCC and always gained concerns in relation to the ability of pathogenic state shifting from the commensal condition. Its commensal condition can develop into an opportunistic pathogen linked explicitly with the initiation of oral neoplasia and the development of OSCC. It has also been reported that Candida invasion is a significant risk factor for the malignant transformation of oral potentially malignant disorder (OPMD) to oral cancer.

In general, the role of Candida albicans in the process of carcinogenesis tends to be complex, such as the role of virulence factors, the host genome, influence on the immune response, and oral dysbiosis. In general, there are seven virulence factors of Candida albicans, mainly phenotype (Candida frequencies, hyphae, sphere, colonies, biofilm formation), genotype (Candida albicans alcohol dehydrogenase 1 (CaADH1) mRNA gene, genotypic diversity of Candida albicans strains, CSH), and metabolic production (acetaldehyde product, lipase, proteinase product, phospholipase, and esterase activity, NMBA production).

Increased colonization of Candida albicans is one of the strong associations with oral epithelial dysplasia and neoplastic transformation leading to the OSCC process. The number of colonies and excessive density of Candida albicans can damage host cells and promote the development of carcinogenesis.

Candida albicans can also affect the progression from OPMD to OSCC. Isolates from the oral leukoplakia group produced significantly higher levels of acetaldehyde than isolates from oral lichen planus when exposed to glucose–ethanol or glucose alone. Another study also confirmed that the leukoplakia with Candida albicans (or Candidal leukoplakia) has a high rate of cancer transformation because it highly expressed a fibroblast activation protein (FAP) and α-smooth muscle actin (α-SMA).

Factors affecting the ability of Candida albicans to accelerate the development of oral carcinogenesis also include virulence factors, protein-degrading ability, and lipolytic activity. The persistence of Candida also depends on the capacity to secrete hydrolytic exoenzymes that facilitate further tissue invasion. It has been shown statistically that Candida albicans proteinase, phospholipase, and lipase activity were higher in oral cancer patients.

Dental Hygiene and Related Factors: There is inverse association between oral hygiene and incidence of oral cancer. Poor oral hygiene and prolonged irritation from sharp teeth have been viewed for their possible role in the development of oral cancer. Poor oral hygiene and dental sepsis is thought to promote carcinogenic action of tobacco. There are several scattered reports on the role of oro-dental factors in the causation of oral cancer, but the hypothesis still lacks major evidence.

Nutritional Factors: Dietary deficiencies are also suggested to play a role in the development of oral cancer. This, however, requires more clinical and experimental evidence for establishment of causal association with the development of oral cancer. Some workers have reported lower risk of oral cancer with higher intake of fruits and vegetables.

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Chapter 3: Oral Precancerous Lesions

Dr (Prof) Ambrish Kaushal

Precancerous lesions of oral mucosa, known as potentially malignant disorders in recent years, are consists of a group of diseases, which should be diagnosed in the early stage. The most common oral precancerous lesions are oral leukoplakia, oral submucous fibrosis (OSMF), and oral erythroplakia. Actinic cheilitis, some miscellaneous inherited diseases such as xeroderma pigmentosum and Fanconi's anemia, and immunodeficiency are another potentially malignant disorders for oral carcinoma as well as these three diseases.

Early detection of premalignant lesions and oral cancer is very important. Therefore, miscellaneous modalities such as oral cavity examination, supravital staining, oral cytology and optical technologies including spectroscopy, fluorescence spectroscopy, elastic scattering (reflectance) spectroscopy, Raman spectroscopy, fluorescence imaging, optical coherence tomography, narrow-band imaging, and multimodal optical imaging may be used. It is thought that the following criteria should be taken into consideration in terms of the importance of early diagnosis: (1) symptomatic and/or non-symptomatic nonhealing lesions of oral mucosa; (2) history of smoking, chewing tobacco, alcohol consumption, oral HPV infection, drug use, long-term exposure to sunlight; (3) advanced age; (4) the presence of immunodeficiency; (5) the presence of genetic disease; and (6) poor oral hygiene.

Oral Leukoplakia

Leukoplakia is defined as ―A white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer‖. Clinically, leukoplakia may affect any part of the oral and oropharyngeal cavity and can be divided into two subtypes including homogeneous and non-homogeneous types. Homogenous lesions are characterized by uniformly flat, thin, uniformly white in colour and shows shallow cracks of the surface keratin. Nonhomogenous lesions have been defined as a white and red lesion (known as erythroleukoplakia) that may be either irregularly flat (speckled) or nodular (Figure 1). Verrucous leukoplakia is yet another type of non-homogenous leukoplakia.

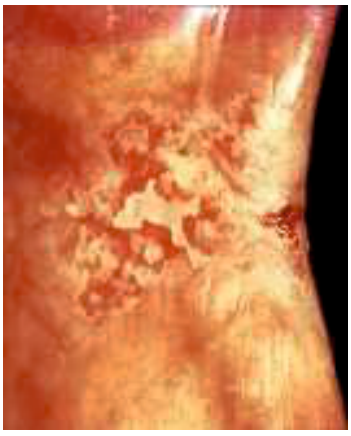

Figure 1: Erythroleukoplakia

Proliferative verrucous leukoplakia, which is a form of verrucous leukoplakia, was first described by Hansen et al in 1985 and characterized by multifocal presentation. It has a strong potential for malignant transformation and is resistance to treatment. Oral leukoplakia should be distinguished from miscellaneous benign and/or potentially malignant disorders that may be seen white or predominantly white diseases of the oral mucosa. The diseases should be considered in the differential diagnosis including aspirin burn, chemical injury, oral pseudomembranous and hyperplastic candidiasis, frictional lesions, oral hairy leukoplakia, leukoedema, linea alba, lupus erythematosus, morsicatiobuccarum, papilloma and allied lesions, mucous patches in secondary syphilis, tobacco-induced lesions, smoker‘s palate (nicotinic stomatitis), stuff-induced lesion, white sponge nevus, oral lichen planus (OLP), and lichenoid reaction.

Oral Erythroplakia

Erythroplakia is defined as ―A fiery red patch that cannot be characterized clinically or pathologically as any other definable disease‖ (Figure 2). Clinical appearance is characterized by flat or even depressed erythematous change of the mucosa without a patch lesion. Both red and white changes in the same lesion refer to as ―erythroleukoplakia‖. It mainly occurs in the middle aged and the elderly. Male gender is most frequently affected. Mostly, a solitary lesion occurs over the surface of any part of the oral cavity. But the most commonly affected areas were reported as the soft palate, the floor of the mouth, and the buccal mucosa.

Clinically, typical lesion of oral erythroplakia is less than 1.5 cm in diameter, but it also be less than 1 cm and larger than 4 cm. Histopathologically, moderate or severe dysplasia was usually seen in lesion with erythroplakia. Malignant transformation rates is very high (vary from 14% to 50%), so it needs to be treated expeditiously. Oral erythroplakia should be diminished from any disease which clinically appears red colour in oral cavity. Oral candidiasis, oral histoplasmosis, oral tuberculosis, atrophic OLP, lupus erythematosus, pemphigus, pemphigoids, amelanotic melanoma, haemangioma, telangiectasia, lingual varies, Kaposi‘s sarcoma, early squamous cell carcinoma, local irritation, mucositis, drug reaction, median rhomboid glossitis, and oral purpura may be confused with oral erythroplakia.

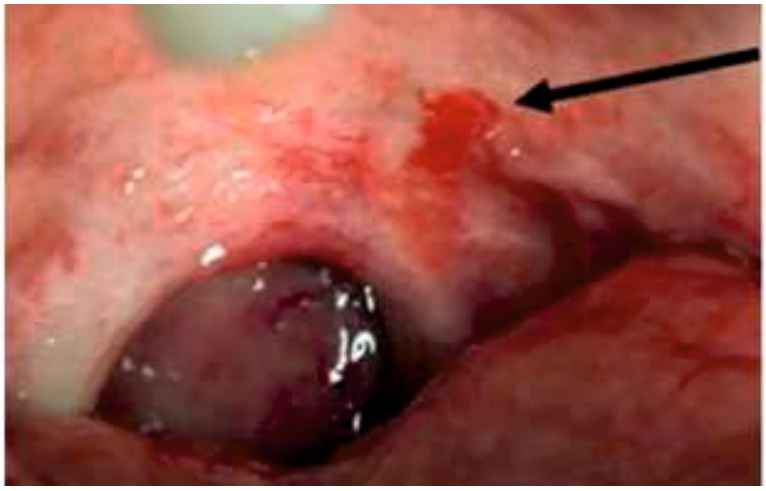

Figure 2: Erythroplakia

Oral Lichen Planus

Lichen planus (LP) is a prevalent inflammatory much cutaneous disease affecting 5% of the population worldwide. The pathogenesis is not well understood but is essentially an autoimmune response to the epidermal basal cell layer mediated by cytotoxic T cells. Characteristically, T cells are seen to infltrate into the lamina propria on microscopy and the damaged basal keratinocytes degrade into apoptotic residues known as civatte bodies (not pathognomonic for LP). Aetiology is unknown, but it is well recognised that appearances of lichen plans can result from a hypersensitivity reaction to nonsteroidal anti-inflammatory, angiotensin-converting enzyme inhibitors and dental amalgam. These reactions are more commonly referred to as lichenoid mucositis. In rare instances, the disease associates with viral hepatitis (B and C), but in most patients LP, there is no triggering factor. Stress is thought to be a contributing factor.

