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University of Al-Mustaqbal
College of Dentistry

DIAGNOSIS AND MANAGEMENT OF ORAL CANCERS

A Graduation Project
Submitted To University of Al-Mustaqbal
College of Dentistry

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In partial fulfillment of the requirements for the ward of the degree of B.D.S

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بسم الله الرحمن الرحيم

يرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ وَاللَّهُ بِمَا تَعْمَلُونَ خَبِيرٍ

صدق الله العظيم

Supervisor Certification

I certify that this project was prepared by the fifth year undergraduate students Ahmed Hussein Fadel,Osama Khader Abbas,Sajjad Laith Ali

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Dedication

In the Name of Allah, the Most Gracious, the Most Merciful, We dedicated this work to our beloved parents for their endless support, to our esteemed professors for their invaluable guidance, To the one who was present in my heart ،and to the patients battling oral cancer, hoping this research contributes to their healing and a better future for dental healthcare.

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1. Introduction

Oral cancer is a malignant neoplasm arising from the lip or oral cavity. It originates from the mucosal lining of various oral structures, including the lips, buccal mucosa, gingiva, teeth, anterior two-thirds of the tongue, floor of the mouth, hard palate, and the retromolar trigone located posterior to the third molars. According to the World Health Organization (WHO) classification, oral cancer encompasses malignant tumors arising in these regions but excludes neoplasms of the tonsils, glands, and major salivary glands.

Anatomically, the oral cavity is closely related to the oropharynx, with defined boundaries such as the inferior margin of the soft palate, the division between the anterior two-thirds and posterior one-third of the tongue, and the anterior tonsillar pillars. Accurate anatomical distinction between these regions is essential for proper diagnosis, staging, and treatment planning, as both the etiology and prognosis may differ significantly between oral cavity and oropharyngeal cancers.

Oral cancer constitutes a major global health concern. When combined with oropharyngeal cancers, it ranks among the six most common malignancies worldwide. Independently, it is the 16th most common cancer and the 15th leading cause of cancer-related mortality, with an age-standardized global incidence of approximately four cases per 100,000 individuals. Overall, oral cancers account for about 2–5% of all malignancies. In 2020 alone, there were an estimated 377,713 new cases and 177,757 deaths globally, reflecting a rising trend and underscoring the significant burden of this disease.

Histopathologically, more than 90% of oral cancers are classified as oral squamous cell carcinoma (OSCC), which originates from the squamous epithelial cells lining the oral mucosa. OSCC represents a substantial proportion of head and neck cancers, accounting for nearly half of all cases. Although less common, other malignancies such as salivary gland tumors, melanomas, and lymphomas may also occur within the oral cavity. Due to the predominance of OSCC, most research efforts have focused on its molecular mechanisms, risk factors, and clinical management, particularly the malignant transformation of oral keratinocytes.

A major challenge in oral cancer management is its persistently poor prognosis, which is closely associated with the stage at diagnosis. The overall mortality rate remains approximately 50%, with little improvement over recent decades despite advances in surgical techniques, radiotherapy, and chemotherapy. This stagnation is largely attributed to the high proportion of cases diagnosed at advanced stages. Early-stage oral cancer is often asymptomatic or presents with subtle mucosal changes, such as white (leukoplakia), red (erythroplakia), or mixed lesions. As the disease progresses, it may manifest as an indurated, raised mass with an ulcerated surface. The absence of pain in early stages frequently leads to delays in seeking medical attention.

Survival outcomes vary markedly depending on the stage at diagnosis. The five-year survival rate for localized disease is approximately 83.7%, but it declines sharply to around 38.5% in cases with distant metastasis. The persistence of relatively unchanged survival rates over time highlights a critical gap in early detection rather than treatment efficacy. Given the accessibility of the oral cavity for direct visual examination, there is a significant opportunity for early diagnosis through routine screening. However, the continued prevalence of late-stage presentation reflects

deficiencies in public awareness, professional training, and the implementation of effective screening strategies.

