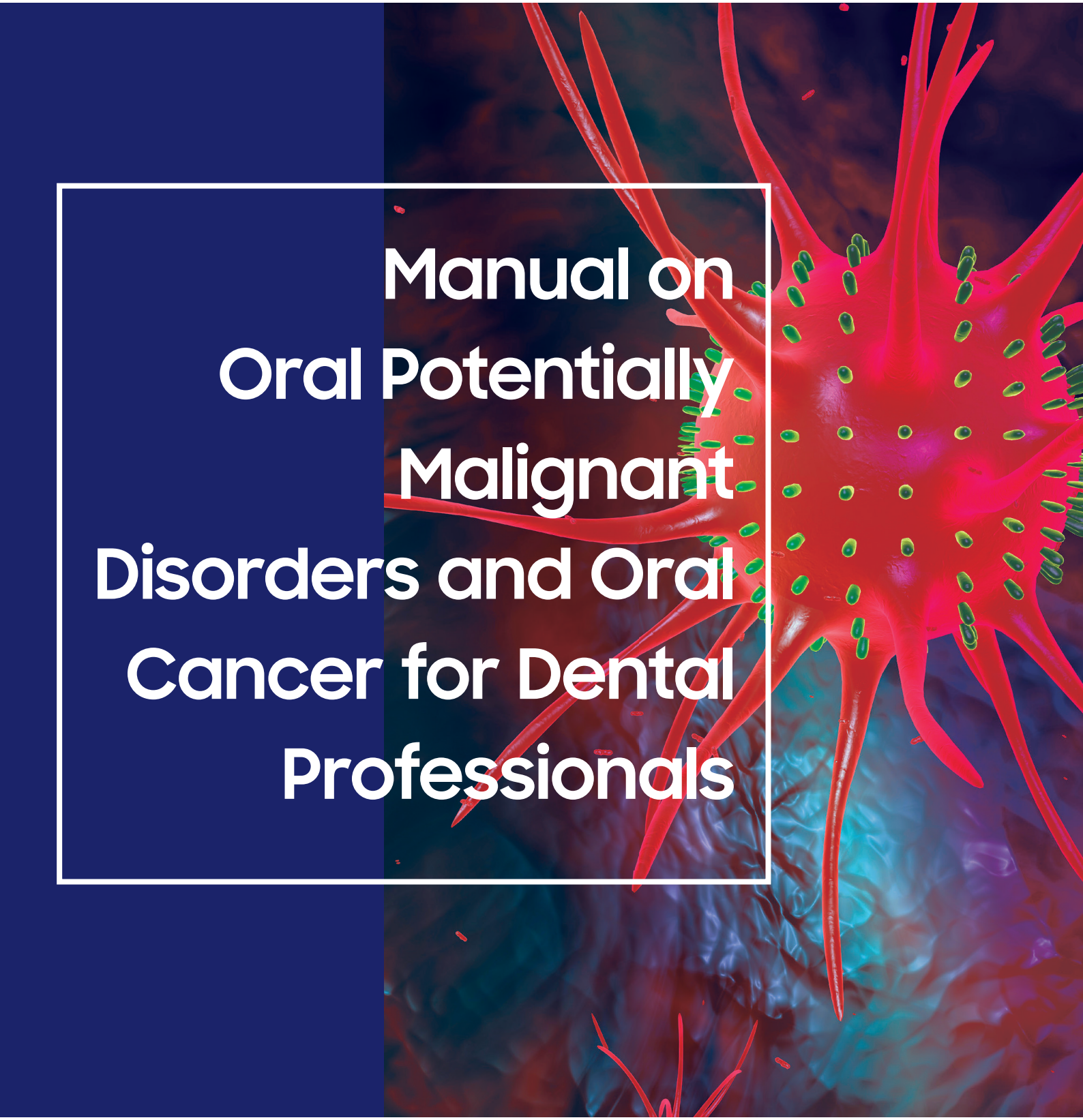
Indian Dental Association

National Oral Cancer Registry



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PRESIDENT'S MESSAGE

Dear Readers,

It gives us immense pride to share this milestone achievement by the Indian Dental Association – the release of our first-ever manual dedicated to the diagnosis, management, and referral of Oral Potentially Malignant Disorders (OPMDs) and oral cancers. This marks the beginning of a series of such initiatives, each aimed at empowering dental professionals across the country with essential knowledge and awareness.

India bears one of the highest burdens of oral cancer globally. The time is now for every Indian dentist to be equipped with the confidence and competence to identify early signs, make accurate diagnoses, manage cases effectively, and refer patients at the right stage to the right care facility. This manual serves as a practical, evidence-based guide for daily clinical use, while also being a valuable resource for research and academic purposes.

With this, we reaffirm our vision: to strengthen our profession with the tools, skills, and confidence needed to save lives – one early diagnosis at a time.

Dr. Subhra Nandy
President, IDA

IMM. PAST PRESIDENT'S MESSAGE

Dear Readers,

Proudly announcing as one of one 'first of many' manuals that we plan to publish. More of such projects are at work.

This manual will act as a guide to anyone and everyone in the dental space when it comes to potential risks of oral cancers. We have experts in the field come together to compile all necessary information regarding this topic, which will act as a reliable handbook in daily dental practice. This book is not only also restricted to dental practice but is a good source for research.

This book promises to definitely help the readers gain the required knowledge in an easily consumable manner. This venture was formulated in an effort to give back to our community, a comprehensive manual for easy understanding and provide a new perspective on this very topic.

Dr. Raveendranath M.
Imm. Past President, IDA

SECRETARY'S MESSAGE

Dear Readers,

It gives me immense pleasure to extend heartfelt congratulations to the Indian Dental Association (IDA), its NOCR Committee, and all the esteemed contributors for the meticulous effort put into crafting this comprehensive manual on the management of Oral Potentially Malignant Disorders (OPMDs). This manual is a significant resource for dental professionals across the country, offering a structured guide to effectively identify, manage, and treat OPMDs within clinical settings.

As tobacco-related OPMDs are a major precursor to oral cancer, this manual will not only equip dentists with the latest knowledge and skillsets but also play a crucial role in public health education. Empowering every dentist with the right tools to intervene early can make a profound difference in reducing the incidence of oral cancer—a growing concern in India. Moreover, it is through initiatives like this that dental professionals can actively contribute to spreading awareness about the dangers of tobacco use and the importance of early detection.

I am confident that this manual will serve as an invaluable reference for practitioners and help foster a stronger commitment toward improving oral health outcomes across the nation. Congratulations once again to the entire team for this noble and timely effort.

Dr. Ashok Dhoble
Hon. Sec. General, IDA

FOREWORD

It is with great pleasure that I write the forward for the manual on “Oral Potentially Malignant Disorders and Oral Cancer”. This is a timely need and an appropriate positive step taken by Indian Dental Association in order to address a major health problem in India. It is a known fact that out of the 400000 oral cancers occuring annually in the world, the majority of them are diagnosed in India compared to other countries. Therefore, it is the duty of the dental fraternity to make sure that they contribute to the management of oral potentially malignant disorders and oral cancer. As Dental surgeon is often the first to encounter these cases, they can play a pivotal role in reducing the burden of oral cancer through early diagnosis which improves the outcome of both OPMD and oral cancer. In that context, training and imparting current knowledge in this area will empower them to recognize suspicious lesions early and accurately. Oral cancer burden in India and South Asia is not just a health problem as it directly involves with significant economic and social implications.

This comprehensive manual covers all aspects of OPMD and Oral cancer management from understanding of aetiology and risk factors, pathogenesis, screening and early detection, clinical features, investigations, histopathology to treatment options. This manual is not just a management guideline document on OPMD and Oral cancer. The detailed coverage of all areas in relation to this major health issue in India will certainly empower all dental professionals on the importance of early detection of OPMD and Oral cancer. If the practicing dental surgeons can impart the knowledge from this manual and put everything what is described into practice, I am sure it will pave the way to reduce the prevalence of OPMD and Oral cancer and better prognosis for all victims of Oral Cancer.

Finally, I would like to appreciate and thank the IDA for the concept and inviting a group of experts to contribute to the relevant sections of the manual making it a reading guide that every dental surgeon should be familiar with and kept in their practices for reference.

Professor W. M. Tilakaratne

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EXECUTIVE SUMMARY

The "**Manual on Oral Potentially Malignant Disorders and Oral Cancer for Dental Professionals**" is a comprehensive resource tailored specifically for dental professionals, offering in-depth insights into the early detection, diagnosis, and management of oral potentially malignant disorders (OPMDs) and oral cancer. This manual serves as an authoritative guide, equipping dental practitioners with the essential knowledge and tools required to address these serious health concerns effectively. It is designed to be a practical tool that extends beyond academic knowledge, enabling dental professionals to make a significant impact on patient outcomes through timely and accurate interventions.

From the perspective of dental professionals, this manual provides a robust, evidence-based compendium that aids in the identification, assessment, and management of OPMDs and oral cancer. It is meticulously structured to ensure that practitioners can understand the clinical features, risk factors, diagnostic procedures, and management protocols associated with these conditions. The manual offers detailed explanations of various OPMDs, including leukoplakia, erythroplakia, and oral submucous fibrosis, among others. Additionally, it covers the etiology, pathogenesis, and progression of oral cancer, emphasizing the critical importance of early detection in improving patient outcomes.

A key aspect of the manual is its provision of step-by-step clinical guidelines that assist dental professionals in conducting thorough oral examinations, recognizing early signs of malignant transformation, and utilizing adjunctive diagnostic tools such as biopsy, imaging, and molecular diagnostics. These guidelines are designed to be integrated into routine dental check-ups, ensuring that early signs of OPMDs and oral cancer are not overlooked. Furthermore, the manual places a strong emphasis on risk assessment and management, guiding dental professionals in identifying high-risk patients and implementing preventive strategies that can significantly reduce the likelihood of malignant transformation. The manual also addresses the importance of effective patient communication, providing strategies for discussing potential diagnoses and treatment plans with patients in a clear and empathetic manner. This includes counseling patients on lifestyle changes, such as tobacco cessation and alcohol reduction, which are critical in reducing the risk of oral cancer. Additionally, the manual highlights the importance of regular follow-ups to monitor patients with OPMDs and ensure early intervention if malignant changes are detected. Recognizing the importance of interdisciplinary collaboration in the management of oral cancer, the manual provides guidance on how dental professionals can work effectively with oncologists, surgeons, and other healthcare providers to ensure a multidisciplinary approach to patient care. This coordinated care is vital for improving patient outcomes, particularly in cases where advanced treatment modalities are required. The inclusion of real-world case studies and best practices within the manual offers valuable insights into the practical application of these guidelines, helping dental professionals navigate common challenges and implement solutions effectively.

The need for this manual is underscored by the significant burden of oral cancer, particularly in countries like India, where the prevalence of risk factors such as tobacco chewing, smoking, and alcohol consumption is high. Despite the widespread occurrence of OPMDs and oral cancer, these conditions often go undiagnosed until they reach advanced stages, leading to poor prognosis and high mortality rates. Dental professionals, who are often the first point of contact for patients, are uniquely positioned to identify early signs of these conditions. This manual is designed to empower them with the knowledge and skills needed to recognize subtle changes in the oral mucosa that may indicate the onset of potentially malignant disorders or oral cancer.

As primary caregivers for oral health, dental professionals are the first line of defense against oral cancer. Their expertise in oral pathology, combined with their ability to perform comprehensive oral

examinations, makes them critical in the early diagnosis and intervention process. The manual emphasizes the importance of early detection, as it is crucial in the successful treatment of oral cancer. By educating patients about the risks associated with OPMDs and oral cancer, dental professionals can play a key role in promoting awareness and encouraging patients to adopt healthier lifestyles, thereby reducing the incidence of these conditions.

The manual also highlights the importance of timely referrals to specialists when OPMDs or oral cancer is suspected. Dental professionals are encouraged to collaborate with oncologists, pathologists, and surgeons to ensure that patients receive comprehensive care. This multidisciplinary approach is vital for improving survival rates and quality of life for patients diagnosed with oral cancer. Additionally, the manual offers guidance on managing treatment and follow-up care, including monitoring for recurrence, managing complications, and providing supportive care to improve patient outcomes.

In a country like India, where oral cancer is a significant public health issue, the role of dental professionals is especially critical. The high prevalence of OPMDs and oral cancer, coupled with limited access to specialized care in rural areas, makes it imperative for dental professionals to be well-equipped with the knowledge and skills to address these challenges. This manual is tailored to the Indian context, taking into account the unique epidemiological patterns, cultural factors, and healthcare infrastructure of the country. It aims to empower dental professionals across India to take a proactive role in the fight against oral cancer, particularly in underserved areas where the burden of disease is highest.

The “Oral Potentially Malignant Disorders and Oral Cancer” manual is an essential tool for dental professionals committed to improving oral health outcomes. By enhancing their ability to detect and manage OPMDs and oral cancer, this manual not only supports the professional development of dental practitioners but also contributes to the broader goal of reducing the burden of oral cancer in India. With the knowledge and strategies provided in this manual, dental professionals can make a significant impact in saving lives and improving the quality of life for countless individuals.

ABBREVIATIONS

Abbreviation	Definition
NCD	Non-Communicable Diseases
OPMD	Oral Potentially Malignant Disorder
WHO	World Health Organization
NOCR	National Oral Cancer Registry
OSF	Oral Submucous Fibrosis
OSCC	Oral Squamous Cell Carcinoma
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
DALY	Disability Adjusted Life Years
YLD	Years Lived with Disability
YLL	Years of Life Lost
GBD	Global Burden of Disease
OLP	Oral Lichen Planus
PVL	Proliferative Verrucous Leukoplakia
MSE	Mouth Self Examination
COE	Clinical Oral Examination
VOE	Visual Oral Examination
EGF	Epidermal Growth Factor
PDGF	Platelet-Derived Growth Factor
TGF	Transforming Growth Factor
CDK	Cyclin Dependent Kinases
VEGF	Vascular Endothelial Growth Factor
OED	Oral Epithelial Dysplasia
NTCP	National Tobacco Control Programme

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Chapter 1

INTRODUCTION

The global prevalence of non-communicable diseases (NCDs) such as cardiovascular and metabolic diseases, diabetes, cancer, and oral health conditions like caries or periodontitis, is a significant concern exacerbated by demographic shifts and epidemiological trends. NCDs contribute significantly to global mortality rates and impose substantial economic burdens on national healthcare systems. They affect people in low- and middle-income countries the most, accounting for over three-quarters of the 32 million NCD-related deaths annually.

Oral cancer ranks among the top 15 most prevalent cancers, all of which are categorized as NCDs.

According to GLOBOCAN data, there was a rise in the estimated global new cases of oral cancer from 354,864 in 2018 to 377,173 in 2020. However, the number of new deaths remained consistent at approximately 177,000 during the same period. 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. In India, Oral cancer ranks among the top three types of cancer.

Annually in India, approximately 77,000 new cases of oral cancer are reported, resulting in around 52,000 deaths, constituting roughly one-fourth of global occurrences.

In South Asia, most oral cancers stem from pre-existing long-standing lesions, now referred to as 'oral potentially malignant disorders' (OPMDs) as acknowledged by Warnakulasuriya et al. in 2007. This recognition stems from the understanding that systemic, cellular, and molecular changes extend beyond specific macroscopically visible oral lesions. In India, tobacco serves as the primary causative factor, leading to visible lesions, with leukoplakia being the most prevalent. This understanding underscores the emphasis on population-based strategies for primary oral cancer prevention and early detection of OPMDs. Habit intervention and follow-up are considered secondary prevention strategies, as proposed by Daftary in 2010.

In 2021, during the Seventy-fourth Session of the World Health Organization (WHO) Regional Committee for South-East Asia, discussions centered on the gaps in advancing oral health in the region. As a result, there was a call for the formulation of a regional action plan for oral health spanning from 2022 to 2030. The plan defines two regional targets to track progress in oral health by 2030:

- Target 1: a 33.3% relative reduction of premature mortality from oral cancer by 2030; and
- Target 2: a 25% relative reduction of prevalence of untreated dental caries of permanent teeth by 2030.

In adherence to the "WHO Global Action Plan for the Prevention and Control of NCDs 2013-2020", India stands out as the first nation to embrace a National Action Plan featuring specific national targets and indicators. These targets are geared towards achieving a 25% reduction in premature deaths from NCDs worldwide by 2025. While the global action plan outlines nine targets for countries, India has introduced an additional tenth target to tackle household air pollution. Within India's National Monitoring Framework for Prevention and Control of NCDs, commitments include a 50% relative decrease in the use of solid fuel in households and a 30% relative decline in the prevalence of current tobacco usage by 2025.

The Indian Dental Association (IDA) established the National Oral Cancer Registry (NOCR) to fulfill its vision of optimal national oral health and its mission of supporting dental professionals and promoting oral health. NOCR generates vital data on oral cancer, empowering research, education, and advocacy efforts to improve early detection and care. By collaborating with stakeholders, NOCR is changing the landscape of oral cancer prevention, aligning with IDA's commitment to ensuring quality oral health care for all Indians.

The "Oral Premalignant Lesion and Oral Cancer Manual" serves as a crucial guide for general dentists, providing essential protocols for the early detection, diagnosis, and management of oral lesions. Dentists, often the first to encounter such cases, play a pivotal role in reducing

the burden of oral cancer through early intervention and improved patient outcomes. Training in oral cancer empowers them to recognize suspicious lesions, educate patients about risk factors, and collaborate with other healthcare providers in multidisciplinary treatment approaches. This manual equips dentists with the knowledge to identify suspicious lesions promptly, ensuring timely referrals and appropriate treatment. In India, where the incidence of oral cancer is rapidly increasing, this resource is indispensable.

Formulated by the expert task force under the NOCR initiative, this manual serves as a comprehensive resource, providing updated technical information and guidelines to the healthcare providers in identifying early signs, OPMDs diagnosis, advanced methods of screening and treatment modalities, and preventive strategies within the Indian context. By promoting standardized practices and interdisciplinary collaboration, it ensures quality care across regions and disciplines within the country. It complements the Indian Dental Association's (IDA) initiative of a national oral cancer registry, enhancing data collection and analysis for better clinical outcomes. By integrating with the registry, the manual supports IDA's vision of effectively managing OPMD and oral cancer in clinical settings, ultimately improving patient care and survival rates.

Chapter 2

CONCEPT OF PREMALIGNANCY

Oral Squamous Cell Carcinoma (OSCC) represents a complex interplay of genetic and environmental factors (such as tobacco) leading to a cascade of cellular changes that may culminate in cancer. The journey from a normal cell to a cancerous one is not abrupt but rather a gradual process marked by a series of genetic mutations, as a result of exposure to carcinogens. These accumulated genetic mutations trigger alterations in the cellular machinery responsible for protein synthesis, leading to biochemical changes within the cells. Over time, the accumulation of these changes can manifest as visible alterations in the structure and morphology of the oral mucosa, signaling the onset of premalignancy. The term "potentially malignant" refers to lesions and conditions in the oral cavity that carry a heightened risk of progressing to cancer. This nomenclature emphasizes the potential rather than the certainty of malignant transformation, distinguishing it from the term "premalignant," which was previously used. Potentially malignant states are identifiable through clinical examination as morphological abnormalities. They are considered precursors to OSCC and signify an increased risk for the individual to develop cancer.

Among the various potentially malignant states, in India, Leukoplakia, Erythroplakia, erosive Lichen Planus, and Oral Submucous fibrosis (OSF) are the most commonly encountered in the oral cavity. It is crucial to understand that not all changes in the oral mucosa that are associated with an increased risk of cancer are premalignant. Some lesions, despite being abnormal, may never progress to cancer. The absence of progression to a neoplasm does not preclude a lesion from being classified as potentially malignant. Modern diagnostic chair-side techniques can detect subtle biochemical changes that precede the development of OSCC. These advancements reinforce the concept that every epithelial cancer originates from a potentially detectable condition, even if not clinically visible, underscoring the importance of vigilant surveillance and early intervention. The oral diagnosis such as Leukoplakia, Erythroplakia, Erosive Lichen Planus and Oral Submucous Fibrosis are diagnosed based on the morphological features of a tissue. The World Health Organization (WHO) classifies oral premalignancies into two broad categories:

Precancerous lesions: These are morphologically altered tissues with a higher likelihood of progressing to oral cancer compared to normal tissues. Common examples include:

Leukoplakia: White patches on the oral mucosa, often painless. It is a predominantly oral, unscrapable, white or greyish white patch or plaque that cannot be characterized clinically or pathologically as any other disorder except for the use of tobacco in any form.

Erythroplakia: A chronic red mucosal macule which cannot be given another specific diagnostic name and cannot be attributed to traumatic, vascular, or inflammatory causes. Such red patches on the oral mucosa, potentially are more concerning than leukoplakia due to a higher transformation rate.

Actinic cheilitis: Chronic inflammation of the lips, typically the lower lip, caused by excessive sun exposure.

Precancerous conditions: These generalized states are not specific lesions but increase the overall risk of developing oral cancer. Examples include:

Oral Submucous Fibrosis: It is best clinically described as a debilitating, progressive, irreversible collagen metabolic disorder, induced often by chronic chewing of areca nut and its commercial preparations. It affects any oral mucosa and may extend occasionally to involve the pharynx, oesophagus and middle ear. It may lead to vesicle formation, ulceration and causes progressive mucosal stiffness and functional morbidity.

Oral Lichen Planus: An autoimmune inflammatory disorder affecting the skin and mucous membranes, including the oral cavity.

Risk Factors for Oral Premalignancy

Several factors can influence your risk of developing oral premalignancy. Some of the most significant include:

a) Tobacco and Areca nut use: Smoking, chewing tobacco, areca nut and smokeless cigarettes all significantly increase the risk.

b) Alcohol consumption: Heavy alcohol use, particularly in combination with tobacco, has a synergistic effect on premalignancy risk.

c) Human papillomavirus (HPV) infection: Certain strains of HPV, particularly HPV16 and HPV18, are linked to an increased risk of oropharyngeal cancer, a type of head and neck cancer affecting the throat and tonsils.

d) Sun exposure: Excessive sun exposure can increase the risk of actinic cheilitis, a premalignant condition affecting the lips.

e) Genetic predisposition: Some individuals may have a genetic susceptibility to developing oral cancer and premalignant lesions.

f) Immunosuppression: Conditions that weaken the immune system, such as HIV/AIDS or medications following organ transplantation, can increase the risk.

Signs and Symptoms of Oral Premalignancy

Early detection of oral premalignancy is crucial for successful treatment. While some premalignant lesions may not cause any symptoms, some common warning signs to be aware of include:

- Persistent white or red patches on the gums, tongue, or inner cheeks.
- Unexplained sores or ulcers in the mouth that doesn't heal within two weeks.
- Pain or burning sensation in the mouth.
- Unusual stiffness or palpable fibrous bands
- Difficulty chewing or swallowing.
- Lumps or bumps in the mouth or neck.
- Numbness in the mouth.

It is important to note that these symptoms can also be associated with other oral conditions.

Diagnosis of Oral Premalignancy

The diagnosis of oral premalignancy typically involves a two-step approach-

a) Clinical examination: A dentist can visually examine your mouth and throat to identify any suspicious lesions.

b) Biopsy: If a suspicious lesion is found, a small tissue sample will be taken through a biopsy and analyzed under a microscope to determine the presence and severity of cellular abnormalities. Depending on the diagnosis, additional tests like imaging studies might be recommended to assess the extent of the lesion.

Chapter 3

CARCINOGENESIS (OVERVIEW)

Carcinogenesis is a multistep process due to the accumulation of numerous changes in genes which result in changes in the phenotypes. Carcinogens are agents that can induce tumors.

Carcinogenesis can be discussed under:

1. Molecular pathogenesis of cancer
2. Chemical carcinogenesis
3. Physical Carcinogenesis
4. Biologic or Viral Oncogenesis

The general concept of Molecular Pathogenesis of cancer is briefly outlined:

1. Monoclonality of tumors. The majority of cancers in humans are caused by mutation or change in genes in a single cell.
2. Field theory of cancer. Whenever a cancer develops in an organ, few cells change and grow into cancer while other cells remain normal.
3. Multi-step process of cancer growth and progression. Carcinogenesis is a gradual multi-step process involved in the further progression of the tumor.
4. Genetic theory of cancer. The growth of normal and abnormal cells is under genetic control.
5. Genetic regulators of normal and abnormal mitosis. In normal cell growth, four regulatory genes control mitosis as well as cell aging, terminating in cell death by apoptosis:

i) Proto-oncogenes are growth-promoting genes.

ii) Anti-oncogenes are growth-inhibiting or growth-suppressor genes.

iii) Genes that regulate apoptosis control the programmed cell death.

iv) DNA repair genes that control repair.

Abnormalities in these result in the transformation of cells, cell proliferation, mutations, escape of cell death, and cancer.

Cancers continue to undergo Darwinian selection and therefore continue to evolve. Tumors start from a monoclonal origin but they become genetically heterogenous when they appear clinically because of multiple mutations.

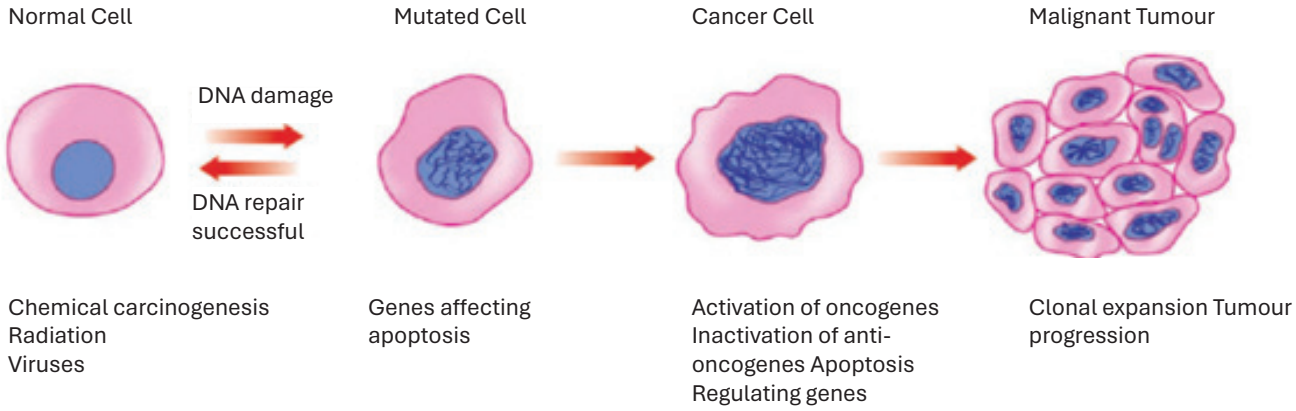


Fig.1: Molecular basis of cancer

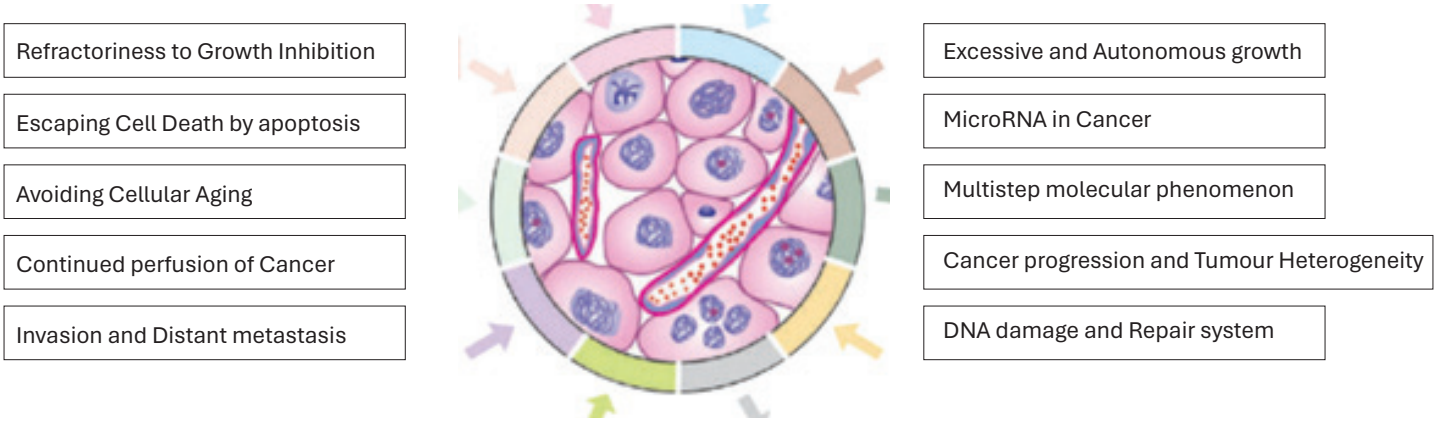


Fig.2: Hallmarks of cancer

Hallmarks of Cancer

Ten fundamental changes are seen in the cells of cancer which are considered Hallmarks of cancer which are seen in the figure.

1. Self-Sufficiency in Growth Signals

2. Insensitivity to growth-inhibitory signals

i. Growth Factors

ii. Growth Factor Receptors

iii. Downstream Signal-Transducing Proteins

iv. Nuclear Transcription Factors

There are two important cell cycle checkpoints: At the G1/S transition and the G2/M transition.

1. The cyclin D genes are overexpressed in many cancers, like the breast, esophagus, liver, lymphomas, and plasma cell tumors.
2. CDKIs are disabled by mutation or gene silencing in many human malignancies. There are cell senescence and apoptosis, that oppose oncogene-mediated cell growth.
3. RB (Retinoblastoma gene): Governor of the cell cycle
4. TP53: Guardian of the genome
5. TGF-β, Contact inhibition, and APC-β- Catenin pathways

3. Altered cellular metabolism and reduced cellular aging

Warburg metabolism favors pro-growth metabolism and changes in the metabolism that favor the growth of cells.

4. Evasion of apoptosis

Evasion of cell death by cancers mainly involves loss of p53 function.

5. Limitless replicative potential (Immortality)

6. Sustained Angiogenesis

Vascularity plays an important role in tumor growth by balancing between angiogenic and antiangiogenic factors which are produced by tumor cells or stromal cells.

7. Invasion and Metastasis

Cells invade tissues by: Cell-to-cell contacts loosen; the Extracellular matrix degrades, cells getting attached to new Extracellular matrix components, and results in cellular migration.

8. Evasion of Immune Surveillance

The immune system of the body can identify the tumour cells as foreign and can be destroyed.

9. Multistep molecular mechanisms

There will be a mutation of some of the genes that regulate some of these cellular traits.

10. MicroRNAs in cancer: Oncomirs

Single-stranded non-coding RNA molecules with a length of only 22 nucleotides are called microRNAs (miRNAs) which function as tumor suppressors, tumor promoters, and pro-apoptotic.

Chemical Carcinogenesis

Skin and lung cancer occurs in arsenic workers.

1. Direct-acting carcinogens - These are chemical substances like alkylating agents, and acylating agents that can induce cellular transformation directly.

II. Indirect-acting carcinogens or procarcinogens - These require metabolic conversion within the body to become ultimate carcinogens.

Initiation of Carcinogenesis

1. The target cell will become the Initiated cell following Metabolic activation in the liver .
2. Reactive electrophiles. Direct-acting carcinogens are intrinsically electrophilic, and indirect-acting substances are electron-deficient after metabolic activation.
3. Target molecules. The cell will become “initiated” with a change in DNA.
4. The initiated cell. The damage becomes permanent and irreversible only if the altered cell undergoes at least one cycle of proliferation.
5. Promotion of carcinogenesis
6. Progression of carcinogenesis

Progression of cancer is the stage when a mutated proliferated cell shows cancer features

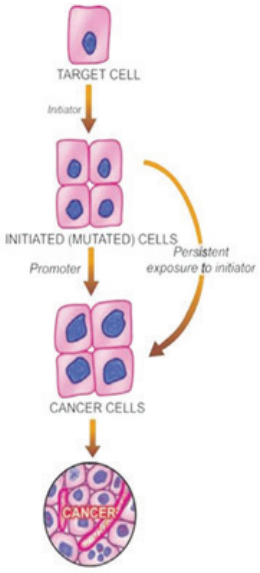


Fig.3: Initiation of Chemical carcinogenesis

Physical Carcinogenesis

Physical agents in carcinogenesis are divided into 2 groups:

1. The most important physical agents involved in carcinogenesis are types of radiation. Non-ionizing radiations are electromagnetic, with low penetration, and present a real danger to eyes and skin - Ultraviolet A and B radiations. This can enhance chemical carcinogenesis also.
2. Various forms of injuries from the less important type of non-radiation physical agents.

Viral Carcinogenesis

About 20% of all cancers are caused due to persistent virus infection. The persistence of DNA or RNA viruses is the first step in the multistep process of cancer development. RNA viruses have a very high mutation rate (e.g. HIV, HCV) than DNA viruses. Viral infections (including oncogenic viruses) can be transmitted by one of the 3 routes:

i) Horizontal transmission. Viral infections pass from one to another by direct contact, ingestion of contaminated water or food, or by inhalation.

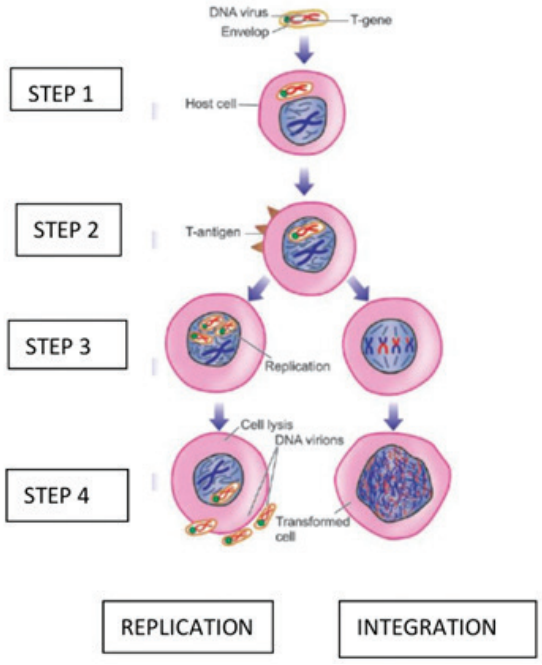


Fig.4: Mode of DNA viral oncogenesis

ii) By parenteral route: By inoculation as in inter-human spread from animals and insects to humans.

iii) Vertical transmission: The infection is genetically transmitted from infected parents to offspring.

Oncogenic viruses fall into 2 broad groups. Viruses that contain Deoxyribonucleic acid (DNA) and those that contain Ribonucleic acid (RNA).

1. Mode of DNA viral oncogenesis.

Host cells infected by DNA oncogenic viruses may multiply or undergo i) Replication. Virus DNA will join with the nucleus ii) Integration.

Oncogenic RNA Viruses

Mode of RNA viral oncogenesis

There will be two identical strands of RNA in retroviruses and there will be an enzyme, Reverse transcriptase. The three components of virus particles are then assembled at the plasma membrane of the host cell and the virus particles are released by budding off from the plasma membrane, thus completing the process of replication.