Commonly, oral lichen planus (OLP) presents as reticular white patterns on the buccal mucosa or the tongue known as Wickham‘s striae (Figure 3). Many varieties and presentations are recognised such as desquamative gingivitis, plaque form and an unusual form that presents with vesicular bullae. An erosive form is also recognised giving the appearance of the highrisk erythroplakia and mixed red and white lesions. Some authors use the term erosive OLP to refer to the ulcerated type of lesion and erythematous OLP as the commoner type which affects atrophied buccal mucosa (usually seen with reticular lesions). Distribution is usually symmetrical, a feature it shares with discoid lupus.

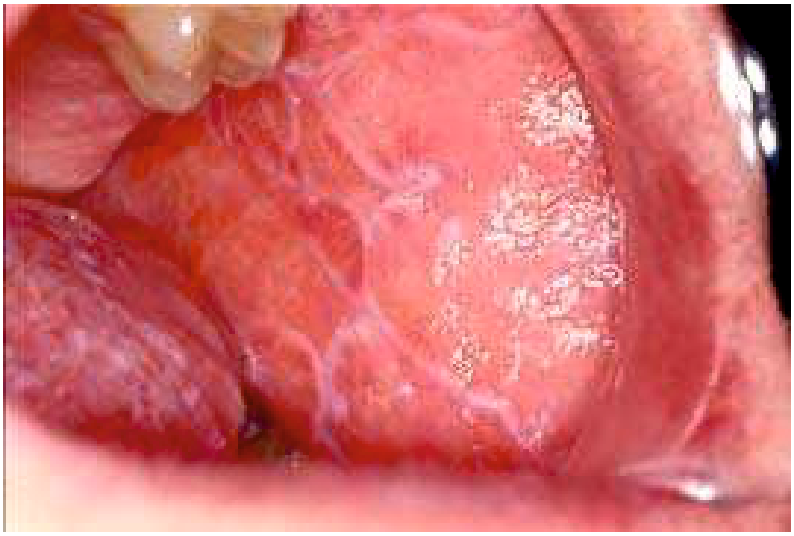

Figure 3: Oral lichen Planus

The highest risk subsites were predominantly the tongue (51%) and the buccal mucosa (32%). Malignant transformation was three times as likely in females as it was in men. It is proposed that changes at lower-power magnification of oral leukoplakia resemble lichen planus or that lichenoid changes in epithelial dysplasia are common. Clinically, there is overlap between the clinical appearance of the various types of OLP and between erythroleukoplakia and verrucous leukoplakia. A diagnosis of OLP is more likely in symmetric lesions, but only a biopsy

demonstrating epithelial dysplasia would confirm truly high-risk lesions. Correlation between malignant change and certain subtypes of OLP, namely, the erosive and plaque-like forms, has not been consistent.

Oral Submucous Fibrosis (OSMF)

Oral submucous fibrosis is progressive scarring disorder linked to the use of betel products (paan) (Figure 4). Additional risk for oral squamous cell carcinoma is conferred by the addition of slaked lime to the betel quid or concurrent use of tobacco. The active ingredients in paan include arecoline, copper and polyphenol fragments (flavanols, tannins) which stimulate an intense acute inflammatory response characterised by a polymorphic infiltrate and vascular dilatation. This gives way to a chronic immune response and constrictive vascular changes that end with obliteration of blood vessels in the affected region. Over time, this leads to an epithelial to mesenchymal transition mediated by TGF-β. Fibroblasts are activated, and collagen is deposited steadily replacing the submucous tissues with hyalinised cartilage almost devoid of cellular components. Several genes are known to associate with the risk of developing submucous fibrosis including MMP3 gene promoter region and CYP1A1/CYP2E1 genes, but the genetic basis for transformation into squamous cell carcinoma is not currently defined.

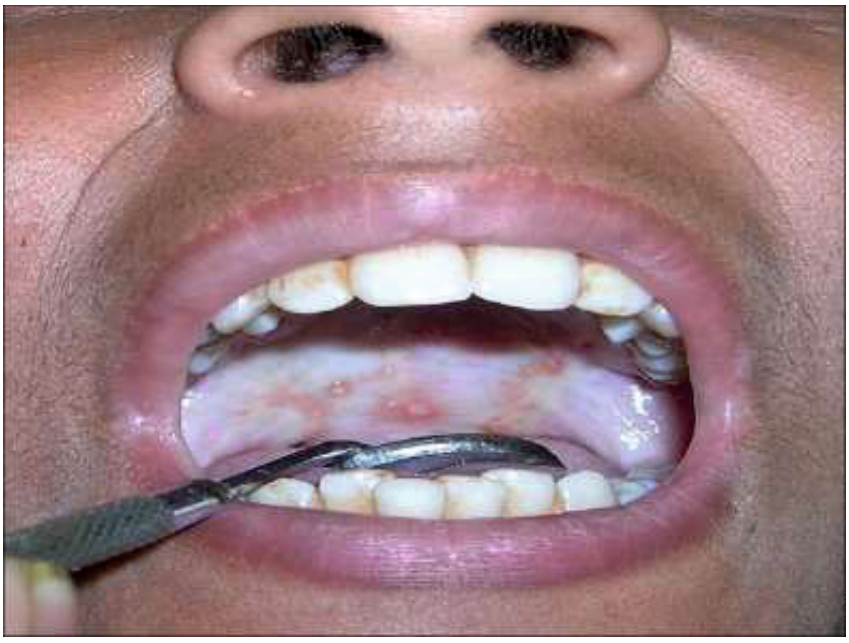

Figure 4: Oral Submucous Fibrosis showing restricted mouth opening

Consumption of paan is common in Southeast Asia and the Western Pacific but is now also seen in Europe and North America. It is estimated that more than half a billion persons consume betel worldwide. Early presentation reflects the early histological picture with non-specific inflammatory mucosal changes. The diagnosis becomes clearer when early changes are replaced by the characteristic hypo-vascular blanched appearance with a fibrous texture although these changes may be patchy or reticular causing potential confusion with unrelated mucosal changes (e.g. lichen planus). In general, submucous fibrosis tends to present in young adults

(predominantly males) with worsening trismus (37.2% of patients), painful dysesthesia (25.9%), excess salivation (22.5% of patients) and recurrent ulceration. Clinical findings on examination are white patches particularly in the buccal mucosa (20.8%) and the palate (17.7%) followed by the floor of mouth and the retromolar trigone. Clinical signs develop within 3–5 years following commencement of chewing betel preparations. Patients are 19 times as likely to develop oral cancer particularly with betel quid containing tobacco. Malignant transformation rates are reportedly 4–13%.

Conservative and medical measures are considered for the early clinical stages. This includes physiotherapy, immune modulators steroids and promoters of blood flow such as pentoxifylline. Many other medical treatments are reported but none with definitive clinical benefit.

Nicotine Stomatitis

Nicotine stomatitis is a thickened, hyperkeratotic alteration of the palatal mucosa that is most frequently related to pipe smoking (Figure 5). The palatal mucosa becomes thickened and hyperkeratotic, sometimes developing a fissured surface. The surface often develops papular elevations with red centres, which represent the inflamed openings of the minor salivary gland ducts. The term nicotine stomatitis is actually a misnomer because it isn‘t the nicotine that causes the changes; the changes are caused by the intense heat generated from the smoking. Nicotine stomatitis is seen more often in pipe smokers because of the great amount of heat that is generated from the pipestem. Although nicotine stomatitis is a tobacco related it is not considered to be premalignant and it is readily reversible with discontinuation of the tobacco habit.