2. Pathophysiology of Oral Cancer

Oral cancer, predominantly represented by oral squamous cell carcinoma (OSCC), originates from the epithelial lining of the oral cavity and results from a complex interaction between genetic mutations, epigenetic alterations, and environmental influences. Its development follows a multistep progression, beginning with normal epithelium transforming into premalignant lesions such as leukoplakia or erythroplakia, which may subsequently evolve into invasive carcinoma.

This process is driven by disruptions in key molecular pathways that regulate cellular proliferation, differentiation, apoptosis, and immune surveillance. Understanding these mechanisms is essential for the development of targeted therapeutic strategies and improved clinical outcomes.

2.1 Genetic Mutations and Molecular Drivers

The pathogenesis of oral cancer is fundamentally linked to genetic alterations affecting oncogenes, tumor suppressor genes, and DNA repair systems. These changes result in loss of growth control and malignant transformation.

2.1.1 Tumor Suppressor Gene Mutations

Inactivation of tumor suppressor genes is a critical event in oral carcinogenesis. Among these, **TP53**, which encodes the p53 protein, plays

a pivotal role in regulating the cell cycle, DNA repair, and apoptosis. Mutations in TP53 are frequently observed in OSCC, leading to loss of its protective function as the "guardian of the genome." Consequently, cells with DNA damage continue to proliferate, promoting genomic instability.

Another important tumor suppressor gene is **CDKN2A**, which encodes the p16 protein, a key regulator of cell cycle progression. Loss of p16 activity—either through mutation or epigenetic silencing—removes an essential checkpoint, allowing uncontrolled cell division. In HPV-associated cancers, however, p16 is often overexpressed and serves as a useful biomarker.

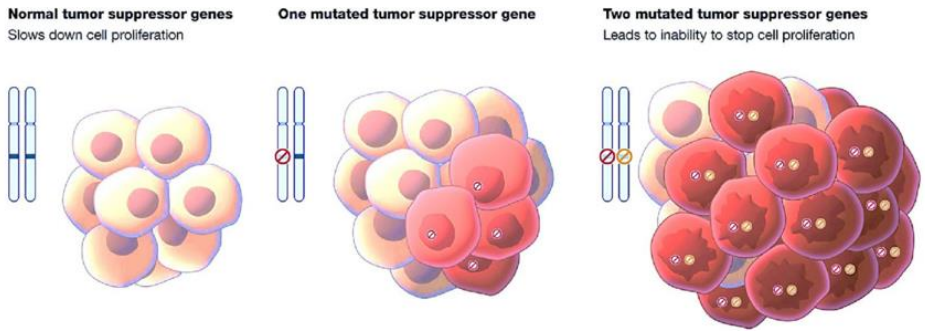


figure 1Normal and mutated tumor suppressor genes

2.1.2 Oncogenes and Cell Signaling Pathways

Activation of oncogenes plays a major role in driving oral cancer progression through dysregulated signaling pathways. One of the most commonly overexpressed oncogenes in OSCC is the **epidermal growth factor receptor (EGFR)**. Upon activation, EGFR stimulates downstream pathways such as **PI3K/AKT/mTOR** and **MAPK/ERK**, which enhance cell proliferation, survival, and invasion.

Overexpression of EGFR is associated with poor prognosis and resistance to conventional therapies, making it an important therapeutic target (e.g., cetuximab).

Additionally, the **PI3K/AKT/mTOR pathway** is frequently altered due to mutations in genes such as *PIK3CA* and *PTEN*. Hyperactivation of this pathway contributes to tumor aggressiveness by promoting cell growth, metabolism, and survival, and it represents a promising target for novel therapies.