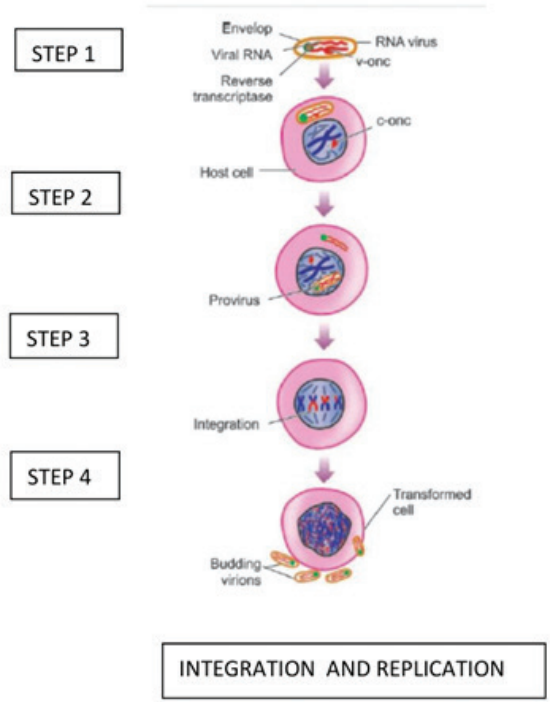


Fig.5: Mode of RNA Viral oncogenesis

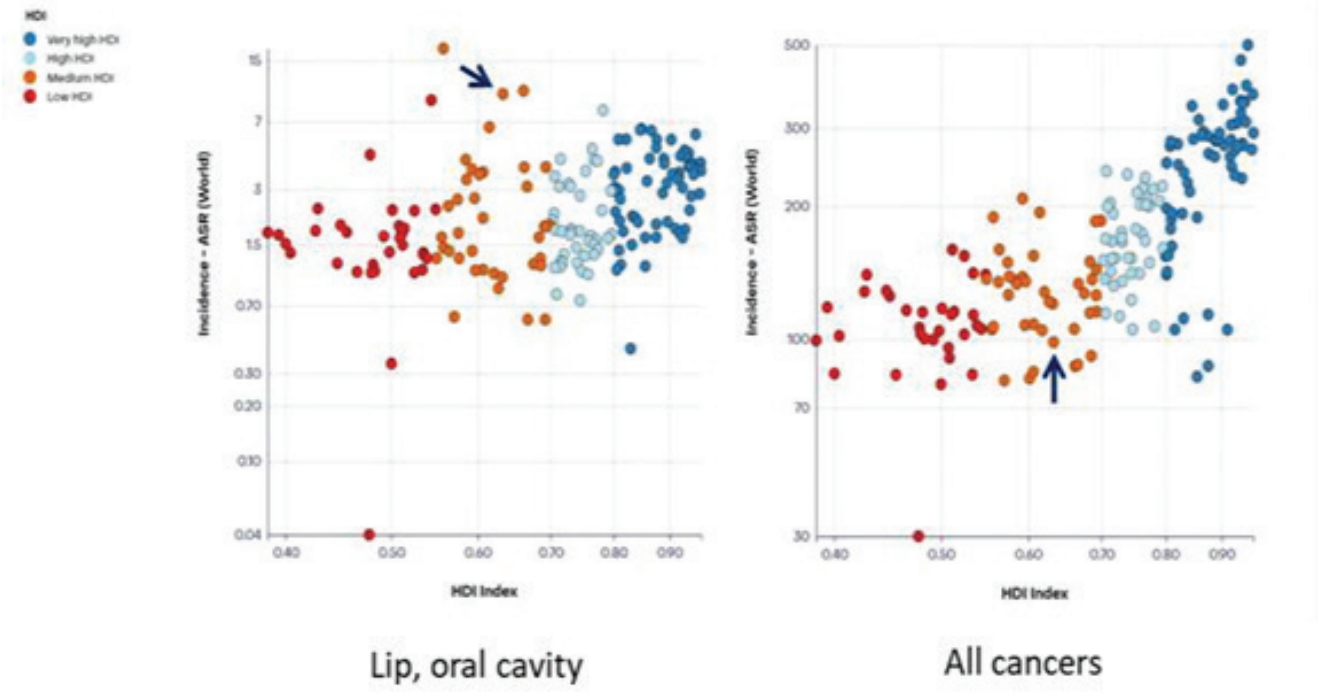
Chapter 4

ORAL CANCER BURDEN IN INDIA & THE NEED TO ADDRESS THE BURDEN

Over the past few decades, cancer has emerged as one of the significant challenges to the health systems worldwide. World Health Organization's (WHO) 2019 estimates suggest that cancers account for the first or second leading cause of death in more than 60% of the countries globally. According to the International Agency for Research on Cancer's (IARC) GLOBOCAN estimates of cancer incidence and mortality, there were 19.97 million new cancer cases and 9.74 million cancer deaths in the year 2022. The GLOBOCAN 2022 incidence and mortality estimates for cancers in India were 1.41 million and 0.91 million, respectively. Oral cancer is among the most common types of cancer in India. To provide a thorough rationale for the need to address the oral cancer burden and to prioritize this area in the national health agenda, the burden of oral cancer in India can be better summarized in terms of its incidence and mortality rates, disability-adjusted life years (DALYs), Years Lived with Disability (YLDs), Years of Life Lost (YLLs) of oral cancer, the health care costs incurred for oral cancer care, and productivity loss.

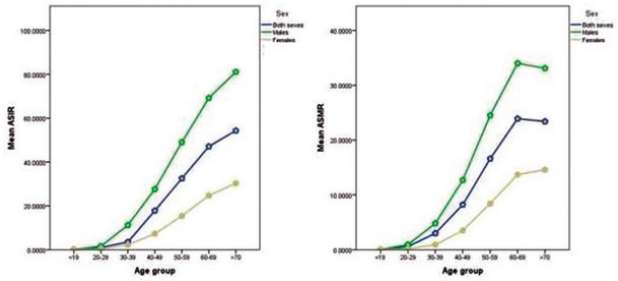
Oral Cancer Incidence and Mortality Rates in India

In India, oral cancer is the second most incident cancer accounting for 10.17% of all the incident cancer cases, thus constituting a significant public health concern in the country. Among males, it is the most common cancer accounting for 15.59% of all incident cancers. As per GLOBOCAN 2022 estimates, the age-standardized incidence rate of the cancers of the lip, and oral cavity in India is 9.9 per 1, 00,000 with an age-standardized mortality rate of 5.6 per 1, 00,000.



The differential relative positions of India in the age standardized incidence rates of cancers of lip, oral cavity, oropharynx versus all cancers (created in GLOBOCAN Dataviz using the 2022 estimates).

Within the Indian context, it is important to focus on the differential incidence and mortality rates of oral cancer by age to better articulate the prevention strategies in an informed manner. The figure below presents the age-standardized incidence and mortality rates per 1, 00,000 among the Indian population by age group, where a prominent rise in the incidence and mortality rates can be observed between 49 and 59 years. Another noteworthy observation from the GLOBOCAN 2022 estimates is that India ranks first in the world in terms of the age-standardized incidence rate of cancers of the lip, and oral cavity among the 20-39-year-old population, which forms a very important age group in defining the nation's development. With reference to the estimated cumulative risk, India ranks third in the world with an estimated cumulative risk percentage of 1.6, however, the cumulative risk % for cancers of the lip, and oral cavity is highest for India up to the age of 44 years.



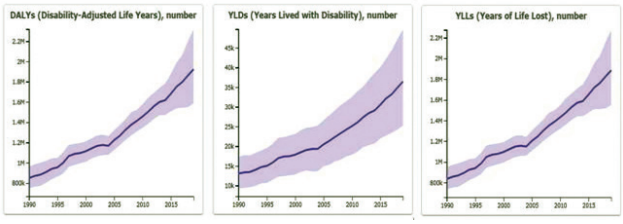
Age-standardized incidence and mortality rates per 1, 00,000 among the Indian population by age group (created using the GLOBOCAN 2022 estimates)

GLOBOCAN projections show that there will be a 69.1% rise in the incidence of oral cancer cases by 2045 compared to 2022, reaching an absolute annual incidence of 2,43,150. By 2045, the oral cancer mortality rate is estimated to increase by 69.5%; these numbers are 83.9% and 99% in the >50 and >60 years age groups, respectively. The corresponding projected percentage rise in the incidence of breast cancer, the most common cancer in India, is only 65.7% underscoring the emergence of oral cancer as the rapidly increasing type of cancer in India posing a striking challenge to the Indian health system.

With due regard for and sensitivity towards the efforts of the International Agency for Research on Cancer (IARC) and the national cancer registries, it is to be acknowledged that the reported incidence and mortality rates could be gross underestimates of the actual scenario in light of the inequitable distribution of cancer registries and pronounced disparities in access to cancer screening services.

DALYs, YLDs, and YLLs of Oral Cancer in India

Literature suggests that there is a significant negative influence of oral health on the quality of life among oral cancer patients. With reference to the Disability Adjusted Life Years (DALY), an important indicator of the burden of a disease/health condition, there had been a 126.83% rise in the DALYs of oral cancer in India over the past three decades as opposed to an increase by 92.89% at the global level during this period. Figure 3 shows the trends of the number of Years Lived with Disability (YLDs), Years of Life Lost (YLLs), and DALYs of oral cancer from 1990 to 2019 among the Indian



Trends of oral cancer DALYs, YLDs, and YLLs from 1990 to 2019 among the Indian population (created using the GBD Vizhub using the 1990-2019 metrics)

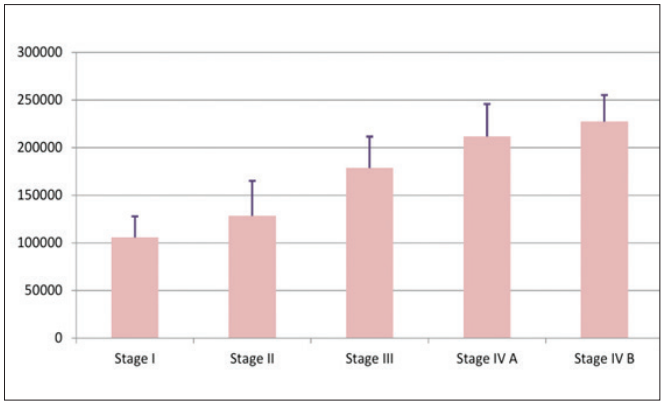
population with confidence bands representing the uncertainty.

Health Care Costs and Productivity Loss

Besides the burden imposed by oral cancer in terms of morbidity and mortality, the fiscal burden inflicted on a nation's health system is a prominent area to focus on. It is estimated that India spent around 322 million US dollars for oral cancer treatment in the year 2020. This expenditure is projected to be 3.2 billion US dollars over the next 10 years even without accounting for any cost inflation. India reported the highest productivity loss due to premature death and morbidity from oral cancer with a staggering total of 740 million US dollars. With relatively high age-specific oral cancer

incidence among the younger Indian population, these productivity losses are only bound to increase causing a catastrophic economic loss, owing to the loss or compromise in productivity from the most yielding age groups.

In a first-of-its-kind study to ascertain the cost of illness for oral cancer in India, using a bottom-up methodology that prospectively collected data on the costs incurred for services as they were used, Singh AG et al. provided cost distribution for oral cancer care in India. The figure below presents the cost per unit based on the stage of oral cancer. The fact that almost 60-80% of oral cancer cases present at an advanced stage only escalates the financial burden on the system. Emphasizing the straining economic impact of oral cancer treatment and promoting the potential that screening for and early detection of oral potentially malignant disorders (OPMDs) hold in reducing the incidence and the



Costs incurred per unit for treatment of oral cancer based on its stage (created using the data reported by Singh AG et al., 2021)

corresponding health expenditure for treatment of advanced stages of oral cancer is quintessential in the advocacy for prioritizing oral cancer in the Indian cancer control strategies.

In view of the significant burden imposed by oral cancer on individuals, corresponding families, and the nation's progress, it is pertinent that prevention of oral cancer be identified as an absolute priority. Raising public awareness on the common risk factors for oral cancer in India that include tobacco consumption, alcohol, and areca nut use, eliminating or curtailing the exposure to these risk factors by developing cost-effective measures, training the populations in oral self-examination, articulation of feasible strategies for population-based screening of OPMDs and oral cancer, ensuring universal access to quality oral cancer care, promoting clinical and public health research in the field of oral cancer are among the effective strategies to combat the oral cancer challenge in India.

Chapter 5

ETIOPATHOGENESIS

New WHO 2002 classification

Oral potentially malignant disorders and oral epithelial dysplasia.

Oral potentially malignant disorders

Oral epithelial dysplasia

Proliferative verrucous leukoplakia

Submucous fibrosis

HPV-associated dysplasia

Leukoplakia

Leukoplakia is “a clinical term for a white plaque of questionable risk after having excluded other known diseases or disorders that carry no increased risk for cancer”

Etiology and Risk Factors

- Smoke (mainly) or smokeless form together with chronic alcohol consumption,
- Ultraviolet radiation,
- Ill-fitted dentures,
- Bacterial infections,
- Epstein Barr virus (EBV)
- Candida species and
- Herbal plant extracts

Alterations (insertions/deletions/mutations) with inside the chromosomal location(s) with tumor suppressor genes or proto-oncogenes boom the carcinogenic capacity of OPMDs.

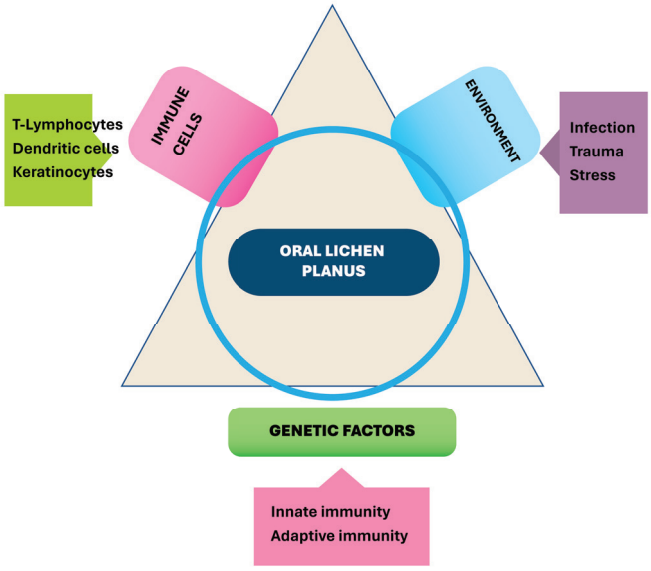
- Chromosomal deletion in 3p14 and 9p21
- Deletion in 4q, 8p, 11q, and 17p region
- Mutation of p53 can disrupt its regulatory function and lead to uncontrolled cell growth.

**(For Diagnostic- Therapeutic Algorithm for Leukoplakia Ref. Appendix 4)*

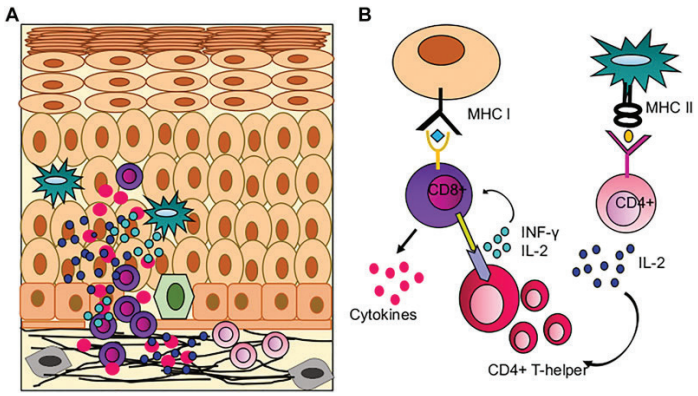
Oral Lichen Planus

OLP is known as a disease of unknown etiology, however, probable causative factors

- Genetic Susceptibility,
- Immunological Illnesses
- Malnutrition
- Psychological
- Infection



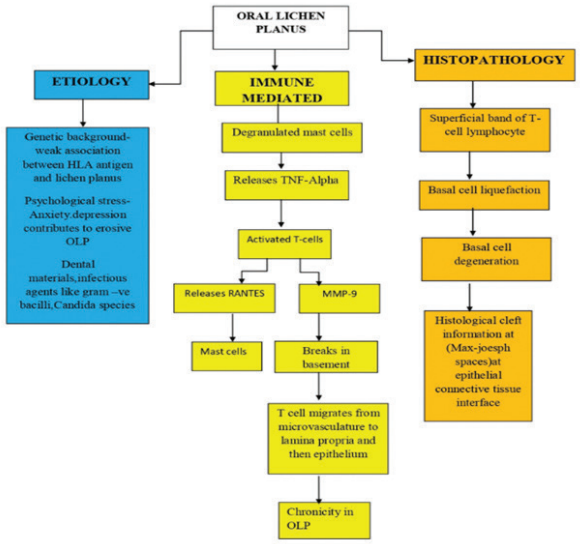
Pathogenesis at A) Cellular & B) Molecular Levels



Immune cells in OLP pathogenesis;

(A) Immune infiltration in OLP, CD8+ T cells mediated hyper-immune activation leading to apoptosis of basal keratinocytes.

(B) Possible mechanism of hyper immune response in buccal mucosa, where CD8+ T cells are activated by oral keratinocytes and CD4+ T cells.



Schematic Image showing an overview of Oral Lichen Planus

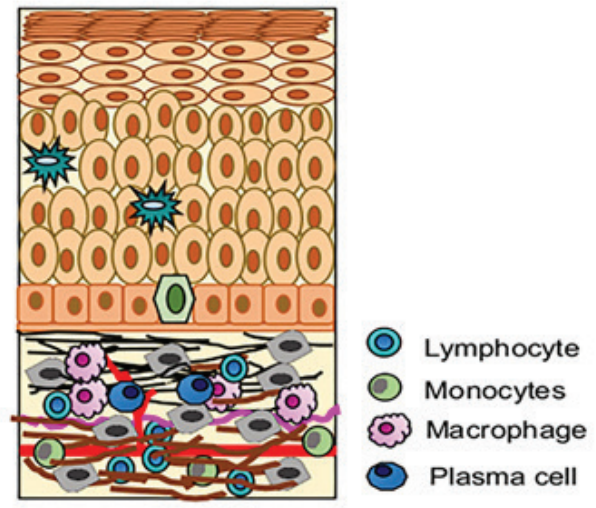
Oral Submucous Fibrosis

Oral submucous fibrosis (OSMF) is a fibrotic condition of oral mucosa characterized by epithelial immune cell infiltration followed by a fibro-elastic change in the lamina propria and submucosa leading to stiffness of the oral mucosa.

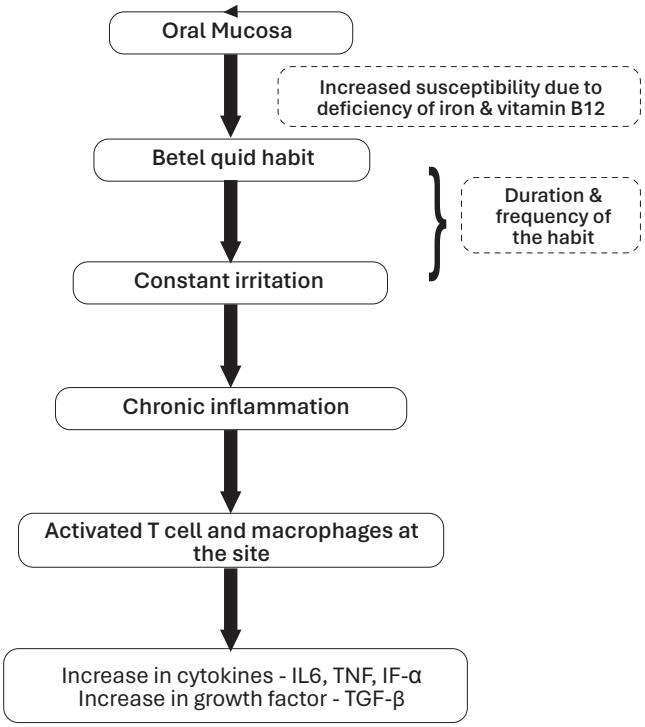
Etiology:

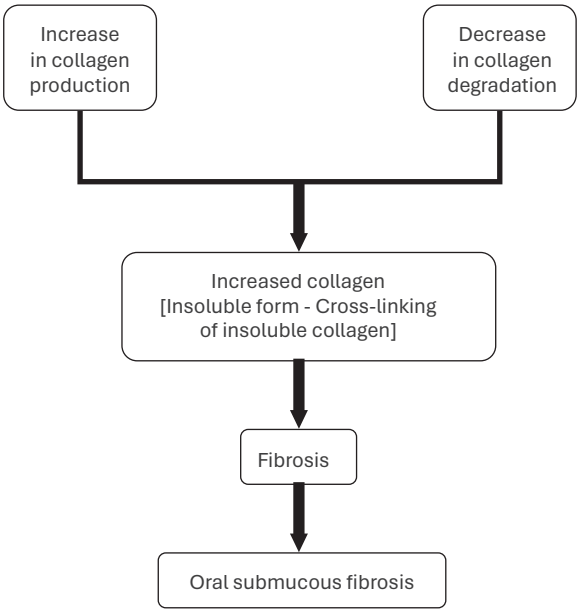
- Areca Nut Products
- Chilies
- Genetic Factors
- Immune Reactions
- Nutritional deficiencies

At Cellular Level



Hyperkeratotic epithelial cells in OSMF. Immune activation in OSMF show the presence of different types of immune infiltrates in sub mucous layer. Increase in fibroblast cells leads to high production of collagen fibers (brown bar) leading to fibrosis of oral mucosa.





(Courtesy: Upama Sishan – ETIOPATHOGENESIS OF OSMF)

Actinic Cheilitis

When sun or UV radiation exposure Ultra Violet light B (UVB)-induced transformed keratinocytes grow clonally, with molecular and genomic alterations.

Prolonged UV light radiation eliminates the tumor suppressor gene p53, resulting in excessive proliferation of defective cells. This gene mutation becomes more prevalent as actinic cheilitis and actinic keratoses progress to SCC.

Proliferative Verrucous Leukoplakia

The etiology is unclear but the underlying genetic alteration can also be a major cause for the lesion. Genetic alteration involves a change in ploidy level, Loss of heterozygosity (LOH), Allelic loss at 9p21, alteration in p53, higher expression of Mcm2 levels, and delayed G0-G1 is also noted.

Discoid Lupus Erythematosus

The inflammatory connective tissue disease lupus erythematosus is a kind of widespread autoimmunity marked by immune complexes and pathogenic autoantibodies that are thought to be caused by a reduction in immunological tolerance. It is evident that, in contrast to systemic lupus erythematosus, Th1 cells predominate in cutaneous inflammatory infiltrates. However, the evidence for discoid lupus erythematosus without associated SLE (CDLE) does not indicate whether circulating inflammatory cells and autoantibodies are involved in the pathogenesis.

Oral Cancer

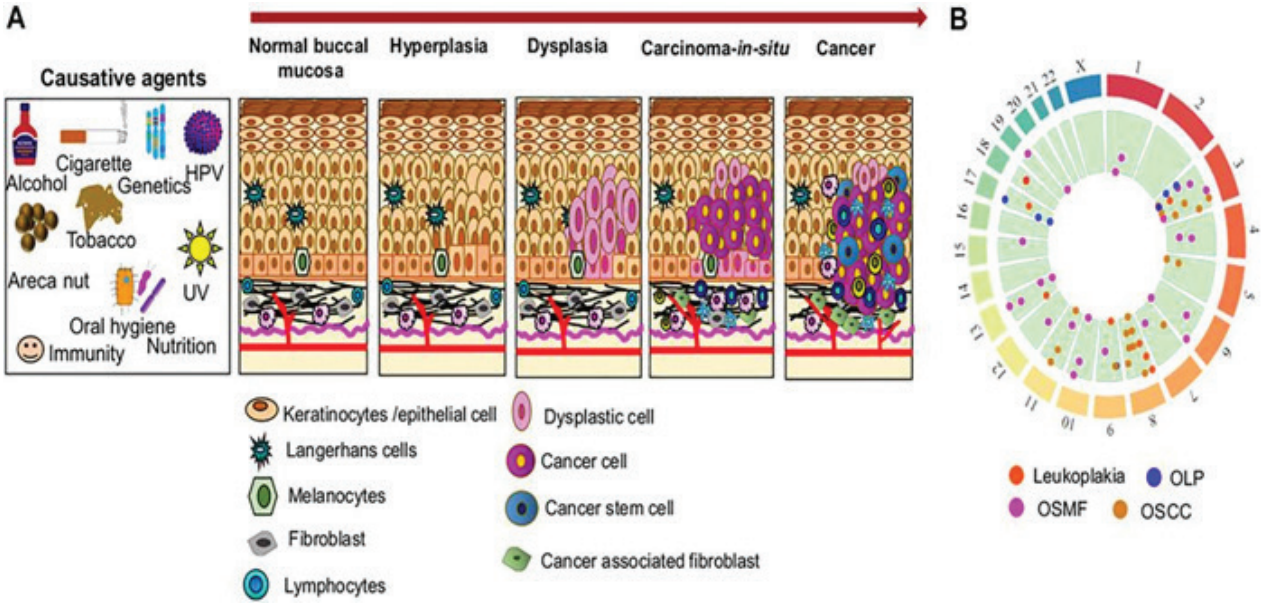
"Oral cancer, a disease of epithelial origin, is associated with multifactorial etiology, such as genetic, epigenetic, habitual (tobacco/areca nut/cigarette/alcohol), and microbial factors, which often vary with geographical regions or ethnic groups. A series of histopathological changes have been documented in normal mucosa during oral cancer progression. These changes include hyperplasia, dysplasia, carcinoma in situ, and, finally, oral cancer."

Oral carcinogenesis like any other cancer is a progressive disease and normal epithelium passes through stages starting from dysplasia to finally transforming into invasive phenotypes. Although all types of carcinomas are seen in the oral cavity, the most common form of OC is squamous cell carcinoma. Use of genetic and proteomic approach in recent years have revealed the molecular pathological picture of OC. There is active search to identify genetic alterations in oncogenes or tumour suppressor genes, role of genomic instability and epigenetic modifications and to generate a gene expression profile in oral oncogenesis.

Overview Of OPMDs and Risk Factors causing Oral Squamous Cell Carcinoma

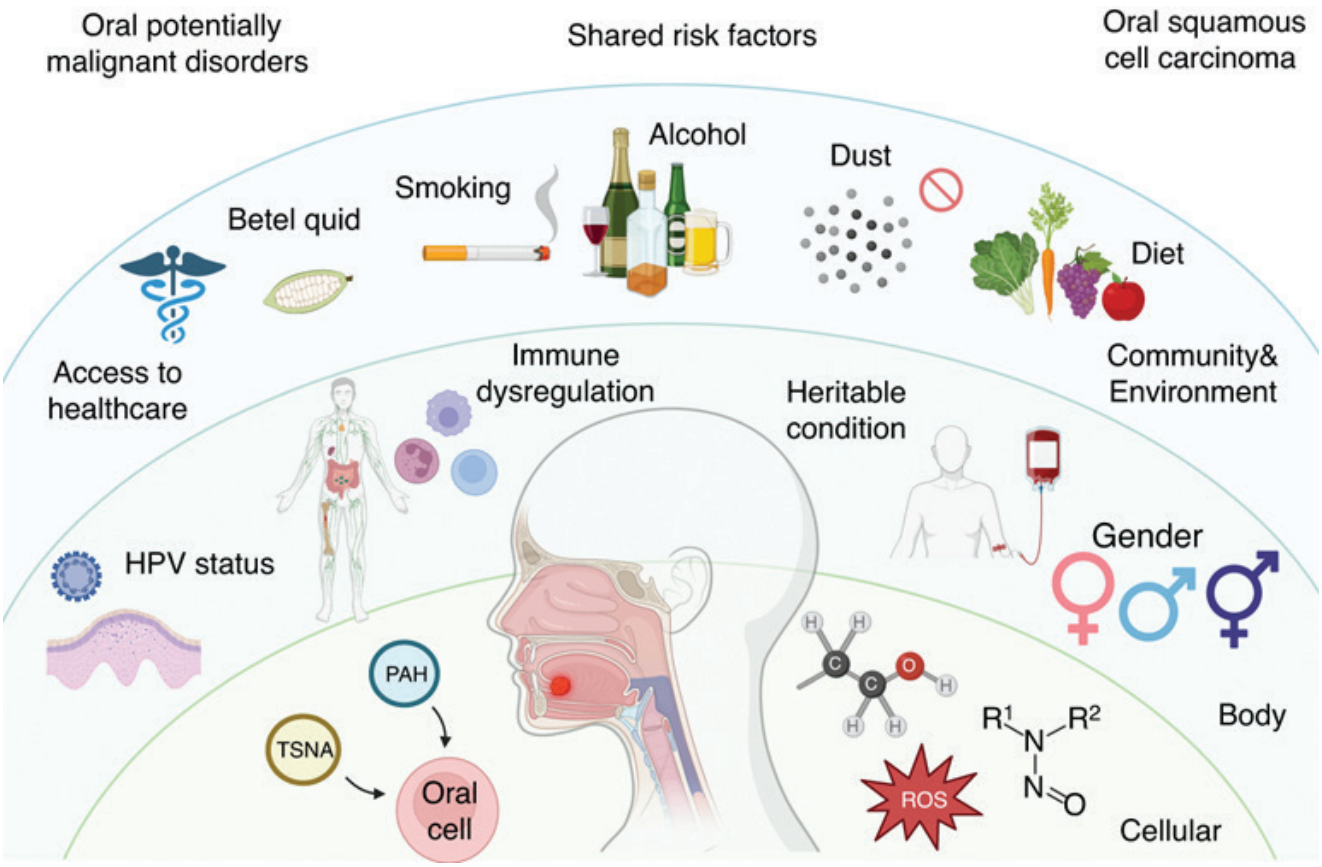
Risk factors of OPMDs and OSCC

The initiation and development of OPMDs and OSCC share similar risk factors, including smoking, alcohol abuse, betel quid (BQ) chewing, human papillomavirus (HPV) infection, nutritional insufficiency, immune deficiency, and hereditary conditions. OPMDs oral potentially malignant disorders, OSCC oral squamous cell carcinoma, PAH polycyclic aromatic hydrocarbons, ROS reactive oxygen species, TSNA tobacco-specific nitrosamines (as diagrammatically portrayed below).



Histological Representation of Oral Cancer

(Courtesy: Kumari P, Debta P, Dixit A. Oral Potentially Malignant Disorders: Etiology, Pathogenesis, and Transformation Into Oral Cancer. Front Pharmacol. 2022 Apr 20;13:825266. doi: 10.3389/fphar.2022.825266. PMID: 35517828; PMCID: PMC9065478)



Risk factors of OPMDs and OSCC. The initiation and development of OPMDs and OSCC share similar risk factors, including smoking, alcohol abuse, betel quid (BQ) chewing, human papillomavirus (HPV) infection, nutritional insufficiency, immune deficiency, and hereditary conditions. OPMDs oral potentially malignant disorders, OSCC oral squamous cell carcinoma, PAH polycyclic aromatic hydrocarbons, ROS reactive oxygen species, TSNA tobacco-specific nitrosamines

(Courtesy : Ram, H. et al. Oral cancer: risk factors and molecular pathogenesis. J. Maxillofac. Oral Surg. 10, 132–137 (2011)

Chapter 6

RISK FACTORS FOR OPMDs AND ORAL CANCER

A risk factor is anything that enhances a person's chance of getting a disease such as cancer. Different cancers have different risk factors. Some risk factors, like smoking, can be altered. Others, like a person's age, or family history, can't be changed. Risk factors don't tell us everything. Having a risk factor or even many doesn't mean that the person will get the disease, and many people who get the disease have limited or no known risk factors. Oropharyngeal cancers are often grouped with other cancers in the head and neck area and these cancers often have many of the same risk factors as follows

Risk factors for OPMDs and Oral Cancer	
1) Epigenetic Factors	1. Smokeless and Smoking Tobacco Use
	2. Areca Nut Chewing
	3. Alcohol
	4. Diet and Nutrition
	5. Viruses
	6. Fungal Infections
	7. Syphilis
	8. Radiation
	9. Age
	10. Gender
	11. Ultraviolet (UV) light
2) Genetic Factors	
3) Unproven or Controversial Risk Factors	1. Mouthwash
	2. Irritation from dentures
	3. Oral health

Epigentic Factors

Smokeless and Smoking Tobacco Use

Tobacco smoking is considered the main causal factor for oral cancer. Besides, the World Health Organization (WHO) has labeled smokeless tobacco (SLT) as a carcinogenic agent relationship between smoking and oral cancer has been established by epidemiological studies. The most significant carcinogens in tobacco smoke are the aromatic hydrocarbon benz-pyrene and the tobacco-specificnitrosamines (TSNs) namely 4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN), and their metabolites covalently bind with deoxyribonucleic acid of keratinocyte stem cells forming DNA adducts. These adducts are accountable for critical mutations involved in DNA replication.

The use of smokeless tobacco has become dominant all over the world. Smokeless tobacco is placed inside the oral cavity in contact with the mucous membranes, where the nicotine is absorbed to deliver the desired effect. Smokeless tobacco has been used in many forms in different parts of the world, for instance, the use of oral snuff is more common in the West and the Middle East. Betel quid chewing in a variety of forms & various ingredients is widespread in Asia, where it has been a custom and cultural habit since tobacco reached India via the Portuguese, Consumption of smokeless form of tobacco causes mainly oral precancer and cancer. The habit of oral snuff (referred to as snuff-dipping) causes a condition called 'snuff-dipper's cancer' classically designated as verrucous carcinoma. Prevention can be done through Counselling by healthcare practitioners and pharmacotherapy (nicotine replacement, varenicline, and/or bupropion) for smoking cessation.

Areca Nut Chewing

Areca nut, because it is often wrapped in betel leaf, is now regarded as a type 1 carcinogen. It is chewed raw, dried, or roasted, or as part of betel quid, by millions of people and use is spreading across the Pacific, as well as in emigrant Asian communities worldwide. Inexpensive, prepackaged areca nut products, such as pan masala are of recent concern, especially among youth. The presence of tobacco in the betel quid adds considerably to the carcinogenicity. Ceasing areca

nut consumption through counseling would prevent roughly half of the oral cancers.

Alcohol

Epidemiological studies indicate that drinking alcoholic beverages increases the risk of oral cancer twofold to sixfold and is an independent risk factor, with risk increasing with the quantity consumed. The numerous pathways by which alcohol may exert carcinogenic influence include topical exposure leading to a direct effect on cell membranes, variation in enzymes that metabolize alcohol, altered cell permeability, and/or systemic effects, such as immunological deficiency, nutritional deficiency, and disturbed liver function. Alcohol consumption has been shown to act synergistically with tobacco in the increased risk of development of oral potentially malignant and oral cancer.

Few studies have been accomplished to analyze with patients who drink alcohol but are non-smokers and in patients who smoke but are non-drinkers. In one such study, alcohol has been found to be an independent risk factor for oral leukoplakia in the Indian population. However, similar studies assessing the oral epithelial dysplasia occurrence in alcohol drinkers who are nonsmokers, found that the role of alcohol in the development of oral epithelial dysplasia is critical only when considered in conjunction with tobacco.