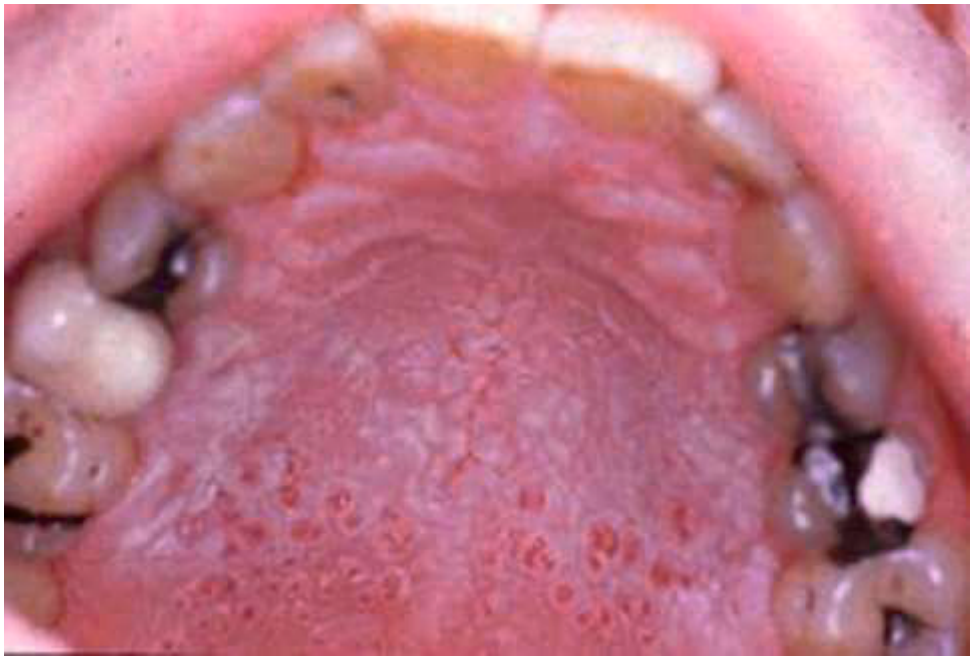

Figure 5: Nicotine stomatitis

Palatal lesion in reverse smokers

In some Southeast Asian and South American countries, individuals practice a habit known as reverse smoking in which the lit end of the cigarette or cigar is placed in the mouth. This habit creates a more severe heat related alteration of the palatal mucosa known as reverse smoker‘s palate, which has been associated with a significant risk of malignant transformation (Figure 6).

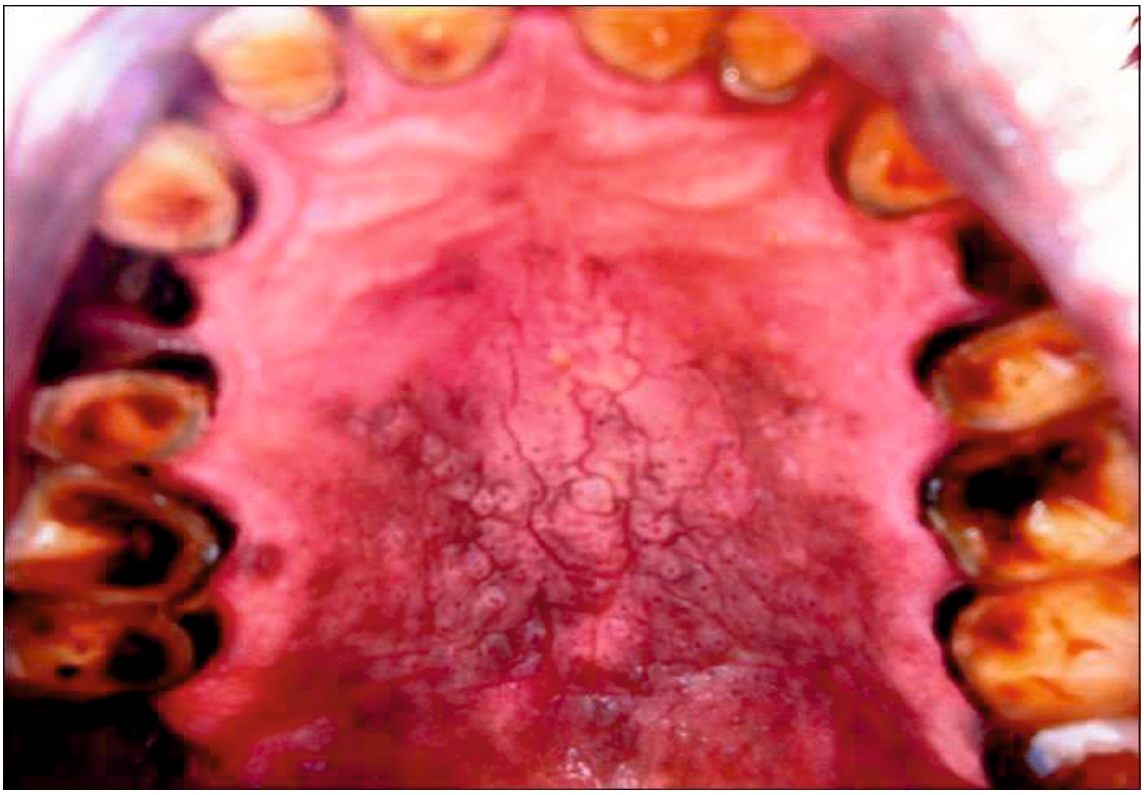

Figure 6: Palatal lesion with reverse smoking

Actinic keratosis

Actinic keratosis is considered to represent a potentially malignant condition which arises in many sites including lips (Figure 7). It is commonly associated with exposure to sun. In Actinic keratosis average rate of progression to invasive cancer ranges from 0.025 to 16% per year.32 A provisional diagnosis may be made on clinical grounds, but definitive diagnosis requires biopsy.

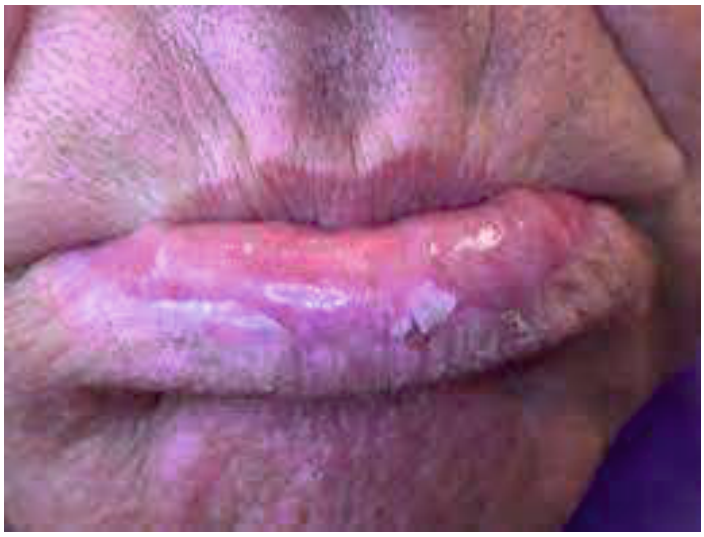

Figure 7: Actinic keratosis of the lip

Tobacco pouch keratosis

Another specific tobacco-related oral mucosal alteration occurs in association with smokeless tobacco use, either from snuff or chewing tobacco (Figure 8). Such lesions typically occur in the buccal or labial vestibule where the tobacco is held, but they can also extend onto the adjacent gingiva and buccal mucosa. Early lesions may show slight wrinkling that disappears when the tissues are stretched. Other lesions may appear as hyperkeratotic, granular patches. Advanced lesions exhibit greatly thickened zones of greyish white mucosa with well-developed folds and fissures. Overall, it is estimated that 15 percent of chewing tobacco users and 60 percent of snuff users will develop clinical lesions. Microscopically, smokeless tobacco keratoses show hyperkeratosis and acanthosis of the mucosal epithelium. True epithelial dysplasia is uncommon; when dysplasia is found, it is usually mild in degree. However, significant dysplasia or squamous cell carcinoma occasionally may be discovered. Most tobacco pouch keratoses are readily reversible within two to six weeks after cessation of the tobacco habit.

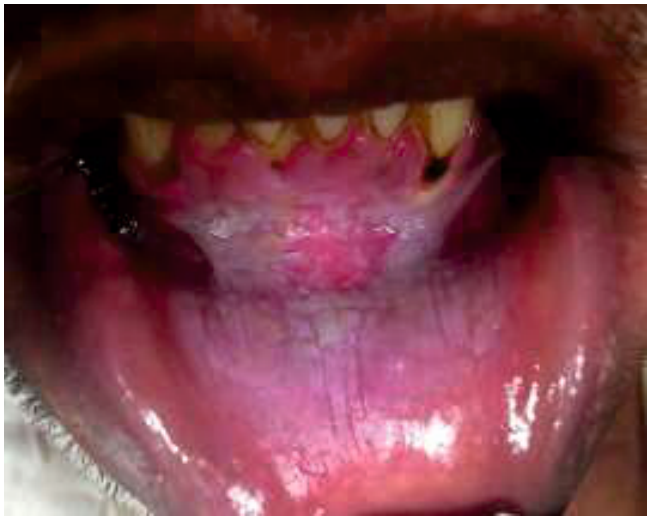

Figure 8: Tobacco pouch keratosis of the lower lip and gingiva

Hereditary disorders

Two conditions that may have an increased risk of malignancy in the mouth are dyskeratosis congenital (DC) (Figure 9) and Epidermolysis Bullosa Figure 10). They are rare hereditary conditions. Most cases of DC are X-linked and affect males. Patients with DC often develop white plaques on the dorsal tongue which may be confused with leukoplakia, but the absence of habits and their young age may point to the hereditary nature of this disorder. Malignant change within the areas of white patches is reported.