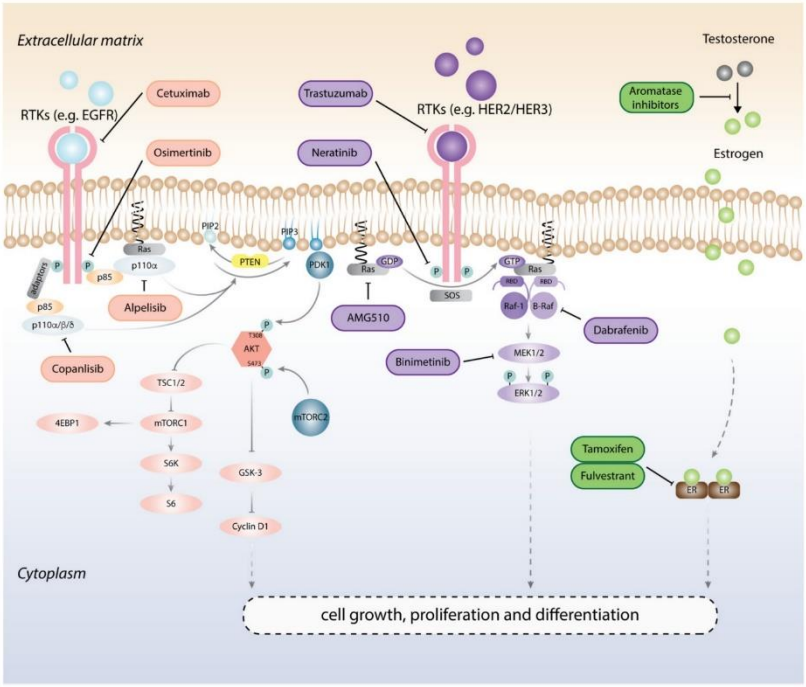


Figure 2 Signaling Pathways in Cancer

2.1.3 Human Papillomavirus (HPV)

A subset of oropharyngeal cancers is linked to infection with high-risk human papillomavirus (HPV), particularly type 16. HPV-related cancers have a distinct molecular mechanism compared to traditional OSCC.

The viral oncoproteins **E6** and **E7** inactivate tumor suppressor proteins p53 and retinoblastoma protein (pRb), respectively, leading to uncontrolled cell proliferation. Notably, HPV-positive cancers generally have a better prognosis and improved response to treatment compared to HPV-negative tumors.

2.2 Epithelial–Mesenchymal Transition (EMT) and Invasion

The transition from localized disease to invasive and metastatic cancer is largely mediated by **epithelial–mesenchymal transition (EMT)**. During this process, epithelial cells lose their polarity and adhesion properties and acquire mesenchymal characteristics, including enhanced motility and invasiveness.

EMT is regulated by signaling pathways such as **TGF-β**, **Wnt**, and **Notch**, which are frequently dysregulated in oral cancer. A hallmark of EMT is the downregulation of **E-cadherin** and upregulation of **N-cadherin** and **vimentin**, facilitating tumor cell detachment, invasion, and metastasis.

2.3 Tumor Microenvironment (TME) and Immune Evasion

The tumor microenvironment (TME) plays a vital role in oral cancer progression, invasion, and resistance to therapy. It consists of cancer-associated fibroblasts, immune cells, endothelial cells, and the extracellular matrix, all of which interact dynamically with tumor cells.

A key feature of the TME is **immune evasion**, where tumors suppress the host immune response. This is commonly mediated through the upregulation of immune checkpoint molecules such as **PD-L1**, which binds to **PD-1** receptors on T cells, inhibiting their activity. Immune checkpoint

inhibitors such as pembrolizumab and nivolumab have demonstrated effectiveness in restoring anti-tumor immunity.

Furthermore, the TME facilitates tumor invasion through the secretion of **matrix metalloproteinases (MMPs)**, which degrade the extracellular matrix. Tumor hypoxia also promotes angiogenesis and contributes to treatment resistance, making the TME a critical therapeutic target.

3. Etiological Risk Factors and Epidemiology

Oral cancer is a multifactorial disease influenced by environmental, lifestyle, viral, and genetic factors.

3.1 Principal Carcinogenic Exposures

The most significant risk factors for oral cancer are tobacco use and alcohol consumption, which together account for the majority of cases.