Pharmacotherapy for alcohol use disorder (approved agents include naltrexone, acamprosate, nalmefene, and disulfiram) and cognitive behavioural therapy, or other forms of evidence-based counseling, have been shown to improve alcohol cessation rates.

Age

Cancers of the oropharynx usually take many years to develop, so they are not common in young people. Most patients with oral cancers are older than 55 years when the cancers are first found. HPV-linked cancers tend to be identified in people younger than 50. Oral screening interventions have found a greater detection of early-stage cases and progression of the disease.

Gender

Oropharyngeal cancers are twice as common in men than in women. This might be because more likely to use tobacco and alcohol by men in the past. HPV-related oropharyngeal cancers are also seen more frequently in men.

Diet and Nutrition

The working group of the International Agency for Research on Cancer (IARC) has declared that low intake of fruits and vegetables predisposes to increased risk of cancer development. Regular consumption of more fruit and vegetables, particularly of carrots, green peppers and fresh tomatoes, were associated with reduced risk of oropharyngeal cancer. Substantial evidence has shown that certain micronutrients decrease the risk of cancer development. They include vitamins A (retinol), C (AA), and E (α-tocopherol); carotenoids (β-carotene); potassium; & selenium (38–43). β-carotene, retinol, retinoids, vitamin C (AA), and vitamin E (α-tocopherol) are antioxidants that are essential in reducing free radical reactions that can cause DNA mutations, changes in enzymatic activity, and lipid peroxidation of cellular membranes.

Dietary factors and Cultural risk factors appear to interplay in the progress of oral cancer and precancer. Studies have shown the association between smoking and the lowering of serum levels of nutrients. For instance, cigarette smokers had lower levels of β-carotene than nonsmokers, and also smoking modified the association between dietary and serum β-carotene. The habit of quid chewing has also been shown to reduce serum levels of vitamins A, C, B12, folate, and β-carotene in quid chewers than non-quid-chewers.

Antioxidants like vitamin C, E, and carotenoids. Vitamin A, isotretinoin (13-cis retinoic acid), green tea extract, and some medicinal herbs have been used as chemo-preventive agents. Studies have shown that consumption of probiotics was also useful for chemo-prevention.

Viruses

Viruses have been strongly associated with the development of malignant tumors of the oral squamous epithelium. Viral infections of latent or chronic nature are usually responsible for inducing malignant transformation by interfering with the host's cell cycle machinery and these viral genes & gene products may affect proliferation and cell growth. Certain viral genes are proto-oncogenes which become oncogenes when

inserted into the host's DNA and ultimately resulting in malignant transformation. The prototypic viruses implicated in oral cancer development are human herpes virus (Epstein–Barr virus (EBV)).

HPV vaccination is currently approved as a two-dose routine vaccine beginning at ages 11 and 12. Vaccination has shown a reduction in the prevalence of oral HPV 6, 11, 16, and 18 by 88.2%.

Fungal Infections

Infections caused by Candida species, in particular, Candida albicans have been associated with the pathogenesis of oral potentially malignant lesions. Superficial fungal hyphae of Candida albicans have been found superimposed on leukoplakia, particularly nodular leukoplakia, many of which have undergone malignant transformation. Candida species are commensals in the oral cavity that become opportunistic during the host's immunosuppression due to drug therapy or systemic diseases. Besides immunocompromised individuals, Candida infection can coexist or be associated with other risk factors like iron deficiency and in chronic smokers which may prove synergistic in the development of oral cancer.

Syphilis

Tertiary syphilis has been known to predispose to the initiation and development of oral cancer along with additional risk factors such as tobacco & alcohol. However nowadays, tertiary syphilis is rare in clinical practice as the infection is diagnosed & treated before the onset of the tertiary stage. The data on the causal association between syphilis and oral cancer is weak. There are reports of 19 and 6% serological positivity for syphilis among tongue cancer patients.

Ultraviolet (UV) light

Sunlight is the main source of ultraviolet light for most people. Cancers of the lips are more common in people who are outdoor workers where they are exposed to sunlight for extended periods of time. Use of solar protection agents can prevent the risk associated with UV radiation

Radiation

Substantial evidence exists for an association between exposure to ionizing radiation and the later development of tumors of salivary glands. The tumorigenic effects of therapeutic radiation to the head & neck on the salivary gland tissue have been evaluated.

Genetic Factors

It is currently established that up to 10% of all cancers have a strong hereditary component. The role of genetic components in the development of oral cancer is being suggested by several studies showing familial clustering. Evaluation of specific genetic polymorphism in key genes involved in oral carcinogenesis has been the major area of study. Glutathione S-transferase M1 (GSTM1) null genotype seems to be the most dependable polymorphic susceptibility marker for head & neck cancer including oral cancer. Meta-analyses by Tripathy and Roy showed that the GSTM1 null genotype conferred a 20–50% significantly increased head & neck oral squamous cell carcinoma risk. However, a population-based study to determine the genetic or familial disposition to oral cancers is limited by the coexisting risk factors like smoking & alcohol. It is also thought that certain individuals inherit the susceptibility of inability to metabolize carcinogens or procarcinogens and/or an impaired capacity to repair the DNA damage.

Unproven or Controversial Risk Factors

Mouthwash

Several studies have recommended that mouthwash with high alcohol content might be linked to a higher risk of oropharyngeal cancers. However recent research has questioned these results. Studying this possible link is complicated by the fact that people who smoke and frequent drinkers are more likely to use mouthwash than people who neither smoke nor drink.

Irritation from dentures

It's been suggested that long-term irritation of the lining mucosa of the mouth caused by poorly fitting dentures is a risk factor for the development of oral cancer. However several studies have found no increased risk in denture wearers overall. Poorly fitting dentures can tend to trap agents that have been proven to cause oral cancer, such as alcohol & tobacco particles, so denture wearers should have them checked by a dentist regularly to ensure a good fit. All denture wearers should remove their dentures at night, and clean and rinse them thoroughly every day.

Oral Health

Studies have suggested the overall health of the mouth, teeth, & gums may influence oral cavity and oropharyngeal cancer risk because of changes in the normal bacteria in the mouth. Poor oral hygiene maintenance, which can lead to loss of tooth, may also be linked to these cancers. Overall survival may also be affected. Further research is needed, but regular dental visits, as well as brushing & flossing may lessen these risks and have many other health benefits too.

**(Refer Appendix 6 for a poster on risk factors for OPMDs/cancer)*

Effect of Risk Factors on Quality of Life

Patients with these risk factors will have lower Health-related quality of life than normal individuals which also affects Vitality, Social Functioning, and Role-Emotional Health and various CNS manifestations like Depressive symptoms were also associated. While smoking, alcohol intake, and depression may be episodically treated; standardized protocols and aggressive intervention strategies can be implemented in these populations to eliminate the adverse effects.

Key Message

Numerous risk factors might be involved in the development oral potentially malignant disorders and oral cancer. Amongst tobacco smoking, alcohol consumption, and HPV are the most studied risk factors. Moreover, inflammation and genetic susceptibility are believed to play a crucial role. Several studies have focused on oral cancer risk factors. Nevertheless many patients are identified with oral cancer despite abstaining from known lifestyle or environmental risk factors, where factors like genetic susceptibility are believed to play the causative role. Hence, it is significant for the public and the clinicians to be absolutely conscious of the risk factors for oral cancer and it is prudent for dentists to look cautiously for early signs of oral cancer, while routine examination of the oral cavity particularly in patients with history of known risk factors.

Chapter 7

CLASSIFICATION OF OPMDs

Classification of Precancerous Lesions and Condition (WHO)

According to WHO oral potentially malignant disorders and oral epithelial dysplasia as

World Health Organization (WHO) classifications

Architectural criteria:

- Irregular epithelial stratification
- Loss of polarity of basal cells
- Tear drop shaped rete ridges
- Increased number of mitotic figures
- Abnormal superficial mitosis
- Premature keratinization in single cells
- Keratin pearls within reti ridges
- Loss of epithelial cell cohesion

Cellular criteria:

- Abnormal variation in nuclear size (Anisonucleosis)
- Abnormal variation in nuclear shape (Nuclear pleomorphism)
- Abnormal variation in cell shape (Cellular pleomorphism)
- Increased nuclear – cytoplasmic ratio
- Increased number and size of nucleoli
- Hyperchromatism

(El- Naggar AK, Chan JK, Grandis JR, Takata T, Slootweg PJ. WHO classification of head and neck tumours. WHO/IARC classification of tumours. 4th ed., vol 9, International Agency for research on cancer (IARC) Press;2017.)

Binary System (2006)

Low risk – No / Questionable / Mild epithelial dysplasia

High risk – Moderate epithelial dysplasia / Severe epithelial dysplasia

(Waranakulasuriya S, Reibel J, Bouquot J, Dabelsteen E. Oral epithelial dysplasia classification system: Predictive value, utility, weakness and scope for improvement. J Oral Pathol Med 2008;37:127-33)

Leukoplakia

Based on the clinical type	Homogeneous leukoplakia
	Non-homogeneous leukoplakia
Based on aetiology	Tobacco associated
	Idiopathic
Based on extent	Localized
	Generalized

Histopathological Classifications of Leukoplakia (Epithelial Dysplasia)

Edward Odell et al in 2021, did a review study on oral epithelial dysplasia recognition, grading, and clinical significance, aimed to describe current views on the histological interpretation of epithelial dysplasia in OPMDs, with emphasis on leukoplakia and erythroplakia, and their relationship to malignant transformation and treatment, concluded that the current clinical management of oral epithelial dysplasia is discussed based on histopathology point of view.

Sonia Gupta et al in 2020, did a review article about the current challenges & diagnostic pitfalls in the grading of dysplasia in oral potentially malignant disorders by including different grading systems of oral epithelial dysplasia and concluded that even though the WHO 2017 grading of OED is currently acceptable it has its limitations, so extensive robust research has to be done to propose a reliable and reproducible method of grading of OED.

Omar kujan et al in 2006, conducted a study to assess the evaluation of a new binary system for grading as well as in predicting the malignant progression of oral epithelial dysplasia, based on utilizing 96 oral epithelial biopsies with known clinical outcomes by three oral pathologists and one general pathologist as low risk and high-risk lesions based on architectural and cytological changes and concluded that it has better prognostic value for the clinicians to take critical decisions, particularly in the cases of moderate dysplasia due to its sensitivity and specificity.

Binary System: This Binary system was graded according to Kujan O et al. in 2005. They graded them as high-risk lesions and low-risk lesions.

- **High-risk lesions:** Potential susceptibility for malignancy- based on observing at least four architectural changes and five cytological changes.
- **Low-risk lesions:** less likely to have potential vulnerability for malignancy- correlated with observation of less than five cytological changes or less than four architectural changes (Barnes L, Eveson JW, Reichart P, Sidransky D. World Health Organization Classification of Tumors. Pathology and genetics of head and neck tumors. IARC Press: Lyon 2005; 12:177-79)

WHO grading of epithelial Dysplasia in 2005

Depending upon cytology and architecture changes in the epithelium

- **Hyperplasia**: It is described as an increase in the number of cells. This may lead to the increased thickness of the spinous layer or acanthosis in the basal and parabasal cell layers and termed it basal cell hyperplasia. The epithelial architecture shows regular stratification and there is no cellular atypical.
- **Mild Dysplasia:** Fewer nuclear abnormalities, most distinct in the lower third of the epithelial thickness. Cells show normal maturation and stratification. A few but no abnormal mitoses may be present in the para-basal layers.
- **Moderate Dysplasia:** More distinct nuclear abnormalities are seen in two-thirds of the basal epithelium. Stratification and cell maturation are seen in the upper layers. Increased mitosis is evident in the parabasal and intermediate layers but none is abnormal.
- **Severe Dysplasia:** Marked nuclear abnormalities involving more than two-thirds of the epithelium. Abnormal mitosis may be present in the upper layers. Maturation and stratification were still present in the most superficial layers.
- **Carcinoma in situ:** Dysplastic features shows entire thickness or almost the full thickness of the squamous epithelium and also cellular features of carcinoma without stromal invasion. Requires top-to-bottom change with undifferentiated, primitive cells from the basal layer to the topmost layers. *(Source: Barnes L, Eveson JW, Reichart P, Sidransky D. World Health Organization Classification of Tumors. Pathology and genetics of head and neck tumors. IARC Press: Lyon 2005; 12:177-79).*

Neville et al. in 1995 graded epithelial dysplasia as follows:

- **Mild epithelial dysplasia:** Hyperchromatic and slightly pleomorphic nuclei are noted in the basal and supra-basal cell layers of stratified squamous epithelium.
- **Moderate epithelial dysplasia:** Dysplastic changes extend from the basal layer to the spinous layer's mid-portion and are characterized by hyperchromatism of the nucleus, pleomorphism, and cellular crowding. Hyperkeratosis on the epithelial cell layer along with a prominent granular cell layer.
- **Severe epithelial Dysplasia:** Cellular crowding and disordered arrangement throughout most of the epithelial thickness, although slight maturation and flattening of the cells are present at the epithelial surface. Epithelial cells mature very little as they progress toward the hyperparakeratotic surface.
- **Carcinoma in situ:** When the entire thickness of the epithelium is involved, the term carcinoma in situ is used. Dysplastic cells extend from the basal layer to the mucosa's surface with no invasion into the underlying connective tissue. *(Smith CJ, Pindborg JJ. Histological grading of oral epithelial atypia by the use of photographic standards. Copenhagen: C. Hamburgers Bogtrykkeri 1995; 8: 5-30)*

Kramer IRH et al., in 1980 did a grading system that proposes an epithelium is more likely to show dysplasia with two or more features following

World Health Organization (WHO) in 1978 A collaborating reference center established by the WHO in the year 1967 to organize and redefine lesions that should be considered oral pre-cancer and determine their relative risk of becoming malignant. The WHO defined and listed twelve characteristics of epithelial dysplasia and graded epithelial dysplasia as mild epithelial dysplasia, moderate epithelial dysplasia, and severe epithelial dysplasia and published the histopathological typing of precancer and cancer of

the oral mucosa. The distinct histological features are listed.

- Loss of polarity of basal cells
- Basaloid appearance in more than one layer of cells
- An increase in the nuclear-cytoplasmic ratio
- Drop-shaped rete-pegs
- Irregular epithelial stratification
- Increased number of mitotic figures
- Abnormal mitotic figures in the middle third of the epithelium
- Cellular polymorphism
- Nuclear hyperchromatism

Drop-shaped Rete-pegs	Rete-pegs are wider in the deeper portions than they are more superficially.
Basal cell hyperplasia	The basal layer development shows several cells thick.
Irregular epithelial stratification or disturbed maturational sequence	This denotes disturbance in cellular stratification from the para basal or basal cell layer to the surface.
Cellular pleomorphism	Variation in size and shape of the cells.
Nuclear hyperchromatism	The nuclei in the cells are darkly stained due to an increase in DNA synthesis.
Prominent nucleoli	In some dysplastic epithelial and some carcinomas, the nuclei become more extensive and denser.
Increase in the nuclear-cytoplasmic ratio	The nucleus enlarges and occupies a greater part of the cell than the cytoplasm
Cell crowding	Increased in the number of cells per unit area due to basal cellular hyperplasia.
Increased Mitosis	It is the increase in the frequency of mitotic figures.
Mitosis in upper layers	The spread of mitotic activity to the epithelium's higher levels.
Abnormal Mitosis:	The appearance of mitotic figures in various forms other than normal in any one layer of epithelium, e.g. Tripolar mitotic figures.
Loss of cellular adhesion or cohesion	The cells lose cohesion due to dysregulation in desmosomal attachment
Intra epithelial keratinization	There is abnormal keratin formation within the cytoplasm of individual cells or groups of cells.

- Enlarged nucleoli
- Reduction of cellular cohesion
- Keratinization of single cells or cell groups in the prickle cell layer.

Banoczy J and Csiba A in 1976 in this system based on using criteria suggested by Mehta et al in 1971.Irregular epithelial stratification, with acanthosis or both, increased number of mitotic figures, increased nuclear-cytoplasmic ratio, Loss of polarity of cells, Nuclear pleomorphism, hyperchromatism, keratinization of single cells or cell groups in the prickle cell layer and loss of intercellular adherence.

They graded epithelial dysplasia as mild epithelial dysplasia based on any two features listed histological changes were present. Moderate epithelial dysplasia - when two to four histological features were present. Severe epithelial dysplasia- five or more histological changes were present.

Oral Sub Mucous Fibrosis

Based on Clinical Features of Oral Sub Mucous Fibrosis

- Mathur and Jha (1993)
- Ranganathan K et al., (2001)

Classification Based on Histopathological Features

- Utsunomya H et al., (2005)
- Haider et al., (2000)

Classification Based on Both Clinical and Histopathological Features

- Khanna JN et al., (1995)

Classification Based on Clinical Features

Mathur and Jha in 2006 classified clinical features of oral sub-mucous fibrosis into three stages

- **Stage 1: Early oral sub-mucous fibrosis**
  - Mild blanching
  - No restriction in mouth opening
  - No restriction in tongue protrusion, measuring from the mesio-incisal angle of an upper central incisor to the lip of the tongue when maximum protraction of the tongue
  - The burning sensation only on ingesting spicy food, hot liquids, etc.

- **Stage 2: Moderate oral sub-mucous fibrosis**
  - Moderate to severe blanching
  - Mouth opening was reduced by 33% tongue protrusion was reduced by 33% and flexibility also demonstrably decreased
  - Burning sensation even in the absence of stimuli
  - Presence of palpable bands.
  - Lymphadenopathy, either unilateral or bilateral.
  - Demonstrable anemia on hematological examination.
- Stage 3: Severe oral sub-mucous fibrosis
  - Very severe burning sensation, patients unable to perform day-to-day work
  - More than 66% reduction in mouth opening, check flexibility, and tongue protrusion
  - In many cases, the tongue may appear fixed, and ulcerative lesions may appear
  - Lymphadenopathy evident bilaterally.

Ranganathan K et al., in 2001 divided oral sub-mucous fibrosis based on mouth opening as follows

- **Group I:** only symptoms, with no demonstrable restriction of mouth opening
- **Group II** L Limited mouth opening 20 mm and above
- **Group III** : Mouth opening less than 20 mm
- **Group IV:** Oral sub mucous fibrosis advanced with limited mouth opening. Precancerous or cancerous changes seen throughout the mucosa

Desa J V In 1957 divided oral sub-mucous fibrosis into three stages based on clinical presentation

- Stage I: Stomatitis and vesiculation
- Stage II: Fibrosis
- Stage III: as its sequelae

Utsunomiya H, Tilakratne W.M, Oshiro K et al., in 2005 histo-pathologically divided oral sub mucous fibrosis based on the concept of pindborg and Sirsat and modified it as follows-

- **Early stage:** Large number of lymphocytes in sub epithelial, connective tissue, zone along with myxoedematous changes.
- **Intermediate stage:** granulation changes close to the muscle layer and hyalinization appears in sub epithelial zone where blood vessels are compressed by fibrous bundles. Reduced inflammatory cells in sub epithelial layer
- **Advanced stage:** inflammatory cell infiltrates hardly seen. The number of blood vessels is dramatically small in the sub-epithelial zone. Marked fibrous areas with hyaline changes extending from sub-epithelial to superficial muscle layers. Atrophic, degenerative changes start in muscle fibrosis.

Haider et al. In 2000 did histopathological grading of oral sub-mucous fibrosis

- **Very early stage (Stage I)** finely fibrillar collagen dispersed with marked edema. Plump young, fibroblast containing abundant cytoplasm. Blood vessels are dilated and congested. Inflammatory cells, mainly polymorph nuclear leukocytes with occasional eosinophils are found.
- **Early stage (Stage II):** Juxta epithelial area shows early hyalinization. Collagen is still in separate thick bundles. Moderate number of plump young fibroblasts is present. Dilated and congested blood vessels. Inflammatory cells are primarily lymphocytes, eosinophils, and occasionally plasma cells.
- **Moderately advanced stage (Stage III):** collagen is moderately hyalinised thickened collagen bundles are separated by slight residual edema. Fibroblastic response is less marked. Blood vessels are either normal or compressed. Inflammatory exudates consist of lymphocytes and plasma cells
- Advanced stage (Stage IV): collagen is completely hyalinized. Smooth sheets with no separate bundles of collagen are seen. Edema is absent. The hyalinised area is devoid of fibroblasts. Blood vessels are completely obliterated or narrowed. Inflammatory cells are lymphocytes and plasma cells.

Classification Based on Clinical and Histopathological Features

Khanna JN and Andrade NN in 1995 developed a group classification system for the surgical management of oral sub-mucous fibrosis

- **Group I:** Very early cases: common symptoms are burning sensation in the mouth, acute ulceration, and recurrent stomatitis and not associated with mouth opening limitation

Histopathology: fine fibrillar collagen network interspread with marked edema, blood vessels dilated and congested, large aggregate of plump young fibroblasts present with abundant cytoplasm, inflammatory cells mainly consist of poly morpho nuclear leukocytes with few eosinophils. The epithelium is normal.

- **Group II:** Early Cases: Buccal mucosa appears mottled and marble-like, widespread sheets of fibrosis palpable, interincisal distance of 26 to 35 mm

  Histopathology: Juxta epithelial hyalinization present, collagen present as thickened but separate bundles, blood vessels dilated and congested, young fibroblasts seen, moderate number inflammatory cells mainly consisting of polymorphonuclear leukocytes with few eosinophils and occasional plasma cells, flattening or shortening of epithelial rete ridges evident with varying degree of keratinization.

- **Group III:** Moderate to advanced cases: Trismus interincisal distance of 15 to 25 mm, buccal mucosa appears pale and firmly attached to underlying tissues, atrophy of vermilion border, vertical fibrous bands palpable at the soft palate, pterygomandibular raphe and anterior faucial pillars

  Histopathology: Juxta–epithelial hyalinization present, thickened collagen bundles, residual edema, constricted blood vessels, mature fibroblast with scanty cytoplasm and spindle-shaped nuclei, inflammatory excaudate which consists of lymphocytes and plasma cells, epithelium markedly atrophic with loss of rete ridges, muscle fibers seen in thickened and dense collagen fibers.

- **Group IV A:** Advanced cases: severe trismus, inter incisal distance of less than 15 mm, thickened faucial pillars, shrunken uvula. Restricted tongue movements. The presence of a circular band around the entire lip and mouth

- **Group IV B:** Advanced cases: presence of hyperkeratosis leukoplakia and / or squamous cell carcinoma

  Histopathology: Collagen fibers will become hyalinized smooth sheet, extensive fibrosis obliterate the mucosal blood vessels, eliminated melanocytes, absent fibroblasts within the hyalinised zones, total loss of epithelial rete ridges, and presence of mild to moderate atypia and extensive degeneration of muscle fibers.

Chapter 8

GRADING SYSTEMS

Background

Oral cancer encompasses malignancies that manifest in various parts of the oral cavity, including the tongue (dorsum, ventral or lateral surfaces), buccal and lingual mucosa, lips, palate, floor of the mouth, alveolar mucosa, and gingiva. Oral cancer most often arises due to factors such as tobacco smoking, smokeless tobacco use, alcohol consumption, or human papillomavirus (HPV) infection. Clinically, oral cancer may present as ulcers, swellings, ulcerative swellings, white or red lesions, or a combination of these manifestations. Additionally, oral cancer may extend to involve regional lymph nodes, such as those located in the submental, submandibular, and sublingual areas, and lymph node groups in the neck are described by levels I to VII. *(Ref. Appendix 1). The most common cancer of the oral cavity is Oral Squamous Cell Carcinoma (OSCC).

Upon diagnosing cancer within the oral cavity, dental and oral surgeons employ a structured clinical assessment known as staging to ascertain the extent of malignancy spread. Staging serves as a clinical assessment method aimed at determining the cancer's stage, providing crucial insights into its severity, and guiding treatment decisions for optimal management. Grading pertains to the microscopic evaluation of histopathological characteristics in OSCC, delineating different grades based on specific microscopic features indicative of various levels of cancer aggressiveness. These grades serve as prognostic indicators, offering insight into the likely outcomes, whether good (favorable) or worse (unfavorable).

Staging of oral cancer:

The most popularly used oral cancer staging system is the TNM staging system by the American Joint Committee on Cancer. TNM staging is based on three important parameters namely (1) tumor Size, (2) nodal (nearby lymph node) involvement, and (3) status of metastasis (cancer spread to different parts of the body). Cancer staging is done by an alphanumeric system i.e. TNM and each of the parameters are assigned with numerical code these numbers are called stage grouping.

Oral and Oro-pharyngeal cancers are known to be associated with Human Papilloma Virus DNA called HPV 16 positive cancers (p16 positive). American Joint Committee on Cancer (AJCC) proposed TNM staging of oral and Oro-pharyngeal cancers as p16-positive and p16-negative cancers. It is also worth noting that the prognosis is better on p16 positive cancers than on p16 negative cancers. The context of this chapter is focused on oral cancers and the incidence of p16 positivity is comparatively lower among oral cancers while comparing to pharyngeal cancers. In addition, the focus of the chapter is to target general dental practitioners. Hence the p16 negative TNM staging is discussed in this chapter, and which is essential and adequate for general dentistry practitioners.

T: Tumor Size

Tumor size is evaluated using five numerical grades (0-4) determined by measuring the lesion. T0 indicates no evidence of a primary tumor, while Tis represents carcinoma in situ. T1 signifies a tumor 2 cm or less, T2 is for tumors larger than 2 cm but not exceeding 4 cm, and T3 indicates tumors greater than 4 cm. T4a denotes invasion through cortical bone or into deep muscles, while T4b indicates invasion into deeper structures or encasement of arteries.

Description of Tumor grouping based on the size

Tumor size grouping	Descriptor of Tumour size grouping
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a (lip)	Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin (chin or nose)

T4a (oral cavity)	Tumor invades through cortical bone, into deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face
T4b (lip and oral cavity)	Tumor invades masticator space, pterygoid plates, or skull base; or encases internal carotid artery

N: Nodal Involvement

Nodal involvement is assessed with three numerical grades (0-3) based on the extent of lymph node involvement on either the same side or both sides. N0 indicates no lymph node metastasis, while NX indicates that regional lymph nodes cannot be assessed, and N1 represents metastasis in a single lymph node on one side, measuring 3 cm or less. N2 is further divided: N2a signifies metastasis in a single lymph node, 3-6 cm in size, N2b denotes metastasis in multiple lymph nodes on one side, none larger than 6 cm, and N2c represents metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm. N3a indicates a lymph node larger than 6 cm but hasn't spread outside, while N3b signifies lymph node involvement larger than 3 cm with spreading beyond the node.

Description of nodal grouping based on the involvement of lymph nodes

Nodal involvement grouping	Descriptor of nodal involvement grouping
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis as specified in N2a, 2b, 2c below
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension. (Midline nodes are considered as ipsilateral lymph nodes)
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3a	Metastasis in a lymph node more than 6 cm in greatest dimension but has not grown outside of the lymph node
N3b	Metastasis in a lymph node larger than 3 cm in greatest dimension and has grown outside the lymph node.

M: Metastasis

Metastasis status is graded as 0 or 1, indicating the absence or presence of distant site involvement of oral cancer, respectively.

Description of nodal grouping based on the involvement of lymph nodes

Metastasis grouping	Descriptor of metastasis grouping
M0	No distant metastasis
M1	Presence of distant metastasis

AJCC Staging of Oral Cancer in TNM Assessment

Following these assessments of TNM and various groupings, the AJCC categorizes oral cancer into stages 0 to IV. As the classification group increases, the prognosis tends to worsen. In simple words, Stage IV carries a poorer prognosis compared to Stage I. In other words, the lower number indicates the cancer has less spread, and the higher number indicates that the cancer spread is more.

AJCC staging of TNM assessment of p16 negative oral cancers

AJCC Stage	Grouping		
	Tumor Size T	Nodal involvement N	Metastasis B
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	OR		
	T3	N0, N1	M0

Stage IVA	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IVB	Any T	N3a / N3b	M0
	OR		
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Grading of Oral Cancer

Grading involves the microscopic evaluation of histologically diagnosed oral squamous cell carcinoma. It categorizes tumors based on the presence of keratin pearls and the resemblance of atypical/malignant neoplastic cells to the parental cells of squamous epithelium. These tumors are graded into well, moderately, and poorly differentiated squamous cell carcinoma. Well-differentiated oral squamous cell carcinomas typically have a good prognosis, whereas the poorly differentiated type tends to have a poorer prognosis.

Grading of Oral Squamous Cell Carcinoma

Grading Criteria	Well-differentiated	Moderately differentiated	Poorly differentiated
Keratin pearls	Extensive Keratin pearls	Show less keratin pearls	Minimal keratin pearls
Comparison of resemblance of malignant cells with normal squamous epithelium	Malignant or atypical cells resembles normal squamous epithelium	Malignant or atypical cells have moderate resemblance with normal squamous epithelium. More nuclear pleomorphism and mitotic activity.	Malignant or atypical cells have poor resemblance with normal squamous epithelium. Prominent mitotic activity

Oral Cancer TNM Staging Form

The TNM staging system for oral cancer plays a crucial role in guiding treatment decisions and predicting prognosis. In dental practice, utilizing a TNM staging form ensures comprehensive assessment and documentation of the extent of the disease. Dentists can use this form during initial patient evaluation, especially if suspicious lesions are present in the oral cavity. By systematically documenting tumor size (T), regional lymph node involvement (N), and distant metastasis (M), dentists can accurately stage the disease, which is essential for treatment planning and prognosis estimation. The form facilitates standardized reporting of key clinical findings, promoting effective communication among dental professionals, oncologists, and other healthcare providers involved in the patient's care. Additionally, the use of a TNM staging form in general dentistry practice emphasizes the importance of early detection and management of oral cancer, ultimately improving patient outcomes and survival rates.

In conclusion, the TNM staging system plays pivotal roles in guiding the diagnosis, treatment, and prognosis of this prevalent malignancy. Through the TNM staging system, clinicians can accurately assess the extent of tumor spread within the oral cavity and to regional lymph nodes, providing crucial insights into the disease's severity and informing treatment decisions.

**(For Oral Cancer TNM Staging Form Ref. Appendix 5)*

Chapter 9

SCREENING MODALITIES FOR ORAL POTENTIALLY MALIGNANT DISORDERS IN DENTAL CLINICS, COLLEGES AND COMMUNITY SETTINGS

Oral Potentially Malignant Disorders (OPMDs) have been defined by the WHO Collaborating Centre for Oral Cancer -Invited experts' workshop in March 2020 as 'any oral mucosal abnormality that is associated with a statistically increased risk of developing oral cancer'. OPMDs present as white, red, and mixed white and red lesions. Clinically, they can appear like plaques, and ulcers with smooth, corrugated, verrucous, granular, and atrophic surface textures. Studies from various parts of the world have reported a varying progression of OPMDs to cancer (1.4% - 49.5% in a recall follow-up of 12 months to 20 years). Risk factors for the development of OPMDs and Oral Cancer in India are the usage of smoked (cigarettes, beedi) and smokeless tobacco (processed form; Pan Parag, Gutka, Cool Lips etc). A recent (2020) National Non-communicable Monitoring Survey (NNMS), the Indian Council of Medical Research, Ministry of Health and Family Welfare, Government of India released a fact sheet stating that 28.6% of the Indian adult population (15 years and above)consumed tobacco daily. Given the fact that the link between tobacco usage and the development of OPMDs/Oral cancer has already been proven in India, dental practitioners, dental students, and primary health care workers must be sensitized to OPMD/ Oral Cancer screening procedures.

Screening for OPMDS

Precursor lesions (OPMDs) precede most oral cancers. Therefore, early screening for OPMDs and their management is essential to prevent the morbidity and mortality associated with Oral cancer. Screening for OPMDs involves recording a detailed case history, and a systematic clinical oral examination, which includes visual inspection and palpation of the oral and para-oral soft and hard tissues including the neck, the use of adjunctive, cytology, and advanced techniques when feasible.

Clinical /Visual oral examination (COE/VOE) involves a systematic examination and palpation of lips, labial mucosa, buccal mucosa, buccal aspects of maxillary and mandibular gingiva, lingual aspects of maxillary and mandibular gingiva, hard and soft palate, oropharynx (tonsils), dorsal, ventral posterolateral surface of the tongue in bright light. The neck should be palpated for lymph node enlargements which may suggest metastasis. Mouth opening should be checked to rule out Oral submucous fibrosis which is known to be associated with the smokeless tobacco and/or betel quid habit. In community settings where accessibility to dental chairs is limited, primary healthcare workers and dental students can be trained to examine the oral cavity with a handheld torch or other sources of light. The findings should be recorded systematically in a form for further recall and follow-up (refer Annexure).

Steps in COE (Clinic, College and Community Settings, COE to be carried out ensuring sterilization and disinfection protocols)

Minimal basic setting:

- Source of lighting,
- Mouth masks,
- Gloves
- Sterile mouth mirrors
- Tongue depressors
- Gauze pieces
- Hand sanitizers
- Recording form

A detailed history should be recorded which should include, a history of previous/current medications (name, dosage, and duration), family history (health conditions), and habits such as smoking, chewing, and alcohol consumption. When recording habit history details of frequency (how many times does the patient smoke/chew/consume per day/week, intensity (number of cigarettes/beedies /packets of panparag/ milliliters of alcohol), and duration of the habit (since how many years, discontinued, relapsed).

The importance of recording a detailed case history is reiterated here

- It guides the clinician through rest of the COE and also gives ample information to the clinician to arrive at the provisional diagnosis.
- It helps the clinician to decide whether the subject requires specialist consultation or not.
- It helps the clinician to follow up with the patient at regular intervals after counseling for tobacco/ alcohol habits

The COE procedure should be explained to the subject and all efforts are to be taken to make the subject comfortable.

In all steps, visual examination is followed by palpation with gloved hands.

a) Examination of lips and labial mucosa

Look for changes in color, consistency, pigmentations, ulcers, and swellings. Examine the corners of the mouth for ulcerations or changes in surface texture. Erosive or atrophic areas on the lip can indicate sun damage and actinic keratosis (OPMD). Evert the lips and examine the labial mucosa which should normally have a wet shiny surface (indicating the presence of adequate salivary secretion)

b) Examination of buccal mucosa

Ask the subject to open the mouth to a finger's breadth, use the mouth mirror to reflect the buccal mucosa, and examine the upper and lower vestibule, look for the linea alba line or the indentations made by the teeth in occlusion. Examine the commissure by shifting the mouth mirror slightly upwards and look for changes in color, surface texture, and consistency. All mucosal tissues and teeth should have shiny moist surfaces indicating adequate salivary secretion, any signs of dryness or dull surface should be noted down and it should alert the clinician or the examiner of some underlying conditions (history of medications, salivary gland dysfunctions, etc).

c) Examination of the tongue

The dorsal surface of the tongue can be examined by asking the subject to protrude the tongue out of the mouth, any changes in color and surface topography should be noted. Pallor, coating, pigmentation, depapillated bald areas, and any other change should alert the clinician to underlying conditions. The extension of the tongue (approximately 1 to 1.5cm from the mandibular central incisors) and the movement of the tongue should also be observed. Any difficulty or reduction of the movement and flexibility should alert the clinician to the anatomical condition like a tongue tie or fibrotic conditions specifically Oral Submucous Fibrosis (specifically when associated with the betel quid chewing habit). The ventral surface is examined by asking the subject to touch the tip of the tongue to the palate. The lateral and posterolateral tongue should be examined by asking the subject to touch the upper teeth or buccal mucosae. A mouth mirror can also be used to examine the posterolateral part of the tongue. These regions should be thoroughly examined as they are difficult to access/visualize and a simple color change that may go unnoticed might indicate an ominous OPMD or Oral Cancer.

d) Examination of gingiva

The labial/buccal aspects of the maxillary and mandibular gingiva are examined by reflecting the mucosa with the mouth mirror. The attached gingiva is firmly attached to the underlying bone. The marginal gingiva is examined for changes in color and consistency. The betel quidding habit induces changes in color and consistency in the vestibular mucosa which may extend into the buccal mucosa and/ or into the marginal gingiva. The lingual and palatal marginal gingiva are examined with the mouth mirror through direct and indirect visions respectively.