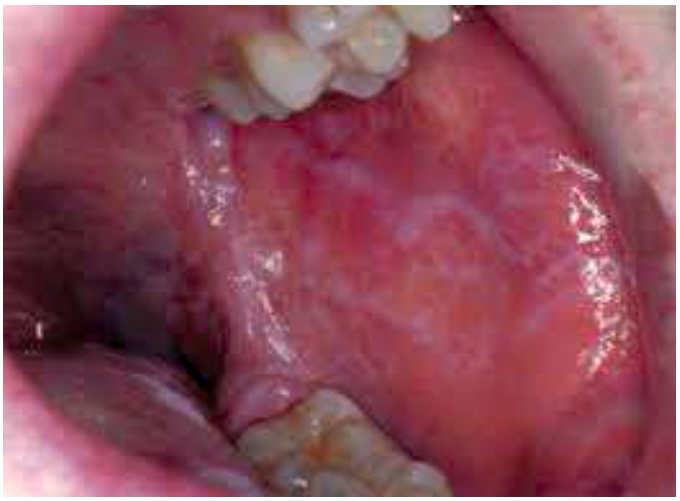

Figure 9: Dyskeratosis congenita

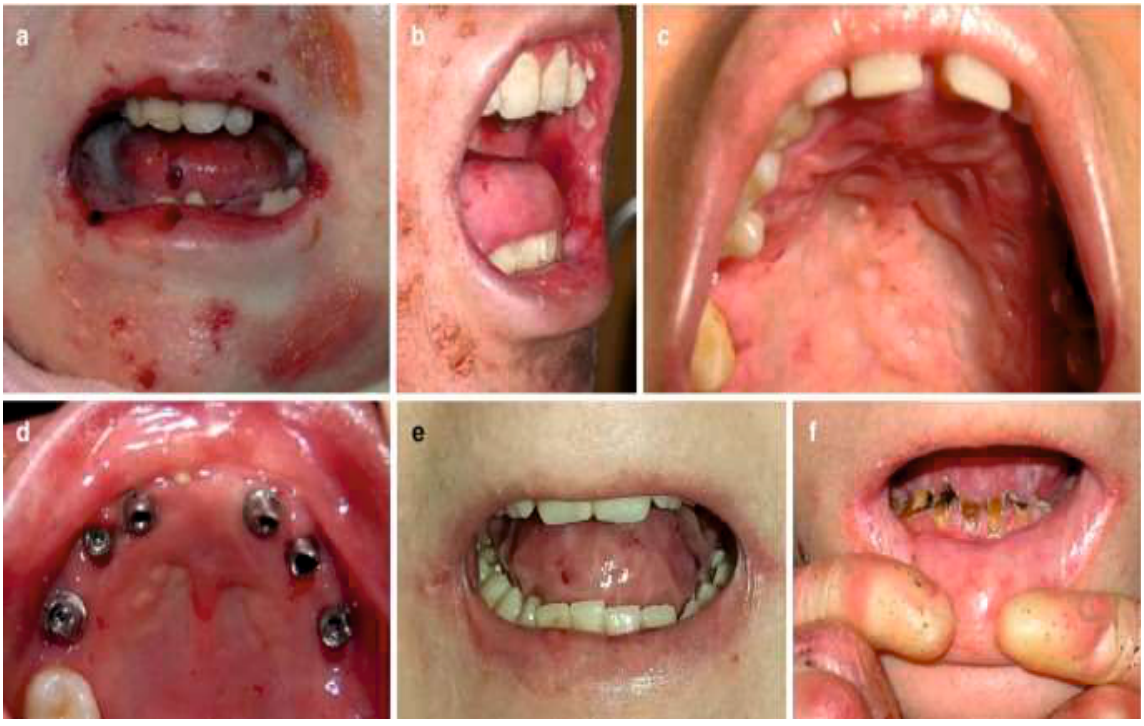

Figure 10: Epidermolysis bullosa of oral cavity

Recent advances in detection of oral precancerous lesions

Vital tissue staining with Tolonium chloride (TB). It is a metachromatic vital dye that may bind preferentially to tissues undergoing rapid cell division (such as inflammatory, regenerative and neoplastic tissue), to sites of DNA change associated with oral PMD or both. The binding results in the staining of abnormal tissue in contrast to adjacent normal mucosa. A meta-analysis summarized 12 studies conducted between 1964 and 1984 and reported an overall sensitivity of 93.5 percent and specificity of 73.3 percent.

Visualization adjuncts. They function under the assumption that mucosal tissues undergoing abnormal metabolic or structural changes have different absorbance and reflectance profiles when exposed to various forms of light or energy.

Described as a chemiluminescent light detection system, ViziLite was developed from predicate devices to detect cervical neoplasia. After receiving an application of acetic acid, sites of epithelial proliferation, having cells with altered nuclear structure, are purported to preferentially reflect the low energy blue-white light emitted by a device generating an ―acetowhite‖ change. The ViziLite system is a part of the ViziLite Plus with Tolonium chloride system.

The Microlux DL system is a multiuse system developed from a blue-white light-emitting diode (LED) and a diffused fiberoptic light guide that generates a low-energy blue light. The Orascoptic DK system is sold as a three-in-one, battery-operated, hand-held LED instrument with an oral lesion screening instrument attachment that is used in concert with a mild acetic acid rinse promoted to improve visualization of oral lesions. The VELscope system is a multiuse device with a handheld scope through which the clinician can scan the mucosa visually for changes in tissue fluorescence. The proposed mechanism of tissue fluorescence is that mucosal tissues have a reflective and absorptive pattern based on naturally occurring fluorophores in the tissue.

Cytopathology. The oral CDx Brush test system uses a specialized brush that collects transepithelial cellular samples composed of free cells and clusters. These samples are fixed onto a glass slide and sent to a laboratory where they are stained (via a modified Papanicolaou test), scanned and analyzed microscopically by means of a computer-based imaging system that can rank cells on the basis of degree of abnormal morphology. A cytopathologist interprets the computerized results. Results are reported as ―negative or benign,‖ ―positive‖ or ―atypical. Oral CDx has been shown to be very accurate All Oral CDx ―atypical‖ and ―positive‖ results should be referred for scalpel biopsy and histology to completely characterize the lesion.

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Chapter 4: Malignant Lesions of Oral Cavity

Dr (Prof) Ambrish Kaushal

Oral Squamous cell Carcinoma:

Introduction: Oral squamous cell carcinoma (OSCC) is the most common oral malignancy, representing up to 80–90% of all malignant neoplasms of the oral cavity. Although oral cancer incidence is highly variable worldwide, it is accepted that oral cavity ranges from the 6th to the 9th most common anatomical location for cancer, depending mostly on the country (and even specific region in some countries) and gender of the patients. Despite this mean incidence, it can represent the most common location for cancer in some specific regions, especially in southeastern Asia. Major etiological and predisposing factors for OSCC include mostly smoking and drinking habits, and ultraviolet radiation (specifically for lip cancer), but several other factors such as human papillomavirus (HPV) and Candida infections, nutritional deficiencies and genetic predisposition have been also associated. OSCC is a disease of adults and elderly and its most common clinical aspect is an ulcerated lesion with necrotic central area surrounded by elevated rolled borders.

Clinical features:

Oral lesions are asymptomatic initially, highlighting the need for oral screening. Most dental professionals carefully examine the oral cavity and oropharynx during routine care and may do a brush biopsy of abnormal areas. The lesions may appear as areas of erythroplakia or leukoplakia and may be exophytic or ulcerated (Figure 1). Cancers are often indurated and firm with a rolled border. As the lesions increase in size, pain, dysarthria, and dysphagia may result.One of the real dangers of this neoplasm, is that in its early stages, it can go unnoticed. Usually at the initial stages it is painless but may develop a burning sensation or pain when it is advanced. Common sites for OSCC to develop are on the tongue, lips and floor of the mouth. Some OSCCs arise in apparently normal mucosa, but others are preceded by clinically obvious premalignant lesions, especially erythroplakia and leukoplakia. Usually, OSCC presents as an ulcer with fissuring or raised exophytic margins. It may also present as a lump, as a red lesion (erythroplakia), as a white or mixed white and red lesion, as a non-healing extraction socket or as a cervical lymph node enlargement, characterized by hardness or fixation. OSCC should be considered where any of these features persist for more than two weeks.