3.1.1 Tobacco: Smoked and Smokeless Forms

Tobacco remains the leading cause of oral cancer. It contains carcinogenic compounds such as nitrosamines, benzopyrenes, and aromatic amines, which form DNA adducts and induce mutations. Smokers have approximately a threefold increased risk compared to non-smokers.

Smokeless tobacco, including chewing tobacco and betel quid with tobacco, also significantly increases risk due to prolonged direct exposure of the oral mucosa to carcinogens.

3.1.2 Alcohol and Its Synergistic Effect

Alcohol acts as an independent risk factor and enhances mucosal permeability, increasing susceptibility to carcinogens. It is metabolized into **acetaldehyde**, a recognized carcinogen that damages DNA and impairs repair mechanisms.

The combined use of alcohol and tobacco produces a strong synergistic effect, dramatically increasing cancer risk—far exceeding the individual effects of each factor alone.

3.1.3 Betel Quid and Areca Nut

Betel quid chewing, common in South Asia, is a major contributor to oral cancer. The **areca nut**, even without tobacco, is classified as a Group 1 carcinogen. The increasing use of commercial products such as gutkha and pan masala has raised significant public health concerns.

3.2 Viral Etiology: HPV

High-risk HPV infection, particularly type 16, is an established cause of a subset of head and neck cancers. While strongly linked to oropharyngeal cancer, its role in oral cavity cancers is less pronounced but still significant.

HPV-associated cancers often occur in younger, non-smoking individuals and are characterized by better prognosis and responsiveness to treatment.

Prevention strategies, particularly vaccination, play a key role in reducing HPV-related cancer burden.

3.3 Other Contributing Risk Factors

Additional factors influencing oral cancer risk include genetic susceptibility, impaired DNA repair capacity, and immunosuppression. Patients undergoing hematopoietic stem cell transplantation, for instance, have a significantly increased risk.

Chronic inflammation, poor oral hygiene, and diets lacking essential nutrients and antioxidants also contribute to disease development.

Epidemiology of Oral Cancer

Oral cancer represents a major and increasing global public health concern, with over 450,000 new cases reported annually. Epidemiological data from 1990 to 2017 demonstrate a steady rise in disease burden, including an increase in age-standardized incidence rates. The global distribution of oral cancer shows significant geographic variation, with certain regions experiencing disproportionately high incidence rates.

In contrast, Iraq is considered one of the countries with relatively low incidence. A large global study conducted in 2017 reported that Iraq had one of the lowest age-standardized incidence rates worldwide, estimated at 0.96 per 100,000 population. This finding was supported by national data from 2014–2018, which reported an even lower incidence rate of approximately 0.4 per 100,000. The highest-risk groups were identified as males and individuals over the age of 40, with the tongue being the most commonly affected anatomical site.

4. Clinical Presentation of Oral Cancer

The clinical presentation of oral squamous cell carcinoma (OSCC) is highly heterogeneous, which complicates early detection and contributes to the high proportion of cases diagnosed at advanced stages. The morphological features of lesions and associated clinical symptoms vary considerably depending on the stage of the disease, the anatomical location involved, and the tumor's pattern of growth.

4.1 Early Manifestations and Precursor Lesions

In its early stages, OSCC is typically subtle and frequently asymptomatic, presenting as minor mucosal alterations that may go unnoticed by both patients and clinicians. Many individuals report no pain at the onset, which reduces the likelihood of seeking prompt medical attention.

Early lesions often develop from or resemble **Oral Potentially Malignant Disorders (OPMDs)**—clinically visible mucosal abnormalities associated with an increased risk of malignant transformation. The most common forms include:

- **Leukoplakia:**
  Appears as a persistent white patch or plaque on the oral mucosa that cannot be scraped off and cannot be clinically or pathologically classified as another condition. Although many cases are benign,

some exhibit epithelial dysplasia and represent the most common precursor to OSCC.