Examination of hard and soft palate: The mucosa of the hard palate is tightly bound to the palatal bone, it is observed by indirect vision with the mouth mirror. The palatine rugae and the mid-palatine raphae are visualized. The posterior part of the hard palate should be carefully examined especially in a subject with a smoking habit; the mucosa of the hard palate is directly subjected to the smoke which may alter the palatal mucosa. Any deviation from the normal pale pink color - red or white lesions, ulcers, should alert the clinician to the smoking habit and the presence of OPMD. The soft palate is examined by depressing the tongue with the mouth mirror and asking the subject to say 'Ha', by this procedure,

the movement of the soft palate and uvula can be noted. A limitation in the movement of the uvula is noted down as this may be a sign of underlying fibrosis (Oral Submucous Fibrosis)

e) Examination of Oropharynx

As a continuation of examining the tongue with the tongue depressor, the oropharynx can be observed, and lymphoid follicles are observed as pale pink nodules in the pharyngeal wall. Tonsils can be visualized on either side at the junction of the oral cavity and pharynx as small mounds between the faucial pillars. Any color change or increase in size should be duly noted.

Clinical examination of Para oral structures

Examination of the cervical, submandibular, and submental lymph nodes

The clinician stands behind the subject, slightly flexes, and bends the neck of the individual to one side and any abnormalities in size, consistency, and tenderness in lymph nodes are examined and noted. Most often, lymph nodes showing swelling and tenderness are secondary to some inflammatory process in the teeth, soft tissue and skin of the head and neck region. If the lymph nodes are painless, fixed to the underlying structures or skin, and hard, it should alert the clinician to other underlying conditions, specifically to metastasis in malignancy. Bimanual palpation of the submandibular and submental region can be performed by standing in front of the subject with the thumb placed intraorally and fingers guiding extra-orally. The parotid glands can be examined by palpating the gland extra-orally in front of the ears extending towards the angle of the mandible. Para parotid lymph nodes can be examined in this method.

The temporomandibular joint is examined by standing in front of the subject with both hands on the joints. The subject is asked to open and close the mouth slowly. Tenderness, crepitations, and clicking in the joints are duly noted.

Mouth Self Examination (MSE)

This is a low-cost technique recommended to the population at large and to the specific population at risk (individuals with a history of smoking, chewing, and alcohol consumption habits) to create awareness of OPMDS and Oral Cancer. The oral cavity is easily accessible for self-examination, and any changes can be promptly brought to the attention of the clinician by the subject. The individuals can be trained to perform MSE.

Steps in MSE

- The subject stands in front of the mirror under bright light. The face, neck, and lips are examined for asymmetry and color change.
- The subject opens the mouth and examines the buccal mucosa, palate, gingiva, tongue, pharynx and teeth by moving the lower and head.
- The individual can also use the forefinger to palpate all the mentioned regions digitally and gently for pain and swelling.
- The risk of over and or underdiagnosis in MSE is a point to be addressed by the clinician.

Adjunctive techniques in screening for OPMDs

Adjunctive techniques aid or facilitate the detection of OPMDs in screening. A screening adjunct is applied to apparently healthy subjects for the sole purpose of helping the screener detect the disease in the population. The primary clinician, can alert the expert about the presence of the suspicious lesion after COE and apply the adjunctive screening technique The expert clinical consultant can use the adjunctive technique to diagnose the lesion. The expert can assess the lesion and determine the incisional and/or excisional biopsy site based on the adjunctive technique.

The adjunctive techniques are:

1) Vital Staining 2) Visualization adjuncts

Basis of vital staining

Dye is applied to the oral mucosa, Toluidine blue has an affinity for Nuclear material and dysplastic cells in OPMDs and Oral Cancers are easily permeable, hence they take up the stain and appear darker. Lugol's Iodine is taken up by glycogen in cells, the normal nonkeratinized mucosa retains the stain whereas hyper ortho-or Para keratinized mucosa may not retain the stain. Extensive research has shown that the interpretation of these staining patterns is unreliable as false positives (Ulcers and regenerating mucosa may take up stain) and false negatives (due to a thick

keratin layer, the dye may not penetrate at all into the mucosa) are often encountered. With these findings in the background, the recent WHO handbook advises against the use of these dyes by general dentists. The staining kits are commercially available in India; they can also be prepared in the laboratory(R).

Basis of Visualization /Optical adjuncts

The devices used in this technique expose the oral mucosa to light of different wavelengths generating optical signals in real time. The premise is that the diseased cells/tissues will generate different wavelengths of light compared to normal cells. Some of the techniques reported in the literature are; Tissue autofluorescence, Narrow-band imaging, and Tissue reflectance.

Technique	Advantages	Disadvantages	Benefits for screening	Relevance to screening
Tissue auto-fluorescence	Non-invasive, handheld, real-time interpretation	Investment cost prohibitive, Darkened room, infection control supplies needed	Minimal	Unclear
Narrow-band imaging	Non-invasive, real-time interpretation	Large, expensive unit, endoscopy equipment requires sterilization between patients	Minimal	Not likely
Tissue reflectance	Non-invasive, handheld, real-time interpretation	Investment cost prohibitive, Darkened room, infection control supplies needed	None	Not relevant

It is suggested the reader go through the IARC HANDBOOK, ORAL CANCER PREVENTION VOLUME 19 for further details about these techniques.

Cytology techniques

Exfoliative cytology and cytobrush biopsy are the two minimally invasive techniques recommended for screening or initial triaging in dental clinics or community healthcare settings when patients refuse a biopsy. These techniques involve the collection of superficial epithelial cells from the surface of the lesion, staining, and visualization in the microscope for features of atypia. The clinician can collect the sample in suspected cases and send it to the expert for further processing and interpretation.

Exfoliative cytology procedure

- Sample collection: A wooden spatula is scraped on the lesion, spread on a glass slide, and fixed in 95% alcohol.
- Processing: These slides are sent to the pathology laboratory for staining and interpretation.
- Cytobrush biopsy:

  Sample collection

  This technique involves, rotating the cytobrush on the lesion on the suspected lesion. The cytobrush is penetrated enough to draw pinpoint blood. Though this may cause discomfort to the patient, it ensures the collection of superficial, intermediate, and basal cells.

Processing

The collected cells can be transported to the laboratory, Immediately fixed in 95% alcohol, stained, and visualized in the microscope. The sample can be centrifuged (cytospin) to get a high yield of cells, and routinely stained for visualization in the microscope. Liquid-based cytology kit, where the brush can be promptly placed in preservative fluid, transported to the laboratory for centrifugation, staining, and flow cytometry. Among the cytological techniques, the liquid-based biopsy is shown in the literature to have a clear yield of cells for interpretation but cost constraints (liquid biopsy kit) are to be considered in resource-limited settings.

Advantages/Recommendations

Cytological techniques for screening are strongly recommended to dental clinics, colleges, and community settings whenever feasible as they are reported to have the highest accuracy when compared to other adjuncts. It is a minimally invasive procedure and can be performed when the patient refuses a biopsy, especially when the dentist has strong suspicion after VOE.

Advanced techniques in screening for OPMDs

Some of the recent advances in OPMD and Oral Cancer research are Quantitative DNA Cytometry, Liquid biopsy DNA study, and Salivaomics/biomarkers study. These techniques identify and quantify subcellular components of dysplastic cells in OPMDs and Oral cancer to predict their prognosis. The subcellular structures, minerals, peptides, proteins, messenger

RNA, tumor DNA, microRNA, cell ageing markers like telomerase, oxidative stress-related molecules, interleukins, etc in cells harvested from cytobrush techniques and saliva. There are promising biomarkers recommended by researchers, but commercial products for use in clinical settings have not yet been promoted.

Artificial Intelligence and Mobile Apps for Oral Cancer Screening: Artificial intelligence and Mobile apps are in development and have shown promising results. Mobile-based apps can be used by primary healthcare workers (PHCW) in remote areas where access to expert consultation is difficult. PHCW can capture images, which can be conveyed to experts for further management. Researchers have used artificial intelligence to improve the efficiency of COE and these are in the early stages of development.

Key Indicators during COE for immediate referral to experts *(Adapted from EW Odell 2017)*

*Initiate tobacco cessation counseling promptly

SL. No.	Indicators
1.	Unexplained non-healing ulcers in the oral mucosa and/or lip persisting for 3 weeks or >
2.	Unexplained, persistent lymph node enlargement in the neck (non-tender) *Rule out the sources of infection in the head and neck region and other recent infections
3.	Red, white, mixed red and white patch/patches in the oral cavity and/lip persisting for 3 weeks or >
4.	Unexplained swelling in the oral cavity or lip persisting for 3 weeks or >
5.	Difficulty in mouth opening, lesser than 4 cm, with a positive history of smokeless tobacco and/or betelnut chewing habit (rule out local factors leading to trismus, TMJ issues, 3rd molar impactions)
6.	History of smoked and smokeless tobacco, betel quid-panparag, etc with alcohol habits
7.	Family history of cancer and cancer-related deaths

**(For Assessment of Oral Mucosal Tissue, Ref Appendix 2)*

Chapter 10

CLINICAL EXAMINATION AND METHODS - 1

In 1978, WHO defined two important terminologies for oral lesions, associated with malignancy. The term "premalignancy" can be described as any lesion, which holds characteristics to turn up into a malignancy; and importantly, not all the malignancies arise from these premalignant lesions.

In the year 2005, Warnakulasurya introduced a new term, "Oral Potentially Malignant Disorders". The definition can be given as, "the risk of malignancy being present in a lesion or condition either during the time of initial diagnosis or at a future date."

1) Oral Leukoplakia

Leukoplakia is one of the most prevalent and extensively researched oral potentially malignant disorders (OPMD) observed in clinical practice and population studies. Several definitions have been suggested for leukoplakia with the most recent provided by the WHO Collaborating Centre in 2007.

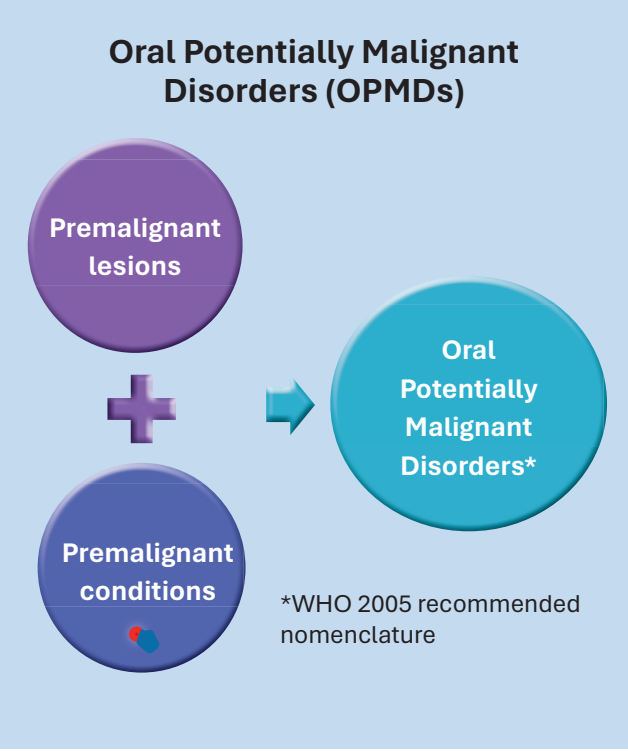


Fig.1: The chart represents OPMDs, according to revised WHO

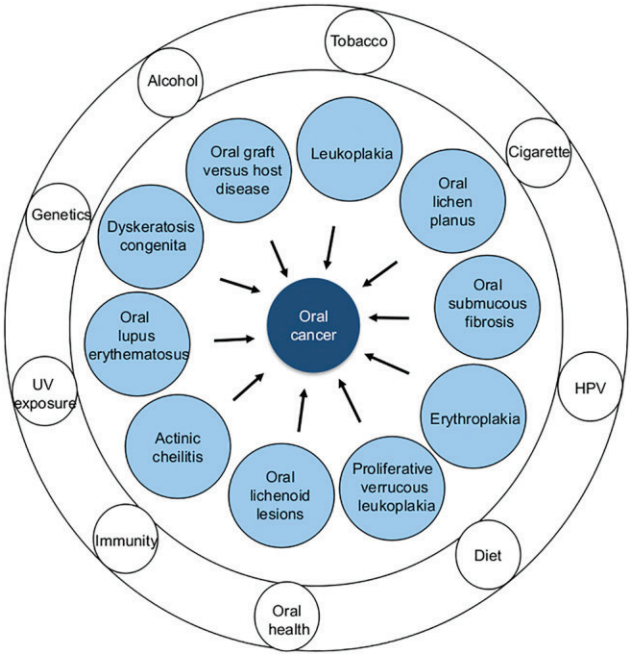


Fig.2: It represents the classification of OPMDs. The outer circle provides the etiological factors for the lesions. The inner circle gives the OPMDs. All these factors contribute to Oral Cancer

According to Warnakulasuriya et al., 2007 leukoplakia is described as, "A predominantly white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer"

The condition is potentially malignant and is strongly associated with tobacco use. This activity describes the evaluation and treatment of oral leukoplakia and the role of the interprofessional team in preventing, recognizing, and managing patients with this condition.

Clinical Features

Leukoplakia commonly occurs in middle to older age people, with a peak incidence of >50 years with male predilection. It most commonly occurs in the vestibule, buccal, palatal surfaces, alveolar ridge, lip, tongue, floor of the oral cavity. The incidence can be given

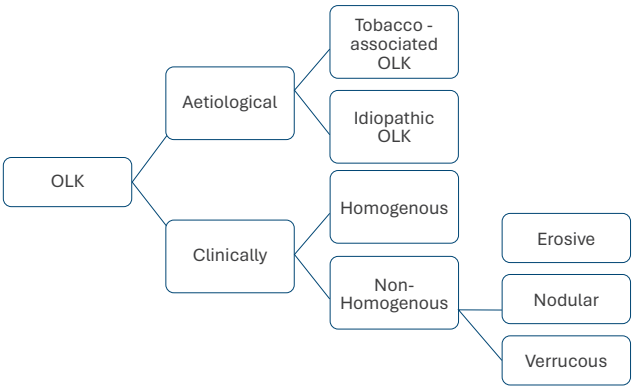


Fig.3: Classification of Leukoplakia given by Axell et al. in 1984

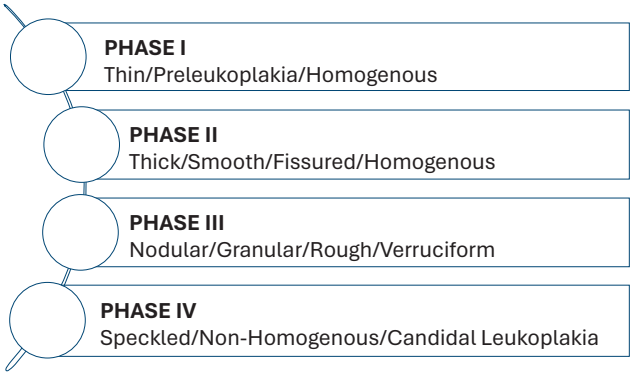


Fig.4: Classification of Leukoplakia based on the clinical presentation, given by Bouquot JE & Whitaker SB

Table 1: Different types of OLK, with clinical features of each type

Clinical Presentation Type	Clinical Features
Phase I	Begins Thin, Grey or Grey-White Plaques Slightly Appear Translucent
Phase II	Thick, Whitish with a "Cracked Mud" Appearance Candida Associated With OLK is known as Candidal Lk
Phase II	Severe when compared to surface irregularities like nodular/ granular/pointed papillary projections
Phase IV	Formation of an erythematous area on whitish plaque suggestive of further progression of lesion toward malignancy

Criteria of Leukoplakia

The criteria for diagnosis of leukoplakia were provided by Warnakulasuriya S, et al, in the year 2020.

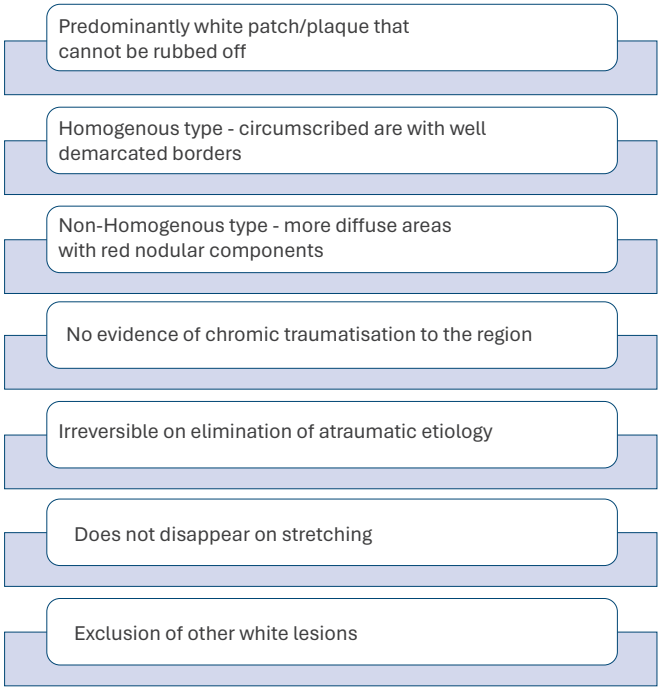


Fig.5: Criteria for diagnosis

by the surfaces in the oral cavity that are more often associated with tobacco and its other products.

Idiopathic Leukoplakia

This term is referred to the lesion, which is diagnosed as OLK, with an unknown cause. The most common involved regions include the lateral border of the tongue

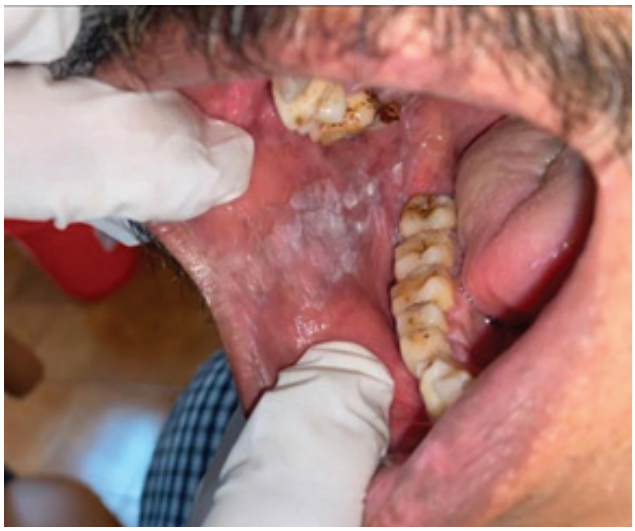


Fig.6: Homogenous variant

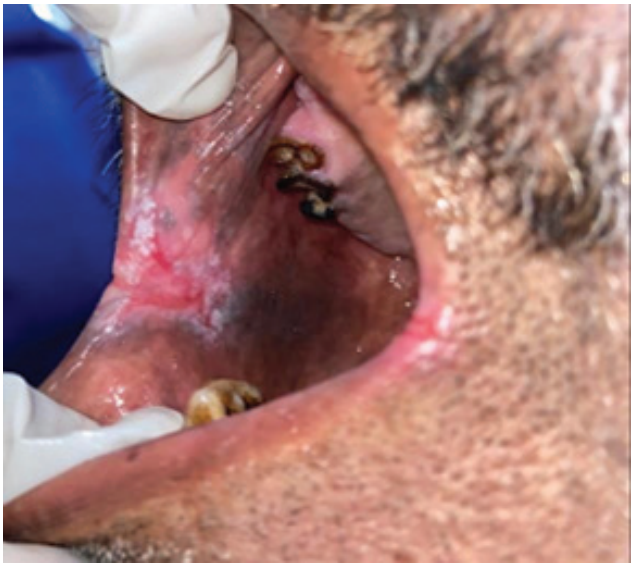


Fig.7: Non-Homogenous variant

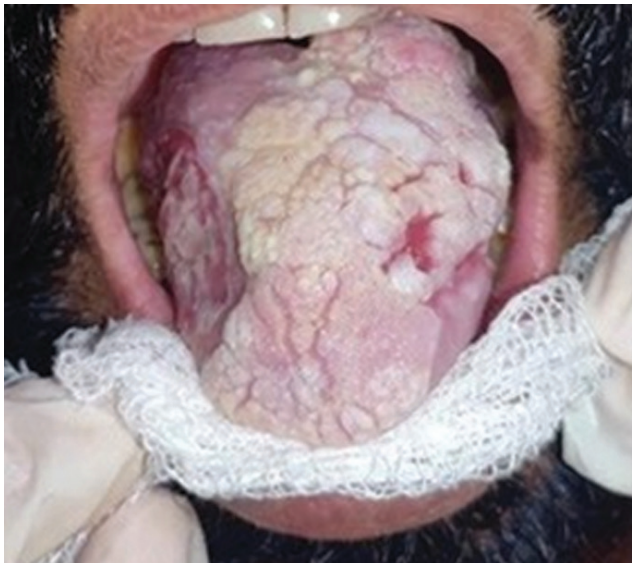


Fig.8: Proliferative Verrucous Leukoplakia

anwd gingiva. These hold the highest rate of malignant transformation.

Even after the treatment, it is considered to have an increased rate of recurrence. Excluding all the etiological factors that are associated with causing OLK, especially the feature of a white patch-like lesion, it can be concluded as "idiopathic leukoplakia". For such cases, a biopsy is essential.

2) Proliferative Verrucous Leukoplakia

It is one of the uncommon types of Leukoplakia, which has a potential to turn into malignancy. The lesion was first described by Hansen.

Clinical Presentation

The lesion is found to be persistent, for about more than 3 years. Clinically, the Proliferative nature is attributed to the progressive, diffuse, and multifocal characteristics; wherein Verrucous represents a warty, long papillary-like exophytic appearance. Muti-focal refers to its existence in 2 or more sites, predominantly in the gingiva, alveolar ridge, and palate.

3) Oral Lichen Planus

It is a chronic immunologic, inflammatory, and mucocutaneous disease that comprises lesions in the skin, mucous membrane, nails, and hair, which ranges from reticular or plaque to erythematous and ulcerative. It is also considered an autoimmune and psychosomatic disorder of oral cavity.

Table 2: Clinical variants with its clinical features

Clinical Variant of OLP	Clinical Features
Papular	Manifest as small white raised areas of 1-2 mm
Reticular	Most common type of OLP presents as interlacing white keratotic lines – wickham's striae with erythematous border May present in different shape like annular (circular), etc.
Plaque-Like	Presents from smooth, flat areas to Irregular, Elevated Areas Clinically Resembles OLK
Atrophic	Presents as Diffuse Red with usually white Striae around the Lesion Striae Radiate Peripherally – Evident at the Margins of Atrophic Zones of the Lesion
Bullous	Rare Form of OLP; Characterized By Large Bullae Ranging from 4 mm to 2 cm Bullae Resembles Pemphigus Vulgaris – Rupture Immediately, Leaving Ulceration on Bed of Inflamed Mucosa
Erosive	Symptomatic; Mix of Erythematous and Ulcerated areas, Surrounded by Finely Radiating Keratotic Striae Involvement of Gingiva – Desquamative Gingivitis

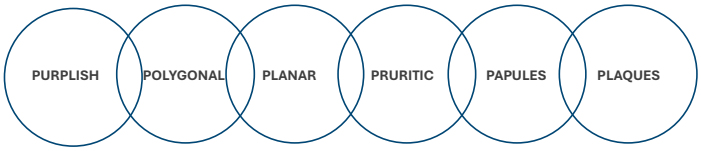


Fig.9: The flowchart represents the Classical Signs of Oral Lichen Planus

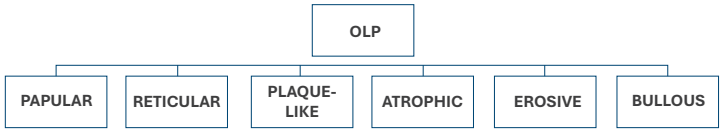


Fig.10: The flowchart describes the classification of Clinical types of Oral Lichen Planus

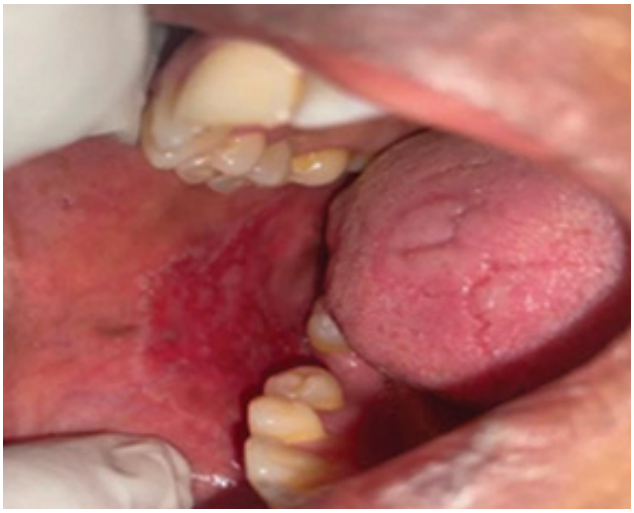


Fig.11: Erosive Pattern

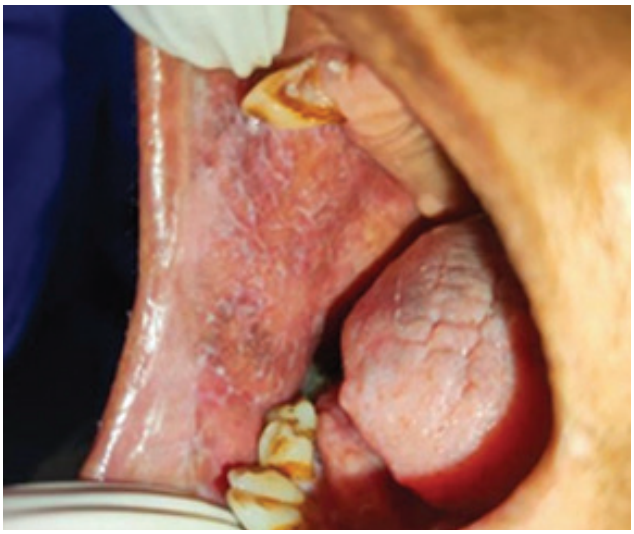


Fig.12: Reticular Pattern

According to Warnakulasurya S, et al., WHO in 2020, Oral Lichen Planus (OLP) is defined as "A chronic inflammatory disorder of unknown etiology with characteristic relapses and remissions, displaying white reticular lesions, accompanied or not by atrophic, erosive and ulcerative and/or plaque type areas. Lesions are frequently bilaterally symmetrical. Desquamative gingivitis may be a feature".

OLP occurs bilaterally, most commonly in the posterior buccal mucosa, tongue, alveolar mucosa and gingiva. The lesions give white striations, named as Wickham's striae (Honiton lace), which are slightly, elevated fine, whitish lines. Desquamative gingivitis can also be appreciated, which is characterized as sensitivity of gums to consumption of hot or spicy food or on brushing, especially in the erosive OLP. Melanin pigmentation can also be seen at times, due to melanocyte stimulation in response to T-lymphocyte infiltrate.

4) Oral Submucous Fibrosis

In 1966, Pindborg JJ, Sirat SM, described Oral Submucous Fibrosis (OSMF) as, "an insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxta-epithelial inflammatory reaction followed by fibro-elastic changes of the lamina propria with epithelial atrophy leading to stiffness of mucosa and causing trismus and inability to eat".

Warnakulasurya S et al, revised the definition of OSMF in 2020 as, "a chronic, insidious disease that affects the oral mucosa, initially resulting in loss of fibroelasticity of the lamina propria and as the disease advances, results in the fibrosis of the lamina propria and submucosa of the oral cavity along with epithelial atrophy."

Clinical Presentation

OSMF is associated commonly with areca nut chewing and chili (capsaicin) consumption too often. It presents with male predilection, noticed in the second to fourth decade of life. The symptoms include – a burning sensation, the appearance of blisters, ulcerations, excessive salivation, and petechiae in the Early OSMF. Blanching and fibrotic bands are noted in Advanced OSMF.

Prodromal Symptoms

This is referred to as a burning sensation in the mouth,

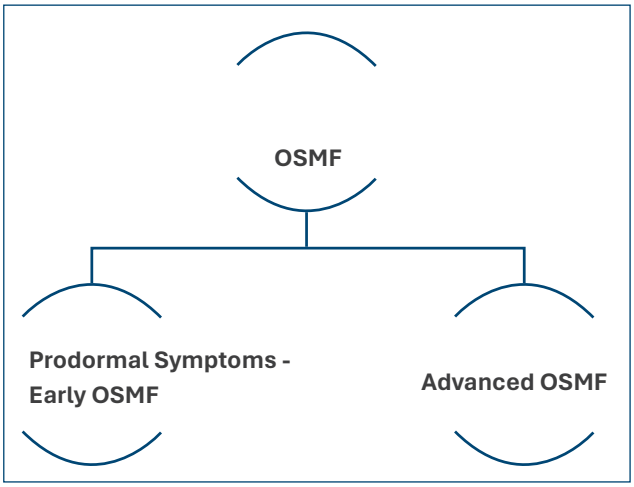


Fig.13: The flowchart picturizes the classification of OSMF based on symptoms

because of atrophy of the epithelium. Blisters are likely to appear notably on the palate. Either ulcerations or recurrent generalized inflammation can be noted. Excessive salivation in certain cases is well-marked. Defective gustatory sensation and dryness of the mouth can also be noted. Small vesicles can be appreciated in the cheek and palatal regions. Petechiae formation due to focal vascular dilatations can be noticed.

Advanced OSMF

It comprises 2 components – Blanching and Fibrotic bands.

a) Blanching

Progression of the disease transforms the oral mucosa to attain blanching and slightly opaque with white fibrous bands. This appearance is mainly because of the impairment of local vascularity as a result of fibrosis. Patterns of blanching can be localized diffuse or reticular. The first involved regions include palate and faucial pillars, but still any area in the oral cavity is likely to get affected. Hyper pigmented areas are seen, adjacent to the zones with loss of pigmentation.

b) Fibrotic bands

The prevalence of bands can be given in descending – faucial bands, buccal bands, labial bands. In the soft palate, the density of the fibrous deposit varies from a slight whitish area with no symptoms to a dense fibrotic area with fixation and shortening. The uvula appears to be deviated and holds hockey stick shape or bud shape. A circular band can be noticed in rima oris. Labial mucosa becomes difficult to evert. Difficulty in mouth opening is caused by pterygomandibular raphe. The inability to whistle or blow and swallow is attributed to buccal mucosa. Referred pain to the ear and nasal voice are considered to be the latter signs. Hearing issues may be caused. Gingiva appears to be bald with a loss of stippling. The tongue is blanched with loss of papillae and in addition, restricted movements.

Fig.14: Picture depicts the measurement of interincisal distance

The Ross Kerr et al. classification of Oral Submucous Fibrosis (OSMF) is a widely used system to stage the progression of OSMF. Here's an overview of the classification:
Stages of OSMF according to Ross Kerr et al.

1. Stage I: The earliest stage, characterized by stomatitis (inflammation of the mucous membranes) and occasional ulcerations.
2. Stage II: Fibrosis (scarring) begins to develop, with the formation of fibrous bands in the buccal mucosa (the lining of the cheeks).
3. Stage III: Fibrosis progresses, with the formation of more prominent fibrous bands and a decrease in mouth opening.
4. Stage IV: Advanced fibrosis, with significant reduction in mouth opening and difficulty in eating and speaking.

Additional Features

The classification also includes additional features to describe the extent of the disease:

- Site involvement: The location and extent of the affected area.
- Mouth opening: The degree of restriction in mouth opening.
- Symptoms: The presence and severity of symptoms such as pain, burning sensation, and difficulty in eating and speaking.The Ross Kerr et al. classification provides a standardized framework for diagnosing and staging OSMF, which helps in planning treatment and monitoring disease progression.

Shahul et al. (2019) proposed a staging system OSMF based on the percentage of reduction in mouth opening. The percentage of reduction in mouth opening (PRMO) was determined by subtracting the maximum mouth opening (MMO) from the three-finger width (TFI) measured in millimeters.

$$PRMO = \frac{TFI - MMO \times 100}{TFI}$$

According to this the proposed clinical staging is given as,

- Stage I < 30%
- Stage II 30–45%
- Stage III > 45%

5) Erythroplakia

"Any lesion of the oral mucosa that presents as bright red velvety plaques, which cannot be characterised clinically or pathologically as any other recognizable condition", as defined by WHO. This term was designed to group the red lesions of the oral mucosa, simulating OLK.

Clinical Features

The occurrence is mostly noted in middle-aged to elderly people, with male predilection. The preferrable sites includes – floor of the mouth, buccal mucosa, soft palate, retro-commissure area in males and mandibular alveolar mucosa, mandibular gingiva and mandibular sulcus in females. Clinically, noted without indurations or any kind of raised lesions. Usually occurs asymptomatic and is referred to as "Erythematous plaques with soft velvety texture". Appearance is predominantly islands of normal mucosa with areas of erythroplakia, with irregular outlines.