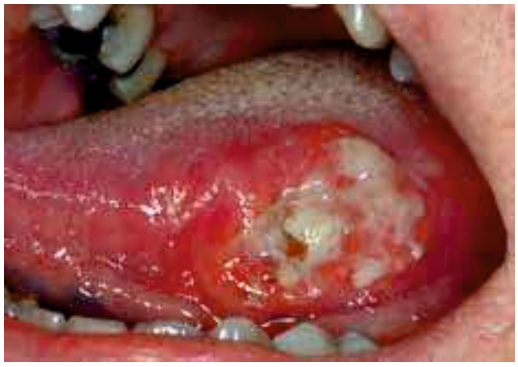

Figure 1: oral Squamous Cell Carcinoma

Field cancerization is a theory of oral carcinogenesis. According to this theory since the oral epithelium is exposed to carcinogenic factors, the entire area is at increased risk for the development of malignant lesions from the accumulation of genetic alterations of oncogenes and tumour suppressor genes. In cancerization field, multiple oral cancers may develop from independent cell clones. This hypothesis has been supported by data from chromosome X inactivation studies, microsatellite analysis, and p53 mutational analysis. However, more recent genetic studies suggested that multiple cancers can be clonally related and derived from expansion of an original clone. These results gave rise to a modification of cancerization field theory, the patch field carcinoma model. According to this model, a stem cell located in the oral epithelium acquires a genetic alteration and generates daughter cells, all of which share the genetic alteration. This patch of cells expands to a size of several centimetres to the surrounding oral mucosa and macroscopically is often undetectable. In some instances, it may appear with distinct morphological characteristics, like leukoplakia or erythroplakia.

Staging of OSCC: TNM staging

TNM staging of OSCC

Primary tumour size (T-status)	
T1	Tumour < 2 cm in greatest dimension.
T2	Tumour more than 2 cm - 4 cm in greatest dimension.
T3	Tumour > 4 cm in greatest dimension.
T4	Tumour invades adjacent structures.
Lymph node metastasis (N-status)	
N0	No regional lymph node metastasis.
N1	Metastasis in a single ipsilateral lymph node. < 3 cm in greatest dimension.
N2a	Metastasis in a single ipsilateral lymph node. 3 – 6 cm in greatest dimension.
N2b	Metastasis in multiple ipsilateral lymph nodes. < 6 cm in greatest dimension.
N2c	Metastasis to bilateral lymph nodes. < 6 cm in greatest dimension.
N3	Metastasis in a lymph node > 6 cm in greatest dimension.
Distant metastasis (M-status)	
M0	No distant metastasis
M1	Distant metastasis
Stage grouping	
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0 or T1/T2/T3 N1 M0
Stage IV	Any T4 lesion. Any N2 or N3. Any M1.

Verrucous carcinoma:

Verrucous carcinoma is a low-grade variant of squamous cell carcinoma (SCC) with specific morphologic, cytokinetic and clinical features. It is a locally aggressive tumour and does not metastasize to regional lymph nodes or to distant sites. Verrucous carcinoma most often arises on mucous membranes of the head and neck region with the oral cavity most commonly involved, particularly buccal mucosa, gum and tongue. Oral verrucous carcinoma accounts for 0.57-16.08% of oral squamous cell carcinoma (SCC) and is predominantly seen in males with the reported mean age at diagnosis between 49 and 69.5 years. Other reported locations in the head and neck region affected by verrucous carcinoma are nasal cavity, paranasal sinuses, nasopharynx, oesophagus and temporal bone.12-14 Verrucous carcinoma on the skin and mucosa of the anogenital region and extremities are described in the literature as well.

Clinical features:

Verrucous carcinoma is characterized by low mitotic activity reflecting in slow growth; hence it can take several years to reach the size that causes symptoms. Patients may report oral discomfort, difficulty chewing or swallowing, and bad breath. Pain usually indicates tumour invasion into the surrounding structures. Oral verrucous carcinoma typically appears as an exophytic broad-based lesion with a cauliflower-like warty surface (Figure 2). Despite its slow growth, it can reach a significant size and infiltrate adjacent tissues such as muscles and bone. However, even when locally advanced, oral verrucous carcinoma has no tendency to metastasize to regional lymph nodes and distant sites. Cervical lymphadenopathy is commonly seen at initial clinical or radiological examination and is mostly considered reactive secondary to inflammation at the tumour-stromal interface.

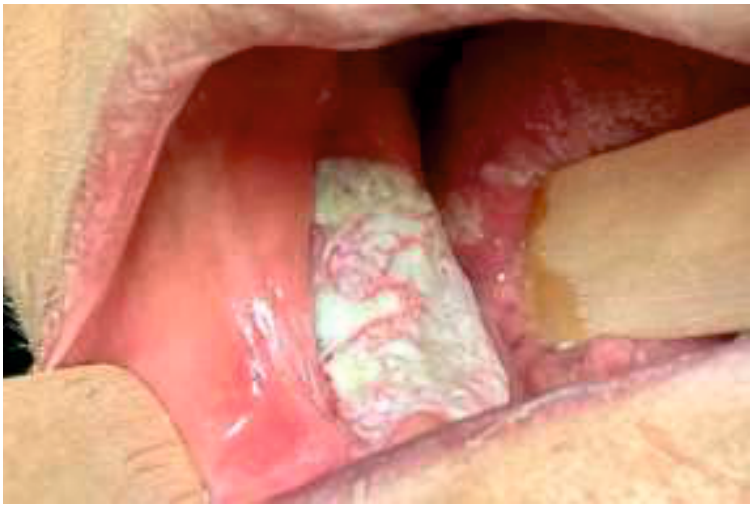

Figure 2: Verrucous Carcinoma

Various mucosal abnormalities including verrucous hyperplasia and dysplasia are frequently found adjacent to the oral verrucous carcinoma supporting the view that verrucous carcinoma develops from precursor lesions. Patients with oral verrucous carcinoma are also at high risk of developing metachronous second primary tumours. This can be explained with the concept of field cancerization which postulates that prolonged exposure of the upper aerodigestive tract to

carcinogens leads to genomic instability even beyond the area of clinically and histopathologically evident mucosal changes.

Basal Cell Carcinoma:

Basal cell carcinoma (BCC) is the most common cutaneous cancer. It accounts for approximately 80% of all cutaneous cancers, and the incidence is increasing all over the world as a result of ultraviolet irradiation, as well as the ageing of the population. Despite the high incidence, metastasis is rare (approximately 0.0028–0.55% of cases). Metastasis that does occur is common in the regional lymph nodes, lungs and bone. BCC in the oral cavity, known as intraoral BCC, is extremely rare; the pathohistological findings are similar to those of basaloid squamous cell carcinoma (basaloid SCC), peripheral ameloblastoma and unique odontogenic neoplasms (Figure 3). Intraoral BCCs are most commonly reported in the gingiva, and they manifest with surface ulceration or erythroplakia. BCC in the oral cavity is difficult to diagnose because of its pathohistological similarity to the diseases mentioned earlier. Recently, some immunohistochemistry markers, such as Ber-EP4 and Bcl-2 protein, which are specific markers of BCC cells, have helped establish the diagnosis of BCC.

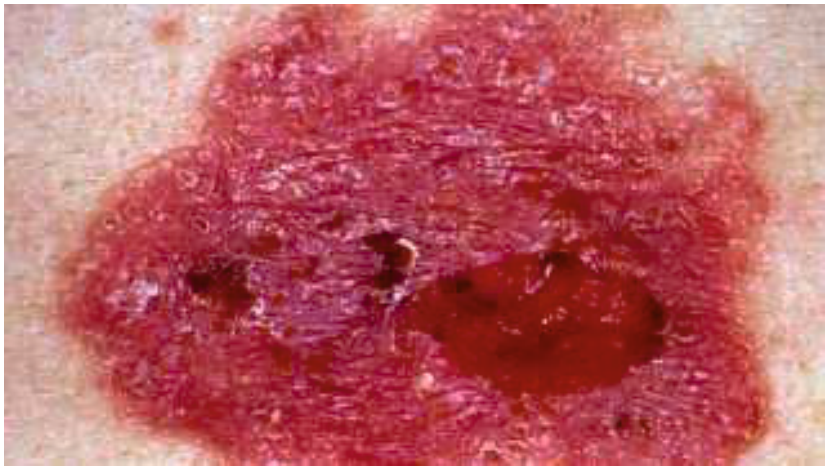

Figure 3: Basal Cell Carcinoma

Basal cell carcinoma on white skin

Basal cell carcinoma is a type of skin cancer that most often develops on areas of skin exposed to the sun, such as the face. On white skin, basal cell carcinoma often looks like a bump that's skin-colored or pink.