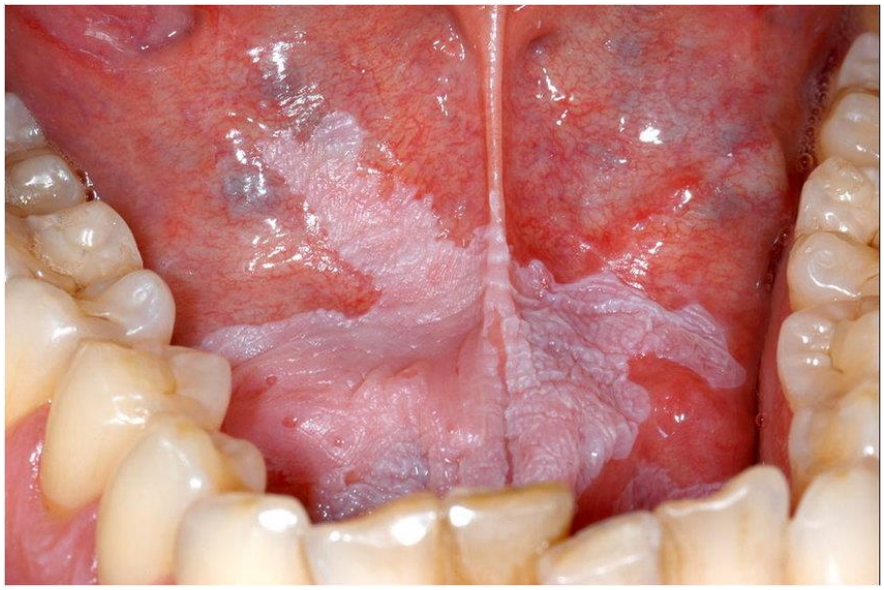


Figure 3 Leukoplakia of the floor of the mouth

- **Erythroplakia:**

  Presents as a flat or slightly depressed, velvety red lesion. Although less common than leukoplakia, it carries a significantly higher risk of malignancy, with many cases demonstrating severe dysplasia or carcinoma in situ upon biopsy.

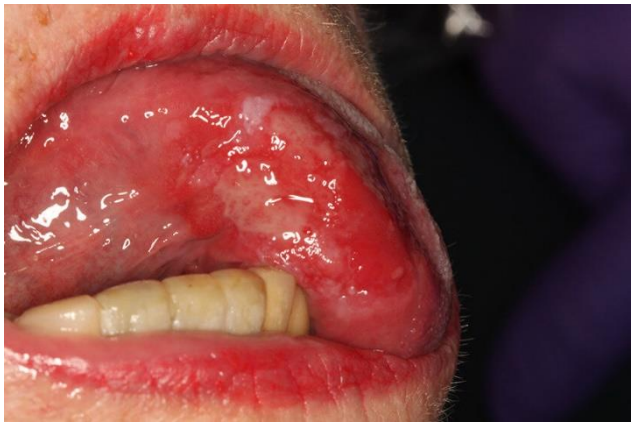


Figure 4 Erythroplakia: a mostly red, ulcerated plaque with a small white area on the superior aspect

- **Erythroleukoplakia (Speckled Leukoplakia):**

A mixed lesion composed of both red and white areas. These non-homogeneous lesions have a higher likelihood of malignant transformation compared to uniformly white lesions.

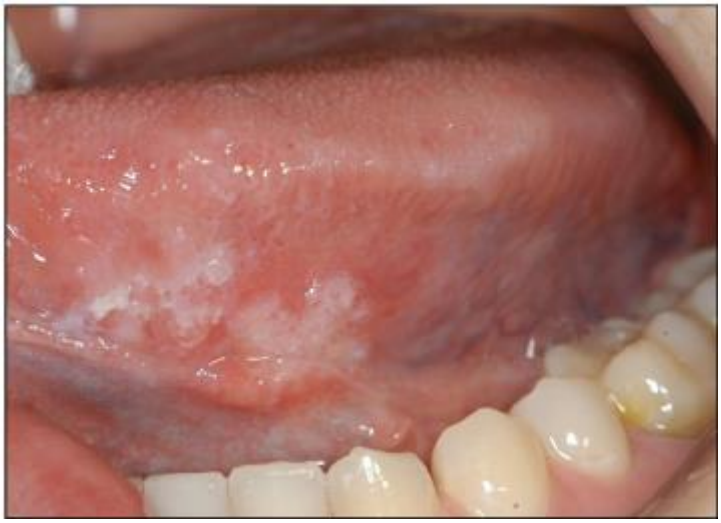


Figure 5 Erythroleukoplakic lesion on the left lateral border of the tongue of patient.