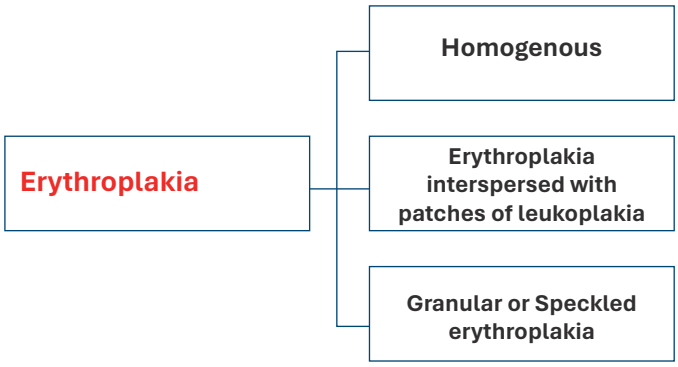


Fig.15: The flowchart shows the classification of Erythroplakia, based on its clinical appearance

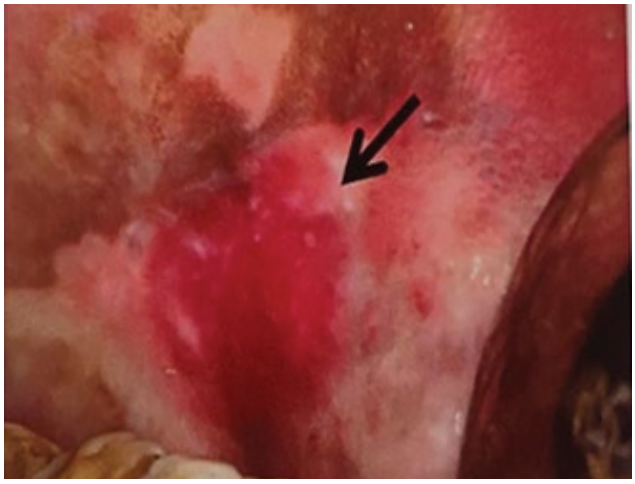


Fig.16: Erythroplakia

6) Oral Lichenoid Reactions

The entity where erythroplakia, simulates leukoplakia; similarly, the oral condition which mimics OLP is described as an Oral Lichenoid Reaction (OLL). Warnakulasurya S, et al., in 2020 defined OLL as, "oral lesions with lichenoid features but lacking the typical clinical or histopathological appearances of OLP, i.e. may show asymmetry or are reactions to dental restorations or are drug-induced". Recently, Aguirre Urizar et al. coined the term "Oral Lichenoid Disease", which complies with both OLP and OLL.

Clinical Features

It is considered to be difficult to differentiate from OLP.

However, the significant features include – unilateral, occurrence, associated with or near restorative material, present as white plaque initially, with transformation to atrophic or erosive type in the near future, with/without pigmentation. A classical Patch test positive is appreciated.

7) Actinic Cheilitis

The condition known as "Sailor's Lip," or Actinic Cheilitis (AC), is a precursor to lip squamous cell carcinoma (SCC). Actinic cheilitis is a premalignant lesion brought on by prolonged sun exposure, much like actinic keratosis. On the lower lip near the vermillion border, it is most frequently seen. It is critical to identify and treat these potentially malignant precursory lesions as soon as possible because squamous cell carcinoma (SCC) on the lips is regarded as a high-risk form of skin cancer, with an 11% chance of metastasis compared to 1% for other body locations.

Clinical Presentation

The classical features of AC include – a persistent white plaque with a “sandpapery” feel on the lips, associated most commonly with lower lips, and blurring of the vermillion border between the cutaneous and mucosal lip. Usually represents to be asymptomatic/painless, but at times gives a burning sensation, numbness, and pain.

8) Oral Lupus Erythematosus (LE)

It represents the classic prototype of an autoimmune disease involving immune complexes. An increased risk of Lupus Erythematosus in siblings as well as an increased disease concordance in monozygous twins provide evidence for a genetic predisposition. Over 80 distinct medications have been linked to the onset of SLE. The drugs associated include – hydralazine, methyldopa, chlorpromazine, isoniazid, quinidine, and procainamide.

Clinical Features

The clinical and histopathological features of the oral lesions seen in (Discoid Lupus Erythematosus) DLE and (Systemic Lupus Erythematosus) SLE are comparable. White, radiating striae that may abruptly end in the center of the lesion, giving it a more erythematous appearance, characterizes a typical clinical lesion. Oral LE does, however, present with a number of clinical manifestations. The tongue, palate, buccal mucosa, and gingiva are the most commonly impacted. Erythematous lesions may predominate in palatal mucosa lesions, and white structures may not be visible. Leprosy-compatible lesions of the oral mucosa could be the initial indication of the illness. Oral lesions have been reported in 20% of patients with LE, though the percentages can range from 9% to 45%.

Recent years have seen the addition of acute cutaneous lupus erythematous and subacute cutaneous lupus erythematosus to the traditional classification of LE into SLE and DLE. Additionally, SLE can coexist with other rheumatologic conditions like mixed connective tissue disorder and secondary Sjogren's syndrome. Well-defined cutaneous lesions with round or oval erythematous plaques with scales and follicular plugging are typical features of the DLE diagnosis. Malar rash, which appears as butterfly-shaped rashes over the nose and cheeks, can develop from these lesions.

9) Dyskeratosis Congenita

Dyskeratosis Congenita is an uncommon and progressive bone marrow failure syndrome, known by several names, including Hoyeraal-Hreidarsson syndrome, Zinsser-Engman-Cole syndrome, and reticulated skin hyperpigmentation. This ailment is precancerous. With X- linked recessive, autosomal dominant, and autosomal recessive subtypes, it is genetically heterogeneous. It has to do with the dysfunction of telomerase. Repeated structures called telomeres are located at the ends of chromosomes and serve to stabilize them. Telomere length decreases with each round of cell division, but the enzyme telomerase makes up for this by keeping germline and stem cell telomeres longer. Telomerase is essential in halting the development of cancer and cellular senescence because telomeres preserve chromosomal stability. Tissues that multiply quickly and require telomere maintenance the most, like bone marrow, are most vulnerable to failure.

Oral Manifestations

OLK is associated with Dyskeratosis Congenita. In addition to OLK, other oral cavity manifestations include taurodontism, severe periodontal disease, hypocalcified teeth, and hyperpigmentation of the buccal mucosa. Another frequently observed

characteristic is crops of vesicles with patches of white necrotic mucosa infected with Candida. The degree of dysplasia can be determined by histopathologically evaluating the oral lesions.

Nearly 20 familial cancer syndromes have been identified, with individuals who inherit genetic predispositions being more likely to develop hematological malignancies and solid tumors at an earlier age and with greater frequency.Examples include Fanconi anemia, xeroderma pigmentosum, Li-Fraumeni syndrome, Bloom's syndrome, ataxia-telangiectasia, and Cowden syndrome.

10) Oral Graft vs Host Disease

Immunocompetent cells from a donor identify and respond to "foreign" tissue antigen in an immunocompromised host, resulting in graft-versus-host disease (GVHD). Despite the use of HLA-matched sibling donors and immunosuppression following grafting, 9–35% of patients receiving standard allogenic bone marrow transplantation experience moderate to severe acute GVHD.

Oral Manifestations

The duration, intensity, and target oral tissue of the attack determine the oral mucosal manifestations of GVHD. GVHD lesions in the mouth can occasionally be the only indications of the illness. It is predicted that oral involvement will occur in 33–75% of patients with acute GVHD and approximately 80% of patients with chronic GVHD. Patients will exhibit a finite reticular network of white striae involving the tongue, labial mucosa, and buccal mucosa, resembling oral lichen planus. Oral mucosal atrophy, ulceration, and xerostomia may occur.

11) Palatal Lesions in Reverse Smokers

Reverse smoking is a traditional tobacco habit prevalent in the rural coastal regions of India. In reverse smoking, the lit end of a cigarette or cigar is placed inside the mouth

Oral Manifestations

White and/or red patches, often stained with nicotine, commonly appear on the hard palate in reverse smokers.

12) Tobacco pouch keratosis

A white patch typically found in the lower buccal grooves of individuals who use smokeless tobacco and habitually retain the tobacco quid in that area (Müller, 2019). While most cases resolve after cessation of the habit, lesions that persist should be classified as leukoplakia.

Chronic hyperplastic candidiasis (CHC) appears as an adherent white patch resulting from a persistent fungal infection, typically caused by Candida albicans. However available evidence on these disorder is insufficient evidence to establish their malignant potential. Consequently, they are not currently recommended for inclusion in the OPMD group of disorders.

Chapter 11

CLINICAL EXAMINATION AND METHODS - 2

The identification of potentially malignant disorders (OPMD) such as leukoplakia, erythroplakia, etc. during a routine oral mucosal examination constitutes one of the most substantial clinical observations in a dental practice. The clinical presentations of OPMDs exhibit diversity, characterized by variations in color (white, red, and a combination of both), texture (plaque, patch, corrugated, verrucous, granular, atrophic), and size.

The clinical presentation may remain unchanged or exhibit alterations, or display either progression or regression over time. Enhancing early detection, recommending suitable investigations, referring to specialists, and implementing appropriate interventions can potentially mitigate the progression of these conditions to invasive cancer. Augmented understanding and enhanced detection of OPMD are crucial for optimal management, thereby enhancing the quality of life for patients.

Clinical Examination

Clinical examination comprises systematic examination of extraoral & intra oral findings. Variations, however trivial have to be recorded. All examination should follow Inspection and Palpation wherever necessary.

Extra Oral Examination

Extraoral findings may indicate related characteristics or an extension of intraoral problem, which include examination of facial symmetry, lip, commissure of lips, and lymph nodes (submandibular, submental & cervical) (Fig.1,2,3,4,5) as nodes are indicators of the possible presence of an inflammatory or malignant process in head and neck region.

The lymph node has to be examined for shape, consistency, border, number, fixity & size. Stony hard consistency and fixity of lymph nodes to the underlying tissue amount to malignancy.

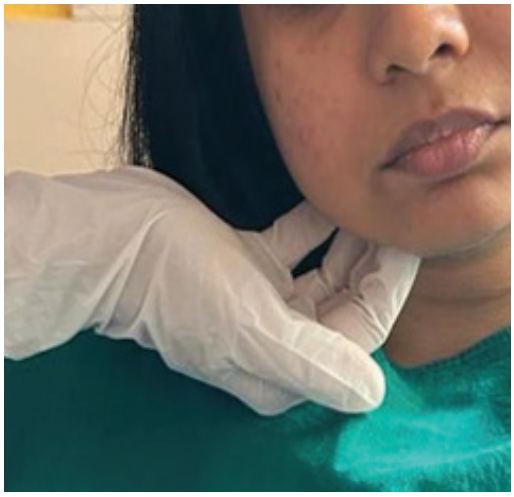


Fig.1: Examination of submandibular lymph nodes

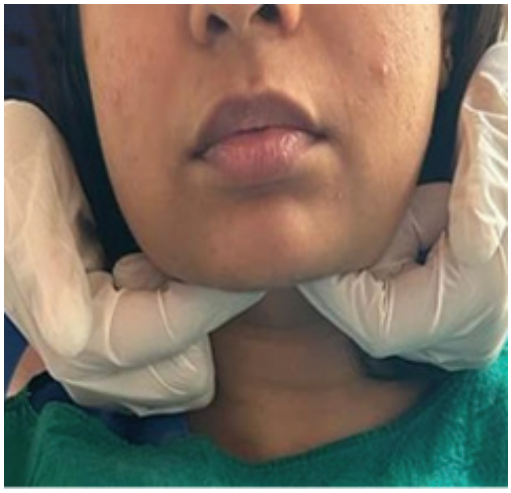


Fig.2: Examination of submental lymph nodes

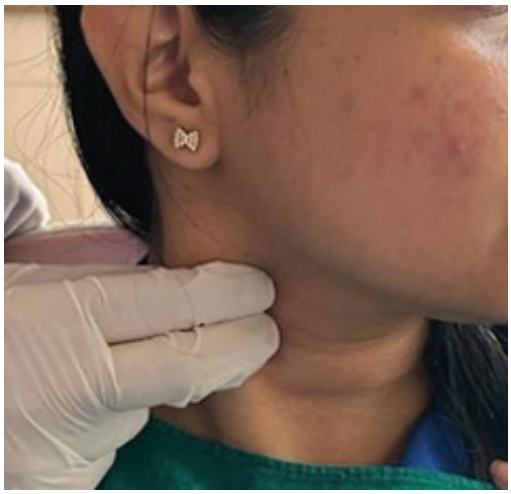


Fig.3 and 4: Examination of lymph node along the sternocleidomastoid muscle. 3, Anterior chain. 4, Posterior chain

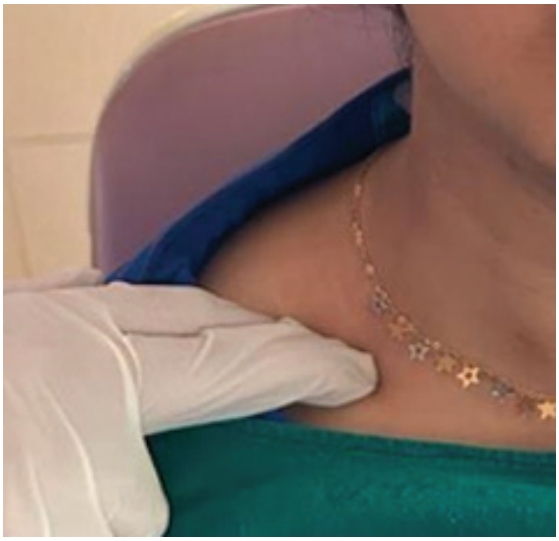


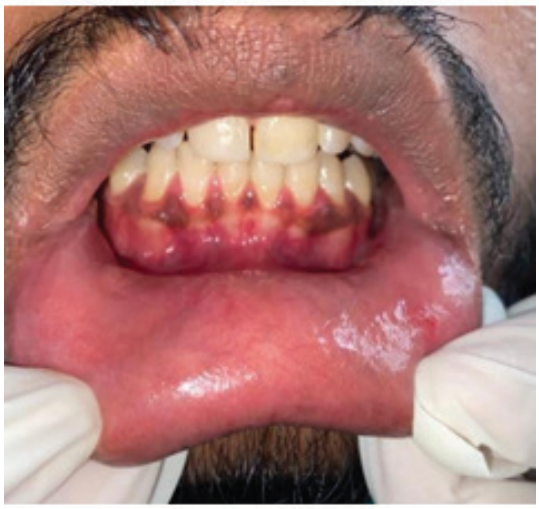
Fig.5: Examination of supraclavicular lymph nodes

Intraoral Examination

A definite pattern can be followed in intra-oral examination starting from labial mucosa (upper & lower) (Fig.6 & 7), buccal mucosa (right and left including retromolar area & faucial pillars) (Fig.8) palate (hard and soft), tongue (Dorsum, ventral surface, left & right lateral border of tongue, root)(Fig 9&10) floor of the mouth & gingiva.

Inspection of OPMD

Morphology describes the form and structure of the lesion. OPMD has to be inspected for its **Site, size, shape, colour, surface texture & extension**



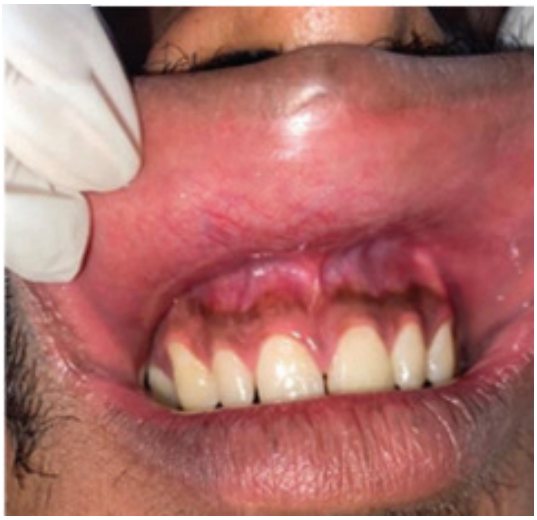


Fig. 6 & 7: inspection of upper and lower labial mucosa

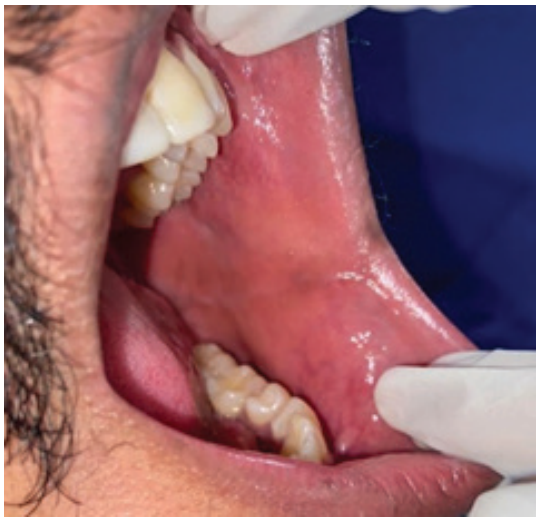


Fig. 8: Examination of the buccal Mucosa

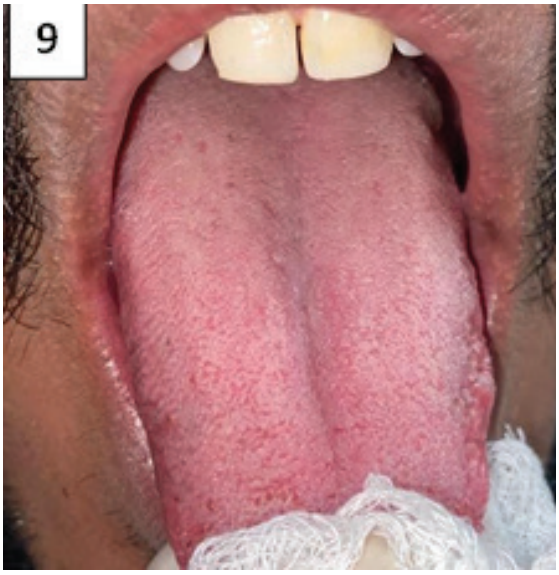


Fig. 9: Examination of dorsal surface of tongue

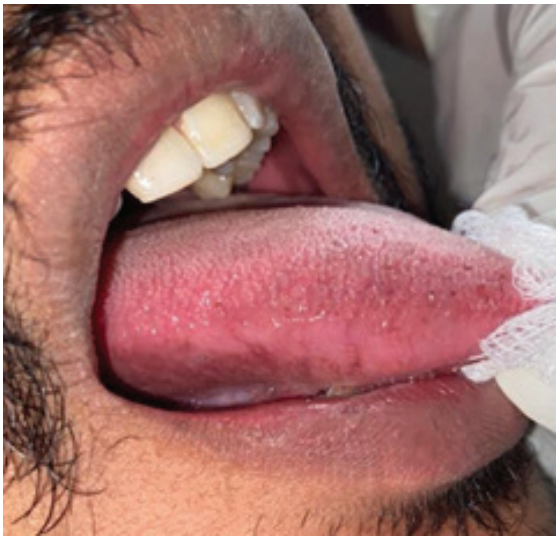


Fig.10: Examination of Lateral Border of tongue

Site: The site of the lesion has to be accurately documented as it is essential for achieving an accurate diagnosis, planning appropriate treatment, monitoring progress, and facilitating communication among healthcare providers, the common site of leukoplakia is more in the retro commissure area & buccal mucosa, Whereas a pouch keratosis can be seen usually in the vestibular sulcus areas.

Size: A small lesion may represent a hyperkeratotic area whereas a larger lesion may be a growing oral squamous cell carcinoma, therefore Approximate size of the lesion should be recorded and confirmed with palpation.

Shape: Certain lesion shows unique shapes as in the case of annular lichen planus and leukoplakia, annular Lichen Planus tends to be circular in shape whereas leukoplakia tends to be irregular. Malignant lesions usually appear irregular in shape. Hence, describing the shape of the lesion leads to providing an accurate diagnosis.

Colour: The color of the lesion can be fully white, fully red, or white interspersed with red. When determining the color of the lesion the predominating color should be selected. If the red and white color are approximately equal the lesion can be indicated as red and white lesions whereas white lesions appear completely white in color & red lesions are completely red. For example, lichen planus shows areas of pigmentation whereas Speckled leukoplakia will show both areas of redness and whiteness.

Surface Texture: Various types of oral lesions present with distinct surface structures. Hence Surface characteristics can provide valuable diagnostic clues. For instance, a lesion with a smooth surface might suggest a different etiology compared to a lesion with a rough or ulcerated surface. Describing whether the surface is smooth, rough, ulcerated, or verrucous helps in narrowing down the differential diagnosis. For example, in OSMF, leukoedema shows a smooth surface whereas leukoplakia often presents as a white patch with a smooth or slightly raised surface. surface can be irregular or ulcerated in case of a malignant lesion.

Extent: Describing the extent of an oral lesion is an important aspect of clinical assessment. Both anteroposterior and supero-inferior extension have to be recorded which helps in knowing the involvement of anatomical structure, diagnosis, treatment planning, monitoring, prognosis, and communication among healthcare providers.

Palpation

Palpation, or the act of examining a patient by touch, is a critical component of the clinical examination of an oral lesion as it provides valuable information about the nature, extent, associated symptoms, and changes over time. All the inspectory findings have to be confirmed with palpation thereby it complements visual inspection and amplifies the clinician's ability to accurately diagnose and manage oral lesions.

Scrapable lesions can be food debris to chemical burns, candidiasis etc. while leukoplakia, lichen planus, OSMF etc. may fall under non scrapable lesions.

Tenderness: The presence or absence of tenderness in an oral lesion is an important clinical feature that can guide diagnosis, treatment planning, monitoring, and prognosis. Homogenous Leukoplakia, Leukoedema, and OSMF tend to be non-tender whereas erosive/ atrophic Lichen Planus and Pseudomembranous candidiasis show tenderness or burning sensation on palpation. Malignancy does not show tenderness on palpation unless it is secondarily infected.

Induration: Induration refers to the hardening of tissues due to increased cellularity or fibrosis. Malignant lesions often exhibit induration due to the infiltration of cancer cells into surrounding tissues. This infiltration causes structural changes and hardening of the affected area. Detecting induration is crucial for identifying potentially malignant lesions early in their development. In oral lesions, induration is commonly associated with neoplastic (cancerous) processes, such as squamous cell carcinoma. Palpating for induration helps differentiate between benign and malignant lesions.

Consistency: The consistency of an oral lesion can help differentiate between benign and malignant conditions. Malignant lesions often exhibit firmness or induration due to tissue infiltration, whereas benign lesions may have a softer consistency.

A thorough examination and documentation of these aspects during inspection & palpation of oral lesions are essential for proper diagnosis and management.

Investigations of Oral Potentially Malignant Disorders

Investigations in Oral Potentially Malignant Disorders (OPMDs) are decisive for accurate diagnosis, risk assessment, and appropriate management. Many OPMDs present with nonspecific clinical features, making it challenging to diagnose based solely on clinical examination. Investigations such as biopsy and histopathological examination are essential for confirming the diagnosis and distinguishing between benign and potentially malignant or malignant lesions and help in stratifying patients based on their risk of progression to oral cancer.

Chair Side Investigations

Vital Staining

Vital staining is the application of a biocompatible dye, in the form of mouth rinse or topical application directly to the affected area of the oral mucosa. Application of the stain could provide information on different lesion properties, identify non-evident lesions, and help to select the best site for a biopsy. The most routine vital stain used in oral medicine is toluidine blue, however, some alternatives involve Methylene blue, Lugol's Iodine, Rose Bengal, etc.

Toluidine blue is a cationic metachromatic dye with an affinity for acidic tissue components, such as nuclei acids. Toluidine blue staining is a technique used to enhance the visualization of suspicious lesions in the oral cavity, particularly those that may be precancerous or cancerous. The steps in toluidine blue staining involve, wiping of affected mucosal surface with 1% acetic acid solution followed by the application of Toluidine blue solution. Areas of the mucosa that potentially show abnormalities or dysplastic or anaplastic cells can retain more stain and appear as a dark blue region. (Fig.11)

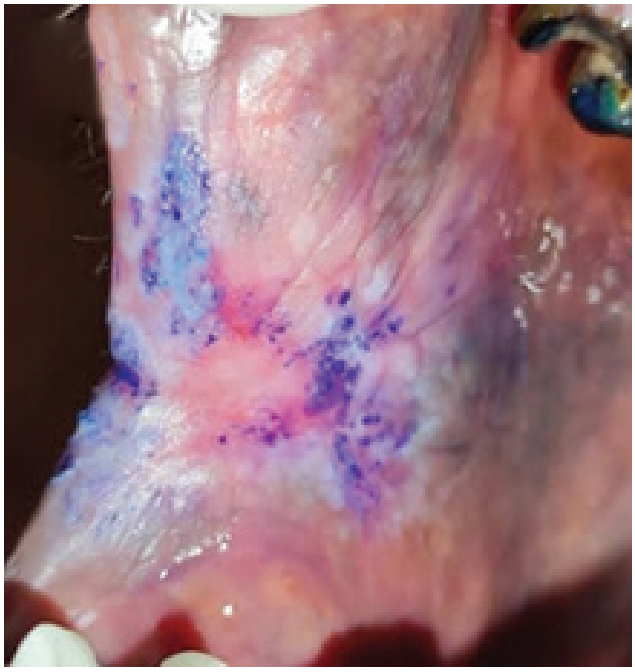


Fig.11: Toluidine blue staining done in a speckled leukoplakia, note areas as dark blue represent dysplastic changes

Methylene blue (MB):

Also recognized as methylthionine chloride or tetramethylthione chloride, methylene blue is an aromatic heterocyclic compound similar to toluidine blue, possessing acidophilic properties. Methylene blue aids in dye retention within cells exhibiting dysplastic characteristics, mirroring the actions of toluidine blue. Its indications and application method resemble those of toluidine blue, potentially offering a more cost-effective and less toxic alternative. However, the lack of evidence regarding its efficacy in oral cancer screening necessitates further research and studies.

Lugol's iodine stain: Lugol's iodine (LI) interacts with glycogen present in the cytoplasm of normal nonkeratinized cells, resulting in a brown-orange color change in tissues. When LI stain is applied to oral potentially malignant disorders (OPMDs), the surrounding normal oral mucosa stains brown while abnormal tissues remain unstained. LI can be utilized alongside toluidine blue, with abnormal tissues staining dark blue and LI highlighting the normal area. However, robust studies demonstrating the effectiveness of LI stain in diagnosing OPMDs are currently lacking.

Optical and light-based systems

The methods entail conveying distinct interactions between incident radiation and tissue, such as absorption, reflection, fluorescence, or scattering, which may indicate potential carcinogenic effects. Chemiluminescence approaches, Autofluorescence approaches, Laser-induced fluorescence examination, and optical coherence tomography are some of them. Optical light-based systems play a vital role in the diagnosis of oral lesions by enabling early detection, providing non-invasive and enhanced visualization, offering real-time imaging, facilitating objective assessment, aiding in lesion differentiation, and promoting patient education.

Chemiluminescence is based on the proportion of light that a mucosal surface is capable of reflecting. Changes in mucosal tissues, such as in OSCC or oral epithelial dysplasia (OED), could show different absorption and reflectance whereas Autofluorescence approach is a phenomenon whereby cells can produce fluorescence when subjected to a specific wavelength of light. This approach can identify lesions that are not visible to the naked eye (occult clinical lesion), and could be used to detect a suspected area of a lesion and for determining adequate surgical margins.

Oral Cytology

Oral cytology is a technique used to study cells collected from the oral cavity for the purpose of microscopic diagnosis of various abnormalities, including premalignant and malignant lesions. This can be considered as auxiliary diagnostic procedure as only isolated or small group of cells are examined. However, the sensitivity of oral cytology is inferior to any type of tissue biopsy. Therefore, an incisional or excision biopsy should be performed to confirm a positive result. The three most common types are exfoliative cytology, transepithelial biopsy (Brush cytology biopsy), and fine-needle aspiration cytology (FNAC).

Exfoliative cytology (EC): The process involves examining cells present in saliva through mouthwash sampling, or cells collected from the surfaces of the oral mucosa using brushing or scraping techniques, typically with a brush (preferred), wooden spatula, blunt instrument, or sharp instrument. It's important to note that many dysplastic cells are situated deeper within the epithelium and may not be adequately represented in surface scrapings. Intensive brushing of the oral epithelium, sometimes to the point of observing bleeding, has led to the development of the Transepithelial cytology technique. Some available commercial tools use this transepithelial cytology technique, including the Oral CDX test, which is a computer-assisted device that uses an algorithm to detect malignant cells, using a circular brush with hard bristles to collect the total depth of the epithelium (superficial, intermediate, and basal).

Biopsy

Biopsy has become a gold standard method for the diagnosis of many lesions and diseases including the investigation of oral malignancy or potentially malignant disorders. It is a surgical procedure where tissue from a living patient is removed and subjected to microscopic examination. It can confirm a provisional diagnosis, make a definitive diagnosis or may exclude other possible diagnoses. Moreover, biopsy may contribute to the assessment of the efficacy of a treatment and help with determining prognosis in malignant or

premalignant lesion. The indications for performing an oral biopsy depend on multiple factors including the clinical and macroscopic characteristics of a lesion, such as evolution of a lesion, macroscopic presentation or refractory response to standard treatments. The biopsy is indicated in case of a suspected malignant lesion, potentially malignant disorder, chronic or persistent lesions of uncertain etiology, lesions showing refractory response to standard treatments, or lesions that interfere with oral function (fibroma, papilloma, etc.). The contraindications to biopsy are primarily related to the general health status of the patient. Biopsy of normal variations of anatomical structures (e.g. racial pigmentation, geographic tongue, Linea Alba, lingual indentations, or Fordyce spots), Irritative/ traumatic lesions that respond to the removal of a local irritant, inflammatory or infectious lesions that respond to specific local treatments, are not indicated. Biopsies can be incisional (only a representative part of the lesion is removed) or excisional (complete excision of the lesion) depending on the amount or area of tissue that is surgically removed. Further categorizations may be used depending on the instruments and specific technique employed (scalpel, punch, core needle), processing of the tissue sample (e.g. fresh, frozen, formalin-fixed paraffin-embedded), type of tissue removed (soft tissue or hard tissue). When conducting soft tissue biopsy, it is preferable to use a scalpel, punch, or forceps for tissue removal instead of electro scalpels, and lasers (such as diode or Nd: YAG, CO2 lasers), as these methods may induce histological artifacts, thereby complicating the diagnosis process.

Incisional biopsy involves the removal of a representative area of the lesion. It should include a representative area and, ideally, adjacent normal tissue. The decision to obtain either abnormal or normal tissue samples depends on the specific nature of the lesion. For instance, when malignancy is suspected, acquiring abnormal tissue is preferred, whereas in blistering disorders, obtaining "normal" adjacent tissue is preferred. In situations involving extensive or large lesions, or when dealing with multiple lesions, incisional or mapping biopsies may be warranted. In heterogeneous lesions (in color, texture, or consistency), multiple incisional biopsies should be performed to obtain different representations of the lesion. Incisional biopsy is considered the gold standard when malignancy is suspected and for oral potentially malignant lesions.

Excisional biopsy is the removal of the entire lesion, with a margin of normal tissue peripherally and at the deeper margin. It is indicated for small lesions (<1cm), such as papillomas, fibromas, granulomas, or in cases of small OPMDs. This allows histological examination & treatment with complete removal of the lesion.

To assist the clinician in choosing a biopsy site diagnostic adjunct tool can be used which involve the use of materials and/or devices to facilitate the detection of the most abnormal part of an oral lesion. Several types of diagnostic adjunct tools are clinically available including vital staining, optical or light-based systems, cytology, and saliva methods.

Salivary adjuncts

Saliva serves as a diagnostic complement for investigating various molecular markers, including antibodies, cytokines, human and microbial nucleic acids (DNA, RNA, microRNA), growth factors, and numerous proteins, notably tumor biomarkers. While several of these markers are either under research or commercially accessible (e.g., CD44 and levels of 'total protein' or M rna biomarkers), there remains inadequate scientific evidence to support their standard utilization in detecting oral potentially malignant disorders (OPMDs) and oral cancer.

Various investigation modalities play a vital role in the diagnosis of oral lesions by enabling early detection, providing non-invasive and enhanced visualization, offering real-time imaging, facilitating objective assessment, aiding in lesion differentiation, and promoting patient education thereby improving the patient's quality of life.

Chapter 12

DIAGNOSIS AND INVESTIGATION

Clinical diagnosis of oral potentially malignant disorders

Oral potentially malignant disorders and their differential diagnosis *(Warnakulasuriya S et.al)*

Oral potentially malignant disorder	Differential diagnosis to be ruled out
Leukoplakia [1]	Pseudomembranous candidiasis [1.a]
	Chemical burn [1.b]
	Frictional keratosis [1.c]
	Chronic hyperplastic candidiasis [1.d]
	Smokeless tobacco induced keratosis [1.e]
	Oral hairy leukoplakia [1.f]
	Leukoedema [1.g]
	White sponge nevus [1.h]
	Nicotinic stomatitis [1.i]
	Uremic stomatitis [1.j]
	Skin graft [1.k]
	Fordyce's granules [1.l]
	Oral lichen planus [1.m]
	Palatal keratosis of reverse smokers [1.n]
	Dyskeratosis Congenita [1.o]
Proliferative verrucous leukoplakia [2]	Early stages resemble like lichen planus
Palatal lesions of reverse smokers [1.n]	Leukoplakia [1]
Dyskeratosis Congenita [1.o]	Leukoplakia [1]
Erythroplakia [3]	Erythematous candidiasis [3a]
	Erythema migrans [3b]
	Other generalized erosive disorders like oral lichen planus, vesiculobullous lesions, lupus erythematosus [3c]
Oral lichen planus (4)	Oral lichenoid lesions [4.a]
	Oral lichenoid contact hypersensitivity reaction [4.a.1]
	Oral lichenoid drug reaction [4.a.2]
	Oral lichenoid lesions secondary to betel quid use [4.a.3]
	Oral lesions of graft vs host reaction [4.b]
	Oral lupus erythematosus [4.c]
	Early stages of proliferative verrucous leukoplakia [4.d]
	Chronic ulcerative stomatitis [4.e]

Oral lichenoid mucositis (4.a)	Oral lichen planus [4]
	Oral lesions of graft vs host reaction [4.b]
	Oral lupus erythematosus [4.c]
	Early stages of proliferative verrucous leukoplakia [4.d]
	Chronic ulcerative stomatitis [4.e]
Oral lesions of graft vs host reaction (4.b)	Oral lichen planus [4]
	Oral lichenoid mucositis [4.a]
	Oral lupus erythematosus [4.c]
Oral lupus erythematosus [4.c]	Oral lichen planus [4]
Actinic cheilitis (5)	
Oral submucous fibrosis (6)	Iron deficiency anemia [6.a]
	Scleroderma [6.b]

*(For Diagnostic algorithm for white patches of oral mucosa, Ref. Appendix 3)

1. Leukoplakia

Leukoplakia is the commonest OPMD. WHO in 2017 defined leukoplakia as a "Predominantly white plaque of questionable risk having excluded other known diseases or disorders that carry no increased risk of cancer." Leukoplakia literally means white patch which has occurred as a result of increased keratinization, when the keratin becomes wet with saliva it appears white in color. Leukoplakia is a clinical diagnosis and it is a diagnosis of exclusion. So in order to reach the clinical diagnosis of leukoplakia all the other white lesions needs to be ruled out.

The WHO expert group on nomenclature and classification of OPMD at the Collaborating Center for Oral Cancer in the UK has proposed the following criteria for the clinical diagnosis of leukoplakia.

- A predominantly white patch/plaque that cannot be rubbed off
- Most homogeneous leukoplakias affect a circumscribed area and have well-demarcated borders. A smaller subset can present with diffuse borders.
- Non-homogeneous leukoplakias typically present with more diffuse borders and may have red or nodular components.
- No evidence of chronic traumatic irritation to the area
- Is not reversible on the elimination of apparent traumatic causes,
- Does not disappear or fade away on stretching (retracting) the tissue

Differential diagnosis to be ruled out in oral leukoplakia

Benign white lesions and normal mucosal variations present as white patches

Scrapable white lesions

1.a. Pseudomembranous candidiasis

The lesions are scrapable leaving a red eroded surface. Patients will have a history of immunocompromised states. Lesions will disappear with anticandidal treatment.