Basal cell carcinoma on brown skin

Basal cell carcinoma is a type of skin cancer that most often develops on areas of skin exposed to the sun, such as the face. On brown and Black skin, basal cell carcinoma often looks like a bump that's brown or glossy black and has a rolled border.

Keratoacanthoma:

Keratoacanthoma (KA) is a common, rapidly growing, locally destructive skin tumour. KAs may regress spontaneously with scarring, but clinically they may be indistinguishable from

well-differentiated squamous cell carcinoma (SCC) and the clinical course may be unpredictable. Thus, many clinicians and pathologists prefer the term SCC, KA-type and recommend surgical excision. Keratoacanthoma is most common in fair-skinned older males with a history of chronic sun exposure. Most patients are over 60 years of age and it is twice as common in males than in females (Figure 4).

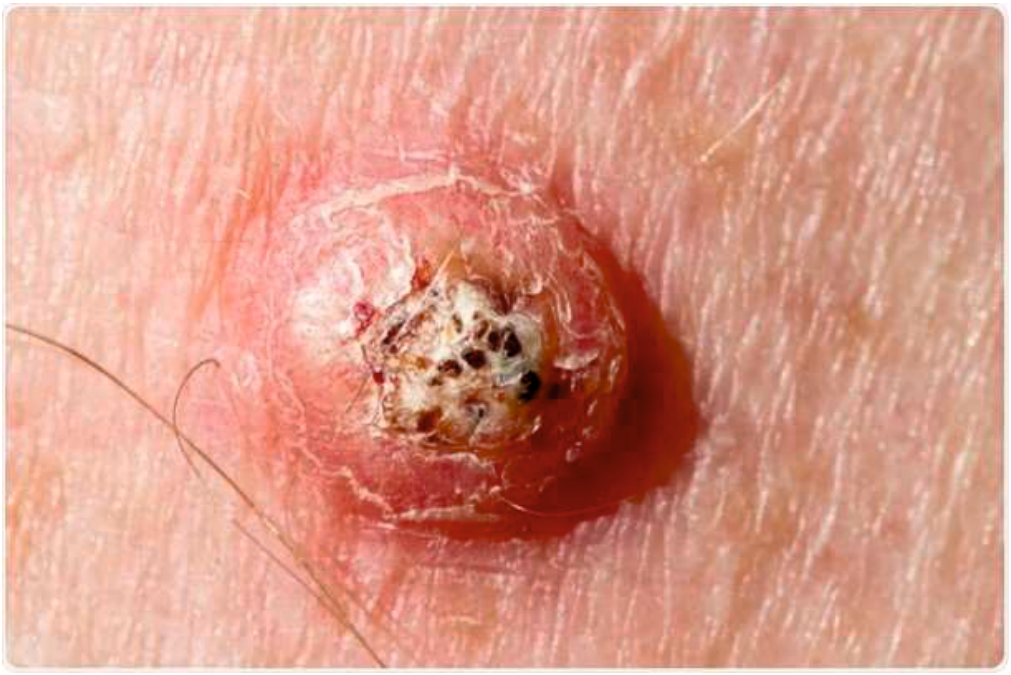

Figure 4: Keratoacanthoma

There is an increased incidence in:

- Patients who are immunocompromised, such as solid organ transplant patients or other patients on long-term immunosuppressive medication
- Patients with genetic cancer syndromes such as:
- Xeroderma pigmentosum
- Muir-Torre syndrome
- Multiple self-healing squamous epithelioma (Ferguson-Smith syndrome)
- Eruptive keratoacanthoma of Grzybowski
- Incontinentiapigmenti
- Patients who received excessive treatment with psoralen-UVA (PUVA) photochemotherapy for psoriasis
- Patients treated for metastatic melanoma with BRAF inhibitors such as vemurafenib and dabrafenib
- Patients treated with hedgehog pathway inhibitors for basal cell carcinoma, such as vismodegib.

Keratoacanthoma arises from the infundibulum of the hair follicle. The specific pathogenetic mechanisms are unclear but may involve aberrant regulation of the WNT signal transduction pathways and mutations in the tumour suppression gene TP53.

The risk factors are probably the same as for squamous cell carcinoma, and include:

- Exposure to ultraviolet light
- Chemical carcinogens (e.g. cigarette smoking, industrial workers exposed to tar, pitch, and mineral oils)
- Cutaneous trauma (e.g. surgery, radiation)
- Human papillomavirus infection.

Keratoacanthomas typically present as a solitary, rapidly growing nodule on sun-exposed skin of the face and upper limbs. Keratoacanthomas are sharply demarcated, firm, erythematous or skin-coloured, with a classic central hyperkeratotic plug and an even shoulder. Removal of the keratotic core will leave a ‗crater'-like appearance to the lesion.

There are several variants and syndromes of keratoacanthoma:

- Solitary keratoacanthoma (most common)
    - Single lesion, growing rapidly within a few weeks up to a diameter of 1–2 cm. After several weeks of stability, the lesion starts to spontaneously regress, eventually leaving a depressed scar. The time from first appearance to complete regression is usually 4–6 months.

- Keratoacanthoma centrifugum marginatum
    - A rare variant of KA, characterised by peripheral expansion and central healing with scarring, often with no tendency to regression. Tumours may reach a diameter of 20 cm or more.
    - Diagnosis may be difficult and they may be confused with inflammatory dermatoses and other tumours.

- Giant keratoacanthoma
    - Typically, a solitary KA grows larger than 2cm.
    - Commonly involves the eyelids or nose.

- Multiple familial keratoacanthoma of Witten and Zak.
    - A rare, autosomal, dominantly-inherited variant of KA that presents in childhood with overlapping features of the Ferguson-Smith and Grzybowski subtypes.
    - It is characterised by multiple tiny papular lesions and larger, more typical KAs.
- Generalised eruptive keratoacanthomas of Grzybowski
- Multiple self-healing squamous epithelioma of Ferguson-Smith disease

The complications of keratoacanthoma include:

- Scarring
- Destruction of adjacent structures
- Ulceration
- Bleeding.

Keratoacanthomas must be distinguished from well-differentiated SCC. Other differential diagnoses include:

- Amelanotic melanoma
- Nodular basal cell carcinoma
- Common warts
- Giant molluscum contagiosum
- Metastatic deposit
- Nodular prurigo.

Nasopharyngeal carcinoma:

Nasopharyngeal carcinoma (NPC), or nasopharynx cancer, is the most common cancer originating in the nasopharynx, most commonly in the postero-lateral nasopharynx or pharyngeal recess (fossa of Rosenmüller), accounting for 50% of cases. NPC occurs in children and adults. NPC differs significantly from other cancers of the head and neck in its occurrence, causes, clinical behavior, and treatment. It is vastly more common in certain regions of East Asia and Africa than elsewhere, with viral, dietary and genetic factors implicated in its causation. It is most common in males. It is a squamous cell carcinoma of an undifferentiated type. Squamous epithelial cells are a flat type of cell found in the skin and the membranes that line some body cavities. Undifferentiated cells are cells that do not have their mature features or functions.

Clinical features:

NPC may present as a lump or a mass on both sides towards the back of the neck (Figure 5). These lumps usually are not tender or painful but appear as a result of the metastatic spread of the cancer to the lymph nodes, thus causing the lymph nodes to swell. Lymph nodes are defined as glands that function as part of the immune system and can be found throughout the body. Swelling of the lymph nodes in the neck is the initial presentation in many people, and the diagnosis of NPC is often made by lymph node biopsy. Signs of nasopharyngeal cancer may appear as headaches, a sore throat, and trouble hearing, breathing, or speaking. Additional symptoms of NPC include facial pain or numbness, blurred or double vision, trouble opening the mouth, or recurring ear infections. If the ear infection does not present with an upper respiratory tract infection, then an examination should be done on the nasopharynx. This is due to the fact that, in adults, ear infections are less common than in children. Signs and symptoms

related to the primary tumor include trismus, pain, otitis media, nasal regurgitation due to paresis (loss of or impaired movement) of the soft palate, hearing loss and cranial nerve palsy (paralysis). Larger growths may produce nasal obstruction or bleeding and a "nasal twang". Metastatic spread may result in bone pain or organ dysfunction. Rarely, a paraneoplastic syndrome of osteoarthropathy (diseases of joints and bones) may occur with widespread disease.