A key clinical guideline is that any oral ulcer, patch, or mass that fails to heal within two to three weeks should be considered suspicious and requires thorough professional evaluation to exclude malignancy.

4.2 Advanced Manifestations and "Red Flag" Symptoms

As oral squamous cell carcinoma (OSCC) advances from a superficial lesion to an invasive malignancy, its clinical presentation becomes more distinct and symptomatic. The most common manifestations of established disease include a persistent non-healing ulcer or an exophytic, proliferative growth.

The Malignant Ulcer:

A characteristic feature of invasive OSCC is a chronic ulcer that does not resolve. Unlike benign traumatic ulcers, malignant ulcers typically present with an irregular shape, elevated and rolled margins, and a firm (indurated) border surrounding a central necrotic or cratered area.

The Exophytic Mass:

In some cases, the lesion may appear as an outward-growing (exophytic) or ulceroproliferative mass. These growths often exhibit a fungating, cauliflower-like appearance or a rough, granular surface texture.

Associated Signs and Symptoms:

As the tumor infiltrates deeper tissues, several important "red flag" features may develop, indicating advanced disease:

• Persistent Pain:

Early lesions are often painless; however, advanced tumors commonly produce continuous localized pain that may radiate to the ear (otalgia).

• Induration and Fixation:

The lesion and surrounding tissues become firm and immobile due to tumor infiltration into underlying structures.

• Unexplained Tooth Mobility:

Loosening of teeth without evident periodontal disease may suggest invasion of the alveolar bone.

• Neurological Symptoms:

Sensory disturbances such as numbness, tingling, or altered sensation (paresthesia) in the tongue or lips may occur نتيجة involvement of sensory nerves.

• Functional Impairment:

Patients may experience difficulty or pain during swallowing (dysphagia), impaired speech (dysarthria), or restricted mouth opening (trismus), all of which indicate deeper involvement of muscles and nerves.

• Cervical Lymphadenopathy:

The presence of a firm, fixed, and typically painless neck mass is suggestive of regional metastasis to the cervical lymph nodes.

5.0 Diagnostic Techniques for Oral Cancer

The diagnosis of oral cancer follows a systematic, multi-step approach that begins with clinical suspicion and progresses to definitive confirmation through histopathological evaluation, followed by accurate staging to inform appropriate treatment strategies.

5.1 Foundational Diagnostic Procedures

The primary basis for diagnosing oral cancer relies on a combination of careful clinical examination and tissue biopsy.

• Clinical Oral Examination (COE):

This represents the first-line diagnostic approach and involves a thorough visual and tactile assessment of all accessible oral and oropharyngeal

tissues under proper illumination. The examination includes palpation of key areas such as the tongue, floor of the mouth, and surrounding soft tissues to detect induration or hidden submucosal lesions. Additionally, evaluation of the cervical lymph nodes through neck palpation is an essential component to identify possible lymphadenopathy.

Table 3 shows important symptoms of oral cancer, which should be looked out for during regular clinical examinations.

Table 1. Clinical Symptoms That May Indicate Oral Cancer

- Non-healing, unresponsive to the induced treatment, localized modification of appearance.
- Rapid growth of lesion in a short period of time
- Pain localized in oral area.
- Bleeding from suspected lesion.
- Tooth mobility.

Clinical symptoms that may indicate oral cancer.

• Biopsy and Histopathology:

A definitive diagnosis of oral cancer can only be established through biopsy followed by histopathological analysis, which remains the gold standard. Performing an incisional biopsy on any suspicious lesion is essential to confirm malignancy. This analysis also determines the histological type (such as squamous cell carcinoma) and evaluates important prognostic factors, including tumor grade and depth of invasion.