1.b. Chemical burn

Present as scrapable white necrotic tissue. Patients will have a known history of exposure to a chemical (e.g. an aspirin tablet or a caustic agent e.g. sodium hypochlorite). The site of the lesion corresponds to chemical injury. The affected area is painful and resolves rapidly as the offending agent is removed.

Non scrapable white lesions

1.c. Frictional keratosis

They are white plaques clearly related to an identifiable source of mechanical irritation. Patients will have a

history of friction or mechanical trauma. The lesions are reversible upon removal of the cause within a two-week period. If the lesion persists it has to be clinically considered as leukoplakia and biopsy has to be performed in order to rule out dysplasia.

1.d. Chronic hyperplastic candidal infection

Presents as a non-scrapable white plaque which can be often confused with leukoplakia. A history of an underlying immunodeficiency state should warn the clinician on the possible differential diagnosis of hyperplastic candidiasis. These lesions will disappear with antifungal treatment.

Many instances the speckled leukoplakias can have colonization of candidal organisms which can aggravate the clinical presentation and symptoms of these lesions. It is recommended to treat these lesions with antifungals before performing biopsy on these lesions.

1.e. Smokeless tobacco induced keratosis

Seen as a white wrinkled patch at the area of tobacco pouching often in the buccal sulcus. Most of these lesions will resolve with the discontinuation of the habit usually within two weeks. If the lesion fails to resolve it has to considered as leukoplakia and biopsy is recommended.

1.f. Oral hairy leukoplakia is an Epstein-Barr virus-induced white lesion seen to develop in immunocompromised individuals. It typically appears as a bilateral vertical streaking with keratosis on the lateral borders of the tongue. They have no potential for malignant transformation. Bilateral keratosis on the lateral border of the tongue and a history of immune deficiency states should help the clinician to identify these lesions.

1.g. Leukoedema is a normal variation of the oral mucosa that presents clinically as a bilateral diffuse white opalescent appearance which occurs due to oedema or wrinkling of the mucosa. The white appearance diminishes when the mucosa is stretched. Leukoedema is seen more prominently in smokers.

1.h. White sponge nevus is a benign hereditary condition often seen in early childhood presenting as white corrugated diffuse spongy plaques often seen bilaterally on the buccal mucosa. Both intraoral and extraoral sites can be involved.

1.i. Nicotinic stomatitis (smokers palate) will present a diffuse leathery greyish-white plaque on the palate with red pointed inflamed openings of minor salivary glands seen in heavy smokers. They have no potential for malignant transformation and will recede after habit cessation.

1.j. Uremic stomatitis: Patients with acute or chronic renal failure can present with white adherent plaques of fibrinous exudate and desquamated epithelial cells due to elevated levels of urea and nitrogenous products in saliva. A positive medical history of renal disease should help the clinician to diagnose this condition.

1.k. Skin grafts can often resemble a leukoplakia. However, a positive history for the same should rule out this differential diagnosis.

1.l. Fordyce's spots/condition presents as yellowish-white elevated circular plaques less than 1 mm in diameter.

Other oral potentially malignant disorders presenting as white patches

1.m. Oral lichen planus

Can be distinguished from leukoplakia because of its characteristic clinical presentation. Lichen planus presents clinically with white papules joined with lines called the Wickham's striae forming a characteristic reticular appearance. Most of them especially erosive types are symptomatic with a burning sensation on taking spicy foods. The lesions are multifocal and will show waxing and waning. Plaque type lichen presents clinically as a white homogenous plaque resembling leukoplakia and they often lack the characteristic Wickham's striae. The common site of occurrence of plaque-type lichen planus is the dorsum of tongue which is a rare site for leukoplakia. Plaque-type lichen planus needs to be ruled out by histopathological examination.

1.n. Palatal keratosis with reverse smokers is classified as a separate entity within the OPMDs since they are considered to have a higher risk of malignant transformation. A positive habit history of reverse smoking will help to identify these lesions.

1.o. Dyskeratosis congenita is an inherited X-linked

recessive disorder showing male predilection. Clinically characterized by abnormal skin pigmentation, nail dystrophy, oral leukoplakia, bone marrow failure, and elevated risks of oral squamous cell carcinomas and haematolymphoid neoplasms. The manifestations will emerge early between the ages of 5 to 12 years. Oral leukoplakia is present at an early age.

2. Proliferative verrucous leukoplakia (PVL)

It is a distinct form of multifocal leukoplakia exhibiting progressive clinical and histological features associated with a high rate of malignant transformation.

The diagnostic criteria for PVL were proposed by Cerero-Lapiedra et al in 2010 as follows

Major Criteria (MC):

A. A leukoplakia lesion with more than two different oral sites, which is most frequently found in the gingiva, alveolar processes, and palate.

B. The existence of a verrucous area.

C. That the lesions have spread or engrossed during the development of the disease.

D. That there has been a recurrence in a previously treated area.

E. Histopathologically, it can range from simple epithelial hyperkeratosis to verrucous hyperplasia, verrucous carcinoma, or oral squamous cell carcinoma, whether in situ or infiltrating.

Minor Criteria (mc):

1. An oral leukoplakia lesion that occupies at least 3 cm when adding all the affected areas.
2. That the patient be female.
3. That the patient (male or female) be a non-smoker.
4. A disease evolution higher than 5 years. (warn 2018, scoping rev PVL)

Diagnosis of PVL:

1. Three major criteria (being E among them) or

2. Two major criteria (being E among them) + two minor criteria.

Differential diagnosis

2.a. The early lesions of PVL can resemble an oral lichenoid lesion. It can appear as flat white lesions without verrucous appearance and can show striae resembling lichenoid reaction.

3. Erythroplakia

It is defined as a "Fiery red patch that cannot be characterized clinically or pathologically as any other definable disease. It presents clinically as a well-defined flat or depressed erythematous area of the mucosa. (1) Erythroplakia is also a diagnosis of exclusion. Biopsy is indicated for erythroplakia to rule out dysplasia or malignancy. Other diseases which presents as a red patch on the oral mucosa needs to be ruled out.

Differential diagnosis to be ruled out

3.a. Erythematous candidiasis (denture sore mouth): The Clinician will be able to recognize this infectious condition from the history of denture-wearing

3.b. Erythema migrans is a benign lesion typically seen in the dorsum of tongue. They present clinically as well demarcated zones of erythema due to the atrophy of filiform papillae. The area of atrophy is surrounded by a yellow white serpentine border. The lesion will heal within few weeks or months and develop in another area.

3.c. Other erosive disorders of the oral cavity like erosive lichen planus, lupus erythematosus, or gingival conditions like desquamative gingivitis can be distinguished from erythroplakia due to its widespread distribution.

4. Oral lichen planus

It is an autoimmune chronic inflammatory mucocutaneous disorder of unknown etiology characterized by white papules joined together to form white lines called Wickham's striae. The various clinical presentations include reticular, papular, erosive, atrophic bullous, and plaque types. They typically have a bilateral symmetrical presentation. The lesions will show waxing and waning. The presence of the typical Wickham's striae helps the clinician to make the diagnosis. Patients with erythematous forms of lichen planus will present with a burning sensation.

The diagnosis of oral lichen planus has to be made with diagnostic criteria endorsed by the WHO working group on oral potentially malignant disorders in 2022.

Clinical criteria

- Presence of bilateral, more or less symmetrical white lesions affecting buccal mucosa, and/or tongue, and/or lip, and/or gingiva
- Presence of white papular lesions and lace-like network of slightly raised white lines (reticular, annular, or linear pattern) with or without erosions and ulcerations.
- Sometimes presents as desquamative gingivitis.

Histologic criteria

- Presence of a well-defined band of predominantly lymphocytic infiltration in the superficial part of the connective tissue.
- Signs of vacuolar degeneration of the basal and/or suprabasal cell layers with keratinocyte apoptosis
- In the atrophic type there is epithelial thinning and sometimes ulceration caused by failure of epithelial regeneration as a result of basal cell destruction. A mixed inflammatory infiltrate may be found.

Differential diagnosis: Other OPMDS with similar clinical appearances

4.a. Oral lichenoid lesions are those oral lesions that have features compatible with, but not typical of oral lichen planus. Oral lichenoid lesions can present with white striae similar to oral lichen planus and erythematous areas can be symptomatic. They may not present in a symmetric bilateral pattern or have the characteristic histologic presentations of oral lichen planus.

Oral lichenoid lesions include

4.a.1. Oral lichenoid contact hypersensitivity reactions are considered delayed hypersensitivity reactions usually to dental restorative materials like amalgam or food allergens. These lesions are unilateral, unlike oral lichen planus. History is very important. Establishing a temporal relationship between restoration placement and the occurrence of the lesion is key to the diagnosis. Mucosal lesions resolve after the removal of the restoration or the allergen.

4.a.2. Oral lichenoid drug reactions are delayed hypersensitivity reactions to drugs or their metabolites. They usually present unilaterally and will have an ulcerative pattern looking very similar to oral lichen planus. The lesions usually develop after several months of drug use. The lesions will resolve after the withdrawal of the drugs.

4.a.3. Oral lichenoid lesions secondary to betel quid use is seen at site of quid placement. It presents with white liner streaks sometimes found arising from a central erosive area. The lesions are found to resolve with the cessation of the habit. A positive habit history of betel quid use and the occurrence of the lesion at the site of quid placement will help the clinician to make the diagnosis.

4.b. Oral lesions of graft vs host reaction are a complication that develops in a patient with a history of bone marrow transplantation. The oral presentation of the lesion resembles an oral lichen planus. but concomitant involvement of other organs like skin and liver and a positive medical history will help to diagnose this condition.

4.c. Oral lupus erythematosus

Is a chronic auto-immune disease which shows three clinical presentations 1) systemic lupus erythematosus, 2) Chronic cutaneous lupus erythematosus (Discoid lupus erythematosus) 3) Subacute cutaneous lupus erythematosus. In systemic lupus erythematosus, 20% of patients show oral manifestations. The oral lesions of lupus erythematosus will resemble like erosive lichen planus showing a central erythematous area with ulceration and peripheral white radiating striae. Systemic lupus erythematosus will show systemic involvement including kidney, cardiac, and skin involvement.

Limited diseases like discoid lupus erythematosus will have skin involvement with oral manifestations. The skin involvement in lupus erythematosus is characterized by the involvement of the malar region producing a butterfly-shaped rash. Sun exposure worsens the condition. The characteristic skin involvement in lupus erythematosus will help to distinguish it from erosive oral lichen planus. Biopsy is needed to distinguish from erosive lichen planus. Confirmatory diagnosis can be done by doing a lupus band test (direct immunofluorescence)

4.d. Early stages of proliferative verrucous leukoplakia can resemble like an oral lichenoid lesion. It can appear as flat white lesions without verrucous appearance and can show striae resembling lichenoid reaction.

Differential diagnosis: Other benign lesions with similar clinical appearances

4.e. Chronic ulcerative stomatitis resembles lichen planus clinically and histologically. Immunofluorescence- DIF IgG directed against nuclei of basal and parabasal epithelial cells. Indirect immunofluorescence is positive against stratified epithelium-specific antinuclear antibodies. Chronic ulcerative stomatitis does not respond to steroids but will respond to hydroxychloroquine.

5. Actinic cheilitis/Actinic keratosis

It is produced by the effect of sunlight on the vermillion border of the lip. The lower lip is commonly affected. It clinically presents as diffuse white flaking plaques or scaly lesions. In mild cases, it appears as dryness of the lips. In advanced stages, redness will appear due to atrophy and ulceration.

6. Oral submucous fibrosis (OSMF)

It is a chronic insidious disease caused by areca nut chewing leading to the fibrosis of the lamina propria. The diseases progress to involve the whole oral cavity. Early lesions are characterized by a burning sensation and the mucosa shows leathery texture and blanching. As the lesion advances there is a loss of resilience of the oral mucosa, the formation of palpable fibrotic bands with patients experiencing limited mouth opening and tongue protrusions. Superimposed over the mucosal changes of OSMF, red and white patches or ulcerations can develop. These areas need to be biopsied to rule out dysplasia or malignancy.

Differential diagnosis

6.a. Iron deficiency anemia is commonly seen in India. Iron deficiency anemia and OSMF can exist as two separate entities and they can have overlapping clinical features. Iron deficiency anemia can show pallor and blanching of the mucosa, mucosal atrophy, and dysphagia similar to OSMF. Sometimes Iron deficiency anemia can co-exist with OSMF. So, a blood examination should be done in patients diagnosed with OSMF in order to rule out iron deficiency anemia.

6.b. Scleroderma is a collagen-related disease with some features similar to OSMF like pale mucosa, reduced mouth opening, and fibrosis of the oral mucosa. However, OSMF lacks the skin and multiorgan involvement seen in scleroderma. In OSMF the changes are confined to oral mucosa and are attributed to areca nut chewing.

Chapter 13

HISTOPATHOLOGIC FEATURES AND FINDINGS

Leukoplakia and Erythroplakia

Leukoplakia and Erythroplakia are clinical terms representing white patch and red patch respectively. Leukoplakias exhibit varying degrees of epithelial changes indicative of the risk of malignant transformation. It is mandatory to biopsy all leukoplakias as biopsy is the gold standard to predict the risk of cancer development in these lesions.

The epithelial changes seen in leukoplakia are:

- **Hyperkeratosis:** Increase in the thickness of the surface keratinized layer.
- **Acanthosis:** Increase in the thickness of the spinous layer
- **Oral Epithelial Dysplasia (OED):** a spectrum of architectural (Fig 1) and cytological (Fig 2) epithelial changes resulting from the accumulation of genetic alterations, usually arising in a range of OPMD and indicating a risk of malignant transformation to OSCC".

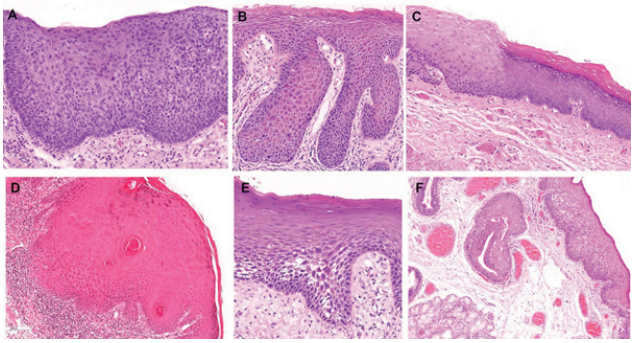


Fig 1: Range of architectural abnormalities seen in OED. (A) Irregular stratification (B) Premature keratinisation. (C) Abrupt transition: a sharp and defined change from normal epithelium to dysplastic epithelium is seen. (D) Keratin pearl formation: (E) Loss cell epithelial cohesion and basal cell polarity: (F) Extension of OED along a salivary duct. . Source: Hankinson P, Mahmood H, Walsh H, Speight PM, Khurram SA. Demystifying oral epithelial dysplasia: a histological guide. Pathology 2024; 56: 11-23.

Clinical Significance:

Lesions clinically diagnosed as leukoplakia could histologically be hyperkeratosis, carcinoma in situ, oral cancer, or most commonly epithelial dysplasia.

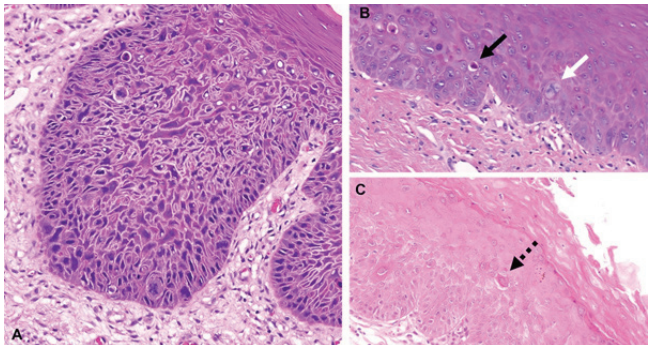


Fig 2: Cytological abnormalities. (A) Severe OED: Abnormal variation in nuclear size and shape, increased mitotic activity, increased nucleus:cytoplasm ratio, atypical mitotic figures, increased number and size of nucleoli, nuclear hyperchromasia and abnormal mitoses. (B) Abnormal mitosis and apoptosis: an apoptotic cell with pyknotic nucleus, brightly eosinophilic cytoplasm and retraction from neighbouring keratinocytes (black arrow); an abnormal mitotic figure with asymmetrical chromatin (white arrow). (C) Single cell keratinisation. Source: Hankinson P, Mahmood H, Walsh H, Speight PM, Khurram SA. Demystifying oral epithelial dysplasia: a histological guide. Pathology 2024; 56: 11-23.

Histopathologically, the presence of features consistent with **"Oral Epithelial Dysplasia" (OED)** is mandatory to characterize these lesions as OPMDs.

Epithelial dysplasia is graded as **Mild, Moderate, and Severe** based on the extent of the dysplastic features in the epithelium.

Mild: Presence of minimum cytological atypia without prominent architectural changes. All the changes seen are restricted to lower one-third of the epithelium (Fig 3A).

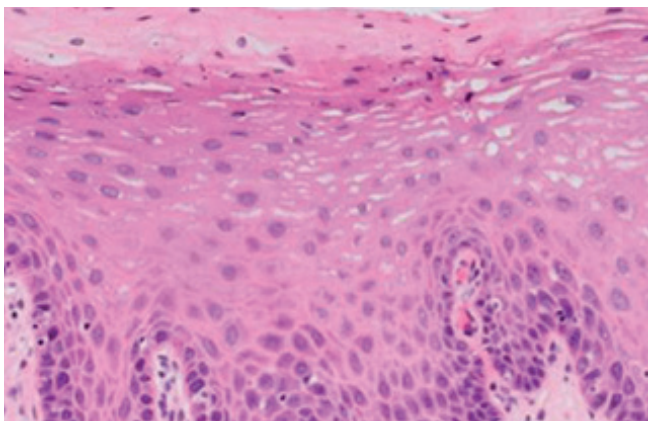


Fig 3A: Mild dysplasia

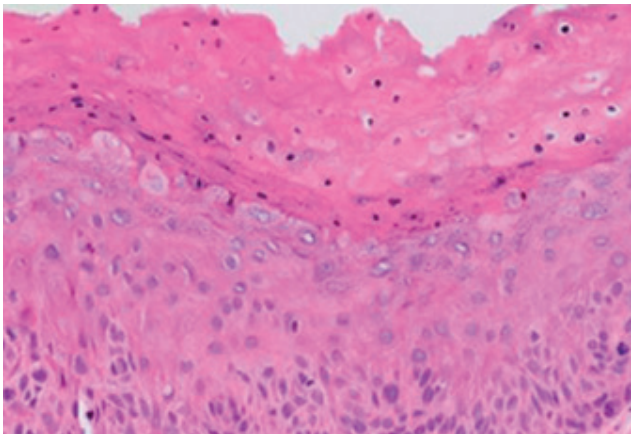


Fig 3B: Moderate dysplasia

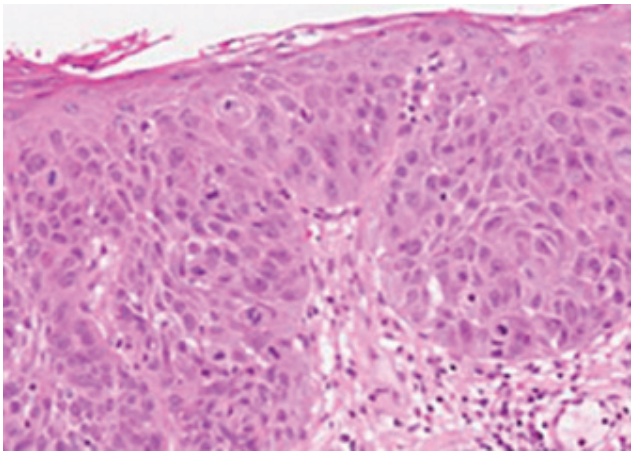


Fig 3C: Severe dysplasia

Fig 3: Histopathological grades of Oral Epithelial Dysplasia. Source: Albuquerque R, Brailo V, Carey B, Diniz-Freitas M, Fricain JC, Lodi G et al, editors. Oral Potentially Malignant Disorders: Healthcare Professional training. London.2022

Moderate: Presence of moderate cytologic atypia such as increased proliferation, prominent cellular and nuclear pleomorphism, and increased and abnormal mitosis extending from the basal cells to the supra-basal layers. Architectural changes include loss of polarity and bulbous rete ridges. All the changes are restricted to the lower half of the epithelium (Fig 3B).

Severe: These lesions exhibit severe cytologic and architectural changes including abnormal keratinization extending to the upper third of the epithelium (Fig 3C).

Interpretation of Histopathology Report/Patient Education:

A histopathology report showing hyperkeratosis or acanthosis represents early changes. Reports showing the presence of dysplasia are of concern. Mild and moderate cases are reversible following cessation of deleterious habits. Severe epithelial dysplasia and carcinoma in situ need to be treated immediately.

Proliferative Verrucous Leukoplakia

Histopathology is not characteristic and diagnosis requires clinicopathologic correlation.

Histopathology reveals prominent hyperkeratosis and granular layer. The keratin is thrown into prominent spikes containing crests and troughs. The presence of cytological atypia depends on the stage of the lesion (Figs 4a and 4b).

Clinical Significance:

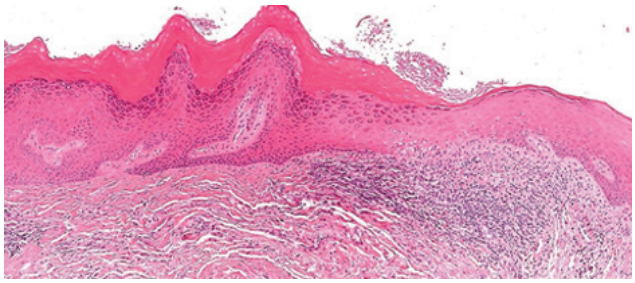


Fig 4a: Early phase lesion:Verrucous hyperplasia consistent with proliferative verrucous leukoplakia (original magnification ×4) showing a verrucous architecture, abrupt transition and no cytological atypia.

Source: Hankinson P, Mahmood H, Walsh H, Speight PM, Khurram SA. Demystifying oral epithelial dysplasia: a histological guide. Pathology 2024; 56: 11-23

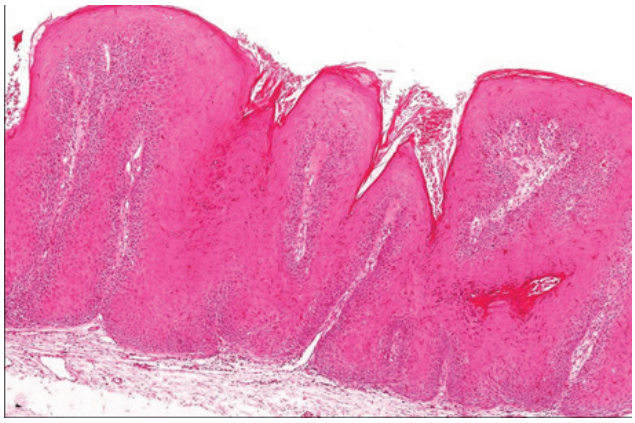


Fig 4b: Progressive Lesion: Verrucous hyperplasia with OED consistent with proliferative verrucous leukoplakia (original magnification ×4) showing bulky endophytic and exophytic proliferation, showing only mild cytological atypia.

Source: Hankinson P, Mahmood H, Walsh H, Speight PM, Khurram SA. Demystifying oral epithelial dysplasia: a histological guide. Pathology 2024; 56: 11-23

Lesions of PVL clinically and histopathologically resemble Verrucous hyperplasia and Verrucous carcinoma.

Interpretation of Histopathology Report/Patient Education:

Proliferative Verrucous Leukoplakia (PVL) is a high-risk form of Leukoplakia characterized by multiple keratotic plaques presenting with irregular surface projections. Lesions reported as PVL need immediate surgical removal and long-term follow-up as it has a high propensity for recurrence and malignant transformation

Oral Submucous Fibrosis

- Atrophic epithelium (with or without dysplasia)
- Flattened epithelial-connective tissue junction,
- Dense sub-epithelial connective tissue exhibiting "juxta-epithelial" hyalinization (Fig. 5)
- Sparse inflammatory cells and vascularity
- As the lesions progress towards cancer, they may show histopathological features of epithelial dysplasia

Interpretation of Histopathology Report/Patient Education

Oral Submucous fibrosis is an Oral Potentially Malignant disorder. The presence of dysplastic features in histopathology indicates an increased risk of transformation into Oral Squamous cell carcinoma.

The patient must be educated about its malignant transformation potential and counseled to discontinue the habit.

Oral Lichen Planus

- Orthokeratosis or Parakeratosis may be present.

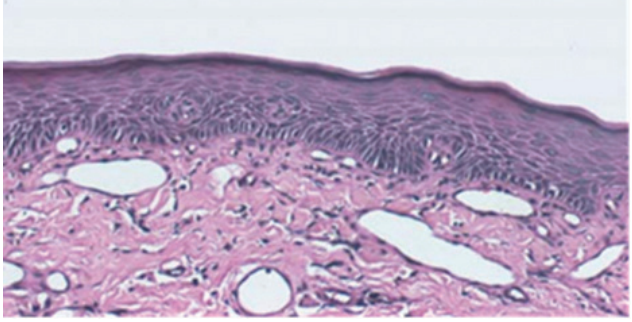


Fig 5: Histopathology of Oral Submucous Fibrosis

- The rete ridges may be atrophic or hyperplastic, but classically have a 'saw tooth' appearance with hydropic degeneration of the basal cells of the epithelium (Fig. 6).
- The degenerated basal keratinocytes appear as eosinophilic structures called Colloid or Civatte or Hyaline bodies.
- The subepithelial connective tissue exhibits a dense band of T lymphocytes.
- An artefactual split formation may occur at the level of the basement membrane (Max Joseph Cleft).

Clinical Significance:

- Epithelial atypia is generally not seen in oral lichen planus, but in lesions with superimposed candidiasis, few atypical features may be noted. Such lesions have to be re-evaluated after the treatment of candidal infection.

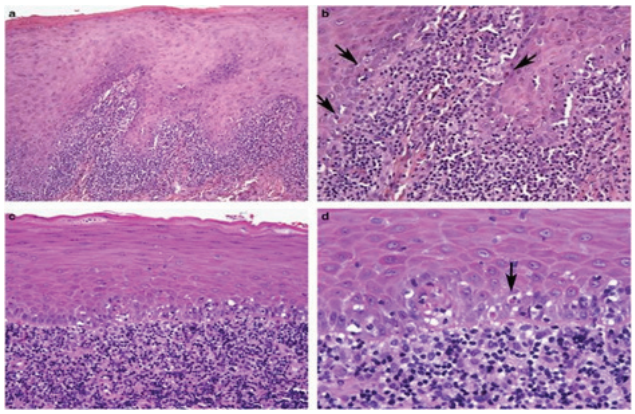


Fig 6: Histopathologic features of the reticular form of oral lichen planus. 'saw-tooth' rete ridge morphology, and a dense band-like chronic inflammatory cell infiltrate in the superficial lamina propria (a, H&E stain, original magnification × 100). Arrows in (b) show keratinocyte apoptosis represented as a colloid (Civatte) body (arrows) (b, H&E stain, original magnification × 250). Arrows in (d) shows premature dyskeratosis. *Source: Miller S. Oral lichenoid lesions: distinguishing the benign from the deadly. Modern Pathology 2017; 30: S54-S67.*

Oral Lichenoid lesions

Histopathologically, Oral Lichenoid lesions are similar to Lichen planus. The distinguishing features include 1. A mixed lichenoid inflammatory infiltrate consisting of eosinophils and plasma cells 2. The inflammatory infiltrate is distributed deeper in the sections and particularly in perivascular location (Fig. 7).

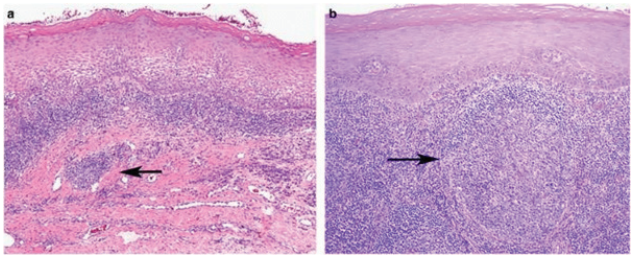


Fig.7: Oral lichenoid drug reaction. Acanthosis and inflammatory exocytosis is seen along with perivascular inflammation (arrow). (a, H&E stain, original magnification × 100). Oral lichenoid contact reaction to dental amalgam often has a dense lymphocytic infiltrate, which can form tertiary lymphoid follicles (arrow) (b, H&E stain, original magnification× 100).

Source: Miller S. Oral lichenoid lesions: distinguishing the benign from the deadly. Modern Pathology 2017; 30: S54-S67

Actinic Cheilitis

- Atrophic epithelium with varying degrees of keratosis.
- Mild subepithelial inflammatory infiltrate
- Characteristic smooth, homogenous, basophilic zone is present in the form of a subepithelial band. This is called solar elastosis and represents the alteration of collagen and elastic fibers in response to UV radiation.
- Dysplasia may be present.

Interpretation of Histopathology Report/Patient Education:

A histopathology report of Actinic cheilitis implies severe epithelial damage due to sun exposure. The presence of dysplasia indicates a high risk of malignant transformation. Patients must be educated to completely avoid exposure to direct sunlight.

Discoid Lupus Erythematosus

- The surface epithelium exhibits hyperkeratosis and degeneration of the basal cell layer.
- In the skin, keratin plugging of hair follicles occurs.
- The underlying connective tissue shows dense aggregates of chronic inflammatory cell infiltrate and perivascular inflammation.

Interpretation of Histopathology Report/Patient Education:

- Some of the microscopic features of lupus erythematosus are similar to oral lichen planus; however, presence of patchy deposit of PAS positive material in the basement membrane zone and more diffuse, deep inflammatory infiltrate in the connective tissue are distinguishing features of LE.

Oral Graft Versus Host Reaction

- The microscopic features of GVHD are similar to lichen planus.
- The tissues show hyperkeratosis, pointed rete ridges, basal cell degeneration and subepithelial inflammation.
- The inflammatory response in GVHD is not as intense as in lichen planus.
- In advanced cases, abnormal deposition of collagen is seen in the connective tissue.
- Minor salivary gland tissue shows periductal inflammation in early stages with acinar destruction and periductal fibrosis in later stages.

Oral Squamous cell carcinoma

- Invasion is the hallmark of cancer.
- The histopathology of squamous cell carcinoma is characterized by break in the continuity of the basement membrane, infiltrating islands, cords and sheets of dysplastic squamous epithelial cells in the connective tissue in addition to the presence of dysplastic features in the surface epithelium.
- Based on the degree of resemblance to site of origin and the extent of differentiation and production of keratin, OSCC is graded as Well-differentiated, Moderately differentiated and Poorly differentiated.

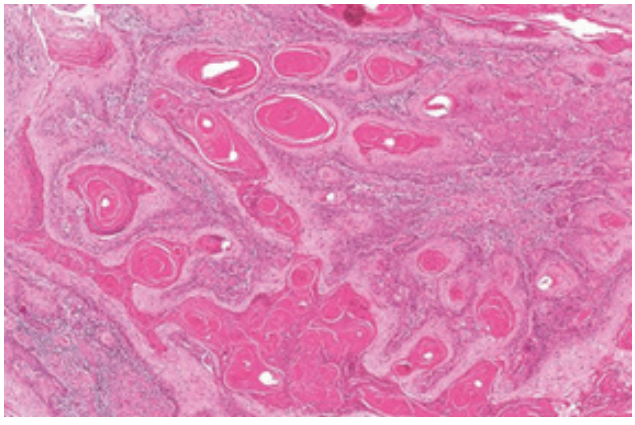


Fig 8a: Well-differentiated OSCC

Well-differentiated: Low grade mature lesion which bears close relationship to its tissue of origin and presence of keratin pearls - foci of concentrically layered keratinized cells (Fig. 8a).

Moderately differentiated: Tumors with an intermediate microscopic appearance between well and poorly differentiated forms (Fig. 8b).

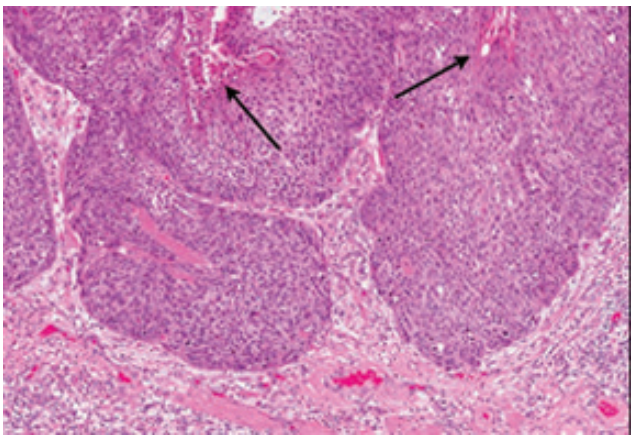


Fig 8b: Moderately-differentiated OSCC

Poorly differentiated: High grade immature (cellular and nuclear pleomorphism) lesion which bears little or no resemblance to tissue of origin with little or no keratin production. They exhibit invasive growth and early metastasis (Fig8c).

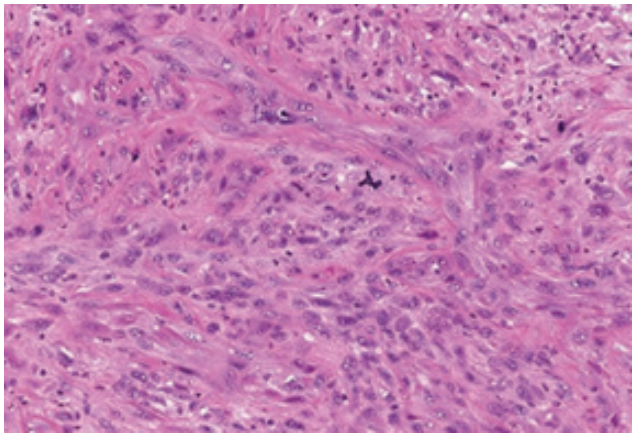


Fig 8c: Poorly-differentiated OSCC

Interpretation of Histopathology Report/Patient Education:

A histopathology report of Oral Squamous cell carcinoma is of major concern and warrants immediate treatment. Prognosis and survival rate of these patients is reflected by the histopathological grades with Poorly-differentiated OSCC bearing the worst prognosis followed by moderately -differentiated OSCC. Well-differentiated OSCC has better prognosis and improved survival rate.

Chapter 14

DIFFERENT TREATMENT MODALITIES AND THEIR INDICATIONS

Management of oral potentially malignant disorders (OPMD)

Oral lichen planus (OLP), leukoplakia, and Oral Sub mucous Fibrosis (OSMF) are three distinct oral potentially malignant disorders (OPMDs) that require careful management to prevent complications and reduce the risk of malignant transformation.

ORAL LICHEN PLANUS

MANAGEMENT:

LIFESTYLE CHANGES:

Good Oral Hygiene:

Maintaining proper oral hygiene is essential for alleviating symptoms and preventing infections.