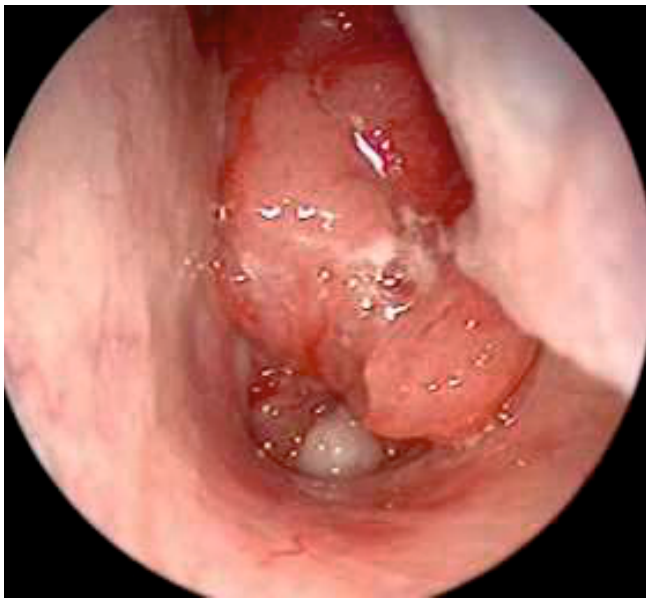

Figure 5: Nasopharyngeal carcinoma

Etiology:

NPC is caused by a combination of factors: viral, environmental influences, and heredity. The viral influence is associated with infection with Epstein–Barr virus (EBV). The Epstein-Barr virus is one of the most common viruses. 95% of all people are exposed to this virus by the time they are 30–40 years old. The World Health Organization does not have set preventative measures for this virus because it is so easily spread and is worldwide. Very rarely does Epstein-Barr virus lead to cancer, which suggests a variety of influencing factors. Other likely causes include genetic susceptibility and consumption of food (in particular salted fish) containing carcinogenic volatile nitrosamines. Various mutations that activate NF-κB signalling have been reported in almost half of NPC cases investigated.

The association between Epstein-Barr virus and nasopharyngeal carcinoma is unequivocal in World Health Organization (WHO) types II and III tumors but less well-established for WHO type I (WHO-I) NPC, where preliminary evaluation has suggested that human papillomavirus (HPV) may be associated.[10] EBV DNA was detectable in the blood plasma samples of 96% of patients with non-keratinizing NPC, compared with only 7% in controls.[6] The detection of nuclear antigen associated with Epstein-Barr virus (EBNA) and viral DNA in NPC type 2 and 3, has revealed that EBV can infect epithelial cells and is associated with their transformation. The cause of NPC (particularly the endemic form) seems

to follow a multi-step process, in which EBV, ethnic background, and environmental carcinogens all seem to play an important role. More importantly, EBV DNA levels appear to correlate with treatment response and may predict disease recurrence, suggesting that they may be an independent indicator of prognosis. The mechanism by which EBV alters nasopharyngeal cells is being elucidated to provide a rational therapeutic target.

It is also being investigated as to whether or not chronic sinusitis could be a potential cause of cancer of the nasopharynx. It is hypothesised that this may happen in a way similar to how chronic inflammatory conditions in other parts of the body, such as esophagitis sometimes leading to Barrett's esophagus because of conditions such as gastroesophageal reflux disease.

Classification:

The World Health Organization (WHO) has identified three subtypes of nasopharyngeal carcinoma

- type 1: squamous cell carcinoma, typically found in older adults
- type 2: non-keratinizing carcinoma
- type 3: undifferentiated carcinoma

Type 3 is most commonly found among younger children and adolescents, with a few type 2 cases. Both type 2 and 3 have been found to be associated with elevated levels of Epstein-Barr virus titers, but not type 1. Additionally, type 2 and type 3 may be followed with an influx of inflammatory cells, including lymphocytes, plasma cells, and eosinophils – a condition referred to as lymphoepithelioma.

Staging:

Staging of nasopharyngeal carcinoma is based on clinical and radiologic examination. Most patients present with Stage III or IV disease.

Stage I is a small tumor confined to nasopharynx.

Stage II is a tumor extending in the local area, or that with any evidence of limited neck (nodal) disease.

Stage III is a large tumor with or without neck disease, or a tumor with bilateral neck disease.

Stage IV is a large tumour involving intracranial or infratemporal regions, an extensive neck disease, and/or any distant metastasis.

Adenosquamous carcinoma:

Adenosquamous carcinoma is a rare, aggressive malignant epithelial neoplasm of the oral cavity. The WHO has defined adenosquamous carcinoma as a malignant tumour characterized by the simultaneous presence of both true adenocarcinoma and squamous carcinoma, with the two components occurring in close proximity, but generally distinct.

There are different theories regarding histogenesis of adenosquamous carcinoma of the oral cavity. Some authors suggested that adenosquamous carcinoma arises from cells of the salivary gland, while some authors suggested that adenosquamous carcinoma might originate from the reverse cells or basal cell of the squamous epithelium from which it undergoes various differentiation.An experimental model of adenosquamous carcinoma has recently been done suggesting that this tumour does not originate from salivary or seromucous glands and providing support for its origin from the reserve cells of the squamous epithelium.

In the head and neck region, larynx is the most common site of occurrence for adenosquamous carcinoma with 48.4% followed by the oral cavity at 30%. Within the oral cavity, the most common locations are the floor of the mouth, tongue, alveolus, palate and upper lip (Figure 6). It has a strong male predilection of 6:1 of male to female ratio. Similar to squamous cell carcinoma, adenosquamous carcinoma has a broad incidence age of 22 to 80 years. Common complaint of patients reported to the clinician is pain because of the tendency of spreading by perineural invasion of the neoplasm. Other common symptoms are tongue numbness and bleeding. Clinically it presents as keratotic ulcer to nodular, exophytic, indurated or undulated masses.

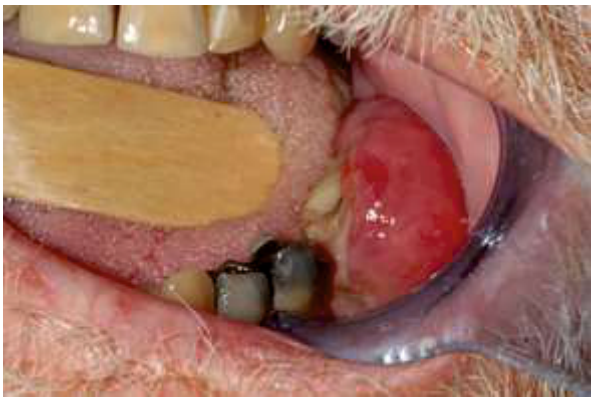

Figure 6: Adenosquamous Carcinoma of Oral cavity

The histopathological features of adenosquamous carcinoma are composed of an admixture or separate areas of squamous cell carcinoma and adenocarcinoma. The squamous epithelium requires two or more of the following features:

1. Intercellular bridging

2. Keratin pearl formation

3. Parakeratotic differentiation

4. Individual cell keratinisation and

5. Cellular arrangements showing pavement or mosaic pattern. The glandular epithelium required demonstration of intracytoplasmic or intraductal sialomucin by high iron diamine – alcian blue or periodic acid–Schiff stain retention after diastase digestion and Mayer's mucicarmine.

Differential diagnosis for adenosquamous carcinoma includes mucoepidermoid carcinoma, acantholytic squamous cell carcinoma, basaloid squamous cell carcinoma, conventional squamous cell carcinoma and necrotizing sialometaplasia. Like adenosquamous carcinoma, mucoepidermoid carcinoma also shows biphasic morphology, consisting of glandular and epidermoid neoplastic components. High-grade mucoepidermoid carcinoma shows epidermoid cells without keratin formation. Adenosquamous carcinoma shows dysplastic features like nuclear pleomorphism, mitotic figures and keratin pearl formation while mucoepidermoid carcinoma will not show.

Other differential diagnosis is adenoid squamous cell carcinoma, variant of conventional squamous cell carcinoma with pseudoglandular formation because of central acantholysis. In adenoid squamous cell carcinoma, there is no intracytoplasmic mucin or well-formed areas of ductal adenocarcinoma.

The next differential diagnosis is basaloid squamous cell carcinoma, a variant of conventional squamous cell carcinoma. Basaloid squamous cell carcinoma is composed of large, rounded, solid clusters of basaloid cells with comedo necrosis, whereas such areas are not seen in adenosquamous carcinoma. Another differential diagnosis is conventional squamous cell carcinoma invading and/or entrapping non-tumorous mucoserous glands. In this, retention of the normal lobular architecture of the mucoserous glands and lack of any significant cytologic atypia of the glands is seen.