5.2 Adjunctive Diagnostic Aids

A variety of adjunctive diagnostic methods have been introduced to support clinicians in detecting suspicious oral lesions that may not be readily visible under conventional white light examination. These techniques also aid in identifying the most representative site for biopsy, thereby minimizing the likelihood of false-negative outcomes.

Vital Staining:

This technique involves the application of specific dyes to the oral mucosa to highlight abnormal tissue changes.

• Toluidine Blue:

Toluidine blue is a metachromatic dye that has an affinity for nucleic acids (DNA and RNA), which are present in higher concentrations within dysplastic and malignant cells. Areas that retain the dye appear as dark royal blue, assisting clinicians in targeting the most biologically active

regions of a lesion for biopsy. Although this method demonstrates high sensitivity, its specificity is relatively limited.

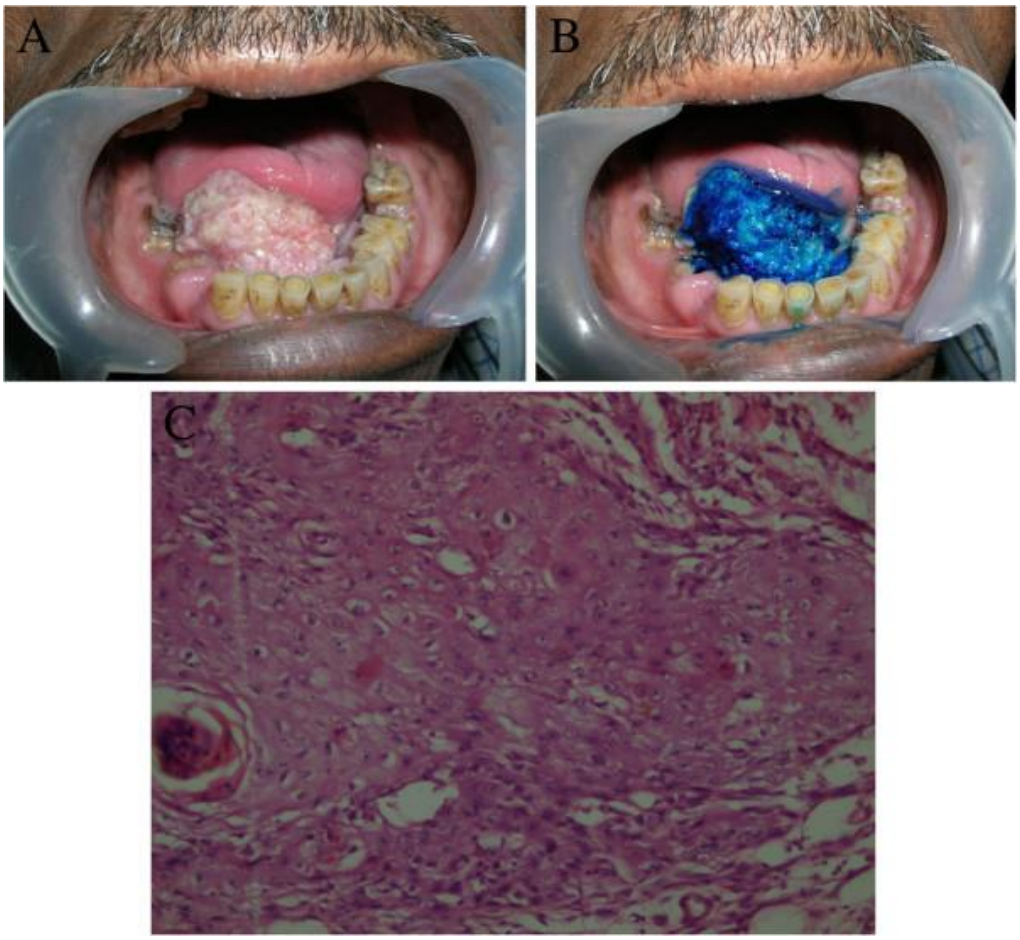
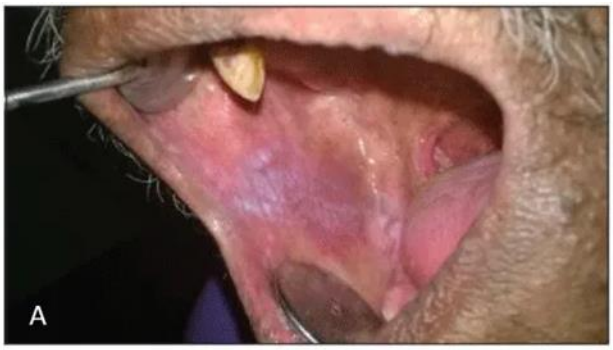