Diet:

Refrain from consuming spicy, salty, or acidic foods that can exacerbate symptoms. A soft diet may be suggested to minimize irritation to the mucosal lining. Also, it is advisable to avoid alcohol and tobacco.

Stress management:

Recent research has emphasized the link between oral lichen planus and psychological stress, especially in relation to increased levels of anxiety and depression. Incorporating mental stress management techniques such as exercise, yoga, and meditation into treatment regimens has been shown to enhance the effectiveness of oral lichen planus therapies.

Pharmacotherapy

Asymptomatic variants of oral lichen planus, such as plaque and reticular forms, do not necessitate any symptomatic treatment; however, consistent follow-up is essential. Symptomatic oral lichen planus, including atrophic and erosive types, primarily involves the use of topical or systemic corticosteroids

Topical corticosteroids

To treat mild to moderate cases

Drugs used: 0.1%Triamcinalone Acetonide,0.025% or 0.05% Clobetasol propionate

Side Effects: Topical administration results in fewer adverse effects, such as candidiasis and atrophy of the oral mucosa. In such cases, topical corticosteroids in combination with topical anti-fungal agents can be advised.

INTRALESIONAL INJECTIONS

Patients with widespread form of lichen planus are advised intralesional injections.

Drugs used:

Triamcinolone acetonide hydrocortisone, dexamethasone, and methylprednisolone.

Recommended injection:

A dosage of 0.2-0.4 ml of a 10 mg/ml triamcinolone acetonide solution is administered once a week for a total of 2-3 doses. This treatment is combined with oral prednisolone, starting with a daily dose of 15-30 mg for two weeks. The oral prednisolone dosage is then gradually reduced to 5 mg per day and discontinued in the third week.

SYSTEMIC CORTICOSTEROIDS

Systemic corticosteroids are recommended for the management of severe and extensive cases of symptomatic oral lichen planus, particularly for atrophic and erosive forms, also when topical treatments have proven ineffective.

Drugs used:

Methylprednisolone or prednisone may be administered at a dosage of 5-60 mg per day. The initial dosage typically starts at either 10 or 20 mg per day for a duration of two weeks, after which the dosage should be gradually tapered.

Side effects:

Adrenocortical suppression, hypertension, hyperglycaemia, weight gain, mood alteration, insomnia, gastrointestinal irritation, osteoporosis.

PULSE THERAPY:

It aids in reducing the adverse side effects associated

with excessive corticosteroid use.

Recommended dose:

Administer 5 mg of betamethasone as a single morning dose following breakfast for two consecutive days each week, continuing until the disease is controlled and the signs and symptoms improve.

OTHER TREATMENT MODALITIES:

IMMUNOSUPPRESSANTS, IMMUNOMODULATORS AND OTHER AGENTS:

These agents are used in cases with contraindications for systemic steroids (Herpetic infections, glaucoma, pregnancy, HIV, tuberculosis, diabetes mellitus or hypertension).

Calcineurin inhibitors:

Cyclosporine, tacrolimus and pimecrolimus.
Levamisole: The levamisole was administered at a dose of 50 mg thrice daily for three consecutive days for 3 months.

Retinoids:

Exhibit immune-modulating effects by alleviating the white striae and associated symptoms in severe cases.

Topical and systemic retinoids: Tretinoin, isotretinoin and fenretinide,

Dapsone: 100mg per day for 3 months

Mycophenolates: Recent studies have used a 2% mucoadhesive patch containing mycophenolate mofetil for the management of symptomatic lichen planus.

ALTERNATIVE MANAGEMENT THERAPIES

Platelet rich plasma:

PRP, or platelet-rich plasma, is derived from the patient's own blood and is characterized by a high concentration of platelets and elevated levels of coagulation factors. Due to its anti-inflammatory properties, ability to promote healing, and biological safety, PRP presents a promising alternative treatment option for oral lichen planus (OLP).

PUVA therapy:

Methoxypsoralen is administered orally, after which the affected areas receive two hours of intraoral UV radiation.

Photodynamic therapy:

It uses a photosensitizing compound like methylene blue, activated at a specific wavelength of laser light.

Laser therapy:

Different lasers used are 980-nm Diode laser, CO2 laser, 904-nm pulsed infrared rays, low-dose excimer 308-nm laser with the UV-B rays

HERBAL MODALITIES:

Turmeric: Turmeric exhibit antiviral, antibacterial, anti-inflammatory properties.

Aloe vera: 70% aloe mucilage in hydrophilic gel base thrice a day on erosive and ulcerative lesions of OLP for 8 weeks showed great responses according to the literature.

Tulsi: Tulsi also has an ability to prevent the effects of metabolic stress by regulating blood glucose, blood pressure, lipid levels and psychological stress through positive effect on memory and cognitive function.

ANTIOXIDANTS

Vitamin A, Vitamin D, Vitamin E, Vitamin C, Lycopene, Raspberry leaf extract have been used to manage oral lichen planus.[1-6]

ORAL LEUKOPLAKIA

MANAGEMENT:

The main objective of treating oral leukoplakia is to prevent the risk of malignant transformation.

HABIT CESSATION:

The first step in treating leukoplakia involves the cessation of smoking and alcohol consumption, which may lead to the regression or complete resolution of the lesion. patients should be advised on maintaining a healthy diet and proper oral hygiene.

CONSERVATIVE TREATMENT:

The management of leukoplakia may involve the use of chemopreventive agents or antioxidants, including vitamins A, C, and E, fenretinide (a vitamin A analogue), carotenoids such as beta-carotene and lycopene, bleomycin, protease inhibitors, anti-inflammatory medications, green tea, and curcumin. These substances can help prevent carcinogenesis..

BIOPSY:

Clinical evaluation is conducted after 2-3 weeks to evaluate the reduction in size of lesions in both low-risk and high-risk leukoplakia cases. A period of 6–8 weeks is deemed appropriate to monitor for any potential regression of the lesion. If the lesion does not regress within 6–8 weeks, a biopsy must be taken. In cases of mild, moderate or severe dysplasia, both conservative and surgical treatment is advised.

SURGICAL TREATMENT:

Surgical treatment includes conventional surgery, electrocoagulation, cryosurgery, and laser surgery (excision or evaporation).

OTHER TREATMENT MODALITIES:

Photodynamic therapy :

A photosensitizer is delivered systemically through intravenous injection and is activated when exposed to low-power visible light at a specific wavelength corresponding to the drug.
Photosensitizers: Photofrin ,5- Aminolaevulinic acid (ALA),Verteporfin, Foscan.

Electrocoagulation:

Cryosurgery: Controlled tissue damage induced by low temperatures.

Materials used: - liquid nitrogen (N) or dinitrogen dioxide (N_2O_2)(7-9)
ORAL SUBMUCOUS FIBROSIS

LIFESTYLE CHANGES:

The primary focus of the treatment involves the cessation of habits such as gutkha, paan, paan masala, areca nuts, and chili chewing. Encourage the patient to quit the habit at an early stage of Oral Submucous Fibrosis (OSMF).

PHYSICAL THERAPY:

Exercise programs (mouth-specific), splints, and other tools are all forms of physiotherapy that can be used to manage OSMF.

PHARMACOTHERAPY:

Antioxidants(micro and macronutrients) including iron, copper, calcium, zinc, magnesium, and selenium as well as vitamins A, B, C, D, and E, can significantly lower the levels of free radicals. Lycopene, beta carotene, Alpha-lipoic acid, Alpha-tocopherol, Selenium, zinc also has the antioxidant properties.

Intralesional injections:

Drugs used:

Corticosteroids, Placentrex and Fibrinolytic Drug Injections.

Injection of Dexamethasone (4 mg) and 1500 IU of hyaluronidase with 2% lignocaine biweekly for 4 weeks.
OR
2ml Placental extract (Inj. Placentrex) was given locally in the predetermined areas, once a week up to a total duration of one month.

POST OPERATIVE PHYSIOTHERAPY:

Wooden tongue spatulas may be positioned between the molar teeth and gradually increased in number to enhance the extent of mouth opening. This practice should be performed for three minutes, three times daily, over a minimum duration of three months. Tongue protrusion and cheek flexibility also helps in mouth opening. Patients receiving biweekly injections and performing physiotherapy exercises significantly effective in managing OSMF.

SURGICAL THERAPY:

Surgical therapy is recommended for patients exhibiting significant trismus and/or biopsy findings that indicate dysplastic or neoplastic alterations.

OTHER TREATMENT MODALITIES:

LASERS:

The most common lasers used are Er:YCCG laser, KTP 532, and the diode lasers.

PENTOXIFILLINE:

400 mg 3 times a day for 7 months

INTERFERON GAMMA INTRALESIONAL INJECTIONS:

Injection of interferon gamma (0.01- 10.0 U/mL) 3 times a day for 6 months[10-13]

Management of oral cancer

Management strategies for oral cancer involve a multidisciplinary approach aimed at effectively treating the tumor, preserving function and aesthetics, and improving the overall quality of life for patients. These

strategies encompass various treatment modalities tailored to the individual patient's needs, tumor characteristics, and stage of the disease.

Surgery: Surgical intervention is often the primary treatment modality for oral cancer, particularly for early-stage tumors. The goal of surgery is to remove the tumor while preserving as much healthy tissue and function as possible. Depending on the location and extent of the tumor, surgical options may include wide local excision, neck dissection to remove affected lymph nodes, or reconstruction of defects using tissue flaps or grafts.

Radiotherapy: Radiotherapy, either alone or in combination with surgery, is commonly used for the treatment of oral cancer. It involves the use of high-energy radiation beams to destroy cancer cells and shrink tumors. Radiotherapy may be used as the primary treatment for patients who are not surgical candidates or as adjuvant therapy following surgery to eliminate remaining cancer cells.

Chemotherapy: Chemotherapy may be used as an adjunctive treatment to surgery and/or radiotherapy in cases where cancer has spread to other parts of the body or as part of a neoadjuvant regimen to shrink tumors before surgery. Chemotherapeutic drugs, such as cisplatin and 5-fluorouracil, are administered either intravenously or orally to target and kill cancer cells.

Targeted Therapy: Targeted therapy involves the use of drugs that specifically target certain molecules or pathways involved in cancer growth and progression. These drugs may be used alone or in combination with other treatments and can help to improve treatment outcomes and reduce side effects.

Immunotherapy: Immunotherapy is a newer approach to cancer treatment that harnesses the body's immune system to recognize and destroy cancer cells. Drugs known as immune checkpoint inhibitors, such as pembrolizumab and nivolumab, are used to block inhibitory signals that allow cancer cells to evade the immune system, thereby enhancing the body's ability to fight the tumors

Supportive Care: Supportive care plays a crucial role in the management of oral cancer, focusing on symptom management, pain control, and improving the quality of life for patients. This may include nutritional support, pain management, speech and swallowing therapy, and psychosocial support for patients and their families.

Palliative Care: For patients with advanced or metastatic disease, palliative care aims to relieve symptoms, manage pain, and improve overall comfort and quality of life. Palliative care is provided in conjunction with other cancer treatments and may involve a multidisciplinary team of healthcare professionals, including physicians, nurses, social workers, and counselors.

Overall, the management of oral cancer requires a coordinated and individualized approach, with treatment decisions based on the specific characteristics of the tumor, the patient's overall health and preferences, and the expertise of the treating healthcare team. Continued research and advancements in treatment modalities are essential to improve outcomes and quality of life for patients with oral cancer.

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Chapter 15

DENTAL MANAGEMENT OF ORAL AND OROPHARYNGEAL CANCER PATIENTS PLANNED FOR RADIOTHERAPY AND CHEMOTHERAPY

Patients with malignancy in the head and neck region, including the oral cavity and nasopharynx, are likely to receive radiation as part of their treatment. The quantity of radiation delivered is usually between 45 to 70 Gy given over a period of 4 to 6 weeks in divided fractions about 5 times a week. The radiation therapy is usually planned in combination with surgery or chemotherapy and may be given before or after the other treatments. Combination therapy is expected to improve the prognosis of treatment.

Radiation therapy (RT) is usually administered through the use of high-energy beams. Radiation exposure interferes with the capacity for the multiplication of cells. The malignant cells are particularly susceptible to such radiation and their ability to reproduce is severely limited as compared to normal cells which usually recover over a period of time.

A cancer specialist called the radiation oncologist is concerned with the management of patients requiring radiation therapy and they usually plan the treatment in a multi-disciplinary team including Head and Neck Surgeons, Medical Oncologists (who plan the chemotherapy schedules), and Palliation therapy specialists (who take care of patients who have advanced cancers which are beyond treatment). A combination of chemotherapy and radiation is sometimes required for patients with advanced cancers and is called chemoradiotherapy.

The region to be radiated is usually planned in advance to optimise the dose of radiation to the site affected by malignancy and reduce the radiation reaching normal tissues. This planning is guided by Medical Physicists. The area to be radiated on the skin is usually marked on the face and neck.

Intensity Modulated Radiation Therapy (IMRT) is a method of delivering precise levels of radiation to the intended target tissues and spare the unaffected tissues, as far as possible, using 3- D computer controlled linear accelerators. Critical tissues like the brain stem, spinal cord or salivary glands can be avoided if not involved in the malignancy. It is expected to reduce the xerostomia following RT because it can reduce damage to the parotid glands and is therefore expected to improve the quality of life. However, this method of treatment is more expensive than conventional Radiation therapy. Head and Neck radiotherapy is associated with several complications related to the mouth and teeth and therefore the dentist is very much involved in the care of these patients. The issues related to the mouth are discussed in this article and also the role of the dentist in the prevention and management of complications following radiotherapy.

Side Effects of Radiation on the Head and Neck

Mucositis: Patients experience soreness of the mouth and throat, during the period of radiation, due to damage of the mucosal tissues. This inflammation is called Radiation-induced mucositis and may result in ulceration of the mouth and pain secondary to the exposed tissues. This usually responds to pain medications and mouthwashes or oral gels. Oral candidiasis may occur as a consequence of alteration of the normal flora and changes in the oral pH. This can usually be treated with local antifungals. During radiation, the patient should avoid hot, spicy, and dry foods and keep the mouth moist.

If the ulceration is severe (grade 4 mucositis) hospitalization and parenteral nutrition support may be required along with temporary stopping of the radiation. Thankfully, the mucositis usually settles spontaneously within about 4 weeks of completing the radiation.

Skin reactions: The intensity of skin reactions is related to the dose and intensity of radiation and is usually managed with skin creams. Hair loss occurs due to radiation and may be permanent in the radiated region of the face. Hyperpigmentation of the treated skin may also be noticed in some patients receiving RT.

Xerostomia: Dryness of the mouth occurs progressively

due to atrophy of the salivary glands affected by radiation. This, in turn, affects the speech, swallowing, oral hygiene, and the overall quality of life of the patient.

Radiation caries: Xerostomia reduces the lubricant and natural hygiene functions of saliva resulting in food debris accumulating around the teeth. In addition, pH changes perhaps due to xerostomia and the tendency of patients to take a sugary (See Case 1) and pasty diet result in decalcification of the surface enamel and development of caries even on the smooth surfaces and cuspal tips or incisal edges which is typical of "Radiation Caries". The incidence of patients developing dental caries within 2 years of receiving radiation to the Head and Neck region is considered to be about 37 %.

Case 1

A 62-year-old female patient was seen with multiple carious teeth, 1 year after radiation to the head and neck. She was found to have trismus, poor oral hygiene, dryness of the mouth and caries at the incisal edges, cuspal tips and cervical level along with root stumps. She gave a history of consumption of a soft semi-liquid diet with added sugar. (See Fig. 1)

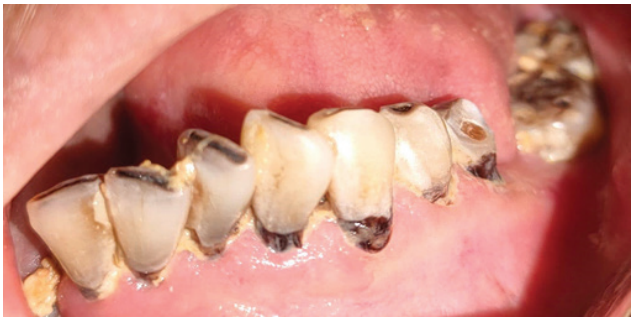


Fig.1

Patients should be instructed about the importance of maintaining oral hygiene and avoiding a cariogenic diet, as far as possible. Dryness of the mouth and decreased taste sensation cause patients to increase their cariogenic diet intake. Although xerostomia affects almost all the patients receiving radiation, caries is not, however, inevitable and can be avoided by good preventive measures and motivation of patients.

Patients should be encouraged to take care of the teeth especially since they may be low in motivation and even be depressed after a long course of radiation. They can be advised about the use of fluoride-containing dentifrices and mouthwashes. Frequent rinsing of the mouth with plain water and adequate hydration will reduce the subjective feelings of mouth dryness.

Osteoradionecrosis (ORN): Osteomyelitis of the jaws, especially the mandible, may occur following a minor infection of the teeth in the line of radiation. The blood supply to the alveolus and mandible is affected by the radiation-induced changes in the microcirculation. The capacity of the bone to heal is impaired and the infection progresses resulting in destruction or sequestration of the bone. The primary infection could be due to a pulpal infection secondary to caries of the teeth or a periodontal infection. Delayed healing (See case 2) and socket infection following extraction shortly before (less than 1 week) or after radiotherapy may also end in osteoradionecrosis.

Case 2

A 55-year-old male presented with a painful non-healing socket following extraction done 2 months before for a carious tooth. He received head and neck radiation 5 years earlier and the x-ray showed a crater-like defect leading to a diagnosis of early localized osteoradionecrosis. (See Fig. 2)

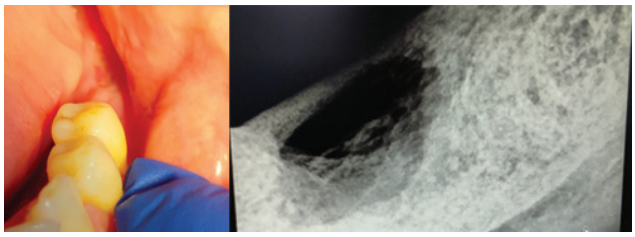


Fig.2

Management of early osteoradionecrosis (bone necrotic area less than 2.5 cm) is by conservative measures which encourage spontaneous gingival coverage of the raw bone. Progressive destruction of bone would result in pathological fractures of the jaw requiring resection of the affected bone and often reconstruction with microvascular free flaps.

Trismus: Difficulty in opening the mouth may be encountered by patients who have had extensive surgery, involving the deep masticator muscles, followed by radiation, The radiation-induced fibrosis in the area results in trismus which can seriously affect the quality of life of these patients. Modern methods of

RT including IMRT are expected to reduce the incidence of trismus following treatment.

Side effects of Chemotherapy

Low blood cell counts occur in patients receiving chemotherapy. Prior to invasive procedures like extraction or scaling patients on chemotherapy should have their blood counts checked because the drugs affect the hematopoietic system. Patients with platelet count of less than 75,000 cells/cu mm or leukocytes less than 1000/cu mm may need to have their procedures postponed till the counts improve.

Practice Guidelines: Dental management before radiation therapy.

Patients who are planned for RT in the head and neck region should be screened in the dental department to identify any infected or potentially infected foci that could result in ORN. Teeth with non-restorable advanced caries or root caries, root stumps, and mobile teeth should be extracted. Restorations should be done in teeth with early carious lesions not involving the pulp. Teeth with a suspected pulp exposure after caries excavation may undergo root canal therapy (RCT) if they do not have apical lesions, since the lesions may not heal following RT. This should be done only if the patient is motivated to retain the teeth and has good oral hygiene. Endodontics has been reported to be successful in a few patients with pulp involvement, but no apical disease, prior to radiation.

It is also advisable to remove all the third molars unless they are deeply impacted and asymptomatic because it is often difficult to maintain hygiene around the third molars and they may be the initial locations for caries or periodontal disease after RT.

Teeth in the line of radiation e.g. the mandibular posterior teeth on the side of carcinoma on the lateral surface of the tongue, should also be extracted since the teeth and bone are exposed to a high level of radiation. This is especially so if the patient is planned for brachytherapy (RT delivered using radiation sources at the site of malignancy itself) since the chances of spontaneous necrosis of the bone are higher when exposed to intensive localized RT. Another reason for extraction is the possibility of recurrent trauma to the tongue at the operated site due to repeated contact with the retained teeth and the possibility of recurrence. Chronic dental trauma itself may have oncogenic potential.

Patients should be explained the reason for the dental procedures since they are often confused about the reason for extensive dental treatment being done before RT. Extractions should be completed 1 week before starting radiation.

If patients refuse any needed dental procedures, they may be asked to give a written undertaking accepting their responsibility for the consequences in spite of being informed about the risks.

Scaling should be done prior to RT and patients counselled with regard to brushing technique and the importance of maintaining oral hygiene. They should also understand the need to avoid a cariogenic diet.

Tobacco users should be counseled about the need to stop the habit and the poor prognosis in terms of wound healing and recurrence of malignancy in patients who stay on the habit. This advice should be re-emphasized after completion of RT and on follow-up visits.

Post Radiation Dental Care

After a course of radiation, the patients may be encouraged to visit their dentists on a regular basis to treat or prevent dental diseases. The treating dentist has an important role in encouraging the patient not only with regard to dental care but also with regards to having a positive outlook on their future. Dental health is an important aspect of the patient's quality of life.

Due to the effects of the radiation on the salivary glands' patients will develop xerostomia. Saliva substitutes are available for use. However, patients may still feel dryness and stickiness after applying the solution in the mouth and should be advised to keep their mouths moist by rinsing often and drinking small amounts of water throughout the day or whenever the mouth feels dry. They should maintain good oral hygiene and avoid cariogenic foods. Occasionally, the patient may take a soft and sweet diet because of the dry mouth, mucositis, and loss of taste sensation. The mushy foods collect around the teeth and because the natural cleansing by saliva is lost or reduced caries develops rapidly on the exposed tooth surfaces. They should be cautioned about this tendency and encouraged to eat an adequate and well-balanced diet.

If caries develops it should be detected early and treated. Glass ionomer cements are beneficial because

of the slow release of fluorides into the surrounding enamel. Patients can be encouraged to use fluoridated mouthwash daily in addition to using fluoridated toothpaste.

Advanced caries may result in infection and abscess formation. In such cases, the infected tooth or teeth would require to be removed. The patient should be warned about the possible consequences of osteoradionecrosis and explained the need to extract the tooth to prevent the spread of the infection. After obtaining informed consent, the offending tooth should be extracted under antibiotics, preferably Augmentin and Metronidazole.

Provision of dentures after radiotherapy is difficult because of the xerostomia which affects denture retention and friability of the soft tissues. Dental implants also have a significant risk of failure following radiation.

In conclusion, the dental management of oral cancer patients planned for radiotherapy and chemotherapy is crucial for ensuring optimal outcomes and minimizing treatment-related complications. Dentists play a pivotal role in the multidisciplinary team approach to cancer care, addressing the unique oral health challenges faced by these patients. Through comprehensive pre-treatment evaluation, meticulous dental treatment planning, and timely intervention, dentists can minimize the risk of radiation-induced oral complications such as mucositis, xerostomia, dental caries or osteoradionecrosis. Moreover, proactive management of oral health before, during, and after cancer treatment can improve patients' quality of life and overall treatment outcomes. It is imperative for dentists to collaborate closely with oncologists and other healthcare professionals to provide holistic care for oral cancer patients. By adopting a patient-centered approach and integrating evidence-based dental protocols into cancer treatment plans, dentists can contribute significantly to enhancing the oral health and well-being of cancer patients undergoing radiotherapy and chemotherapy.

*(For Sample Dental Clearance form for Radiation/ Chemotherapy, Ref. Appendix 7)

Chapter 16

STRATEGIES FOR PREVENTION OF ORAL CANCER

Oral cancer is one of the preventable forms of cancer. In India, the incidence of oral cancer is very high compared to the rest of the world. Cancers of the lip, oral cavity, and oropharynx are among the most common cancers, with approximately 400,000 incident cases globally. Oral cancer has a particular predilection in South Central Asia due to exposure to high-risk factors. In India, cancer of the lip and oral cavity is rated second most amongst males and fifth in females. The mortality rate/per annum for lip and oral cavity cancers is 72,616 (10.09%) and the age-standardized five-year prevalence rate is 2,65,255 (19.59%).

Oral leukoplakia, Oral submucous fibrosis, and Oral lichen planus are potentially malignant disorders with a risk of transition to OSCC. Moreover, though the lesion per se may not transform into OSCC, it may serve as a surrogate clinical lesion to identify individuals at risk of developing OSCC. Most of these disorders may be asymptomatic in the early stages of their evolution and can be detected on routine oral examination. It is essential, therefore, that community dentists are knowledgeable about the clinical features and diagnostic aspects of OPMDs to further investigate and, where appropriate, make referrals to specialists for treatment.

There is a wide range of genetic, environmental, and behavioral factors that contribute to the risk of oral cancer. Risks are dominated by tobacco, both smoked and smokeless, areca nut, and alcohol consumption. In addition, a small proportion of oral cancer globally is caused by the Human Papilloma Virus (HPV) and other viruses. Nutrition deficiency, poor oral and dental hygiene, trauma, as well as environmental and genetic factors also contribute to the risk factors of oral cancer.

Primary Prevention Strategies Primary prevention in oral cancer aims to reduce the incidence by cessation of exposure to risk factors especially tobacco and alcohol or increasing an individual's resistance to them.

Figure.1: Most Common Smokeless Tobacco and Areca Nut Products Worldwide

Premade		Custom-made
Manufactured	**Cottage industry**	**Vendor/individual**
Product examples: • Chewing tobacco (plug/twist/loose leaf) • Creamy snuff • Dissolvables • Dry snuff • Gundahku/ Gundahka • Khaini • Moist snuff • Kiwam • Rapé • Red toothpowder	**Product examples** • Dohra • Gutka • Mainpuri • Nass/Naswar • Nasway • Betel quid (paan) • Rapé • Shammah • Toombak • Tuibur	**Product examples:** • Gundahku/ Gundahka • Iqmik • Nass/Naswar • Nasway • Betel quid (paan) • Rapé • Shammah • Tapkeer • Tobacco leaf • Tombol

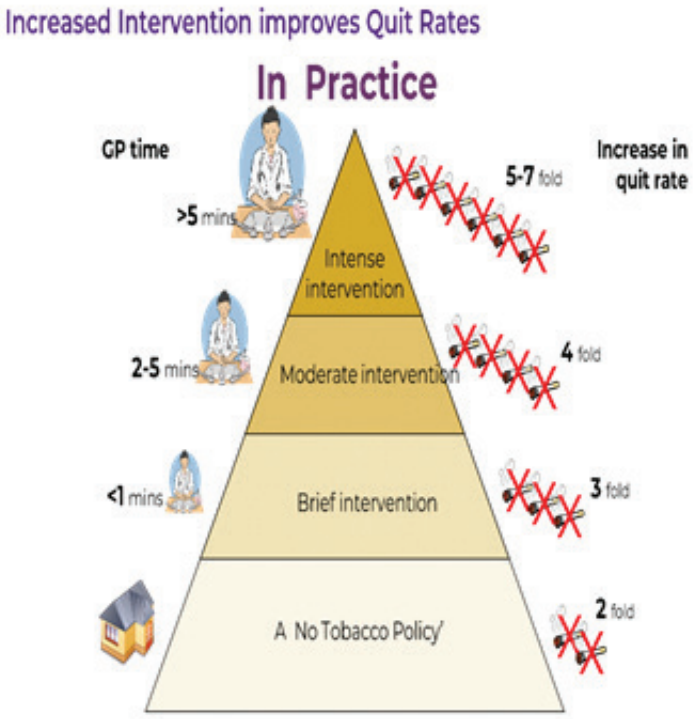
Some premade ingredients are used to make custom-made products: twist, zarda, toombak, gudahku/gudahka, and kiwam

Diverse types of smokeless tobacco product in South East Asia

(Sources: All images except for betel quid (paan) courtesy of Clifford Watson, Centers for Disease Control and Prevention. Image of betel quid (paan) courtesy of World Health Organization South-East Asia Regional Office and Dhirendra N. Sinha).

Figure.2: Evaluation of the Evidence of Interventions and Strategies for Prevention of Oral Cancer

Intervention	Evaluation
Primary Prevention	
Cessation of exposure to Risk factor	
Tobacco Smoking	Sufficient
Use of Smokeless tobacco	Inadequate
Use of areca nut (including betel) with or without tobacco	Sufficient
Alcohol consumption	Sufficient
Cessation Intervention for smokeless tobacco	
Behavioural Intervention	Sufficient in adults, Limited in youth
Pharmacologic intervention	
Combined behavioural and pharmacologic interventions	Limited
Secondary prevention†	Limited
Clinical oral Examination in high-risk populations	Group B



Tobacco use: A major risk factor for Non-Communicable Diseases (NCDs)

Tobacco is a prominent risk factor for 6 to 8 leading causes of death and almost 40% of Non-Communicable Diseases (NCDs) including cancers, cardiovascular diseases, and lung disorders are directly attributable to tobacco use. The burden of NCDs is increasing in low-income and middle-income countries like India and contributing to poverty, loss of productivity, and increase in health costs. The NCDs disproportionately affect poor individuals, thus further increasing inequalities, and in the process, are becoming a major barrier to the development and achievement of Sustainable Development Goals.

The number of deaths every year in India which is attributable to tobacco use is almost 8-9 lakhs. A majority of cardiovascular diseases and lung disorders are directly attributable to tobacco use. Other diseases that are associated with tobacco use are stroke, cataracts, peripheral vascular diseases, etc. Moreover, some studies show that tobacco use also leads to impotence. Tobacco use by pregnant women leads to low-birth-weight babies, premature deliveries, stillbirths, and birth defects.

If the current trends continue and if effective steps are not taken to control tobacco consumption, it is estimated that by the year 2020, tobacco use will account for 13% of all deaths in India every year. Further, according to the WHO Global Report on "Tobacco Attributable Mortality" 2012, seven percent of all deaths (for ages 30 and over) in India are attributable to tobacco use.

Tobacco and Oral Cancers

As per the report of the Indian Council of Medical Research (ICMR), nearly 50% of cancers in males and 25% in females in India, and more than 80% of all oral cancers are directly attributed to tobacco use. Oral cancer accounts for approximately a third of all cancers in India. Around 200,000 new cases of oral cancer are diagnosed annually with a majority of these cases estimated to be advanced at presentation.

India is the second largest producer and consumer of tobacco and a variety of forms of tobacco use is unique to India. Apart from the smoked forms that include cigarettes, bidis, and cigars, a plethora of smokeless forms of consumption exist in the country. India is unique because it has a very large population with a diversity

seen nowhere else in the world regarding multiple cultural practices, traditions, languages, and belief systems. This diversity poses a significant challenge in the communication of healthcare information to a large audience and it is even more challenging when dealing with a disease like cancer. Due to the differences in ethnicity, culture, lifestyle, and socio-economic status, there exists a strong possibility of differences in risk factors related to cancer. For example, the use of areca nut has been shown to cause oral submucous fibrosis, a precursor to oral cancer and periodontal disorders.

Areca nut, popularly as supari in many parts of India, is one of the most common forms of smokeless tobacco. Areca nut plays multiple important roles in the socio-cultural context and economic conditions of the people in India. India is the largest producer of areca nut in the world accounting for approximately 55% of total global production. Therefore, understanding the chewing practice of areca nut along with other similar local practices is very important to address this existing tobacco problem.

Tobacco Control Legislation and Guidelines - India

Highlights

- The Government of India enacted its comprehensive tobacco control law the Cigarettes and Other Tobacco Products (Prohibition of Advertisement and Regulation of Trade and Commerce, Production, Supply and Distribution) Act, 2003 (COTPA 2003) in 2004, to make provisions to effect a reduction in tobacco use.
- Various Rules were notified for effective regulation of tobacco products from time to time. (Ref. Appendix 8) These provided for the prohibition of -
    - Smoking in public places,
    - Sales of tobacco products to and by minors,
    - Sale of tobacco products within 100 yards of educational institutions and,
    - Direct and indirect advertising and promotion of tobacco products.
    - Apart from these provisions, the display of statutory warnings on tobacco packs was also implemented. The same has now been revised for 85% of the packing area to be covered with the warnings along with the display of the national quit-line number.
- India has also effectively implemented rules for restricting the depiction of tobacco products in films and television programs. It is mandatory to display the statutory warning during the display of tobacco products in films & television programs and anti-tobacco video spots & disclaimers at the beginning and middle of the films.
- Smokeless Tobacco Products such as Gutkha, Zarda, Khaini, etc. have been prohibited vide the Food Safety and Standards (Prohibition and Restrictions on Sales) Regulation, 2011 under the Food Safety and Standards Act, 2006.
- Tobacco control efforts of India gained a fresh impetus with the launch of the National Tobacco Control Programme (NTCP) in 2007-08. NTCP

Signage for tobacco-free workplace

Signage at the tobacco vendor

is a comprehensive programme, which not only provides a robust framework for the implementation of tobacco control laws/initiatives but also focuses on community engagement, school programmes, IEC and advocacy.

- Various cessation services have been set up under the NTCP. A national Quitline was launched in 2016. The capacities of the Quitline have now been expanded to cater to the higher volume of calls from prospective quitters given the display of the Quitline number on tobacco packs.
- The Quitline caters to around 2.5 lakh telephone calls every month. Over 400 Tobacco Cessation Centers have been set up. "mCessation" services are also being provided through a mobile app.

2. SECONDARY PREVENTION

Secondary prevention of oral cancer includes screening to detect potentially malignant disorders (OPMD) and oral cancer at an early stage. The key goals are to effectively detect and slow or stop disease progression early and to "down-stage" the disease. This should eventually translate into a reduction in mortality and morbidity. There are two broad scenarios where secondary prevention strategies can be implemented – in the clinic and the field i.e. screening. All secondary prevention should start with education and self-examination, followed by a thorough examination by a trained healthcare worker/professional. A Cochrane review 2013 reported on the effectiveness of screening and early detection of oral cancer or OPMD in reducing oral cancer mortality.

Table-2: Screening model and recommendation

Screening Model	Criteria for Screening	Recommendations
Population vs home visit vs invitation	Studies reported good coverage and compliance to home-to-home screening (95%- 98%) – India, Sri Lanka Poor compliance with invitational screening (UK, Japan) Low compliance to attend referral center for confirmation of diagnosis Most studies do not incorporate a risk prediction model to identify and screen "at-risk" patients Most studies did not provide a series of multiple screenings at regular intervals.	A behaviour change communication campaign could increase compliance Provide repeated screening at regular intervals Use a risk prediction model to preferential screen at-risk population Use mobile technology to take and send clinical images of screen-positive patients to experts for quick consultations. Develop artificial intelligence to analyze clinical images generated during a screening Use mobile screening units that can travel from village to village.
Integrated with medical screening	Reduces the cost of the program. The project would need coordination to integrate with medical screeners.	To increase yield, integrate with screenings for tobacco/ alcohol-related disorders. Provide appropriate training, especially for oral cavity cancer, to increase accuracy
Opportunistic screening	Largely performed in dental offices and not in other primary care settings. A workforce is available but needs additional training; cost neutral. No benefit to people with poor access to care or those who attend primary care clinics irregularly.	Develop tool kits and e-learning modules to train screeners. National practice-based networks should be established for data collection and future research. Develop risk prediction models for primary care to assess risk profile.