The next differential diagnosis is benign necrotizing sialometaplasia, associated with minor salivary glands and also seen are intraductal proliferation of metaplastic squamous cells, partial necrosis of salivary glands and vascular proliferation.

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Chapter 5: Management of carcinoma of oral cavity

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Oral cavity includes lips, buccal mucosa, floor of mouth(FOM), anterior 2/3 of tongue, upper and lower alveolus, retromolartrigone, gingivolabial and gingivolingual sulcus and hard palate.Management of CAOC is multidisciplinary which includes surgery,chemotherapy,radiotherapy,targeted and immunotherapy. The goal of treatment is to cure cancer with preservation / restoration of speech and mastication, swallowing, externalappearance.

Magnetic resonance imaging (MRI) is usually indicated to soft tissue delineation. It is also used for assessing medullary bone involvement, and perineural invasion. MRI is the investigation of choicefor tongue cancer as it is helpful in identifying tumor thickness, involvement of the contralateral side, and involvement of extrinsic muscles. With recent addition of depth of invasion in the AJCC classification for staging, MRI has proven its role. CT scan is recommended for oral lesion specially to access bony erosion

Oral cancers usually metastasize first to the lung, preoperative chest imaging is a part of initial pre-operative work-up. This can be in the form of either plain film or 3D imaging such as computed tomography (CT). Fluorodeoxyglucose positron emission tomography (FDG-PET) scan has emerged as the imaging modality of choice in patient with recurrence and high clinical suspicion for distant metastasis

Management of Primary site

Main modality of treatment of oral cancer is surgery, Radiotherapy can be given for small lesion with good and equal results. Surgical treatment will be considered separately for each anatomical site. Type of surgery depends on primarysite and extent of disease. Goal of treatment is to achieve R0 resection with minimal margin of 1 cm.Reconstruction of defect is performed simultaneously, depending on size and location of defect to achieve better function and cosmoses. Early T stage lesion areresectable but most of T4 disease especially T4B are unresectable. Criteria for unresectablity are high infratemporal fossa involvement, Erosion of skull base, pterygoid plate, sphenoid bone and widening of foramen ovale.

Management of neck

Seven levels of lymph nodes present in neck. Level I to V lymph node along with sternocleidomastoid muscle ,the omohyoid muscle ,internal and external jugular vein ,spinal accessary nerve submandibular gland removed in classic radical neck dissection. Radical neck dissection can be modified by preserving certain structures like sternocledomastoid muscle, internal jugular vein and spinal accessary nerve in intent to decrease morbidity and improving functional outcome without compromising disease control. There are three types of modified neck dissections type I, spinal accessory nerve spared; typeII, spinal accessaery nerve and internal jugular vein spared; typeIII,all three spared. Selective lymph node dissection included

resection of lymph node which is at highest risk of Spread, for example supraomohyoid neck dissection (SOND) in which level I,II and III lymph node dissection performed .

Incidence of subclinical nodal disease i,e cN0 depends of stage and site of primary disease for instance, T1 disease has low risk (<20%) as compare to T4 disease (>30%),oral ca tongue has higher risk as compare to buccal mucosa. Modified or selective lymph node dissection recommended for cN0 neck ,selected clinically positive cases(mobile ,<2-3 cm),primary lesion with high risk of subclinical disease like ca tongue .Close observation may be consider for cN0 to avoid unnecessary treatment .selective neck dissection can also be perform in such cases .patient is kept on close follow up and may be later manage by surgery and /or RT if nodal metastasis develop. Hematoma, seroma,lymphedema, wound infection, carotid exposure and rupture are the few complication of neck dissection.Criteria for unresectablity are encasement of internal carotid artery >270 degree,Involvement of mediastinal structures,Involvement of prevertebral fascia or cervical vertebrae.

Adjuvanttreatment

Postoperative adjuvant treatment includes radiation and concurrent chemoradiation (chemotherapyand radiotherapy given simultaneously) .it is considered when there is a high risk of recurrence. radiotherapy should be started within 6-8 week of surgery. Indication of postoperative radiotherapy includes close margin (<5mm), positive margin, single positive lymph nodes, T3and T4 disease. Extracapsular extension (ECE), Perineural invasion (PNI), multiple positive lymph nodes are the indications for adjuvant chemoradiation.

Surgical management according to anatomical sites

Lip

Wide local excision with minimal possible margin of 5mm is the ultimate goal of treatment. Surgical excision of small lesion leaves essentially noaesthetic or functional debility. Larger lesions requiresreconstruction in orderto achieve satisfactorycosmoses and functionalityespecially oral competence, facial expression, clarity in speech etc. Small lesion can be reconstructed by v platy but larger lesion requires reconstruction usually by local flaps with surrounding skin and soft tissue and opposite lip provide sufficient tissue for functional and cosmetic outcome. For very large defect like composite resection or complete lip resection may require free flapreconstruction. Abbes estlander flap,Karapandzic flap, V -Y plasty, nasolabial flap are the few example of local flap depending on site and size oftum or.

Tongue

Tongue is highly vascularized organ and most common site is lateral border. Tongue lesion should be resected very cautiously as lesion may be much larger then that it appears clinically hence resection should be performed after palpating induration. Partial, subtotal and total glossectomy can be performed depending on size of lesion. Small lesion can be easily close primarily, while larger defect need to be reconstructed mostly by free flaps. The most

commonly used flap is radial forearm free flap and anterolateral thigh free flap. The other uncommon examples for free tissue transfer are lateral arm flap, gracilis flap and local flap such as FAMM flap and submental flap. Lesions in middle third can be approach by paramedian mandibulotomy. Glossectomy with marginal orsegmental mandibulectomy can be perform depending on extent of lesion in order to achieve adequate margin.

Lower alveolus, Gingivobuccal sulcus, Buccal mucosa, Retromolar trigone(RMT)

Surgery for buccal mucosa depend on size and extent of disease. Small lesion away from alveolus can be resected with safe margins withoutremoving alveolar bone. For lesions is close to alveolus, decision for marginal or segmental mandibulectomy or upperalveolectomy has to be made. Iflesion is minimallyaway (<1cm) from lower alveolus then marginal mandibulectomy can be performed provided CT showed no mandibular erosion.

Marginal mandibulectomy is oncologically safe procedure providing safe margin of resection in carcinoma oralcavity when lesion abuts mandible or lie over alveolus with no radiological mandibular infiltration.it is an adequate procedure which achieves good disease control.

Lower alveolus lesion should be managed by segmental mandibulectomy or hemimandibulectomy depending on extent of mandibularerosion. Management of central lower alveolus involvement is a difficult disease to treat. It needs a complex and lengthy reconstructive procedure. the free fibula is the best option for such defects.

Primary SCC of the RMT is not very rare, these tumors generally present at an advanced stage because of their unique anatomical location.They are seated at the junction of the mandible, the alveolar arcus, the tonsillar pillar, the buccal space, the masticator space, the base of the tongue or the palate, they may easily invade all these structures simultaneously at an early period . More importantly, since there is only a thin mucosal barrier between the RMT tumor border and the underlying bone, bone involvement is a common feature of these tumors that upstage even small lesions to T4. Most of the RMT tumors reported in the literature were advanced atpresentation.these tumor treated by bite composite resection (segmental madibulectomy and maxillectomy).prognosis is usually poor.

Reconstruction depends on size, site, availability of local tissue, affordability and functional expectation. Locoregional flaps are pectoralis major myocutanious ,deltopectoral ,nasolabial, submantle ,hypohyoid and forehead. Bestoutcome for mandibular reconstruction can be achieve by free fibular flap. Other less commonly used flaps are free radial ,free gracalis ,free anterolateral thigh flaps .

Hard Palate

Tumors of the hard palate are less common and are mostly of minor salivary gland etiology. Posterior alveolus lesion cab be managed by upper alveolectomy or inferior partial maxillectomy. These Lesions have a higher tendency to locally invade the orbital floor and skull

base or through various neurovascular bundles (greater palatine foramen, sphenopalatine foramen, palatovaginal canal. reconstruction can be avoided by placing dental obturator. Premaxilla provides support for the nose and midface hence lesions involving anterior alveolus and hard palate will require bony reconstruction to prevent midface deformity.

Maxilectomy classifies in different classes ,Class I, limited maxillectomy with involvement of one wall; Class II, subtotal maxillectomy with involvement of at least two walls including the palate, subdivided further into anterior, inferior medial, and lateral types; Class III, total maxillectomy which was complete resection of maxilla with or without orbital involvement.

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19. Treatment Outcomes for Primary Retromolar Trigone Carcinoma: A Single Institution ExperienceUygar Levent Demircorresponding author and Halide Öztürk Yanaşma


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