Figure 6 Presentation of a true-positive staining on the floor of the mouth.

• Lugol's Iodine:

Lugol's iodine stains glycogen-rich normal epithelial cells a dark brown color. In contrast, dysplastic and malignant cells, which are deficient in glycogen, fail to absorb the stain and appear as pale or unstained regions against the surrounding brown-stained healthy tissue.



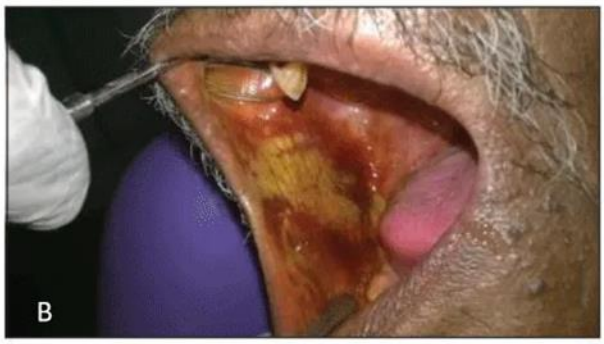


Figure 7: A: lesion present on the buccal mucosa. B: lesion is stained with lugol's iodine solution. The margins appeared to be ill defined shows prominent after staining

5.3 Imaging for Staging and Treatment Planning

Following confirmation of a cancer diagnosis, imaging modalities play a crucial role in determining the extent of disease (staging), which is essential for appropriate treatment planning.

• Radiography:

Conventional radiographic techniques, including dental and panoramic imaging, provide preliminary information regarding tumor invasion into the jaws. Typical findings may include poorly defined osteolytic lesions and cortical bone destruction.

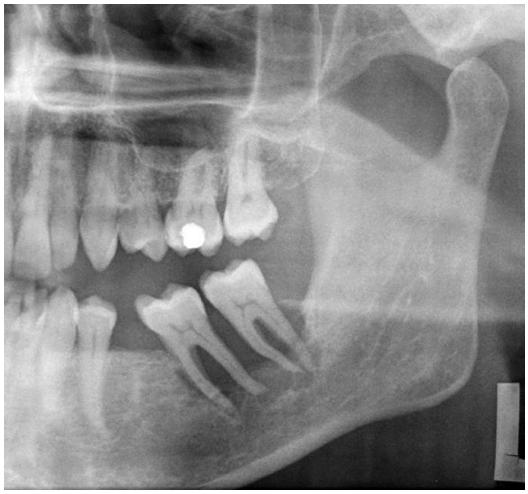


Figure 8 Imaging patients with cancer of the oral cavity

• **Advanced Cross-Sectional Imaging:**

o Computed Tomography (CT):

CT imaging is particularly valuable for assessing cortical bone involvement and is highly effective in detecting metastatic spread to cervical lymph nodes. Additionally, chest CT scans are routinely performed in advanced cases to evaluate for possible pulmonary metastases.

o Magnetic Resonance Imaging (MRI):

MRI offers superior soft tissue resolution compared to CT and is the preferred modality for evaluating the precise extent of the primary tumor. It is especially useful in assessing invasion into tongue muscles, the floor of the mouth, bone marrow, and in identifying perineural spread.

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