Screening Model	Criteria for Screening	Recommendations
High-risk screening	Provides the best cost-effectiveness	Combine with risk factor health promotion and treatment programs to achieve compliance.
Industrial/Workplace	Most reported studies are on white-collar workers Compliance is better than in other models	Dentists working in industries to receive Continuing Professional Development packages on oral cancer screening
Mouth self-examination (MSE)	High negative predictive value. Leaflets are inadequate in instructing how to perform MSE A high volume of self-referrals to specialist centers.	Visual media (instead of printed leaflets) may improve accuracy. MSE is to be demonstrated at dental visits by auxiliaries.

*(For 5 R technique to motivate a client who is not willing to quit tobacco, Ref. Appendix 11)

Table-3: Different diagnostic tests used as adjuncts for Oral Cancer Screening

Technique	Example	Mechanism
Vital tissue staining	Toluidine blue, tolonium chloride	Stain nucleic acids that are abundant in precancer and cancer cells
Cytology	OralCDx	Collection of a trans-epithelial sample using a non-laceration device and stained with a modified Papanicolau test. These were viewed as a histology section
Light-based – Chemiluminescence	ViziLite plus,	Due to the higher nucleus/ cytoplasmic ratio in dysplastic and malignant epithelium
Light-based – Tissue fluorescence imaging	ViziLite, VELscope,	Cellular atypia changes the concentration and distribution of fluorophores, which will impact the tissue reaction to light
Light-based – Tissue fluorescence spectroscopy		Spectrograph receives, records, and analyses data eliminating any subjectivity
Biomarkers analysis		Saliva, blood, and serum, based on genomics/epigenomics, proteomics, transcriptomics, metabolomics, and microbiomics

*(For Guidance on an action plan for tobacco users willing to quit, Ref. Appendix 11)

Management of most common OPMDs

A) Low-Risk Leukoplakia

i) Essential treatment

- Betel quid/areca nut use, Tobacco, alcohol cessation
- Counselling through motivational interviewing and lifestyle modification
- Dietary modulation - daily consumption of green leafy vegetables (75 gm daily) and seasonal fruits like mango, guava, papaya
- Topical antifungal - Clotrimazole 1% for 7 days for red and white leukoplakia
- Topical Vitamin A application of 25,000 IU twice daily for 90 days
- Referral mapping - Designated referral center for patient management
- Regular surveillance

ii) Optional Treatment
(in addition to the above measures)

- Laser ablation
- Electrocauterization

B) High-risk Leukoplakia

i) Essential Treatment

- Betel quid/areca nut use, tobacco, alcohol cessation counseling
- Dietary modulation - daily consumption of green leafy vegetables (75 gm daily) and seasonal fruits like mango, guava, papaya

Biopsy

If biopsy shows -

- Moderate/Severe epithelial dysplasia or carcinoma in situ
- Conventional surgical excision with or without grafting
- For larger homogeneous lesions (>4 cm) - wait and watch through rigid surveillance
- Regular surveillance

ii) Optional Treatment (in addition to the above measures)

- Laser ablation Co2 laser
- Nd: YAG laser therapy potassium-titanyl-phosphate
- Photodynamic therapy - Aminolevulinic acid (10%, 20%) twice a week for 3 months

C) OSMF Grade 1,2 (Mouth opening >20 mm)

i) Cessation of habit & Physiotherapy

ii) Optional treatment

- Clostridium collagenase
- Imatinib
- Microwave diathermy, ultrasound

D) Grade 3 OSMF (Mouth opening <20 mm)

i) Essential Treatment

- Cessation of habit
- Physiotherapy

ii) Optional treatment

- Reconstruction with tissue flaps
- Temporal muscle myotomy
- Coronoidectomy

E) Non-dysplastic OLP

i) Essential Treatment

- Psychometric evaluation and counselling
- Topical triamcinolone acetonide- 0.1% thrice daily for 2 weeks (monitor for symptoms alleviation) or
- Clobetasol propionate 0.05% in orabase) 2-3 times/day/3 weeks

ii) Optional treatment

- Topical application of cyclosporine, topical tacrolimus 0.1%, and topical retinoic acid (0.05%) in oral base Low-level laser therapy - 630-980 nm wavelength, power output - 20-300 mW, and duration - 10 s-15 min
- Photodynamic therapy with aminolaevulinic acid (10%, 20%) once/twice a week, 2-10 min, 1-8 sessions PUVA (psoralen and ultraviolet A radiation) therapy Oral administration of 0.6 mg/kg 8-methoxy psoralen followed by long-wave ultraviolet light irradiation. The therapy is given 12 times at intervals of 2-3 days

* (For Intervention Method Algorithm for Quitting Tobacco Use, Ref. Appendix 9)

*(For Challenges faced to client during lapse and relapse, Ref. Appendix 12)

In conclusion, there is an urgent need to strengthen primary prevention which policymakers need to address it. The current evidence highlights that prevention strategies for oral cancer should address the risk factors mainly cessation of tobacco (smoking, smokeless form, areca nut), and alcohol. Behaviour change communication intervention focusing on etiologies of oral cancer should be designed which be more context-specific and non-confrontational.

Screening programs should target high-risk groups and downstream efforts need to strengthen the care continuum about diagnosis and treatment. Tobacco control efforts through the implementation of the COTPA (Cigarettes and Other Tobacco Products Act 2003) and its subsequent amendments are needed.

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APPENDICES

Appendix 1: Lymph Node Levels of the Neck

Level	Description of Lymph node levels of the neck
I	Level I nodes are situated beneath the mylohyoid muscle and above the lower margin of the hyoid bone, along with the anterior and posterior borders of the submandibular glands. Submental nodes, known as Level Ia, lie between the two anterior bellies of the digastric muscle. Level Ib refers to submandibular nodes positioned posterolateral to the anterior belly of the digastric muscle.
II	Moving to Level II, nodes are found along the internal jugular vein (IJV) or the deep cervical chain, extending from the base of the skull to the carotid bifurcation. Level IIa is contiguous with the IJV, located anterior (medial) to the vertical plane defined by cranial nerve XI (CN XI). Level II b is distinguished by a fat plane separating the nodes and the vein, situated posterior (lateral) to the vertical plane defined by CN XI.
III	Level III nodes encompass the IJV, spanning from the lower margins of the hyoid to the lower margins of the cricoid, positioned anterior to the posterior border of the sternocleidomastoid (SCM) muscle, and lateral to the medial margin of the common carotid artery (CCA) and internal carotid artery (ICA).
IV	Deep cervical (IJV) chain nodes, extending from the lower margin of the cricoid to the clavicle, constitute Level IV, situated lateral to the medial margin of the CCA and anterior and medial to an oblique line drawn through the posterior edge of the SCM and the posterior edge of the anterior scalene muscle.
V	Level V nodes, located in the posterior triangle (spinal accessory), are further divided into Va and Vb. Va encompasses the superior half, extending posteriorly from the base of the skull to the inferior border of the cricoid, while Vb constitutes the inferior half, extending posteriorly from the level of the inferior border of the cricoid to the level of the clavicles.
VI	Level VI encompasses the pretracheal and prelaryngeal lymph nodes, situated anterior to the visceral space and extending from the inferior margin of the hyoid bone to the manubrium.
VII	Level VII includes the superior mediastinal lymph nodes, positioned between the CCAs, extending from below the superior aspect of the manubrium to the level of the brachiocephalic vein.

Appendix 2: Assessment of Oral Mucosal Tissue

Assessment of Oral Mucosal Tissue

Name _____

For office use
Reg./OP Number

Address and Contact no.: _____

Examination Date

Age ☐☐ Sex ☐ Day ☐☐ Month ☐☐ Year

	Ulcer	White	Red	Swelling	Pigmented	Other
a. Upper lip	☐	☐	☐	☐	☐	☐
b. Lower lip	☐	☐	☐	☐	☐	☐
c. R commissure	☐	☐	☐	☐	☐	☐
d. L commissure	☐	☐	☐	☐	☐	☐
e. Upper labial mucosa	☐	☐	☐	☐	☐	☐
f. Upper sulci	☐	☐	☐	☐	☐	☐
g. Upper gingivae	☐	☐	☐	☐	☐	☐
h. Hard palate	☐	☐	☐	☐	☐	☐
i. Soft palate	☐	☐	☐	☐	☐	☐
j. Pharynx and tonsillar area	☐	☐	☐	☐	☐	☐
k. Tongue - dorsum	☐	☐	☐	☐	☐	☐
l. Tongue - R lateral border	☐	☐	☐	☐	☐	☐
m. Tongue - L lateral border	☐	☐	☐	☐	☐	☐
n. Tongue - ventral	☐	☐	☐	☐	☐	☐
o. Floor of mouth	☐	☐	☐	☐	☐	☐
p. R buccal mucosa	☐	☐	☐	☐	☐	☐
q. L buccal mucosa	☐	☐	☐	☐	☐	☐
r. Lower gingivae	☐	☐	☐	☐	☐	☐
s. Lower sulci	☐	☐	☐	☐	☐	☐
t. Lower labial mucosa	☐	☐	☐	☐	☐	☐

Abnormal findings Yes ☐ No ☐

If yes, use the list on the left and / or the diagram overleaf to note details of any abnormal finding.

Referral (Please tick)

No referral required ☐

Non-urgent referral ☐ Urgent referral ☐

History of habits:

Smoking: Y/N
No.of cigarettes/Beedie/Others (specify):

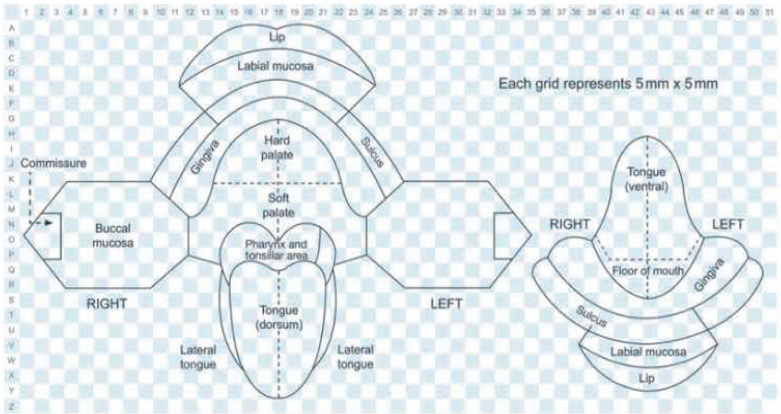
Duration(months/years):
Chewing: Y/N
No. of packets Pan Parag/Betel quid/Others(specify):

Spitting/Swallowing/Quidding
Duration of quidding
Duration of Habit:
Alcohol: Y/N
Type:
Quantity:
Duration:

Signature of Practitioner _____ **Date** _____

Assessment of Oral Mucosal Tissue

Record the extent of any pathology on the mouth map:



Description of the lesion

Monitoring 1

Date	Signature of Practitioner

Has lesion changed since previous examination? Yes ☐ No ☐

Lesion description / Notes

Monitoring 2

Date	Signature of Practitioner

Has lesion changed since previous examination? Yes ☐ No ☐

Lesion description / Notes

Monitoring 3

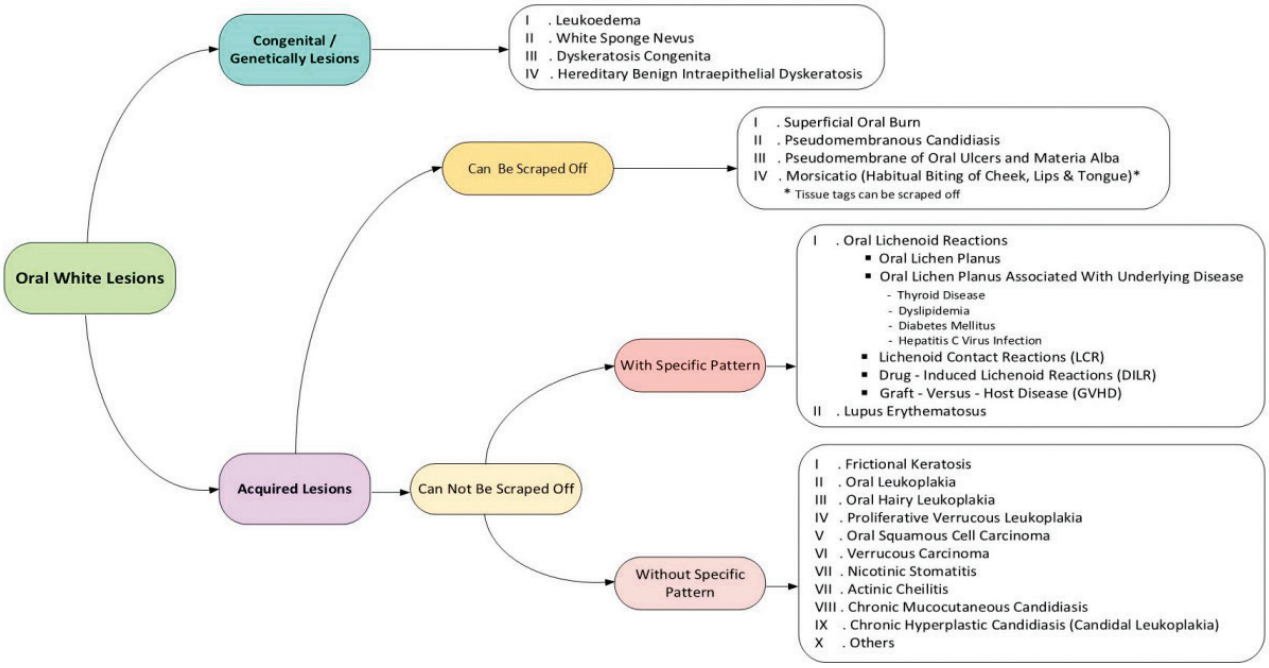
Date	Signature of Practitioner

Has lesion changed since previous examination? Yes ☐ No ☐

Lesion description / Notes

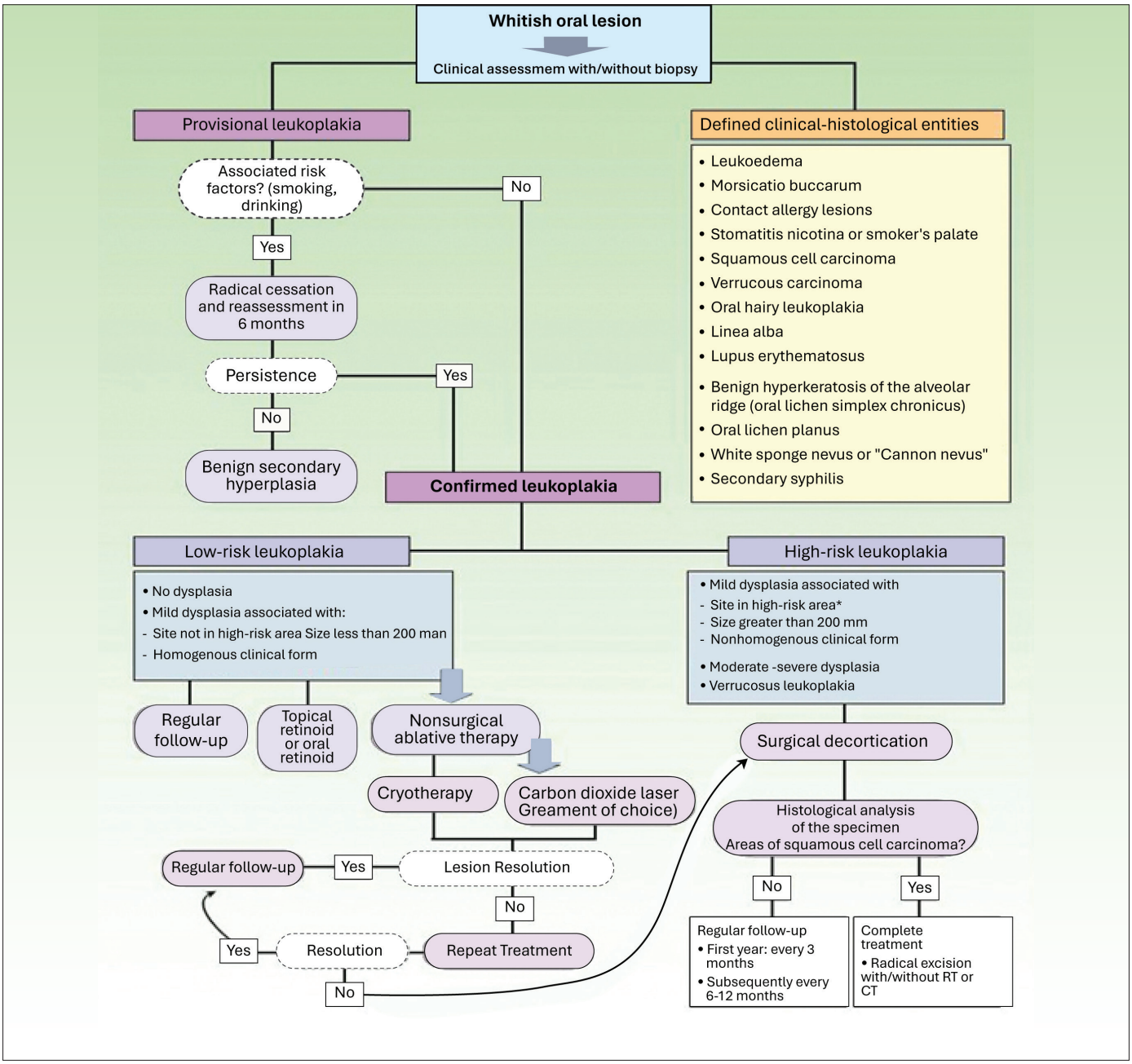
Signature of Practitioner _____ **Date** _____

Appendix 3: Diagnostic algorithm for white patches of oral mucosa



(Courtesy: Mortazavi H, Safi Y, Baharvand M, Jafari S, Anbari F, Rahmani S.
Oral white lesions: an updated clinical diagnostic decision tree. Dentistry journal. 2019 Feb 7;7(1):15)

Appendix 4: Diagnostic- Therapeutic Algorithm for Leukoplakia



CT indicates chemotherapy; RT, systemic radiotherapy

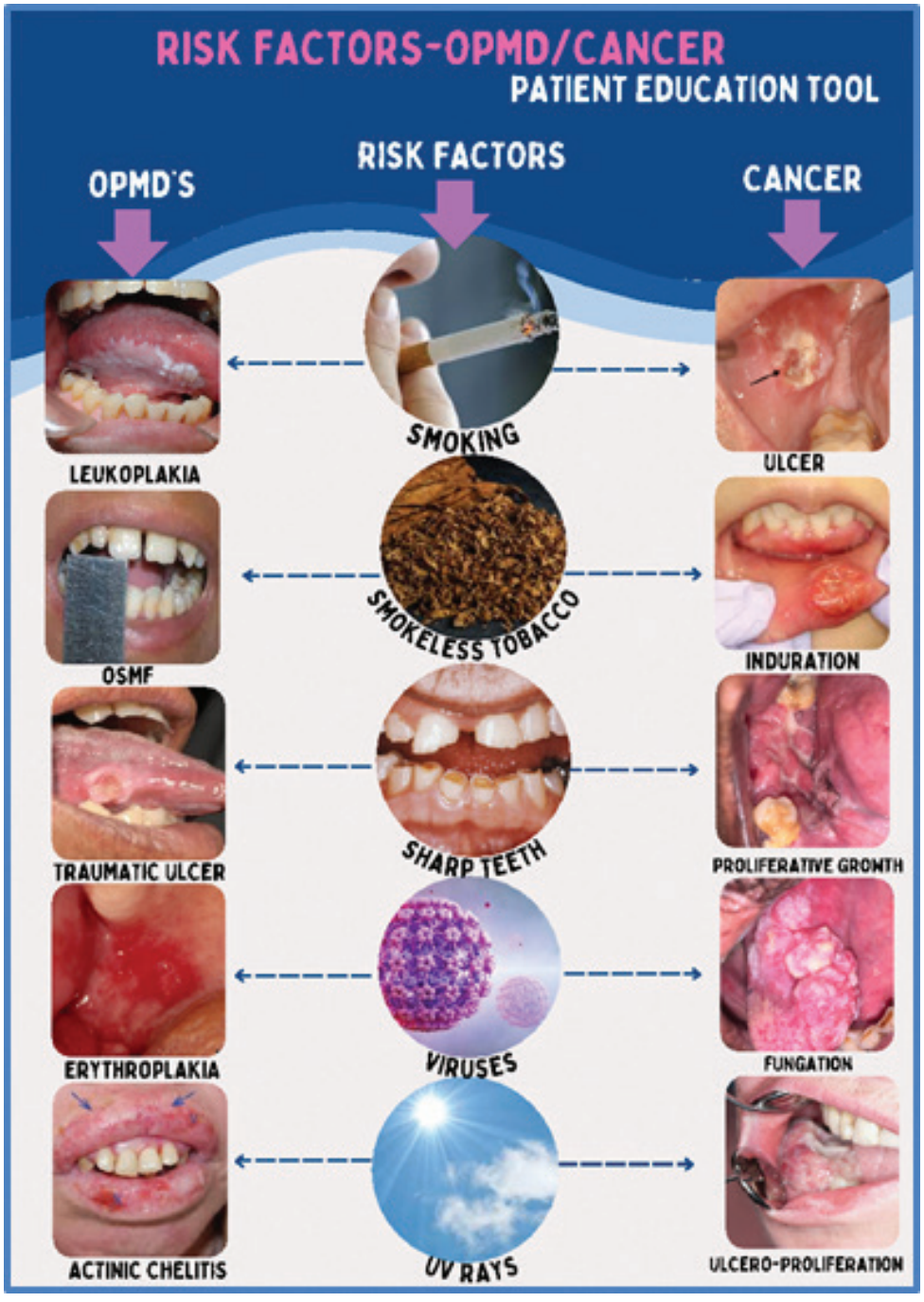
(Courtesy: Martorell-Calatayud, R. Botella- Estrada,a J.V. Bagán-Sebastián,b O. Sanmartín-Jiménez,a and Guillén- Baronaa C. Oral Leukoplakia: Clinical, Histopathologic, and Molecular Features and Therapeutic Approach. Acta Dermosifiliogr. 2009; 100:669-84)

Appendix 5: Oral Cancer TNM Staging Form

Assessment of TNM Staging of Patient with Oral Cancer		
Patient Reg No.		Date of Diagnosis of Oral Cancer
Name		Gender
Age		Chief Complaint
TNM Staging Characteristics		
Step 1:	**T – Assessment of Tumor Size**	
Check the box	Tumor Size Grouping	
	TX: Primary tumor cannot be assessed	
	T0: No evidence of primary tumor	
	Tis: Carcinoma in situ	
	T1: Tumor 2 cm or less in greatest dimension	
	T2: Tumor more than 2 cm but not more than 4 cm in greatest dimension	
	T3: Tumor more than 4 cm in greatest dimension	
	T4a (lip): Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin (chin or nose)	
	T4a (oral cavity): Tumor invades through cortical bone, into deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face	
	T4b (lip and oral cavity): Tumor invades masticator space, pterygoid plates, or skull base; or encases internal carotid artery	
Step 2:	**N: Assessment of Regional Lymph Nodes**	
Check the box	**Nodal Involvement Grouping**	
	NX: Regional lymph nodes cannot be assessed	
	N0: No regional lymph node metastasis	
	N1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension	
	N2: Metastasis as specified in N2a, N2b, N2c below	
	N2a: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension	
	N2b: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension	

	N2c: Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension	
	Metastasis in a lymph node more than 6 cm in greatest dimension but has not grown outside of the lymph node	
	Metastasis in a lymph node larger than 3 cm in greatest dimension and has grown outside the lymph node.	
Step 3:	**M: Assessment of Metastasis**	
Check the box	**Distant Metastasis Grouping**	
	M0: No distant metastasis	
	M1: Distant metastasis	
AJCC Staging of TNM Assessment of Oral Cancer:		
Check the box	**AJCC Staging of TNM Assessment of Oral Cancer**	
	Stage 0: Tis, N0, M0	
	Stage I: T1, N0, M0	
	Stage II: T2, N0, M0	
	Stage III: T3, N0, M0; T1, T2, T3, N1, M0	
	Stage IVA: T4a, N0, M0; T4a, N1, M0; T1, T2, T3, T4a, N2, M0	
	Stage IVB: T4b, Any N, M0; Any T, N3, M0	
	Stage IVC: Any T, Any N, M1	
Name of the Dentist	**Signature of the Dentist**	**Date of TNM Assessment**

Appendix 6: Poster for patient education regarding risk factors for OPMDs/ Cancer



Appendix 7: Sample Dental Clearance form for Radiation/ Chemotherapy

Patient Name: _____

Date of Birth: _____

Date of Dental Consultation: _____

Dental Examination Findings:

Oral Examination:

Teeth present: Yes / No

Dental caries: Yes / No

Periodontal status: _____

Presence of oral lesions: Yes / No

If yes, please provide details: _____

Oral hygiene status: _____

Radiographic Findings (if available)

Panoramic radiograph: Attached / Not attached

Bitewing radiographs: Attached / Not attached

Periapical radiographs: Attached / Not attached

Dental Treatment Plan:

Dental Treatment Completed:

Dental prophylaxis: Yes / No

Dental fillings: Yes / No

Root canal treatments: Yes / No

Extractions: Yes / No

Dental implants: Yes / No

Other dental treatments:

_____

Recommendations (If any):

_____

Based on the dental examination findings, the patient is considered

- Fit for radiation therapy without any further dental treatment required.
- Fit for radiation therapy but requires the following dental treatments before initiation of therapy.
- Unfit for radiation therapy due to unresolved dental issues. Further dental treatment is necessary before initiating therapy

Comments or Additional Information

Dentist's Note (If any): _____

I certify that I have conducted a comprehensive dental examination of the patient listed above and have provided the necessary dental treatment or clearance as indicated. Please proceed with radiation therapy accordingly.

Dentist's Name: _____

Dentist's Signature: _____

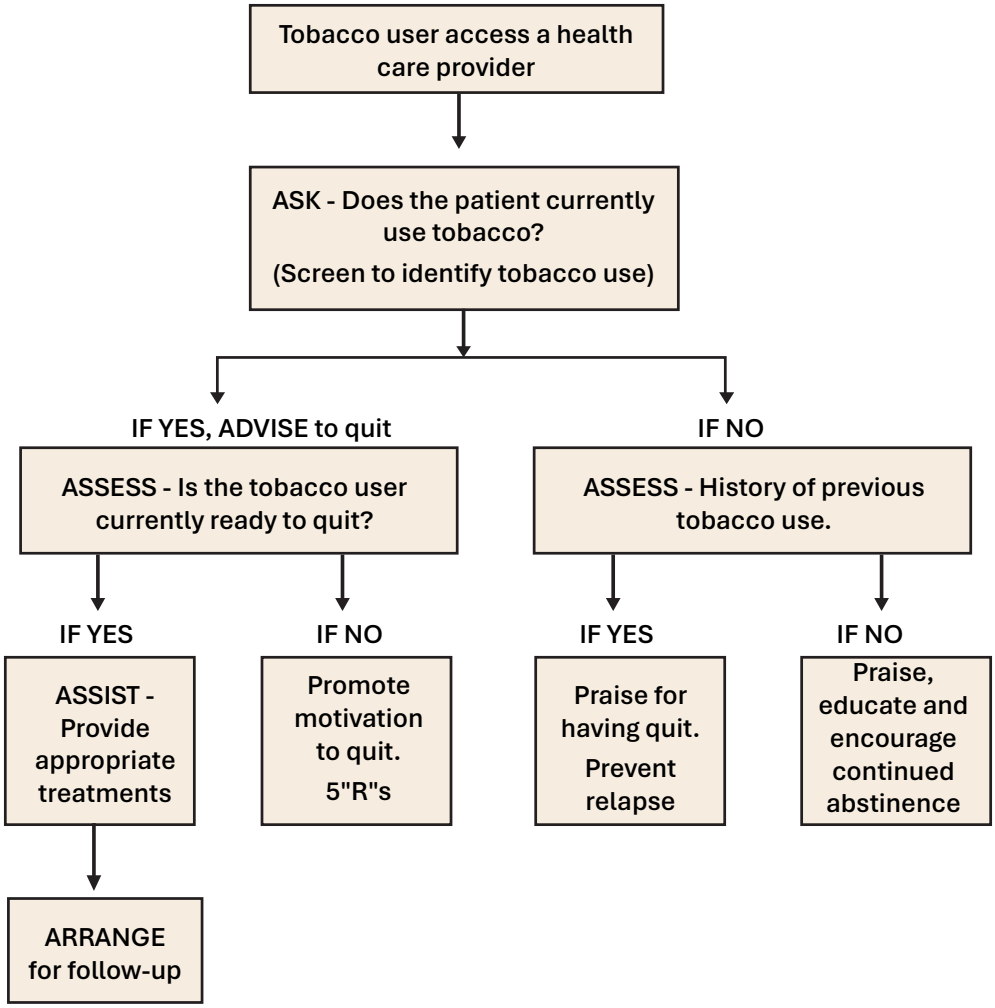
Dental Clinic Address: _____

Date: _____

Appendix 8: Tobacco Control Legislation and Guidelines - India

ACT	Section	Offence	Penalties	
COTPA	Section 4	Smoking in Public Places	Fine up to Rs.200 under section 21	
	Section 6a	Sale of tobacco products to or by minors	Fine up to Rs.200 under section 24	
	Section 6b	Sale of tobacco products within 100 yards of any Educational Institute	Fine up to Rs.200 under section 24	
	Section 5	Direct/indirect advertisement of tobacco products and scholarship/ sponsorship of any event by tobacco companies	Under Section 22- **First Offence:** Fine up to Rs. 1000/- or imprisonment up to two years or both **Subsequent offence:** Fine up to Rs. 5000/- or imprisonment up to five years or both	
	Section 7	Mandatory display of specified health warnings on all tobacco product packs	Under Section 20 – **First Offence for Producer or Manufacturer:** Fine up to Rs 5,000/- or imprisonment up to two years or both. **Subsequent Offence:** Fine up to Rs 10,000/- and imprisonment up to five years	Under Section 20 – **First Offence for Seller or distributor:** Fine up to Rs 1,000/- or imprisonment up to one year or both. **Subsequent Offence:** Fine up to Rs 3,000/- and imprisonment up to two years
Juvenile Justice Act	Section 77	Giving or causing any addictive substance including tobacco to minors	Upto 1 lakh fine and 7 years imprisonment	
Indian Penal Code	Section 268	Creating a Public nuisance that causes any common injury, danger or annoyance to the public	Fine up to Rs. 200/-	
	Section 269	Negligent acts likely to spread infection or disease dangerous to life	Imprisonment up to 6 Months or a Fine or both	
	Section 278	Making atmosphere noxious to health	Fine up to Rs. 500/-	
Food Safety and Standards Act, 2006 (FSSA, 2006)	Regulation 2.3.4 of Food Safety and Standards (Prohibition and Restrictions on Sales) Regulations, 2011	Use of Tobacco and nicotine as ingredients in any food products.	Penalty not exceeding Rs. 10.00 lakh under Section 57 (1) (ii) of FSSA, 2006	

Appendix 9: Intervention Method Algorithm for Quitting Tobacco Use



Appendix 10: 5 R technique to motivate a client who is not willing to quit tobacco

Relevance	• Encourage the tobacco user to consider the personal relevance of cessation. • Consider the disease status (if any), family or social situation, health concerns, age and gender.
Risk	• Discuss short-term, long term and environmental risks of continued tobacco use, including the effects of exposure to second-hand smoke on the family members, especially children. • Relate with the symptoms.
Rewards	• Encourage tobacco users to identify the benefits of cessation. • These may include withdrawal symptoms, fear and concern associated with quitting, depression, lack of social support, weight gain etc. • Discuss strategies to address potential barriers.
Roadblocks	• Barriers the tobacco user may face in his/her quit attempt should be identified. • Withdrawal symptoms, fear and concern associated with quitting, depression, lack of social support, and enjoyment of tobacco are some of the barriers that the tobacco user may face in an attempt.
Repetitions	• This information should be reviewed regularly with tobacco users who are not yet ready to quit. • It is also important for tobacco users who have not yet successfully quit to understand that most people attempting cessation quit several times before finally succeeding in quitting.

Appendix 11: Guidance on an action plan for tobacco users willing to quit

Challenges	Suggested Solutions
Help in making a **QUIT PLAN.**	• Preparations for quitting; Set a quit date; ideally, the quit date should be within 2 weeks. • Tell family, friends, and co-workers about quitting, plan and seek their support. • Anticipate challenges to planned quit attempts, particularly during the critical first few weeks. These include nicotine withdrawal symptoms. • Remove tobacco products from surroundings. • Avoid – Avoid Smoking or Using tobacco in places where a lot of time is spent e.g. workplace. • Avoid all forms of tobacco; do not substitute one tobacco product for another.
Provide practical counselling (Problem solving/skills training)	• Past quit experience-Identify what helped and what failed in previous • (Problem solving/skills training) quit attempts. • Anticipate triggers or challenges in upcoming attempts – Discuss challenges and how the user will successfully overcome them. • Alcohol- The tobacco user should consider limiting/abstaining from alcohol while quitting. • Other tobacco users in the household/ workplace - Quitting is more difficult when there is another smoker/ tobacco user in the household/ workplace. Other housemates/ coworkers/ peers should also be encouraged to quit.
Provide intra-treatment social support	• Provide a supportive environment by encouraging tobacco users in their quit attempts.
Help in obtaining extra treatment and social support	• Provide help in developing social support for quit attempts in the environment outside of treatment. • “Ask your spouse/partner, friends and coworkers to support you in your quit attempt.”
Recommend pharmacotherapy	• Explain how the medications improve success rates and reduce withdrawal symptoms.

Appendix 12: Challenges faced by client during lapse and relapse

Problem	Responses
Lack of support for cessation	• Schedule follow-ups or telephone calls with the tobacco user. • Help in identifying sources of support.
Negative mood or depression	• Provide counselling, prescribe appropriate medications, or refer to a specialist.
Strong or prolonged withdrawal symptoms	• Use an approved pharmacology or adding/combining pharmacologic medications to reduce strong withdrawal symptoms.
Weight gain	• Recommend starting or increasing physical activity. • Emphasize the importance of a healthy diet. • Reassure the tobacco user that weight gain is normal and will not increase beyond a point, and that there is just a need to watch it.
Flagging motivation/ feeling deprived	• Reassure the tobacco user that these feelings are common. • Recommend rewarding activities. • Emphasize that (even a puff or chew) will increase urges.

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We hope this manual will be an essential tool for dental professionals dedicated to improving oral health outcomes. By strengthening their capacity to detect and manage Oral Potentially Malignant Disorders (OPMDs) and oral cancer, we believe this manual will not only support the professional growth of practitioners but also contribute to reducing the burden of oral cancer in India. With the knowledge and strategies outlined here, dental professionals have the potential to make a significant impact, saving lives and enhancing the quality of life for countless individuals.

Disclaimer

NOTES

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